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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 08.067.107

Solicitud de patente a nombre de **WORLD-TRADE IMPORT-EXPORT, WTIE, AG**

Respuesta a la oposición presentada por **PROCAPS S. A y LAFRANCOL S.A.**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53 piso 6, obrando como apoderada de la sociedad Solicitud de patente a nombre de **WORLD-TRADE IMPORT-EXPORT, WTIE, AG**, ubicada en Zug, Suiza, damos respuesta a los oficios No. 04089 y 04090 ambos notificados por fijación en lista el 14 de marzo de 2012, por medio de los cuales se corrió traslado de las oposiciones presentadas por las sociedades PROCAPS S.A. y LAFRANCOL S.A respectivamente, contra la solicitud de patente de la referencia.

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presentamos junto con este memorial nuevo pliego reivindicatorio que consta de 1 reivindicación dirigida a la composición farmacéutica que comprende la combinación sinérgica de besilato de amlodipino y ácido acetilsalicílico en unas cantidades específicas y que contiene además excipientes farmacéuticamente aceptables.

En cuanto a estas modificaciones nos permitimos decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de realzar la novedad y la altura inventiva de la invención en estudio a la luz de los requerimientos de la Decisión 486 de la Comunidad Andina y en respuesta a las objeciones presentadas por los opositores.

Teniendo en cuenta el concepto técnico emitido por el Señor Superintendente Delegado para la propiedad intelectual GianCarlo Marcenaro Jiménez a la doctora Ana Maria Castro Wey, que da alcance a las comunicaciones No. 09-001524 y 09-012566, se presenta únicamente una tasa adicional correspondiente al recibo No. 10-24,975 del 5 de abril de 2010, por modificación de la solicitud, toda vez que la solicitud fue presentada con anterioridad al 1 de enero de 2009.

2. PRETENSIONES DE LAS OPOSICIONES:

Respetuosamente nos permitimos decir que nos oponemos a la pretensión de los escritos de oposiciones por cuanto, como se demuestra más adelante, la invención presentada por mi mandante cumple con los requisitos de novedad, nivel inventivo y aplicación industrial. En consecuencia, se debe otorgar el privilegio de patente de invención y expedir el título correspondiente.

2.1 El opositor PROCAPS S.A. (Opositor 1) argumenta que la solicitud en estudio carecería de novedad y nivel inventivo en vista de las enseñanzas de los documentos D1 (US2003099724)

En relación con la novedad, se hace necesario señalar que artículo 16 de la Decisión 486 establece que: “*Una invención se considera nueva cuando no está comprendida en el estado de la técnica*”

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida...”(el resaltado es nuestro).

Si de acuerdo con el espíritu de la norma legal indicada, la invención no se considera como nueva si está “comprendida” en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la totalidad del invento y no a alguno o a algunos de los componentes que hacen parte de la nueva solicitud.

En efecto, para que la invención pierda su calidad de novedosa, es claro que ella, TODA ELLA, ha de estar contenida en el “*conjunto de conocimientos existentes que son aplicables al proceso industrial*” como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Esto se conoce como NOVEDAD ABSOLUTA, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de forma total con lo revelado en cada uno de los documentos señalados por el opositor, conclusión a la que se llega después de un análisis exhaustivo mediante una comparación entre

el capítulo reivindicatorio de la invención en estudio y cada una de las divulgaciones citadas por el opositor como anterioridades.

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: *“hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria”* (Ibidem, páginas 53 y 54) (El subrayado es nuestro).

Por lo tanto y teniendo en cuenta lo anteriormente expuesto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma **TOTAL** y **ABSOLUTA** en cada uno de los documentos que se mencionan como anterioridad; y

-Que la invención en cuestión puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el **valor agregado** que aporta la invención con sus nuevas características al campo técnico al cual pertenece la solicitud en estudio.

Aplicando lo anterior al caso concreto, para que las razones que aduce el opositor para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención en estudio está comprendida en el estado de la técnica de forma **TOTAL**, lo cual no sucede como más adelante se demostrara.

2.1.1 Argumentos que desvirtúan las objeciones presentadas por el oponente PROCAPS S.A

2.1.1.1. Legítimo interés.

El solicitante considera que el opositor no acredita su legítimo interés para presentar la oposición que nos ocupa, ya que manifiesta que “algunos productos” de su representada se verían afectados directamente ya que contienen en particular Amlodipino Besilato y Acido Acetilsalicílico.

Sin embargo cabe señalar que la presente solicitud de patente versa sobre la **COMBINACION SINERGICA DE DOS ACTIVOS**, que en su conjunto forman un PRODUCTO NUEVO, pero en forma aislada no existiría ninguna afectación para con ninguno de los compuestos que la conforman, por lo que el solicitante considera que el oponente no tiene acreditado su interés legal para presentarse como opositora de la presente solicitud de patente.

2.1.1.2 Fundamentos de la Oposición.

El opositor manifiesta que la presente solicitud carece de novedad en base al documento US 2003099724 denominado D1, ya que dice que la reivindicación 1 y 10 recoge en concreto la combinación de un vasodilatador con un agente antiinflamatorio. Entre los agentes vasodilatadores figura como una opción el amlodipino besilato y entre las opciones de los antiinflamatorios se encuentra el ácido acetilsalicílico.

Sin embargo, aunque dicha patente contempla como opciones de la composición a los activos materia de la presente invención, este documento **NO** describe la presente invención.

De hecho, el D1 describe un compuesto para la **prevención y retraso de la retinopatía diabética**, y la pérdida de agudeza visual y ceguera que puede causar dicha patología. Los compuestos incluyen magnesio, un vasodilatador, aminoguanidina, un agente antiinflamatorio y un antioxidante.

Asimismo, en las reivindicaciones específicamente la No. 25, se establece: *El compuesto de la reivindicación 14 comprende aproximadamente de 40 a 400 mg de carbonato de magnesio, aproximadamente 0.4 a 10 mg de amlodipino besilato, aproximadamente 10 a 50 de aminoguanidina, aproximadamente de 20 a 650 mg de ácido acetilsalicílico, y aproximadamente de 10 a 250 mg de vitamina C.* Todo lo anterior, dirigido al **TRATAMIENTO PARA PREVENIR O RETARDAR LOS ESTADOS PATOLOGICOS RETINALES ASOCIADOS CON RETINOPATIA DIABETICA.**

Sobre este particular, es importante hacer énfasis sobre el hecho que la Retinopatía Diabética (RD) es la principal manifestación del compromiso ocular en los pacientes diabéticos. Ocurre cuando la diabetes daña a los pequeños vasos sanguíneos de la retina, que es el tejido sensible a la luz situado en la parte posterior del ojo. Lo más importante en la retinopatía diabética es el control de la glucosa por medio de una dieta adecuada y terapia farmacológica con normoglucemiantes o hipoglucemiantes.

En claro contraste con lo anterior, la presente invención comprende una combinación sinérgica de amlodipino besilato y ácido acetilsalicílico (en adelante AAS) para el **TRATAMIENTO DE LA HIPERTENSIÓN ARTERIAL SISTÉMICA** Y LA PREVENCIÓN DE EVENTOS VASCULARES DE ORIGEN ISQUÉMICO, ocasionados por la alteración en la elevación en las cifras de presión arterial, aunado a factores de riesgo coronario (como vida sedentaria, obesidad, tabaquismo, síndrome metabólico etc.).

Como se podrá apreciar, ambos medicamentos SON DIFERENTES, por lo que NO SE PUEDE AFIRMAR que uno DESCRIBE al otro, lo cual sería necesario

para poder concluir que no se cumple con el requisito de novedad contemplado en el artículo 16 de la decisión 486 de la Comunidad Andina de Naciones.

De conformidad con el artículo citado, se debe considerar nuevo todo aquello que NO esté comprendido en el estado de la técnica, y el estado de la técnica se considera al conjunto de **conocimientos técnicos** que se hayan hecho públicos por una **descripción** oral o escrita.

Del análisis del documento D1 se establece que EN DICHO DOCUMENTO NO SE DESCRIBE LA PRESENTE INVENCION, y en dicha solicitud NO SE APORTA CONOCIMIENTO ALGUNO RELACIONADO CON UN SINERGISMO DE PARTE DEL AAS HACIA UN BLOQUEADOR DE CANALES DE CALCIO, COMO LO ES EL BESILATO DE AMLODIPINO EN LA HIPERTENSION.

A fin de realizar la valoración de la novedad, es necesario analizar el contenido global de los documentos y no sus aspectos aislados. En el caso que nos ocupa, la anterioridad D1 reporta una composición que **puede contener o no**, amlodipino y ácido acetilsalicílico, pero ADEMÁS está compuesto de carbonato de magnesio, aminoguanidina y vitamina C, dichos activos son necesarios **todos** para conseguir el objetivo para lo cual se reivindica dicha solicitud de patente y dicho objetivo es el TRATAMIENTO PARA PREVENIR O RETARDAR LOS **ESTADOS PATOLOGICOS RETINALES** ASOCIADOS CON LA RETINOPATIA DIABETICA.

La presente invención en cambio está compuesta por la combinación de Amlodipino besilato + Ácido acetilsalicílico para el **TRATAMIENTO DE LA HIPERTENSION ARTERIAL SISTÉMICA** Y LA PREVENCIÓN DE EVENTOS VASCULARES DE ORIGEN ISQUÉMICO.

Un técnico en la materia NO podría considerar que ambos medicamentos son lo mismo y, por lo tanto, pueden ser administrados indistintamente para ambas patologías. Las dosis y las combinaciones de fármacos son determinantes en el momento de indicar su administración. El solicitante considera que D1 de ninguna manera describe los **conocimientos técnicos** aportados por la presente invención.

Del análisis de la solicitud de patente citada D1, se observa que está dirigida a la prevención de la retinopatía diabética, basándose en **los mecanismos de acción secundarios de los calcio antagonistas NO COMO EFECTO ANTIHIPERTENSIVO** como los derivados dihidropiridínicos, los cuales tienen acción en el mejoramiento de la microcirculación, que junto con los otros componentes y antioxidantes MEJORAN LA RETINOPATÍA DIABÉTICA.

En los párrafos **0015 al 0020** se mencionan múltiples factores fisiopatológicos que pueden contribuir a la progresión de la retinopatía diabética entre los que se

encuentra la hiperglucemia (cifras de glucosa elevadas), la cual es característica en los individuos que padecen de diabetes mellitus tipo 1 o 2, y causa daños en la microvasculatura de la retina debido a alteraciones químicas que producen metabolitos tóxicos (endotoxinas).

Si bien en el párrafo **0021** se menciona que la hipertensión arterial PUEDE contribuir a la progresión de la retinopatía diabética es solo UNA PROBABILIDAD, puesto que NO TODOS LOS PACIENTES DIABETICOS SON HIPERTENSOS, NI TODOS LOS HIPERTENSOS SON DIABÉTICOS, ambas pueden ser comorbilidades o NO. Al respecto también se menciona en el párrafo **0022** a la aterosclerosis, y no porque se haya hecho mención de esta patología se debe entender que el medicamento en cuestión es indicado también para el tratamiento de esta última.

De hecho, en el párrafo **0037** se explica expresamente el efecto buscado del activo amlodipino besilato: **“la vasodilatación” acción conocida de los bloqueadores de los canales de calcio**, entre ellos (y no de forma exclusiva) el amlodipino.

En efecto, en el párrafo **0038** se hace mención que otros bloqueadores de los canales de calcio adecuados para su uso como compuestos en la invención de D1 incluyen: nifedipino, nicardipino, felodipino, nimodipino, nisoldipino, isradipino, o bien verapamilo y diltiazem.

En el párrafo **0039** se menciona que para la invención se puede utilizar amlodipino y/o nicardipino especificando que es para LA RETARDACIÓN DE LA RETINOPATÍA DIABÉTICA.

De hecho, a lo largo de toda la descripción de la patente se hace mención de “vasodilatadores”, los cuales incluyen a todos los antihipertensivos, ya que un experto en la materia entiende que esta acción secundaria es conocida de los fármacos que son bloqueadores de los canales de calcio.

Por lo tanto, este efecto vasodilatador es para lo cual está dirigida la propuesta del uso de los fármacos antihipertensivos. Con la invención descrita en D1 **NO** se está buscando el efecto principal de estos fármacos, es decir, como antihipertensivos, ya que las dosis propuestas son infra-terapéuticas (amlodipino desde 0.4 mg.), y no lograrían funcionar como antihipertensivos (como se podrá ver más adelante), pero SI como vasodilatadoras.

En el párrafo **0047** citado por el oponente, referente al **AAS**, en dicho documento están proponiendo su acción en algo ya conocido de este activo: el efecto antiinflamatorio y su acción bloqueadora de la síntesis de tromboxano, además también mencionan y proponen a otros antiinflamatorios no esteroides, los conocidos como “AINES”.

Al respecto, en el párrafo 0048 se describen las dosis de la aspirina como “CANTIDAD EFECTIVA PARA PREVENIR LA AGREGACIÓN PLAQUETARIA”, acción ya conocida de la aspirina. Se describe que la dosis para niños menores de 3 años va de 20 a 84 mg por día, de 80 a 325 mg por día para niños de 3-16 años y de 80 a 650 mg por día para un adulto. Dosis de adulto distinta a la reivindicada en la presente invención.

Asimismo, en el párrafo 0049 se describe que un experto en la materia reconocería que otro AINE podría ser aplicable para esta invención por ejemplo: diclofenaco, diflusal, etodolaco, fenoprofeno, flurbiprofeno, ibuprofeno, indometacina, ketoprofeno, meclofenamato, nabumetona, naproxeno, colín salicilato, oxaprozina, piroxicam, sulindaco y tolmetina. Por lo tanto, se tiene que a diferencia de la presente invención, los fármacos propuestos por la invención D1 SON INTERCAMBIABLES, es decir, no se está proponiendo una combinación sinérgica para LA PREVENCIÓN DE LA RETINOPATIA DIABETICA, ya que la propuesta de esta solicitud D1 es la combinación de fármacos con efectos conocidos, los cuales COMBINADOS DICHS EFECTOS actúan para prevenir la patología mencionada.

Con lo anterior, un experto en la materia entiende que la propuesta de esta invención D1 es LA COMBINACIÓN de 4 elementos: UN VASODILATADOR (el cual puede ser CUALQUIER ANTIHIPERTENSIVO), UN ANTIINFLAMATORIO (que puede ser o no aspirina), UNA AMINO GUANIDINA y UN ANTIOXIDANTE (que puede ser o no vitamina C).

De esta combinación, se entiende que lo que se busca es el retardar la aparición de la RETINOPATIA DIABETICA, en ningún momento se sugiere que esta combinación mejorará la hipertensión arterial, no presenta parámetros al respecto ni se sugiere que se pueda administrar como parte de una terapia a un paciente hipertenso, exclusivamente esta propuesto como PREVENTIVO DE LA RETINOPATÍA DIABÉTICA.

Por lo anterior, el solicitante considera que el D1 NO DESCRIBE LA PRESENTE INVENCION, ya que NO SE RESUELVE EL MISMO PROBLEMA TECNICO, lo cual sería necesario para considerar incumplido el requisito de novedad para el otorgamiento de una patente. La presente invención es la combinación exclusivamente de amlodipino besilato y ácido acetilsalicílico, combinación NO conocida de dichos activos que juntos actúan de manera sinérgica para el CONTROL DE LA HIPERTENSIÓN ARTERIAL.

La novedad de la invención deberá analizarse respecto AL TODO de la invención y no sobre cada una de sus partes. Entre los requisitos indispensables para que una invención pueda ser considerada como objeto de protección por medio de patente, en primer lugar, está su novedad, que significa que una invención es nueva cuando no está comprendida en el estado de la técnica, es

decir que no está contenida, no está incluida, NO ESTA DESCRITA o no forma parte del estado de la técnica.

Es el caso que la presente invención consiste en la combinación sinérgica de Amlodipino y Acido Acetilsalicílico, administrados en una sola unidad de dosificación por vía oral, lo cual da lugar a un producto totalmente desconocido hasta antes del arribo de la presente invención, y el cual presenta un efecto mejorado con respecto a la actividad terapéutica de ambos activos actuando en forma aislada.

A efecto de aportar más elementos para acreditar los requisitos de patentabilidad de la presente invención, se adjunta a la presente carta, el **ANEXO No. 1** correspondiente al estudio titulado “EVALUAR LA EFICACIA Y SEGURIDAD DE LA COMBINACIÓN AMLODIPINO / ÁCIDO ACETILSALICÍLICO EN PACIENTES CON HIPERTENSIÓN ARTERIAL SISTÉMICA, ASOCIADO A FACTORES DE RIESGO CARDIOVASCULAR”. Dicho estudio tuvo el objetivo de evaluar la eficacia y seguridad de la combinación Amlodipino 5 mg y Ácido Acetilsalicílico 75 mg en pacientes con hipertensión arterial sistémica.

Como ya se ha mencionado **no existe precedente, es decir, no existe conocimiento técnico o científico que aporte o evidencie que el acido acetilsalicílico potencializa la actividad antihipertensiva del amlodipino, o de algún otro antihipertensivo.**

Existen en la literatura especializada innumerables artículos relacionados con la actividad antihipertensiva del activo amlodipino besilato. Por otro lado, es conocida la actividad antiplaquetaria del acido acetilsalicílico. Sin embargo, la actuación de este último como potencializador de la actividad antihipertensiva del amlodipino era desconocida hasta antes de la presente invención.

Se ha realizado una selección de los documentos científicos (estudios clínicos) que el solicitante considera especialmente relevantes para el caso que nos ocupa, y en particular para demostrar la mejora y la aportación que tiene el medicamento de la presente invención en relación con el estado de la técnica que le es aplicable.

Se analizaron los resultados reportados en dichos estudios en los que se evaluó al Amlodipino, los cuales fueron efectuados con diversos grupos, etnias, grados de hipertensión, edades de pacientes, además de diferentes factores de riesgo, etc. En todos ellos se encontró superioridad de la combinación frente a la actuación de Amlodipino solo o **INCLUSO COMBINADO CON ALGÚN OTRO ANTIHIPERTENSIVO**, dichos estudios se describen a continuación y se adjuntan al presente como evidencia de la aportación de la presente invención.

En este sentido, es deseo del solicitante adjuntar el artículo **“A randomized Placebo-Controlled Comparison of Amlodipine and Atenolol in Mild to Moderate Systemic Hypertension”** William H. Frishman, Richard Brobyn, Ronald D. Brown, Brian F. Johnson, Robert L. Reeves, and Duane G. Wombolt (ANEXO No. 2). En el cual se comparó Amlodipino con placebo y Atenolol en 125 pacientes con media a moderada hipertensión sistémica. Los pacientes recibieron placebo por 4 semanas, seguido de un tratamiento de una vez al día por 8 semanas de amlodipino y atenolol o placebo (tres grupos de 41, 43 y 41, respectivamente). La dosis media que se administró de amlodipino fue de 8.8 mg diarios. Los resultados alcanzados fueron de -12.8/-10.1 mm Hg para el grupo de amlodipino, meta alcanzada a las 8 semanas de tratamiento. En la página 104, Fig. 1 y página 105, Fig. 2. se pueden apreciar dichos resultados.

Comparando la información de este documento con los resultados de dicho estudio se ve que hay una diferencia significativa en la eficacia del tratamiento de la presente invención en comparación con Amlodipino solo. Con la presente invención se alcanzaron valores de reducción de presión arterial mucho más significativos en comparación con los alcanzados con Amlodipino solo (Amlo/AAS -23.7mm Hg y -14.9 mm Hg, presión sistólica y diastólica, respectivamente). Se sabe que una disminución promedio de 5-6 mm Hg en la presión arterial diastólica y de 10-12 mm Hg para la presión sistólica se asocia a una disminución de un 21% en la mortalidad cardiovascular, de un 48% en accidentes cerebrovasculares fatales y no fatales y una disminución del 14% en la enfermedad coronaria fatal y no fatal.

Otro estudio significativo a fin de demostrar la superioridad de la combinación de la presente invención es el titulado **“Amlodipine and captopril in moderate-severe Essentials hipertensión”** D. Maclean, E.T. Mitchell, R.G. Wilcox, P. Walker and H.M. Tyler. Department of Pharmacology, Ninewells Hospital, Dundee, DD1 9 SY, Queen's Medical Center, Nottingham, and Pfizer Central Research, Sandwich, Kent, UK (ANEXO No. 3). En dicho estudio, se valoró la utilidad de administrar amlodipino a pacientes que no habían sido controlados con dosis bajas de captopril. A 29 pacientes en un doble ciego, controlado con placebo, los cuales no pudieron ser controlados con dosis de 25 mg dos veces al día de captopril, se les administró placebo o bien 10 mg una vez al día de amlodipino.

Los resultados revelan que la reducción máxima de presión arterial que alcanzó la combinación de amlodipino con captopril fue de -22.9/13.5 mm Hg, presión sistólica/diastólica respectivamente. Dichos resultados, aunque se acercan mucho a los alcanzados con la combinación de la presente invención de Amlodipino /AAS con la dosis de 5mg/75mg respectivamente, es importante notar que éstos fueron alcanzados CON LA COMBINACION DE DOS ANTIHIPERTENSIVOS (amlodipino y captopril); por lo tanto, esto evidencia una superioridad de la combinación de la presente invención sobre el arte previo que le aplica.

Otro estudio es el presentado en el **ANEXO No. 4: “A dose-response study of amlodipine in mild to moderate hipertensión”** M. Heikki Frick, D. McGibney & H.M. Tyler From the First Department of Medicine, University Central Hospital, Helsinki, Finland and the Pfizer Central Research, Kent, UK., en el cual se estudió la eficacia del amlodipino en dosis de una vez al día en 205 pacientes con media a moderada hipertensión. El estudio fue conducido a doble ciego en 13 centros. La dosis inicial de amlodipino fue de 1.25, 2.5 y 5 mg respectivamente, las cuales fueron duplicadas después de 4 semanas si no se logró la meta de normo tensión.

En la página 103 tabla 3, se puede observar y comparar los resultados obtenidos en dicho estudio. La dosis máxima de amlodipino, es decir **10 mg diarios** alcanzó una disminución de 23.7 mm Hg, cifra idéntica a la disminución alcanzada con la combinación de la presente invención. Sin embargo, esta disminución se alcanzó con la **dosis máxima del fármaco en cuestión.**

En cambio con la combinación materia de la presente invención, se alcanzó la misma disminución de 23.7 mm Hg que la reportada en dicho estudio, pero con la mitad de dicha dosis (es decir, con 5 mg. cada 24hrs.), por lo que queda evidenciado que la combinación propuesta supera la actuación del amlodipino solo y en consecuencia se está aportando un medicamento potencializado, que supera el estado de la técnica al momento de la invención.

En el **ANEXO No. 5: “Double-blind evaluation of the dose-response relationship of amlodipine in Essentials hipertensión”** Jawahar L. Mehta, MD, PhD, Larry M. Lopez, PharmD, Nicholas D. Vlachakis, MD, Alan H. Gradman, MD, David T. Nash, MD, Mark T. O’Connell, MD, W. Thomas Garland, MD, and Bryant I. Pickering, MD Gainesville, Flu., Los Angeles, Calif., West Haven, Conn., Syracuse, NY., Miami, Flu., New Orleans, La., and Phoenix, Ark. From the University of Florida, Gainesville; University of Southern California, Los Angeles; Cardiology Section, Veterans Administration Medical Center, West Haven; D.T.N. Clinical and Research Laboratory, Syracuse; Department of Medicine, Jackson Memorial Hospital, and University of Miami Medical Center. Supported by funds from Pfizer Research, Groton, Corm. Received for publication Aug. 10, 1992; accepted Dec. 1, 1992. Reprint requests: Jawahar L. Mehta, MD, University of Florida, Division of Cardiology, Box 100277 JHMHG, Gainesville, FL 32610. 1993 by Mosby-Year Book., que fue un estudio multicéntrico, doble ciego, randomizado, paralelo, controlado con placebo para evaluar 4 dosis de amlodipino en pacientes con media a moderada hipertensión, se incluyeron 210 pacientes con hipertensión diastólica y por consecuencia sistólica. Después de 4 semanas de un periodo con placebo, a los pacientes les fueron administrados placebo o amlodipino a dosis de 1.25, 2.5, 5.0 o 10.0 mg diarios cada 24 horas. Se registró la presión y el pulso a la semana 0 y 4 registradas cada 12 horas después de la dosis y de nuevo a las 24 horas. Al final

del estudio los pacientes tratados con todas las dosis de amlodipino mayores a 1.25 mg diarios tuvieron reducción significativa de la presión arterial.

A partir de dicho estudio se puede observar que la presión sistólica fue disminuida con 5 y 10.00 mg diarios de amlodipino (Tabla II, página 1706), los cambios basales/finales se pueden apreciar en la Fig. 1. Con dichos resultados se puede determinar que la terapia con amlodipino en dosificaciones de 2.5, 5.0 y 10.0 mg. diarios fue asociada a una reducción significativa de la presión diastólica y sistólica, pero en ninguna de las dosis probadas se obtuvieron resultados en los niveles que la combinación de la presente invención Amlodipino /Acido acetilsalicílico se lograron.

Como se podrá observar a dosis máximas de amlodipino de 10.0 mg diarios la reducción más significativa fue de -14.1/-10.8 mm Hg, sistólica y diastólica respectivamente. **En cambio con la combinación de la presente invención, se alcanzó una disminución promedio de -23.7 y -14.9 mm Hg, presión sistólica y diastólica respectivamente.** Esto se logró con una dosis de 5.0 mg de amlodipino en combinación con 75 mg de ASA cada 24 hrs, es decir, en este estudio con la dosis igual de la combinación de la presente invención solo se alcanzaron disminuciones de 8.3 y 7.4 mm Hg para presiones sistólica y diastólica, respectivamente.

Estos resultados evidencian la mejora que aporta la combinación de la presente invención para el control de la presión arterial en comparación con el estado de la técnica que existía hasta antes del arribo de la presente invención.

Por su parte en el **ANEXO No. 6** se adjunta un estudio comparativo titulado **“Valsartan, a new angiotensina II antagonist for the treatment of Essentials hipertensión: A comparative study of the efficacy and safety against amlodipine”** Luigi Corea, MD, Ondina Cardoni, MD, Roberto Fogari, MD, Pierfranco Innocenti, MD, Carlo Porcellati, MD, Michele Providenza, MD, Susanne Meilenbrock, BPharm, John Sullivan, BSc, and Frederic Bodin, MD Perugia, Gubbio, Pavia, Carrara, and Gulado Tadino, Italy, and Basel, Switzerland.

El objetivo de este estudio consistió en comparar la eficacia antihipertensiva de Valsartán con Amlodipino. 168 pacientes con media a moderada hipertensión fueron randomizados en un doble ciego y a igual número recibieron 80 mg de Valsartán y 5 mg de Amlodipino por 8 semanas. Cuando no fue controlada la presión se elevó la dosis con 5 mg más de Amlodipino para ambos grupos.

Con los resultados que se observan en la Tabla II, pág. 344, se tiene que con monoterapia a las 4 semanas de tratamiento los valores alcanzados fueron de solo una reducción de -13.3/-10.1 mm Hg, presión sistólica y diastólica respectivamente, y a las 8 semanas para el grupo de Amlodipino solo se tuvo una reducción de -14.8/-11.1 mm Hg, presión sistólica y diastólica respectivamente.

Asimismo, en la semana 12 y, después de terapia adicional, es decir, **después de combinar los fármacos o bien duplicar la dosis inicial se lograron valores de -19.2/-15 mm Hg**, presión sistólica/diastólica respectivamente. Dichos valores son incluso menores a los alcanzados con la combinación materia de la presente invención. Por lo que se puede concluir que Amlodipino combinado con AAS a dosis bajas supera la combinación de incluso dos conocidos antihipertensivos.

En el **ANEXO No. 7** se presenta el estudio titulado **“Efficacy, safety, and effects on hipertensión-associated symptoms of losartan, alone or in combination with hydrochlorothiazide versus amlodipine in patients with mild to moderate hipertensión”** Renate Tiebel, Arnold Valhbruch, and Manfred Stapff. MSD Sharp & Dhme GmbH, Haar bei Muenchen, and Private Practice, Liccstandt, Germany.

En este estudio clínico randomizado, multicéntrico, doble ciego, con tres grupos de tratamiento fue conducido para comparar la eficacia y tolerabilidad de Losartán solo o combinado con Hidroclorotiazida y Amlodipino en pacientes con media a moderada hipertensión. Un total de 935 pacientes fueron randomizados a 3 regímenes de tratamientos: (1) Losartán 50 mg una vez al día con un posible incremento a 100 mg una vez al día. (2) Losartán 50 mg una vez al día con una posible adición de Hidroclorotiazida 12.5 mg una vez al día, o (3) Amlodipino 5 mg una vez al día con un posible incremento a 10 mg una vez al día a la semana 6.

Este estudio arrojó como resultados una disminución después de 12 semanas de tratamiento y con la necesidad de haber aumentado la dosis al doble de la inicial (de 5 a 10 mg de Amlodipino), se lograron cifras de reducción de -18.5/-13.6 mm Hg, presión sistólica y diastólica respectivamente. Lo anterior de nuevo confirma que la combinación de la presente invención logra mejorar parámetros de hipertensión con una dosis media en combinación con dosis baja de AAS.

También es importante analizar lo adjuntado en el **ANEXO No. 8**, principalmente, los resultados que fueron reportados en el estudio titulado **“Haemodynamic and metabolic effects of rilmenidine in hypertensive patients with metabolic syndrome X. A double-blind parallel study versus amlodipine”** Nicola De Lucaa, Raffaele Izzo, Dario Fontanaa, Gianluigi Iovino, Luigi Argenziano, Carmine Vecchione and Bruno Trimarco.

El objetivo de este estudio fue el comparar los efectos del Rilmenidina contra Amlodipino en presión arterial, entre otros. Lo importante de este estudio es que se realizó con pacientes que presentaban “síndrome metabólico”.

Al igual que el estudio del solicitante, la población que fue incluida en este estudio presentaba factores de riesgo coronario que son determinantes para llevar a un control más estricto en la disminución y control la presión arterial. En estos

pacientes es especialmente complicado poder regularizar la presión arterial, sobre todo con dosis bajas de antihipertensivos. Por esta razón resulta ser relevante la comparación de los resultados reportados en este estudio con los datos reportados en el estudio del solicitante con la combinación Amlodipino/Ácido Acetilsalicílico.

Cuando un paciente no ha respondido con dosis bajas efectivas, o dosis medias de antihipertensivos, es común que se eleve la dosis inicial e incluso combinar antihipertensivos a fin de lograr controlar la presión arterial. En este estudio como en muchos otros, la dosis inicial fue de 5.0 mg diarios y posteriormente se duplicó dicha dosis (10 mg cada 24 hrs.). Es importante señalar que la dosis máxima permitida de amlodipino son 10 mg en 24 horas.

Los resultados reportados implican una reducción de -15/-14 mm Hg presiones sistólica y diastólica respectivamente en 4 meses de tratamiento, tomando en cuenta que dichos resultados fueron alcanzados al haber tenido que aumentar la dosis de 5.0 mg a 10.0 mg diarios.

En el estudio del solicitante con una duración de 90 días, NO FUE NECESARIO AJUSTAR DOSIS a ninguno de los pacientes incluidos en el estudio, y la meta se alcanzó en tan solo 4 semanas, con una reducción de 23.7 mm Hg, es decir, con una diferencia significativa y con una dosis de tan solo 5 mg de Amlodipino, que corresponde a la mitad de la dosis administrada en este estudio.

Con la combinación de la presente invención se logran resultados más rápidos y efectivos, y con la dosis de 5mg se logran los resultados que el Amlodipino actuando solo hubiera tenido que ser administrado a 10mg diarios, es decir el doble de dosis y con los efectos secundarios ya conocidos del Amlodipino.

Una de las grandes ventajas que ofrece la combinación de la presente invención es que NO HUBO NECESIDAD DE AJUSTAR LA DOSIS, y la meta se alcanzó rápidamente, en comparación a la actuación de amlodipino solo. En la literatura especializada se puede encontrar que invariablemente hay necesidad de ajustar dosis a efecto de conseguir los resultados deseados, con la combinación de la presente invención, esto NO FUE NECESARIO. Es decir que la combinación de Amlodipino y AAS resultó en un efecto sorprendente al mejorar los parámetros de hipertensión en pacientes con riesgo cardiovascular, donde según las guías de hipertensión hubiera sido necesario administrar la dosis más alta de Amlodipino o bien optar por combinar 2 antihipertensivos a fin de lograr disminuir la presión arterial a niveles normotensos.

A efecto de ilustrar gráficamente los resultados de la combinación de presente invención Amlodipino 5 mg/AAS 75 mg en comparación con los resultados reportados de la eficacia de amlodipino solo, se realizaron gráficas comparativas que evidencian la superioridad de la combinación de la presente

invención. Se anota la significancia estadística con la prueba t-Student al comparar la presión arterial del estudio de la combinación de la presente invención con la presión arterial reportada en algunos de los estudios cotejados (documentos arriba indicados como ANEXOS No. 5, 6 y 8). Se presentan graficas de la PAS, la PAD, la disminución absoluta de la presión arterial en mm de Hg de ambas presiones y la disminución porcentual de la presión arterial en dichos estudios (**ANEXO No. 9**).

Asimismo, se anexan graficas comparativas de la eficacia terapéutica de la combinación de la presente invención comparada con los estudios que se adjuntan como Anexos 5, 6 y 8 mencionados anteriormente (**ANEXO No. 10**).

De las graficas anexas se puede evidenciar que la combinación de la presente invención logró con MENORES DOSIS de ambos activos Amlodipino/ AAS, disminuir significativamente los parámetros de presión arterial, los cuales solo son alcanzados con la dosis máxima de Amlodipino, es decir con 10 mg cada 24 hrs., y además estas cifras de disminución se alcanzaron en MENOR TIEMPO comparado con la monoterapia de Amlodipino a igual dosis, es decir con 5 mg cada 24 hrs.

Ha sido ampliamente documentada en los consensos sobre el tratamiento de la hipertensión arterial, la importancia de la disminución de las cifras de presión arterial. **Disminuir la presión arterial en pacientes con riesgo cardiovascular** (obesidad, vida sedentaria, síndrome metabólico, tabaquismo, diabetes etc.) reduce considerablemente el riesgo de sufrir un evento isquémico como: Infarto al miocardio fatal o no fatal (que el paciente sobreviva quedando con una mala calidad de vida) o hemorragia cerebral fatal o no fatal.

Disminuir las cifras de presión diastólica de 5 a 6 mm de Hg y de 10 a 12 mm de Hg para la presión sistólica, reduce significativamente las complicaciones mencionadas.

Para evitar estas complicaciones se requiere una disminución más significativa para la presión sistólica que para la diastólica, esto se explica porque la presión sistólica es la fuerza con la que se abre la válvula aórtica para expulsar la sangre primeramente a través de la arteria aorta y posteriormente a todas sus ramas. La presión diastólica es consecuencia del aumento de la presión sistólica puesto que se refiere a la resistencia en mm de Hg que soportan las paredes de las arterias al ser expulsada la sangre por la válvula aórtica.

Es importante señalar que entre más factores de riesgo cardiovascular tenga el paciente, el objetivo será llevarlo a valores más apegados a la normalidad, y CON LA PRESENTE INVENCION ESTO FUE LOGRADO, ya que más del 90% de los pacientes llegaron a parámetros dentro de la normalidad a pesar de que el 74.1% de los pacientes tenía más de 3 factores de riesgo, siendo estos resultados mejores que los reportados con Amlodipino solo, incluyendo su manejo con

dosis máximas de 10 mg, e inclusive que los reportados cuando se administraron 2 fármacos antihipertensivos con diferentes mecanismos de acción, como los mencionados en los Anexos 3, 6 y 7.

La presente invención involucra una selección especial de dosis. Tal selección produce un efecto inesperado, que se ve reflejado en la sinergia lograda con la combinación de Amlodipino y Acido acetilsalicílico, que administrada en UNA SOLA UNIDAD DE DOSIFICACIÓN con MENORES CONCENTRACIONES de dichos principios activos comparadas con las prescritas en la práctica médica, produce un EFECTO TERAPÉUTICO EFICAZ Y SEGURO con MAYOR RAPIDEZ en comparación al originado por el Amlodipino y Acido acetilsalicílico prescritos separadamente y durante periodos prolongados de tiempo.

Por lo tanto, el conocimiento científico está irremediablemente precedido por la investigación científica. El conocimiento técnico específico que aporta la presente invención, es decir LA SINERGIA EXISTENTE ENTRE EL AMLODIPINO Y ACIDO ACETILSALICÍLICO PARA EL TRATAMIENTO DE LA HIPERTENSION ARTERIAL SISTEMICA Y PREVIENCION DEL RIESGO DE EVENTOS VASCULARES DE ORIGEN ISQUEMICO, Y LA DOSIS EFECTIVA Y SEGURA DE DICHA COMBINACIÓN, no está descrito (es nuevo) ni se puede deducir de forma obvia o evidente a razón de conocer la actuación de los activos de la combinación de la presente invención por separado (tiene actividad inventiva), así mismo el nuevo capítulo reivindicatorio cumple con el requisito de aplicación industrial.

Por lo tanto, la presente invención cumple con los requisitos de novedad, actividad inventiva y aplicación industrial contemplados en la Ley.

2.1.2 Argumentos que desvirtúan las objeciones presentadas por el oponente LAFRANCOL S.A

2.1.2.1 Legítimo interés.

El solicitante considera que el opositor no acredita su legítimo interés para presentar la oposición que nos ocupa, ya que no manifiesta que tipo de sustancias y composiciones farmacéuticas son las que específicamente le afectarían en detrimento de sus legítimos intereses comerciales y de la libre competencia.

Cabe señalar que la presente solicitud versa sobre la COMBINACION SINERGICA DE DOS COMPUESTOS, que en su conjunto forman un PRODUCTO NUEVO, pero en forma aislada no existiría ninguna afectación para con ninguno de los compuestos que la conforman, por lo que el solicitante considera que el oponente no tiene acreditado su interés legal para presentarse como opositora de la presente solicitud de patente.

2.1.2.12 Fundamentos de la Oposición.

Del análisis de la oposición presentada por el Laboratorio Franco Colombiano LAFRANCOL S.A., no se desprende NINGUN ARGUMENTO MOTIVADO Y FUNDAMENTADO en contra de la combinación materia de la presente invención.

Esto en virtud de que ha desarrollado su argumento considerando que la combinación de la presente solicitud es la compuesta por Amlodipino y Clopidogrel, siendo que la combinación materia de la presente solicitud comprende **AMLODIPINO + ACIDO ACETILSALICÍLICO**.

No obstante lo anterior, su argumento se basa en que afirma que la combinación materia de la presente invención o una combinación de activos conocidos no cumple con los requisitos de patentabilidad.

Sin embargo, la materia de la presente invención, NO VERSA SOBRE LOS ACTIVOS ACTUANDO POR SEPARADO o EN FORMA INDIVIDUAL, es el caso que la combinación de dos activos (aunque éstos sean de dominio público) da lugar a un PRODUCTO NUEVO, el cual tiene efectos diferentes respecto a los activos actuando por separado, es decir, se reivindica un producto completamente nuevo, el cual cumple con los requisitos de patentabilidad y, por lo tanto, tendrá derecho a la obtención de un título patentario que le otorgue el beneficio de exclusividad.

La novedad de la invención deberá analizarse respecto AL TODO de la invención y no sobre cada una de sus partes. Entre los requisitos indispensables para que una invención pueda ser considerada como objeto de protección por medio de patente, en primer lugar, está su novedad, que significa que una invención es nueva cuando no está comprendida en el estado de la técnica, es decir que no está contenida, no está incluida, NO ESTA DESCRITA o no forma parte del estado de la técnica.

Comúnmente cuando una invención comprende varios componentes, la novedad en cada uno de ellos **NO ES UN REQUISITO INDISPENSABLE** ya que pueden ser conocidos individualmente en el estado de la técnica, por lo que se exige que sea su combinación la que dé lugar **A UN PRODUCTO DESCONOCIDO ANTERIORMENTE**. Al respecto, la novedad no es un requisito que deban cumplir todos y cada uno de los componentes que conforman la presente invención, pudiendo incluso ser conocidos individualmente la totalidad de tales elementos, si combinados entre ellos dan lugar a un **MEDICAMENTO DESCONOCIDO ANTERIORMENTE**.

En efecto, ninguna invención aparece de la nada; por el contrario, toda innovación requiere aplicar conocimientos y objetos previamente creados o

descubiertos por la humanidad, los cuales constituirán la materia prima para desarrollar un nuevo producto.

Ahora bien, las reivindicaciones precisan la novedad y altura inventiva del producto que se busca proteger con la patente. De la lectura del capítulo reivindicatorio de la presente solicitud se puede ver que lo reivindicado versa sobre la COMBINACIÓN de los activos AMLODIPINO y ACIDO ACETILSALICILICO y no sobre cada uno de ellos en forma aislada.

Es el caso que la presente invención consiste en la combinación sinérgica de Amlodipino y Acido Acetilsalicílico, administrados en una sola unidad de dosificación por vía oral, lo cual da lugar a un producto totalmente desconocido hasta antes de la presente invención, el cual presenta un efecto mejorado con respecto a la actividad terapéutica de ambos activos actuando en forma aislada.

En cambio el opositor solo argumenta y prueba que dichos activos eran conocidos en forma individual, sin que dicha información tenga relación alguna con la presente invención que consiste en un PRODUCTO NUEVO con efectos mejorados.

NO APORTA NINGUN DOCUMENTO O PRUEBA QUE EVIDENCIE la falta de novedad o actividad inventiva de la presente invención, y esto es claro porque la presente invención ES NUEVA Y TIENE ACTIVIDAD INVENTIVA. Por lo tanto, el solicitante considera que dicha oposición es infundada y temeraria, incumpliendo con lo establecido por el artículo 42 de la Decisión 486 del Tribunal Andino.

Ahora bien, el opositor argumenta que la presente invención no tiene nivel inventivo, es decir, que no implica un salto **CUALITATIVO** en relación con la técnica existente. Este requerimiento presupone que la invención, además de no ser obvia para una persona del oficio normalmente versada en la materia técnica, debe ser siempre el resultado de una actividad creativa del hombre, LO QUE NO IMPIDE QUE SE ALCANCE LA REGLA TÉCNICA PROPUESTA DE UTILIZAR ACTIVOS YA CONOCIDOS en el área técnica correspondiente.

La altura inventiva se define como la ausencia de obviedad en la invención para una persona del oficio normalmente versada en la materia y el hecho de no derivarse de manera evidente del estado de la técnica.

La presente invención versa sobre la sinergia que se presenta al combinar los activos Amlodipino y Acido Acetilsalicílico, y la sinergia de dos componentes SOLO puede ser establecida a través de la investigación. Ningún científico pudiera APORTAR ESTE CONOCIMIENTO TÉCNICO solo con una deducción, deberá haber pasado necesariamente por un proceso de investigación.

Es importante considerar que entre las interacciones que pueden presentarse al pretender combinar dos o más compuestos activos fuera del organismo (*in vitro*) se encuentran las de tipo químico, que se refieren a las incompatibilidades fisicoquímicas que pueden imposibilitar la mezcla de dos o más compuestos activos en una misma forma farmacéutica para conseguir su administración conjunta.

Asimismo, tras la administración *in vivo* de una combinación de dos o más compuestos activos se pueden presentar interacciones farmacológicas de tipo farmacocinético, que se refieren a modificaciones en el efecto farmacológico resultante debido a alteraciones en el proceso de absorción, distribución, metabolismo y excreción causadas por un compuesto activo desencadenante sobre otro compuesto activo contenido en la formulación, provocando variaciones en su efecto; y de tipo farmacodinámico, que son aquellas alteraciones bioquímicas y fisiológicas producidas por un compuesto activo que afecta la respuesta o efecto de otro, principalmente a nivel de su sitio de acción u órgano blanco, aumentándola o disminuyéndola, pero sin alterar la concentración del mismo, logrando originar efectos de potenciación, adición o, por el contrario, antagonismo al disminuir de manera importante la acción farmacológica del compuesto activo afectado.

De igual manera, la combinación de dos o más compuestos activos en diferentes proporciones (concentraciones) puede producir diversos efectos resultantes que abarcan:

- a) la suma de los efectos individuales (parciales) de cada compuesto activo (adición),
- b) el efecto resultante de la combinación es mucho mayor que el efecto esperado de la suma de los efectos de cada compuesto activo individual (potenciación),
- c) la disminución significativa de la acción farmacológica observable de uno o ambos compuestos activos (antagonismo).

Al respecto, es importante señalar que la búsqueda de las concentraciones eficaces de cada compuesto activo es una prioridad necesaria para plantear la combinación de concentraciones idóneas de los compuestos activos en una formulación. En este sentido, la selección de las concentraciones dependerá de la investigación científica, la experimentación fisicoquímica y farmacológica y de la experiencia clínica, es decir, de un mérito inventivo, como es el caso de la concentración propuesta en la presente invención para Amlodipino y Acido Acetilsalicílico, la cual solo en la proporción reivindicada logra un efecto sinérgico que potencializa la eficacia de la composición farmacéutica y mejora la seguridad de la misma.

Es por esto que la combinación óptima de dos o más compuestos activos, en conjunto con los excipientes necesarios para obtener una composición

farmacéutica, no puede ser considerada como obvia o evidente, ya que la eficacia y seguridad de la administración conjunta en una misma forma farmacéutica es desconocida.

La presente invención involucra una selección especial de dosis. Tal selección produce un efecto inesperado, que se ve reflejado en la sinergia lograda con la combinación de Amlodipino y Acido Acetilsalicílico, que administrada en UNA SOLA UNIDAD DE DOSIFICACIÓN con MENORES CONCENTRACIONES de dichos principios activos comparadas con las prescritas en la práctica médica, produce un EFECTO TERAPÉUTICO EFICAZ Y SEGURO con MAYOR RAPIDEZ en comparación al originado por el Amlodipino y Acido Acetilsalicílico prescritos separadamente y durante periodos prolongados de tiempo.

La ley señala que se considera que existe un paso inventivo cuando se está ante la no obviedad. Algo obvio se puede traducir como una situación en la que no es necesaria la investigación para saber el resultado de una teoría o un problema determinado.

Por lo tanto, el conocimiento científico está irremediablemente precedido por la investigación científica. El conocimiento técnico específico que aporta la presente invención, es decir, LA SINERGIA EXISTENTE ENTRE EL AMLODIPINO Y ACIDO ACETILSALICÍLICO PARA EL TRATAMIENTO DE LA HIPERTENSION ARTERIAL SISTEMICA Y PREVIENCION DEL RIESGO DE EVENTOS VASCULARES DE ORIGEN ISQUEMICO, Y LA DOSIS EFECTIVA Y SEGURA DE DICHA COMBINACIÓN, no esta descrito (es nuevo) ni se puede deducir de forma obvia o evidente a razón de conocer la actuación de los activos de la combinación de la presente invención por separado (tiene actividad inventiva).

En consecuencia, la presente invención cumple con los requisitos de novedad, actividad inventiva y aplicación industrial contemplados en la Ley.

En consecuencia, ninguno de los documentos citados por los opositores en el presente caso, puede afectar los requisitos de patentabilidad de la solicitud en estudio.

Habiendo atendido cabalmente las objeciones presentadas por los opositores, atentamente solicitamos se continúe con el trámite administrativo y se analicen los requisitos de patentabilidad de la solicitud en estudio a la luz del nuevo juego de reivindicaciones y se conceda el privilegio de patente de invención o si el examinador considera que subsisten razones para objetar la presente invención, rogamos expedir los exámenes de fondo necesarios con los debidos motivos y razones que sustenten su objeción con el fin de que nuestro mandante tenga la posibilidad de exponer sus argumentos con base en la

interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *“habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares”* y *“(.) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso”,* respectivamente (El subrayado es nuestro).

En consecuencia, pedimos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional

Señor Superintendente,



DILIA RODRIGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá

NOVEDAD DE LA INVENCION

Habiendo descrito la presente invención, se considera como novedad y, por lo tanto se relaciona como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Una composición farmacéutica caracterizada porque comprende la combinación sinérgica de besilato de amlodipino en una cantidad de 5 mg. y ácido acetilsalicílico en una cantidad de 75 mg, además de excipientes farmacéuticamente aceptables, los cuales se encuentran formulados en una sola unidad de dosificación para ser administrada por vía oral.

ANEXO No.1

Estudio titulado “EVALUAR LA EFICACIA Y SEGURIDAD DE LA COMBINACIÓN AMLODIPINO / ÁCIDO ACETILSALICÍLICO EN PACIENTES CON HIPERTENSIÓN ARTERIAL SISTÉMICA, ASOCIADO A FACTORES DE RIESGO CARDIOVASCULAR”.

**Evaluar la eficacia y seguridad de amlodipino / ácido acetilsalicílico en
Pacientes con Hipertensión Arterial sistémica, asociado a factores de riesgo cardiovascular.**

Dr. Raúl Gerardo Velasco Sánchez.

*Médico Cardiólogo adscrito al Departamento de Cardiología del Hospital Universitario Dr. Ángel Leño de la Universidad Autónoma de Guadalajara.

Resumen

Objetivo: Evaluar la eficacia y seguridad con la combinación amlodipino/AAS en pacientes con hipertensión arterial sistémica. **Material y Métodos:** Se incluyeron 60 pacientes con hipertensión arterial (Presión arterial sistólica (Pas) ≥ 140 mm Hg y/o Presión arterial diastólica (Pad) ≥ 90 mm Hg); presión arterial diastólica (Pad) entre 90 y 110 mm Hg y factores de riesgo cardiovascular, quienes requirieron terapia con: bloqueadores de los canales de calcio dihidropiridínicos y antiagregante plaquetario. La aleatorización fue estratificada en tres grupos: Grupo 1: Pad entre 101 y 110 mm Hg; Grupo 2: Pad entre 90 y 100; y Grupo 3: Pad < 90 mm Hg. En la primera y última visita a todos los pacientes se les realizó exámenes de laboratorio: BH, EGO, QS, ES, Perfil de Lípidos, PFH, TP, TPT y Tele de Tórax. **Resultados:** Al término del estudio la Pas disminuyó 23.7 mm Hg y para la Pad 14. mm Hg. No se reportaron eventos adversos serios en ninguna de las visitas o alteración en PFH, TP y TPT. **Conclusión:** El tratamiento combinado amlodipino 5 mg /AAS 75 mg demostró ser eficaz y seguro en el tratamiento de la Hipertensión arterial sistémica.

Palabras claves: Hipertensión arterial sistémica (HAS), amlodipino, ácido acetilsalicílico (AAS), factores de riesgo cardiovascular (FRC).

Abstract

Objective: Evaluate the efficiency and safety of a combination of amlodipine/Acetylsalicylic Acid (ASA), in patients with systemic hypertension. **Methods and Materials:** Sixty patients with systemic hypertension (mean systolic pressure ≥ 140 mm Hg and/or diastolic arterial pressure (DAP) ≥ 90 mm Hg) with DAP of 90-110 mm Hg requiring treatment with calcium channel blockers, dihydropyridines and platelet aggregation inhibitors. Patients were randomized into three test groups: group 1: DAP 101-110 mm Hg, group 2: DAP 90-100 mm Hg and group 3: DAP <90 mm Hg. All patients had standard laboratorial tests and chest x-rays at their first and last office visit. **Results:** The mean systolic pressure had decreased by 23.7 mm Hg and the DAP by 14 mm Hg at the end of the study. No serious side effects were observed during the study. **Conclusion:** Combined treatment using Amlodipine 5 mgs and ASA 75 mgs is effective and safe in the treatment of systemic hypertension. **Key Words:** Systemic Hypertension, Amlodipine, Acetylsalicylic Acid (ASA), Cardiovascular risk factors.

***Correspondencia y solicitud de sobretiros.**

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INTRODUCCIÓN.

La hipertensión arterial sistémica (HAS) representa actualmente un problema de salud a nivel mundial, en la población mexicana de acuerdo a las cifras de ENSALUT 2006 en la población de 20 años o más; la prevalencia resulto de 30.8 %⁽¹⁾. Dada esta estadística el médico debe prevenir el riesgo de complicaciones a corto y largo plazo, enfocándose tanto en la prevención primaria y secundaria de esta enfermedad, además de promover los cambios en el estilo de vida; es de suma importancia el tratamiento farmacológico.⁽²⁾

Los calcio antagonistas dihidropiridínicos, han demostrado su eficacia clínica, como el amlodipino ya que poseen un mecanismo de acción hemodinámicamente beneficioso en hipertensos, pues estos actúan sobre uno de los principales problemas fisiopatológicos, que es el aumento de la resistencia periférica; además se han demostrado los efectos antioxidantes de las dihidropiridinas, ya que protegen al músculo liso vascular de la sobrecarga cálcica y reducen la formación intracelular endotelial de radicales libres de oxígeno demostrando también que reducen la proliferación y migración celular muscular lisa y la agregación plaquetaria^(3,4).

Acción antihipertensiva.

Existen diversos estudios que han demostrado la eficacia antihipertensiva respecto al amlodipino comparado con otro grupo de antihipertensivos, como es el estudio VALUE demostrando un valor preventivo, reduciendo los eventos cardiovasculares alrededor de un 35 % para amlodipino y valsartan, pero el amlodipino mostró un valor preventivo en el IAM significativamente mayor y una tendencia preventiva sobre el ACV⁽⁵⁾.

El estudio CAMELOT sugiere que el amlodipino es útil y seguro en pacientes coronarios. En cuanto a la protección renal el amlodipino también ha demostrado ser eficaz⁽⁶⁾.

Uso de antiagregantes plaquetarios en pacientes con FRC

El AAS (ácido acetilsalicílico) ejerce su efecto principal interfiriendo con la biosíntesis de prostanoides cíclicos como tromboxano A₂, prostaciclina y otras prostaglandinas. Dichos prostanoides, se generan por la oxidación catalizada enzimáticamente del ácido araquidónico; este ácido araquidónico es metabolizado por la enzima prostaglandina H sintetasa en tromboxano y prostaglandinas. Así, el AAS ejerce su efecto antitrombótico mediante la inhibición de la PGH sintasa, conocida como ciclooxigenasa. Han sido descritos otros mecanismos antitrombóticos del AAS, ya que facilita la inhibición de la activación plaquetaria por medio de los neutrófilos por un efecto dependiente del óxido nítrico⁽⁶⁾. Además de sus efectos antitrombóticos otros mecanismos pueden contribuir al beneficio clínico del AAS en el tratamiento de la ECV (enfermedad cardiovascular), dado que previene la oxidación de las LDL⁽⁷⁾, mejora la disfunción endotelial en vasos ateroscleróticos y, en definitiva, actúa como antioxidante⁽⁸⁾.

Mucho se ha comentado sobre la dosis mínima efectiva del AAS en pacientes con ECV; las Guías Europeas de Hipertensión Arterial del 2007⁽⁹⁾, recomiendan dosis bajas de AAS desde 75 mg, estudios como el HOT (Hypertension Optimal Treatment); en el cual se reclutaron 19,193 pacientes, pretendió principalmente conocer cuáles son los niveles de tensión diastólica óptimos a conseguir en pacientes hipertensos, y también analizó el efecto del tratamiento con la administración de 75 mg de AAS frente a placebo. El seguimiento medio fue de 3,8 años. Se definió como evento cardiovascular mayor el IAM, ictus y la muerte cardiovascular de cualquier causa. El menor riesgo cardiovascular se produjo con una Pad 82,6 mm Hg. El grupo de AAS presentó una reducción de la incidencia de IAM del 36%. Los resultados del estudio HOT corroboran por tanto que el mayor beneficio del AAS es una reducción en el número de IAM⁽¹⁰⁾.

En el estudio TPT (Thrombosis Prevention Trial); se reclutaron 5.499 pacientes de con edades comprendidas entre 45 y 69 años. Todos ellos presentaban al menos un 20% de riesgo cardiovascular. Los dos regímenes de tratamiento elegidos consistieron en anticoagulación oral a baja dosis con warfarina y 75 mg de AAS. Los grupos con AAS experimentaron una reducción de IAM de un 20%⁽¹¹⁾.

Tanto los estudios TPT y HOT con dosis bajas de AAS (75 mg) demuestran los beneficios que obtienen los pacientes con riesgo moderado.

Por tanto, se confirma que el beneficio del AAS se eleva cuando el paciente presenta algún factor de riesgo cardiovascular, siendo éste un factor fundamental al momento de prescribir tratamiento con AAS en prevención primaria⁽¹²⁾.

Factores de riesgo cardiovascular y endotelio.

En condiciones normales, las células endoteliales modulan la función vascular regulando el tono vasomotor, controlando el intercambio entre los compartimentos extra e intravascular, inhibiendo la activación y la agregación plaquetaria, la trombogeneidad de la sangre, la adhesión de leucocitos a las células endoteliales y la proliferación y crecimiento de las células del músculo liso. Para que el endotelio pueda ejercer todas estas funciones es necesario la integridad anatómica.

Los llamados factores de riesgo cardiovascular como la hipertensión, hipercolesterolemia, Diabetes mellitus, etc, modifican las condiciones del entorno de las células endoteliales produciendo aumentos de la presión transmural, la fuerza de fricción de la sangre sobre las células endoteliales, las concentraciones de lípidos y cambios en las concentraciones de diversos mensajeros humorales⁽¹³⁾. En estas condiciones, se pierde el papel homeostático que ejerce el endotelio sobre la función vascular como consecuencia de cambios en el patrón de producción y liberación de factores derivados del endotelio, llevando a la disfunción endotelial caracterizada por: 1) Una alteración de

la regulación del tono vasomotor con predominio del tono vasoconstrictor, debido al desequilibrio entre factores relajantes como el óxido nítrico y constrictores, donde las especies reactivas de oxígeno juegan un papel determinante; 2) Una tendencia al crecimiento de la pared vascular que puede ser debido a un aumento del número y/o tamaño de las células musculares lisas y/o fibroblastos, una disminución de la apoptosis de éstas y/o un aumento de la síntesis de matriz extracelular; 3) Un incremento en la permeabilidad del endotelio, con la consiguiente pérdida de la función de barrera selectiva para diversas partículas y macromoléculas; 4) Un aumento de la adhesión de leucocitos debido a la sobre-expresión de moléculas quimiotácticas y de adhesión, junto con una respuesta elevada a citoquinas y liberación de mediadores inflamatorios; 5) Una mayor tendencia a la agregación plaquetaria y la adhesión de éstas a las células endoteliales; 6) Una mayor tendencia a la coagulación y una fibrinólisis ineficaz, que en conjunto llevan a un aumento del riesgo trombótico⁽¹⁴⁾.

El estado protrombótico, se caracteriza por hipercoagulabilidad del plasma, hiperagregabilidad de las plaquetas, aumento de viscosidad de la sangre, reducción del flujo sanguíneo con turbulencia, fibrinólisis alterada y pérdida de las propiedades anticoagulantes naturales de la superficie de las células endoteliales en contacto íntimo con la sangre.

El estado de hipercoagulabilidad se define como la reactividad incrementada del plasma sanguíneo a las superficies trombogénicas. Existe evidencia clínica y epidemiológica de que el estado protrombótico es un predictor importante de enfermedad cardiovascular.

Por lo general, las agresiones que dañan o interrumpen la alineación celular endotelial de los vasos sanguíneos estimulan la formación de lesiones vasculares integradas por células de músculo liso. Después del desgarro celular endotelial uno de los primeros eventos es la generación de trombina en el sitio de la lesión. Esto inicia la activación de las plaquetas y la formación del trombo. Las evidencias existentes sugieren que este trombo puede estimular la proliferación de las células

musculares lisas por factores emanados de él, que incluyen los derivados de plaquetas o macrófagos, los de crecimiento básico de fibroblastos o trombina⁽¹⁵⁾.

La toma de decisiones terapéuticas en los pacientes hipertensos se debe realizar considerando no solo las cifras de presión arterial, sino también la existencia de otros factores de riesgo cardiovascular (FRC) asociados como: Diabetes mellitus tipo 2, obesidad, tabaquismo, vida sedentaria, sexo, edad, dislipidemias, así como presencia y severidad de afectación cardiovascular y renal entre otros.

Dado los beneficios de los calcio antagonistas dihidropiridínicos (como el amlodipino), no solo en el control de la HAS sino también a nivel endotelial y el AAS antes mencionados, se decidió llevar a cabo la combinación de amlodipino / AAS realizando el estudio de eficacia y seguridad, asociado a factores de riesgo cardiovascular.

OBJETIVOS.

Evaluar la eficacia y seguridad de la combinación amlodipino /AAS en pacientes con Hipertensión Arterial Sistémica asociado a factores de riesgo cardiovascular.

Se consideró en este proyecto eficacia clínica cuando los pacientes del Grupo 1 logaran la meta de una Pad <85 mm Hg, y los de los Grupos 2 y 3 una PA< 80mm Hg. La seguridad fue evaluada por la ausencia/presencia de alteraciones en las enzimas hepáticas además de TP y TPT.

MATERIAL Y MÉTODOS.

Grupo de Estudio.

Se incluyeron 60 pacientes con hipertensión arterial documentada (Presión arterial sistólica (Pas) máxima de 160 mm Hg y/o Presión arterial diastólica (Pad) $\geq$ 90 mm Hg); presión arterial diastólica (Pad) entre 90 y 110 mm Hg y factores de riesgo cardiovascular, quienes requirieron terapia a base de bloqueadores de los canales de calcio dihidropiridínicos y antiagregante plaquetario. La aleatorización fue estratificada en tres grupos: Grupo 1 Pad entre 101 y 110 mm de Hg; Grupo 2 Pad entre 90 y 100; y Grupo 3 Pad $<$ 90 mm Hg.

Tipo de estudio.

Estudio Fase III, ciego, prospectivo, longitudinal, no comparativo consistió de 4 fases / etapas: Valoración (1), Evaluación (2), Tratamiento (3) y Visita final de Tratamiento (4).

La elegibilidad para el estudio fue determinada en la Visita de Valoración (Día 0) con base en la presencia de hipertensión arterial ($\geq$ 140/90 mm Hg), presión diastólica (Pad) máxima de 110 mm Hg, y cualquiera de los siguientes factores de riesgo cardiovascular como: tabaquismo, diabetes mellitus tipo 2, enfermedad arterial periférica, accidente cerebro vascular o ataque isquémico transitorio previo (3 meses), colesterol total / HDL colesterol $>$ 6.

Criterios de Inclusión.

Consentimiento informado firmado, edad entre 50 a 70 años, uno de los siguientes factores de riesgo cardiovascular: Diabetes mellitus tipo 2, enfermedad arterial periférica, accidente cerebro vascular o ataque isquémico transitorio previo (3 meses), tabaquismo, cociente entre colesterol total y HDL mayor, riesgo de eventos coronarios de 1.5% o más anual, riesgo coronario global según la Organización Mundial de la Salud (WHO) y la Sociedad Internacional de Hipertensión (ISH) 2004 (riesgo intermedio 15-20%), Presión arterial $<$ 130/90 mm Hg, prueba de embarazo en orina negativa. Mujeres en edad reproductiva deberán seguir un método anticonceptivo definitivo. Historia familiar de enfermedad cardiovascular prematura (hombres menores de 50 años o mujeres menores de 65 años).

Criterios de exclusión.

Hipersensibilidad a dihidropiridinas, enfermedad cardíaca congénita hemodinámicamente significativa, arritmia no controlada, bloqueo de 2do. o 3er grado, anormalidades electrocardiográficas que indiquen isquemia, insuficiencia cardíaca congestiva, angina inestable o evidencia de infarto miocárdico agudo, IAM durante los tres meses previos al ingreso al estudio, presión arterial diastólica > 115 mm Hg, bradicardia significativa (< 50 latidos/ minuto), cirugía coronaria en los tres meses previos, creatinina plasmática 2 mg./dL, condiciones médicas que pueden interferir o ser afectadas adversamente por el desarrollo del presente estudio. Incapacidad de hacer ejercicio por más de 6 minutos. Alcoholismo, drogadicción, desorden mental o de personalidad, pobre motivación u otros problemas mentales o intelectuales que invaliden el consentimiento informado o dificulten el cumplimiento del paciente con el presente estudio. Uso concomitante de otro calcio-antagonista. Haber participado en cualquier otro estudio clínico durante el mes previo al presente. Mujeres embarazadas o lactando. Enfermedad renal o hepática pre-existente. Ingesta actual de terapia anticoagulante y/o antiagregante. Pacientes con alta probabilidad de muerte durante el estudio. Antecedentes de Isquemia cerebral transitoria, trombosis cerebral o encefalopatía hipertensiva. Exudados y hemorragias retinianas, papiledema, antecedentes de úlcera péptica, reflujo gastroesofágico, asma, hipertensión arterial no controlada, deficiencia de G6PD. Tratamiento con sulfonilureas, metotrexato, corticosteroides, espironolactona, furosemida o antigotosos, y vitamina K.

Tratamiento administrado.

Los pacientes incluidos en el estudio recibieron el fármaco de estudio en combinación Amlodipino 5mg/ AAS 75 mg, una tableta por vía oral cada 24 horas durante 90 días.

Se realizó una valoración inicial (al día 0), posteriormente, los 60 pacientes fueron citados al día 30 (2ª Visita de Valoración), al día 60 (3ª Visita de Valoración) y al día 90 (4ª y última Visita de Valoración Final).

Procedimiento.

En la visita inicial se registraron los factores de riesgo cardiovascular agregados (sedentarismo, obesidad, enfermedades cardíacas familiares, tabaquismo, diabetes mellitus tipo 2, colesterol total >240 mg./dL, microalbuminuria, retinopatía hipertensiva, antecedentes de cardiopatía isquémica, antecedentes de AVC y/o enfermedad arterial periférica, datos generales (edad y género), y los antecedentes personales patológicos.

En cada una de las visitas, desde la inicial hasta la final, se llevó a cabo una exploración física del paciente (presión arterial en ambos brazos, peso, talla, índice de masa corporal (IMC), circunferencia de cintura, frecuencia cardíaca, frecuencia respiratoria) y un examen físico por aparatos y sistemas. Se registró asimismo en cada una de las visitas: la terapia concomitante y la presencia de eventos adversos no-serios y serios.

A todos los pacientes se les derivó al laboratorio clínico en la primera Visita de Valoración (día 0), así como en la última Visita (día 90), una vez concluido el estudio para realizar: biometría hemática, examen general de Orina, química sanguínea, electrolitos, perfil de lípidos, perfil Hepático, tiempo de protrombina y tiempo parcial de tromboplastina, además de tele de tórax.

En la última visita se pidió la opinión del médico investigador con respecto a la eficacia clínica, la seguridad y la tolerancia del medicamento de prueba.

RESULTADOS.

El total de pacientes que iniciaron el estudio fue de 60. El 91.7% cumplió con las cuatro visitas programadas, lo que corresponde a un total de 55 pacientes. (**Cuadro I**).

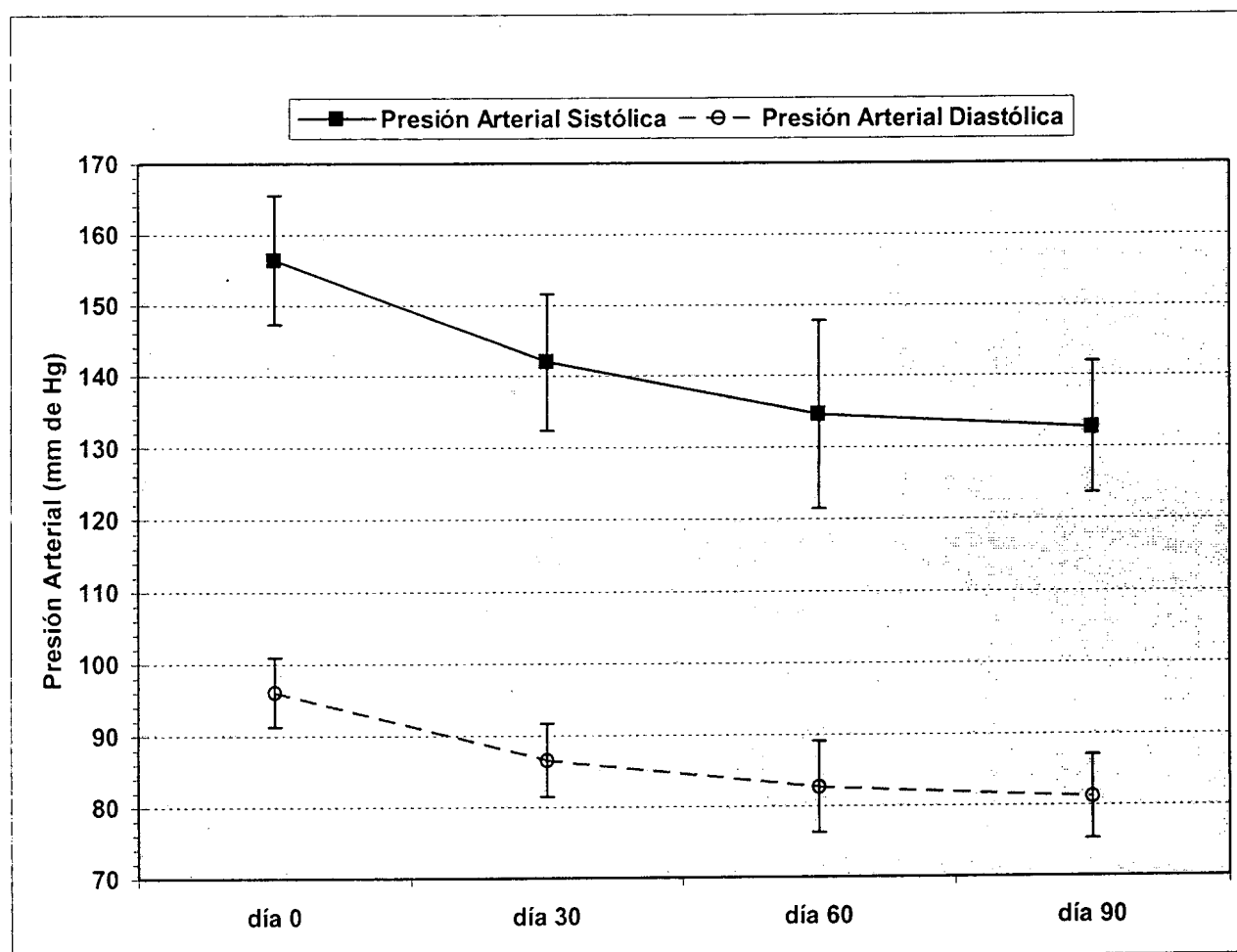
No hubo diferencia estadísticamente significativa entre la edad de hombres y mujeres al utilizar la prueba t de Student para muestras independientes, tampoco al analizar la distribución por grupos de edad entre sexos, mediante la aplicación de la prueba X^2 .

Presión Arterial.

Los pacientes fueron clasificados en tres grupos de acuerdo a la Pad inicial que presentaron, con el fin de estratificarlos según la severidad de la hipertensión arterial. El cual nos muestra el **Cuadro II**.

En el la **Figura 1** se presentan las medidas descriptivas para la presión arterial sistólica y diastólica a lo largo del estudio en cada una de las visitas de los pacientes: día 0, día 30, día 60 y día 90.

Figura 1. Promedio $\pm$ Desviación Estándar de la Presión Arterial (Sistólica y Diastólica - en mm de Hg) en 60 pacientes con Hipertensión Arterial Sistémica que recibieron Amlodipino-AAS durante 90 días de seguimiento.



El análisis de varianza de medidas repetidas resultó estadísticamente significativo tanto para la Pas como para la Pad, lo que nos permite concluir que las medias no fueron iguales a lo largo del tratamiento; al contrastar la Pas inicial y la Pad inicial vs. las presiones subsecuentes, todas presentan cambios significativos con la prueba t de Student para muestras dependientes.

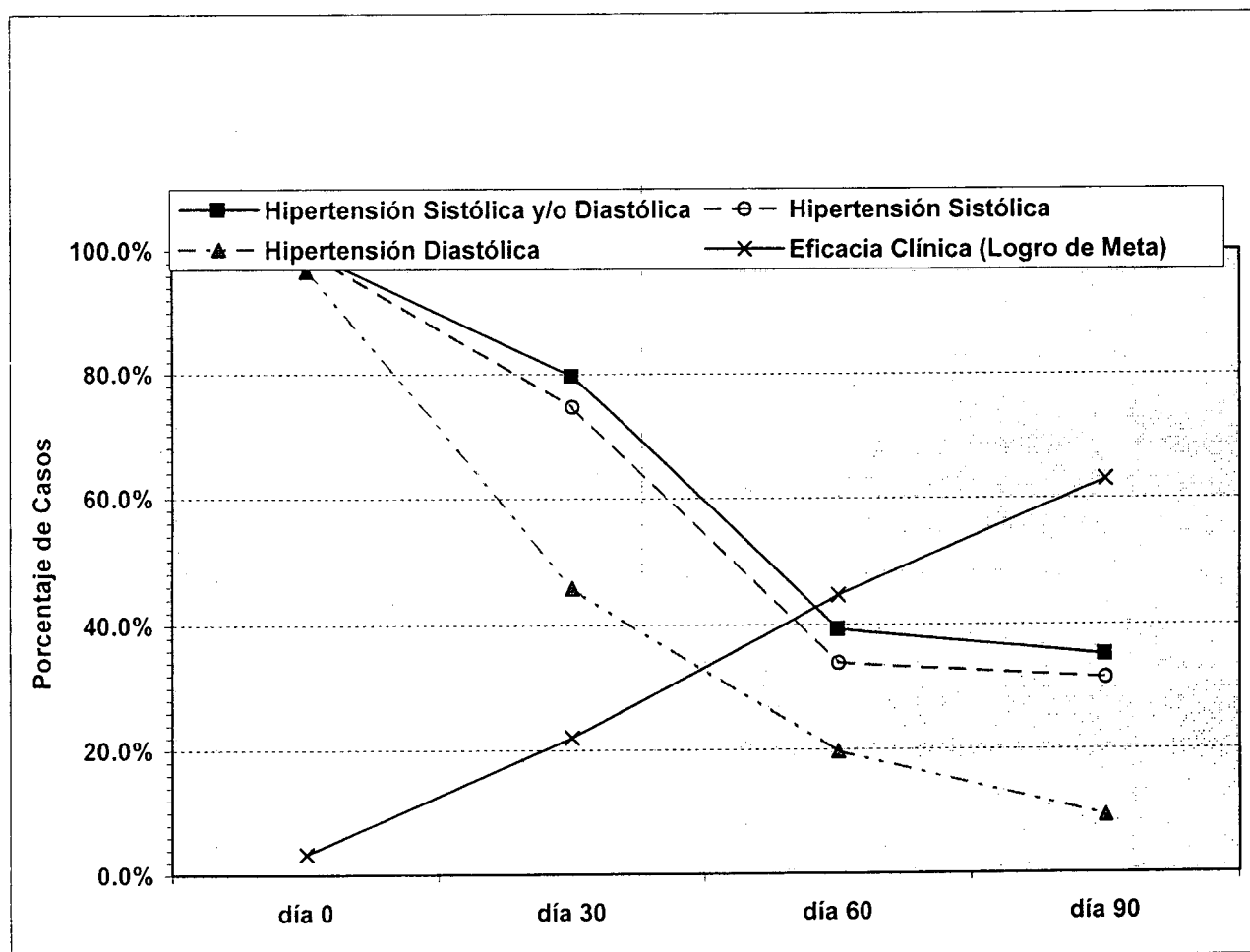
La **Figura 2** nos permiten analizar el comportamiento cualitativo de la presión arterial a lo largo del tratamiento con la combinación Amlodipino/AAS, en estos pacientes hipertensos con factores de riesgo cardiovascular. Inicialmente, el 100% de los pacientes se clasifican como hipertensos, de acuerdo a los valores de la Pas y Pad. Hacia el final del tratamiento (día 90), solo el 35.2% de los pacientes se clasificó como tal dado que la Pas resultó mayor o igual a 140 y/o la Pad mayor o igual a 90 en la última toma.

Sobre la Hipertensión Arterial Sistémica: el 64.8% de los pacientes tratados durante 90 días con la combinación de Amlodipino 5mg/AAS 75 mg presentan cifras de Presión Arterial en rangos de normalidad.

Analizando exclusivamente el comportamiento de la Pas encontramos cifras similares a las anteriores: al inicio el 100% de los pacientes fueron clasificados en rangos de hipertensión sistólica, pues todos ellos presentaron valores mayores o iguales a 140 mm Hg. Al día 90 del estudio, solo el 31.5% de los casos presentaron cifras de presión arterial sistólica mayores o iguales a 140. Conclusión sobre la Pas: el 68.5% de los pacientes presentan cifras de Pas en rangos de normalidad al término del estudio.

Para el caso de la presión arterial diastólica los resultados son relevantes, pues de un 96.7% de casos con cifras de Pad mayores o iguales a 90 mm Hg, al inicio del tratamiento, solo el 9.3% de los casos continuaba al término del tratamiento con niveles de hipertensión diastólica. Conclusión sobre la Pad: el 90.7% de los pacientes presentan cifras de Pad en rangos de normalidad al término del tratamiento con Amlodipino 5mg / AAS 75 mg.

Figura 2. Porcentaje de Casos según tipo de Hipertensión y de logro de eficacia clínica en cada uno de los días de observación, en 60 pacientes con Hipertensión Arterial Sistémica que recibieron Amlodipino/AAS.



Factores de Riesgo Cardiovascular.

Las **Figuras 3 y 4**, nos muestran la frecuencia según el número de factores de riesgo presentados por cada uno de los pacientes..

Figura 3. Prevalencia de Factores de Riesgo Coronario en 60 pacientes con Hipertensión Arterial Sistémica tratados con Amlodipino/AAS durante 90 días.

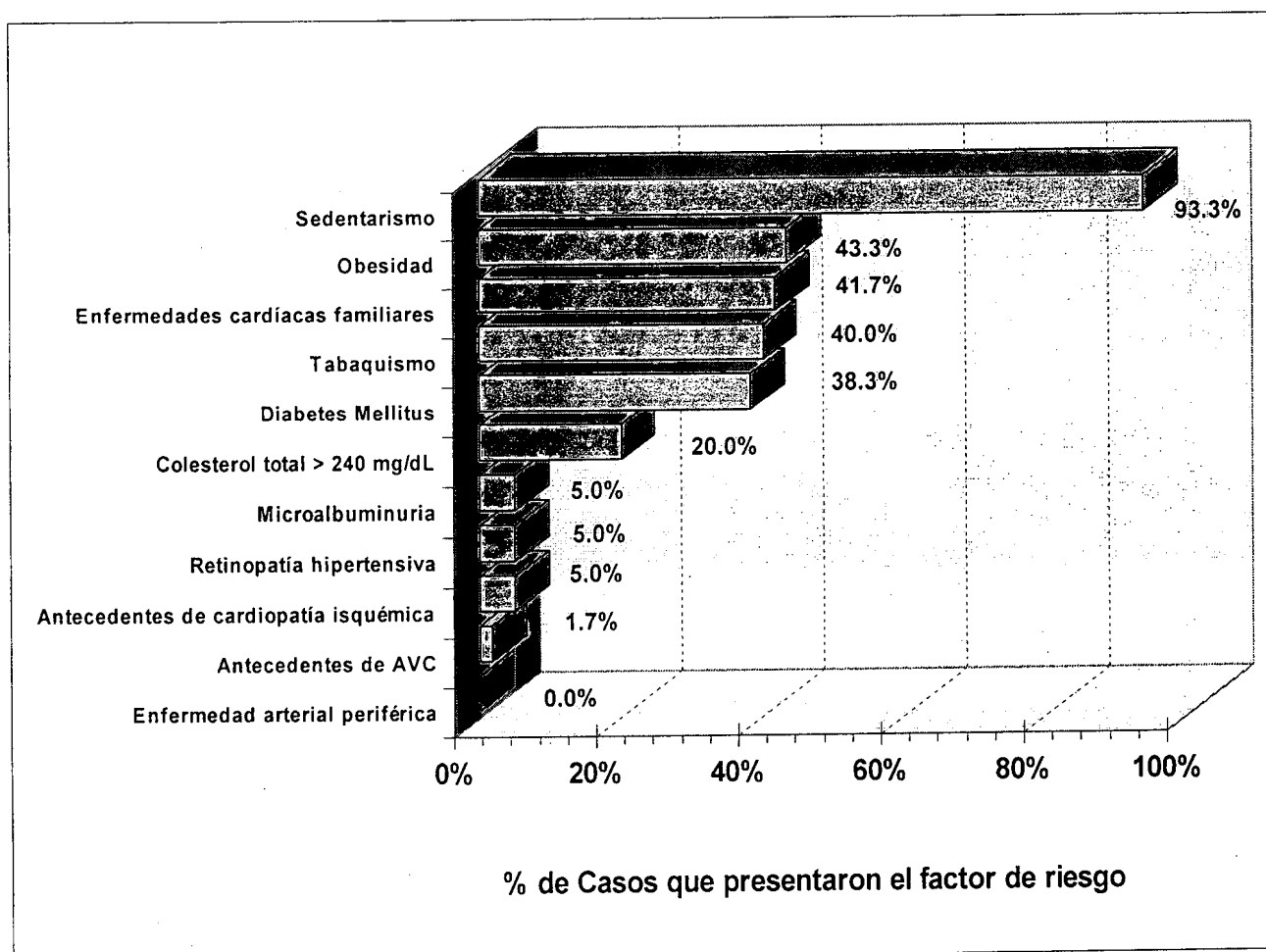
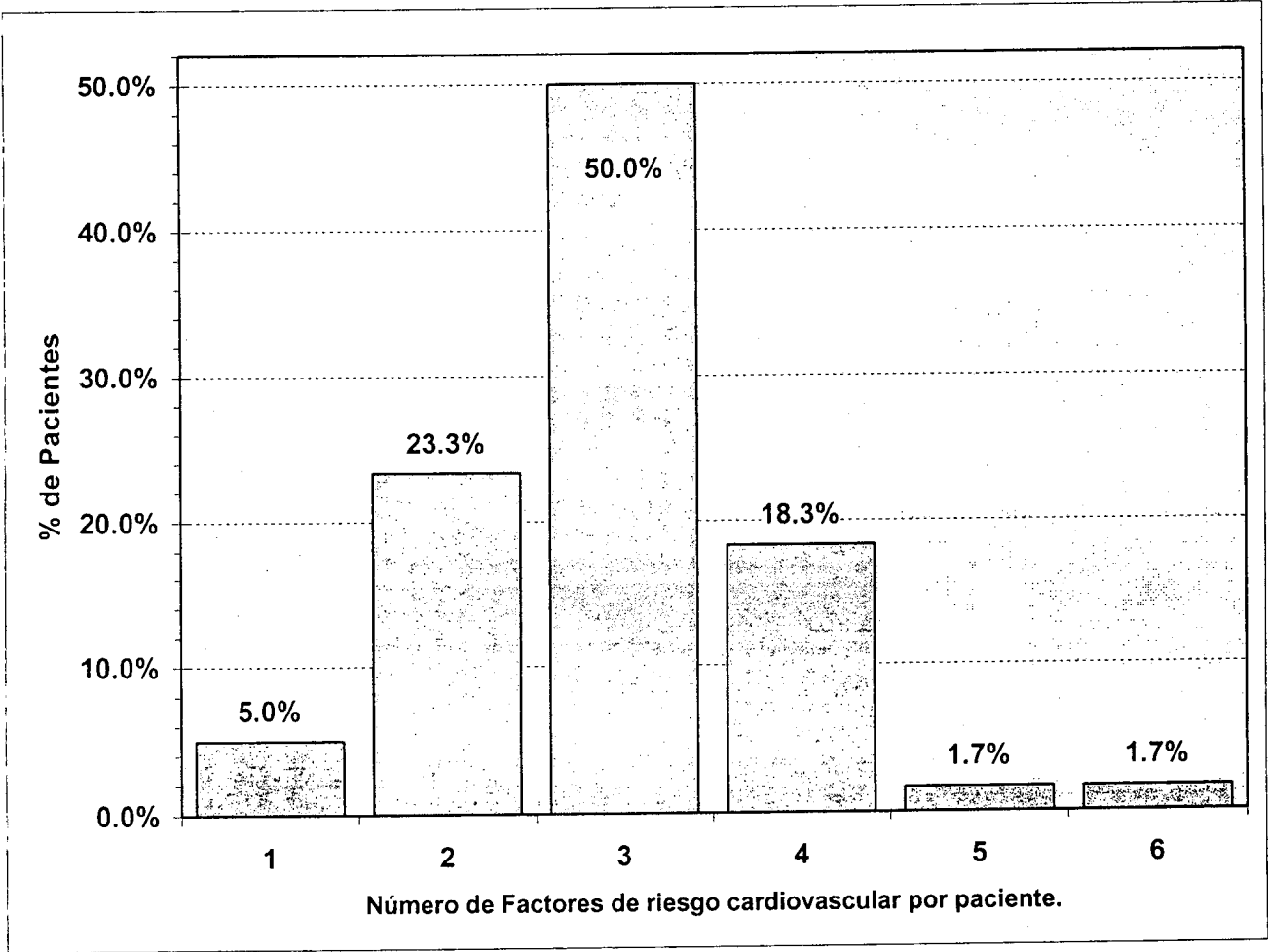


Figura 4. Porcentaje de pacientes hipertensos que recibieron Amlodipino/AAS durante 3 meses, según el número de factores de riesgo cardiovascular que presentan



Terapia Médica concomitante.

Los medicamentos más frecuentemente suspendidos fueron: Enalapril, AAS, captopril, diltiazem, clortalidona, propranolol, y atenolol.

Los medicamentos que más frecuentemente indicó el médico tratante en la visita inicial de valoración que podían continuar, fueron: glibenclamida, metformina, rosuvastatina, metformina con glibenclamida, levotiroxina y pravastatina.

Antecedentes Personales Patológicos.

Los dos principales antecedentes patológicos reportados en la valoración inicial fueron los cardiovasculares con el 63.3% de los pacientes y los endocrino-metabólicos con un 45% de los casos. Con muy baja frecuencia aparecen tabaquismo con el 6.7%, patologías en cabeza, ojos, oídos, nariz y garganta con el 5.7%, y con un caso solamente aparecen las siguientes patologías: periférico vascular, hepatobiliar, genitourinario, musculoesquelético, neurológico, psiquiátrico y alcoholismo. Al comparar las frecuencias de los antecedentes personales patológicos entre sexos solamente se observaron diferencias estadísticamente significativas en endocrino-metabólico en donde las mujeres presentaron una frecuencia relativa casi del doble que la de los hombres.

Examen Físico.

Con respecto al examen físico realizado a los pacientes en cada una de las visitas,. Destaca solamente el hecho de que en solo tres rubros se hayan mencionado anormalidades que correspondieron a: Anormalidades en Cardiovascular, en Pulsaciones Aórticas y en extremidades, todas ellas con frecuencias mínimas en su mayoría solo con un caso reportado.

En cada visita se realizó un examen físico que consistió en medir la presión arterial, que fue la variable central de este estudio y que ya se describió su evolución durante el tratamiento con Amlodipino/AAS. Además de la presión arterial se midieron los siguientes parámetros: peso, talla, índice de masa corporal (IMC), circunferencia de cintura, frecuencia cardíaca y frecuencia respiratoria. (cuadro III)

Podemos decir que al analizar internamente por género esta evolución no hubo cambios estadísticamente significativos, las variaciones observadas son aleatorias y de poca importancia clínica. Hubo diferencias entre hombres y mujeres en peso, talla y cintura, pero esto es perfectamente explicable por la diferente naturaleza de ambos géneros. En los demás parámetros (IMC, cintura, frecuencia cardiaca y respiratoria) no hubo diferencias entre sexos a lo largo del tratamiento.

Química sanguínea.

Química sanguínea (Glucosa, Urea, Creatinina) y electrolitos (Sodio, Potasio y Cloro), no hubo cambios significativos entre los valores báseles y los finales, ni al analizar los datos en forma cuantitativa a través de las medias ni en forma cualitativa analizando las frecuencias de los casos que se clasificaron como bajos, normales y altos.

Perfil de Lípidos.

Nuevamente ocurre lo mismo que en el caso de la química sanguínea y electrolitos, el tratamiento Amlodipino 5 mg/AAS 75 mg no modificó significativamente los niveles de lípidos en sangre, ni al analizar los datos en forma cuantitativa con la prueba t de Student para muestras dependientes ni al analizar la distribución de frecuencias basal-final de los sujetos en las categorías de bajo-normal-alto con la prueba χ^2 y con la prueba de Wilcoxon.

Perfil Hepático.

Los hallazgos más importantes del perfil hepático en estos pacientes son los siguientes: los Cuadros IVa y IV b nos permiten evaluar la normalidad de los pacientes en su perfil hepático. En globulina encontramos diferencias en la distribución de casos bajos-normales-altos entre la clasificación inicial y la final, tanto con la prueba χ^2 como con la prueba de Wilcoxon. El porcentaje de casos con niveles de globulina altos (globulina mayor a 3.2) fue de 43.1% al inicio del tratamiento, este porcentaje disminuyó a 27.8% de individuos con globulina elevada después del tratamiento.

En las demás variables del perfil hepático no se observaron cambios estadísticamente significativos entre las frecuencias iniciales y las finales.

Debemos mencionar por último porcentajes importantes de casos con colesterol elevado (más de 200 mg./dL) tanto en la valoración inicial como en la final del perfil hepático. El porcentaje inicial con colesterol elevado fue del 48.3% al inicio y de 46.3% al final.

Tiempo de Protrombina y Tiempo Parcial de Tromboplastina.

No se observaron alteraciones en: las mediciones del tiempo de protrombina y del tiempo parcial de tromboplastina. El 95% de ellos se mantuvieron dentro de los rangos de normalidad tanto en la evaluación inicial como en la final y no presentaron diferencias significativas entre hombres y mujeres en ningún momento (ver **Cuadro V.**)

Efectos adversos.

En el estudio no se reportaron eventos adversos serios en ninguna de las visitas, ni eventos adversos no serios se muestran en el **Cuadro VI**.

En el **Cuadro VII** se especifican los eventos adversos no serios ocurridos en cada una de las visitas.

Un paciente presentó dos eventos adversos no serios que consistieron en edema facial y edema en miembros pélvicos.

Solamente se reportó un caso con edema generalizado, el evento fue reportado como de intensidad moderada y debido al medicamento de estudio.

En el resto de sujetos con evento adverso no serio la intensidad se reportó como leve, con duración de un día y con probable relación con el medicamento de estudio.

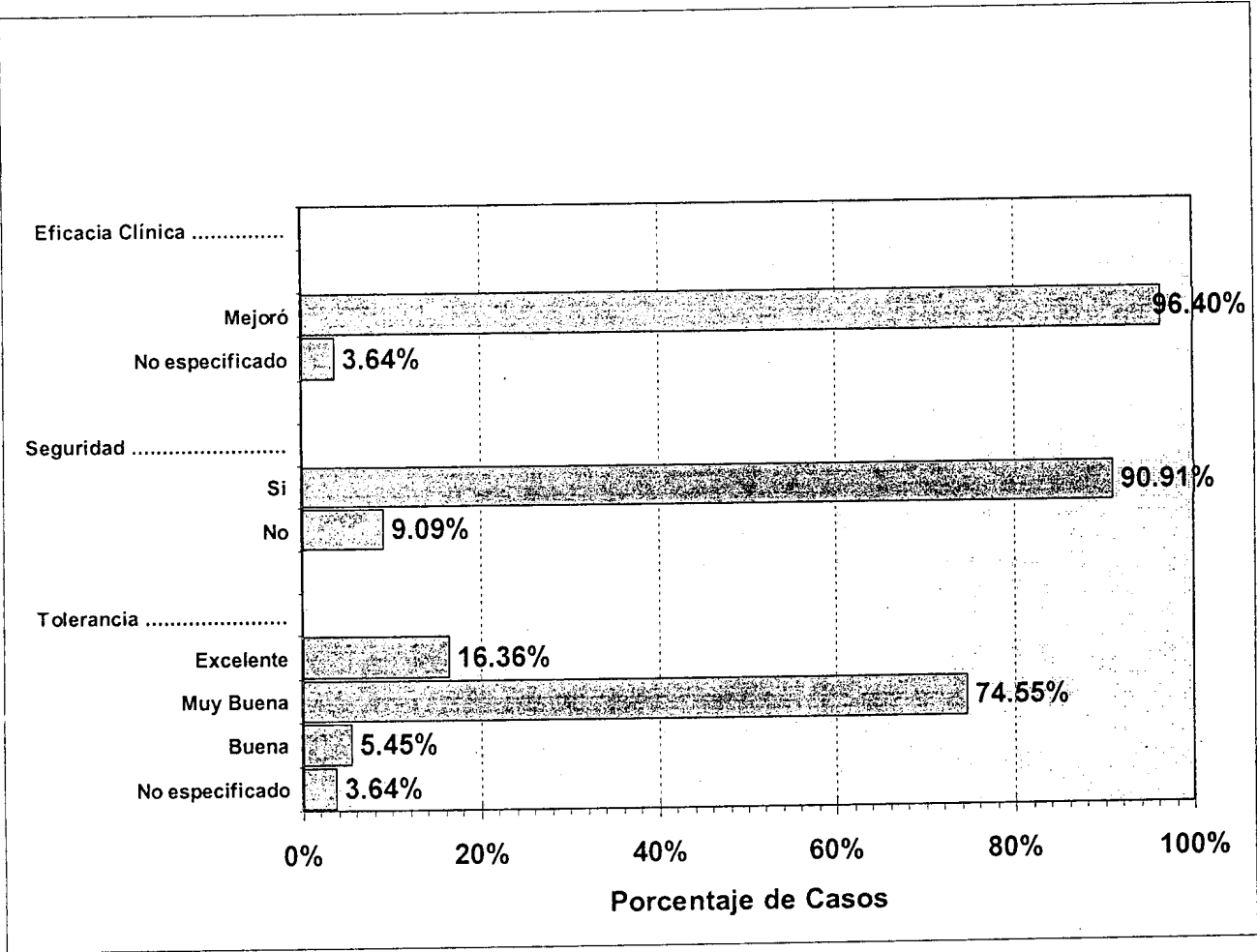
En total 3 pacientes presentaron eventos adversos no serios en la 3a visita. Estos 3 pacientes presentaron cada uno un evento adverso no serio.

En la cuarta visita se reportaron los mismos dos casos (con edema y edema en miembros inferiores) de la tercera visita, en esta ocasión ambos se reportan como leves.

Eficacia Clínica, Seguridad y Tolerancia.

Los médicos investigadores responsables del tratamiento de los 55 pacientes que terminaron el estudio emitieron su opinión con respecto a la eficacia clínica, la seguridad y la tolerancia del medicamento de prueba Amlodipino/AAS, (**Figura 5**).

Fig. 5. Evaluación del Medicamento según los médicos tratantes en lo que respecta a Eficacia Clínica, Seguridad y Tolerancia con Amlodipino 5mg/AAS 75mg.



DISCUSIÓN.

Los beneficios del tratamiento antihipertensivo han sido ampliamente estudiados y catalogados como beneficios dependientes de la reducción de cifras de la presión arterial y los beneficios independientes de éstas. Se sabe que una disminución promedio de 5-6 mm Hg. para presión arterial diastólica y de 10-12 mm Hg. para la sistólica se asocia con una disminución de un 21% en la mortalidad cardiovascular, de un 48% en accidentes cerebrovasculares fatales y no fatales y una disminución del 14% en la enfermedad coronaria fatal y no fatal^(15,16). En los estudios UKPDS, HOT, ABCD, SHEP y SIST-EUR, revelan un porcentaje de reducción de la mortalidad total entre un 18 al 64% como consecuencia de la disminución de las presiones arteriales sistólicas entre 4 y 10 mm Hg y de la diastólica entre 2 y 8 mm Hg^(17,18).

En nuestro estudio la presión arterial sistólica inicial al día 0, partió de un valor promedio de 156.4 ± 9.1 mm Hg y llegó a un valor promedio de 132.7 ± 9.2 mm Hg al día 90, lo que implica una disminución promedio de 23.7 mm Hg.

Para el caso de la Presión arterial diastólica el comportamiento fue como sigue: el promedio inicial fue de 96.1 ± 4.8 y al día 90 el promedio fue de 81.2 ± 5.9 lo cual corresponde a una disminución de 14.9 mm Hg; esto significa que los pacientes obtuvieron el beneficio de la disminución de riesgo cardiovascular antes mencionado.

Dentro de los factores de riesgo presentados en nuestros pacientes, cabe destacar que el 93.3 % de los pacientes llevan vida sedentaria, este es un factor de riesgo dos veces mayor para presentar cardiopatía coronaria y la magnitud de dicho riesgo es semejante al que se observa en la hipercolesterolemia o en el tabaquismo⁽¹⁹⁾.

El 43.3% de la población estudiada presentaron obesidad, como sabemos el anterior padecimiento aunado a la HAS se asocian a disfunción endotelial, disminuyendo la producción de óxido nítrico (ON) siendo este el vasodilatador endógeno más potente el cual interviene en la regulación del tono vascular, inhibición de la agregación y adhesión plaquetaria e inhibe la proliferación de células musculares^(20,21,22).

Un 41.7% de los pacientes presentaron tabaquismo positivo, diversos componentes del tabaco y del humo del tabaco actúan a distintos niveles del organismo, originando alteraciones fisiopatológicas que explican las complicaciones derivadas, mayormente la aceleración del proceso arterioscleroso y las alteraciones vasculares y endoteliales observadas en el fumador, la propia elevación tensional, las alteraciones hemorreológicas y del sistema de coagulación y diversas alteraciones endocrinas hemodinámicas⁽²³⁾.

De estos pacientes el 40% presentaron diabetes mellitus tipo 2, en esta patología, se ha encontrado una elevación de los factores VII, IX, X y XII de la coagulación, ya que los niveles plasmáticos de determinados factores de la coagulación están bajo el control inmediato de la glucosa plasmática o de los niveles de insulina, además, se produce un descenso de la actividad biológica de la antitrombina III (AT-III) en la diabetes⁽²⁴⁾.

Las concentraciones plasmáticas de factor de Von Willebrand (FVW) están elevadas en pacientes diabéticos con o sin complicaciones vasculares. Por tanto, el aumento de su concentración puede contribuir al aumento de la capacidad de adhesión plaquetaria en la diabetes. Además de estas alteraciones en el paciente diabético encontramos: Disminución de la proteína C, aumento de la agregación plaquetaria, aumento de la capacidad de adhesión plaquetaria, aumento de la formación de tromboxano A, deterioro de la actividad fibrinolítica, concentraciones elevadas de PAI-1, glucosilación del plasminógeno fibrinógeno^(24,25).

Todos estos factores de riesgo que presentaron nuestros pacientes subyacen en el desencadenamiento de la enfermedad coronaria y cerebrovascular, siendo éstos las dos principales complicaciones cardiovasculares de la HAS, por lo tanto es de suma importancia el tratamiento farmacológico, además de cambios del estilo de vida.

Como nos muestran los resultados no se presentaron alteraciones significativas en las pruebas de funcionamiento hepático, ni alteraciones en el TP y TPT. Estos últimos parámetros pueden ser

alterados con el consumo de algunos fármacos, entre ellos el AAS entre otros⁽²⁶⁾. El edema fue el evento adverso más común, presentándose en un 10% de los casos.

Cuando realizamos el estudio, una de nuestras limitantes fue que en nuestra ciudad no contábamos con el estudio de agregometría plaquetaria, este estudio es relativamente poco conocido pero eficaz en la detección de anormalidades en la función plaquetaria debido a su alta sensibilidad, permite establecer programas de vigilancia terapéutica cuando se usan antiagregantes plaquetarios como el AAS, además de ser útil para el diagnóstico de enfermedades que afectan la función plaquetaria⁽²⁷⁾.

CONCLUSIONES.

Los resultados del presente estudio de la combinación de Amlodipino 5mg/AAS 75 mg demostraron una eficacia clínica en el 89.1% % de los casos y una seguridad del 90.9 %. Además de no presentarse eventos adversos serios.

Al término del estudio el 64.5% de los pacientes presentaron rangos normales de T/A. De éstos, el 90.7% presentaron rangos normales de Pad y 68.5% presentaron rangos normales en la Pas. No se reportaron eventos adversos serios en ninguna de las visitas o alteración en PFH, TP y TPT.

Está claramente definida, la conducta terapéutica en los casos de factores de riesgo cardiovascular como; obesidad, sedentarismo, diabetes, antecedentes de enfermedad arterial oclusiva, accidentes cerebro-vasculares e incluso ataques isquémicos transitorios; el empleo de hipolipemiantes, antiagregantes plaquetarios, esta fundamentado bajo el mismo principio de protección de riesgos isquémicos, la prescripción a este tipo de pacientes favorece la administración de múltiples fármacos, motivo muy frecuente de falta de apego al tratamiento, ya sea por costos o por olvido, el empleo de un fármaco que contenga dos principios activos que contribuyan al manejo de una de las principales enfermedades crónicas en la actualidad, hace relevante su implicación terapéutica, incrementando el apego al tratamiento y reduciendo el consumo de múltiples drogas.

Los beneficios observados con la combinación Amlodipino 5mg/AAS 75mg en un solo producto contribuye al mejor control de los pacientes hipertensos, disminuyendo el riesgo de las complicaciones propias de la enfermedad, con mínimos efectos adversos.

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Cuadro I. Distribución por edad y género de 60 pacientes que participaron en el estudio.

Grupo de Edad	Masculino		Femenino		Total	
	Número de Pacientes	%	Número de Pacientes	%	Número de Pacientes	%
De 50 a 59 años	10	41.7%	15	41.7%	25	41.7%
De 60 a 69 años	12	50.0%	14	38.9%	26	43.3%
70 años y mayores	2	8.3%	7	19.4%	9	15.0%
Total	24	100.0%	36	100.0%	60	100.0%

$\chi^2 = 1.595$; $p=0.450$; N.S.

Promedio $\pm$ Desv. Est.	61.3 $\pm$ 4.95	60.0 $\pm$ 6.13	61.7 $\pm$ 5.65
(Mínimo - Máximo)	(54 - 71)	(50 - 70)	(50 - 71)
Mediana	60	62	56

Prueba t de Student entre sexos

$t(58) = 0.500$; $p=0.619$; N.S.

Cuadro II. Clasificación de los pacientes por nivel de la presión arterial diastólica inicial.

Nivel de la Presión Arterial Diastólica Inicial (mm de Hg)	No. de Pacientes	%
Menos de 90 mm de Hg	2	3.3%
De 90 a 100 mm de Hg	56	93.4%
Mas de 100 mm de Hg	2	3.3%
Total de pacientes	60	100.0%

Cuadro III. Promedio $\pm$ Desviación estándar de parámetros de la exploración física en pacientes que recibieron Amlodipino/AAS, en el tratamiento de hipertensión arterial sistémica en 4 evaluaciones.

Parametros de exploracion fisica	Visita Inicial (día 0)		2a. Visita (día 30)	
	Masc. (n=24)	Fem. (n=36)	Masc. (n=24)	Fem. (n=35)
Peso (Kg) *	84.2 $\pm$ 13.2	72 $\pm$ 9.8	83.9 $\pm$ 13.9	71.5 $\pm$ 9.7
Talla (cm) *	1.68 $\pm$ 0.07	1.56 $\pm$ 0.07	1.68 $\pm$ 0.07	1.55 $\pm$ 0.07
IMC (Kg/m ²)	29.8 $\pm$ 3.7	29.8 $\pm$ 4.2	29.7 $\pm$ 3.8	29.6 $\pm$ 4.2
Cintura (cm) *	104.7 $\pm$ 9.7	95.5 $\pm$ 10.5	104.7 $\pm$ 10.5	95.5 $\pm$ 10.2
F.Cardíaca (por min.)	67.7 $\pm$ 12	69.3 $\pm$ 9.6	71.3 $\pm$ 10.9	70.3 $\pm$ 8.7
F.Respiratoria (por min.)	16.3 $\pm$ 0.8	17.1 $\pm$ 1.6	17.4 $\pm$ 1.3	17.5 $\pm$ 1.4
	3a. Visita (día 60)		4a. Visita (día 90)	
	Masc. (n=24)	Fem. (n=32)	Masc. (n=23)	Fem. (n=32)
Peso (Kg) *	84.1 $\pm$ 13.6	71.1 $\pm$ 10	83.5 $\pm$ 14.6	71.2 $\pm$ 10.2
Talla (cm) *	1.68 $\pm$ 0.07	1.55 $\pm$ 0.07	1.68 $\pm$ 0.08	1.55 $\pm$ 0.07
IMC (Kg/m ²)	29.8 $\pm$ 3.9	29.6 $\pm$ 4.3	29.6 $\pm$ 4.1	29.5 $\pm$ 4.3
Cintura (cm) *	104.1 $\pm$ 10.1	95.6 $\pm$ 10.4	102.6 $\pm$ 9.8	95 $\pm$ 10.4
F.Cardíaca (por min.)	72.1 $\pm$ 10.5	69.5 $\pm$ 6.9	68.8 $\pm$ 9.5	69.7 $\pm$ 7
F.Respiratoria (por min.)	17.9 $\pm$ 1.4	18.2 $\pm$ 1.5	17.6 $\pm$ 0.8	17.7 $\pm$ 1.3

Cuadro IVa. Clasificación de resultados de laboratorio para perfil hepático.

Clasificación de los sujetos según nivel en cada uno de los parámetros	INICIAL		FINAL		χ^2	p con χ^2	p con Wilcoxon
PERFIL DE LIPIDOS	No.	%	No.	%			
Colesterol (mg/dL)							
Bajo (Menos de 80)	0	0.0%	0	0.0%	0.224	0.636	0.593
Normal (80 a 200)	28	48.3%	29	52.7%			
Alto (Mas de 200)	30	51.7%	26	47.3%			
Triglicéridos (mg/dL)							
Bajo (Menos de 35)	0	0.0%	0	0.0%	0.355	0.551	0.467
Normal (35 a 200)	42	72.4%	37	67.3%			
Alto (Mas de 200)	16	27.6%	18	32.7%			
HDL Colesterol (mg/dL)							
Bajo (Menos de 35)	23	39.7%	23	41.8%	0.982	0.612	0.782
Normal (35 a 65)	34	58.6%	32	58.2%			
Alto (Mas de 65)	1	1.7%	0	0.0%			
LDL Colesterol (mg/dL)							
Normal (0 a 130)	33	56.9%	29	52.7%	0.198	0.656	0.782
Alto (mas de 130)	25	43.1%	26	47.3%			
Indicador de Riesgo Aterosclerosis CoTotal/HDL							
Bajo (Menos de 4)	13	22.4%	8	14.5%	1.487	0.475	0.180
Normal (4 a 7)	34	58.6%	33	60.0%			
Alto (Mas de 7)	11	19.0%	14	25.5%			
Indicador de Riesgo Aterosclerosis LDL/HDL							
Bajo (Menos de 3)	24	41.4%	16	29.1%	2.672	0.263	0.549
Normal (3 a 4)	13	22.4%	19	34.5%			
Alto (mas de 4)	21	36.2%	20	36.4%			

Cuadro IVb. Clasificación de resultados de Laboratorio clínico para Perfil Hepático con relación a TGO (ASP transferasa) TGP (ALA transferasa).

Clasificación de los sujetos según nivel en cada uno de los parámetros	INICIAL		FINAL			p con χ^2	p con Wilcoxon
PERFIL HEPATICO (2a. Parte)	No.	%	No.	%	χ^2		
TGO (ASP Transferasa) (u/L)							
Bajo (Menos de 15)	1	1.7%	0	0.0%	0.932	0.628	0.157
Normal (15 a 46)	55	93.2%	51	94.4%			
Alto (mas de 46)	3	5.1%	3	5.6%			
TGP (ALA Transferasa) (u/L)							
Bajo (Menos de 4)	0	0.0%	0	0.0%	0.863	0.353	0.317
Normal (4 a 66)	56	94.9%	53	98.1%			
Alto (Mas de 66)	3	5.1%	1	1.9%			
Gamma Glutamil Transferasa (UI/L)							
Normal (0 a 78)	56	94.9%	50	92.6%	0.262	0.609	0.564
Alto (mas de 78)	3	5.1%	4	7.4%			

Cuadro V. Promedio $\pm$ desviación estándar del tiempo de protrombina y de tromboplastina en 60 pacientes con hipertensión arterial.

Parámetros Evaluados del Tiempo de Protrombina y Tromboplastina	I N I C I A L					
	Femenino		Masculino		Total	
Tiempo de Protrombina (seg)	12.11 $\pm$ 1.31	35	12.22 $\pm$ 0.80	24	12.15 $\pm$ 1.12	59
Tiempo de Protrombina - Testigo (seg)	11.63 $\pm$ 0.62	35	11.89 $\pm$ 0.50	24 §	11.73 $\pm$ 0.59	59
Tiempo Parcial de Tromboplastina (seg)	31.89 $\pm$ 4.41	35	33.07 $\pm$ 5.16	22	32.35 $\pm$ 4.70	57
Tiempo Parcial de Tromboplastina - Testigo (seg)	34.6 $\pm$ 0.79	23	34.6 $\pm$ 1.00	17	34.6 $\pm$ 0.88	40

Parámetros Evaluados del Tiempo de Protrombina y Tromboplastina	F I N A L					
	Femenino		Masculino		Total	
Tiempo de Protrombina (seg)	11.95 $\pm$ 0.96	32	11.93 $\pm$ 0.97	23	11.94 $\pm$ 0.96	55
Tiempo de Protrombina - Testigo (seg)	11.62 $\pm$ 0.45	32	11.69 $\pm$ 0.51	23 §	11.65 $\pm$ 0.47	55
Tiempo Parcial de Tromboplastina (seg)	31.02 $\pm$ 4.13	31	32.58 $\pm$ 4.50	23	31.68 $\pm$ 4.32	54
Tiempo Parcial de Tromboplastina - Testigo (seg)	34.5 $\pm$ 0.83	19	34.5 $\pm$ 0.76	16	34.5 $\pm$ 0.79	35

§.p <0.05 entre la valoración inicial y final correspondiente utilizando la prueba t de Student para muestras dependientes.

Cuadro VI. Características de los pacientes que recibieron el tratamiento antihipertensivo.

Características de los pacientes	No. de Pacientes	%
Cumplimiento de las cuatro visitas		
Si	55	91.7%
No	5	8.3%
Total	60	100.0%
Pacientes participantes por visita		
1a. Visita (día 0)	60	100.0%
2a. Visita (día 30)	59	98.3%
3a. Visita (día 60)	56	93.3%
Visita final (día 90)	55	91.7%
Pacientes con presencia de evento adverso no serio		
En la 2a. Visita	3	5.1%
En la 3a. Visita	3	5.4%
En la 4a. y última Visita	2	3.6%
Pacientes con presencia de evento adverso serio		
En la 2a. Visita	0	0.0%
En la 3a. Visita	0	0.0%
En la 4a. y última Visita	0	0.0%

Cuadro VII. Eventos adversos no serios presentados por pacientes que recibieron tratamiento con Amlodipino/AAS en el tratamiento de hipertensión arterial sistémica en la 2ª 3ª y 4ª visita (30, 60, y 90 días).

Evento Adverso No Serio	No. de Pacientes	%
En la segunda visita (a los 30 días)		
Edema	1	1.7%
Edema en cara	1	1.7%
Edema en miembros pélvicos	1	1.7%
Irritabilidad	1	1.7%
Total de eventos adversos no serios en la segunda visita (día 30)	4	
En la tercera visita (60 días)		
Edema	1	1.8%
Edema en miembros pélvicos	1	1.8%
Exacerbación de asma	1	1.8%
Total de eventos adversos no serios en la tercera visita (día 60)	3	
En la cuarta visita (90 días)		
Edema	1	1.8%
Edema en miembros pélvicos	1	1.8%
Total de eventos adversos no serios en la cuarta visita (día 90)	2	

Figura 1. Promedio $\pm$ Desviación Estándar de la Presión Arterial (Sistólica y Diastólica en mm de Hg.) en 60 pacientes con Hipertensión Arterial Sistémica que recibieron Amlodipino-AAS durante 90 días de seguimiento.

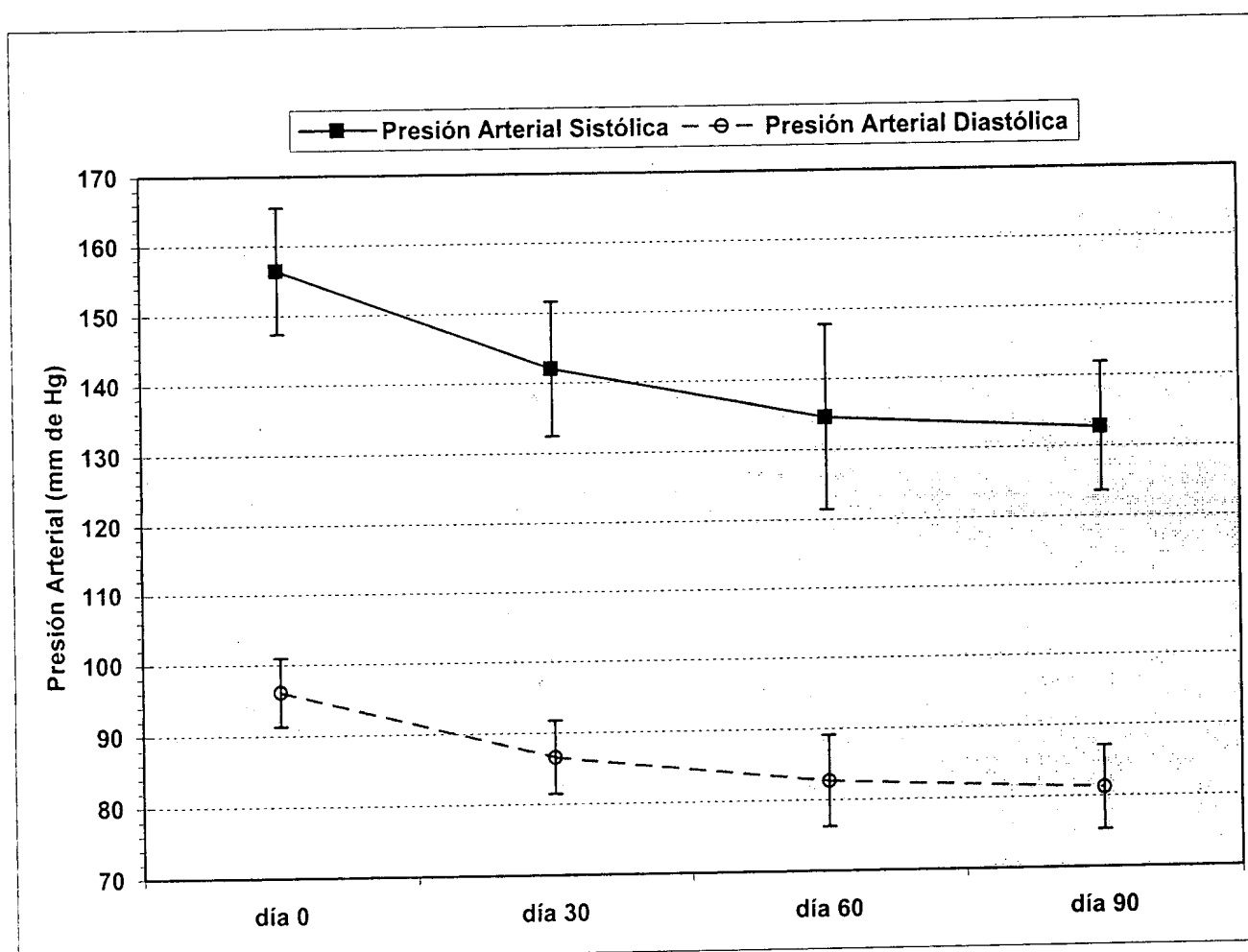


Figura 2. Porcentaje de Casos según tipo de Hipertensión y de logro de eficacia clínica en cada uno de los días de observación, en 60 pacientes con Hipertensión Arterial Sistémica que recibieron Amlodipino/AAS.

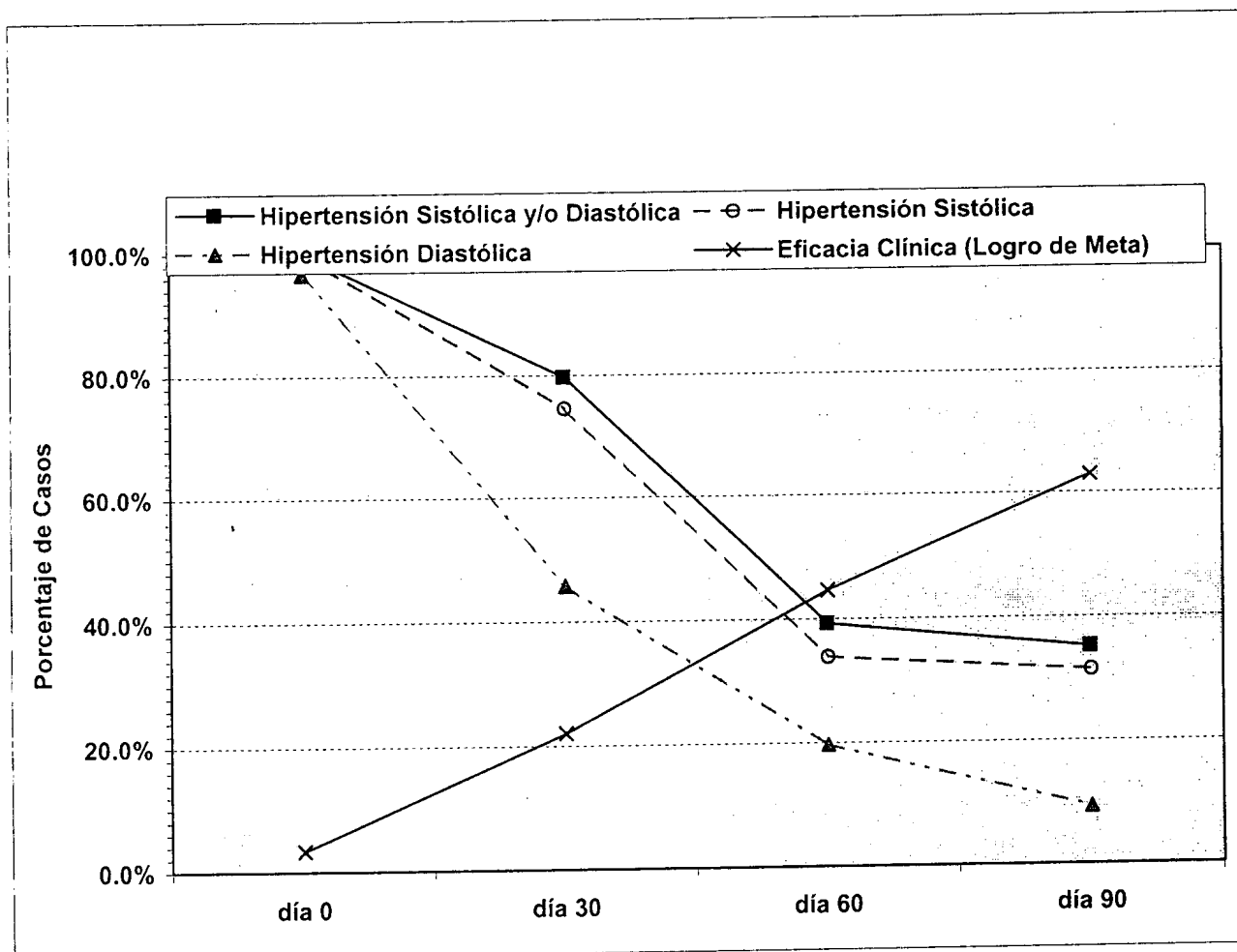


Figura 3. Prevalencia de Factores de Riesgo Coronario en 60 pacientes con Hipertensión Arterial Sistémica tratados con Amlodipino/AAS durante 90 días.

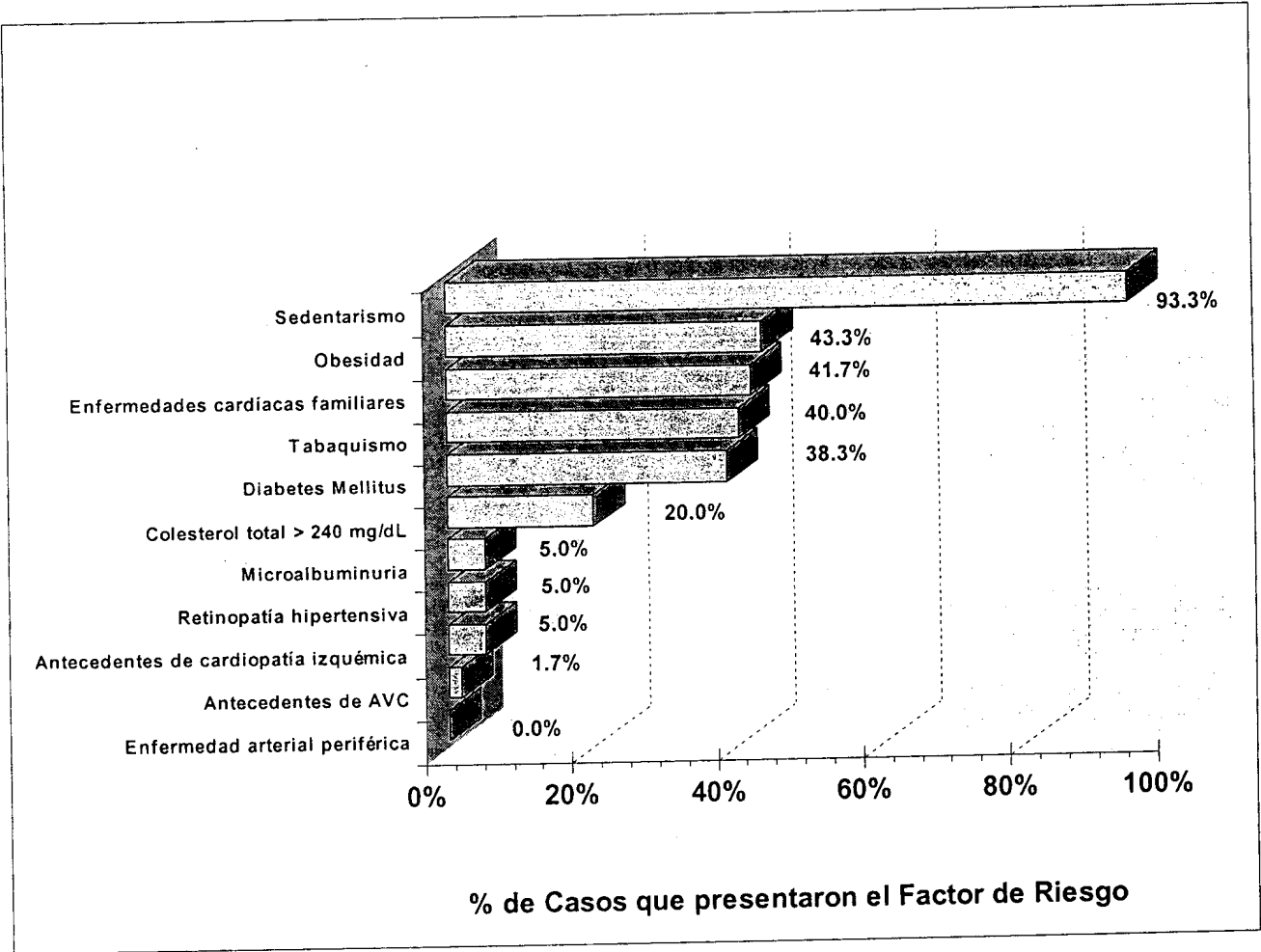


Figura 4. Porcentaje de pacientes hipertensos que recibieron Amlodipino/AAS durante 3 meses, según el número de factores de riesgo cardiovascular que presentan.

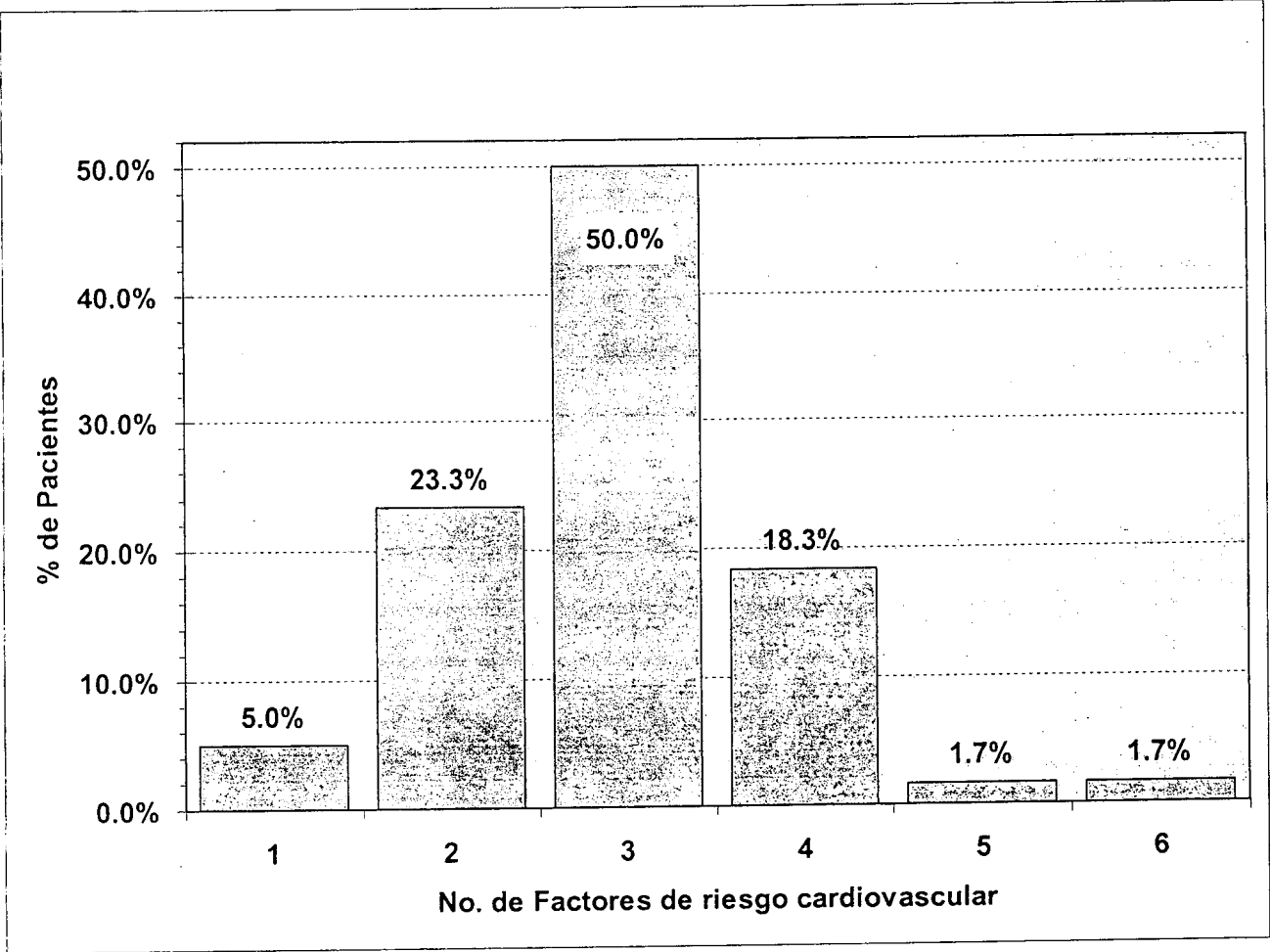
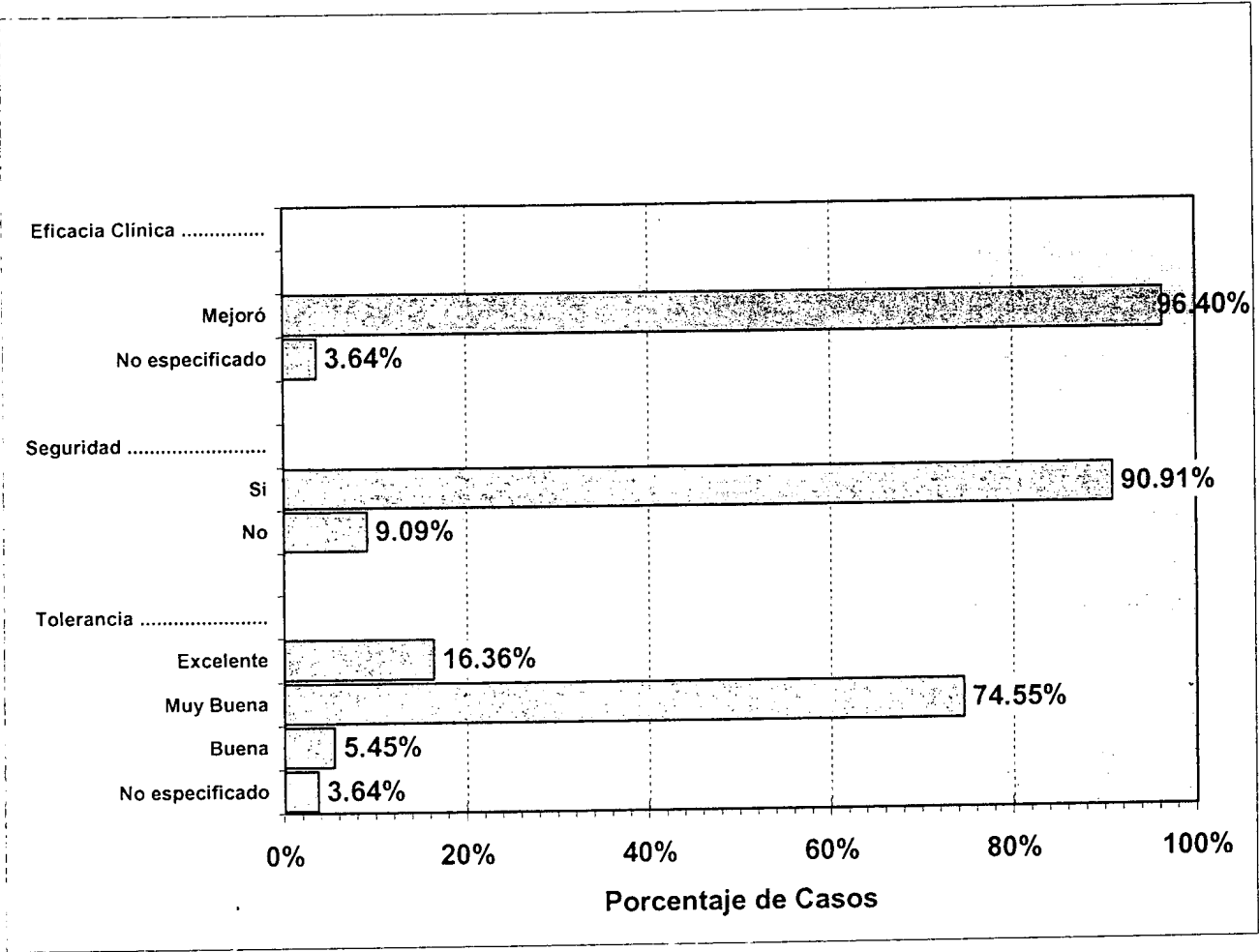


Fig. 5. Evaluación del Medicamento según los médicos tratantes en lo que respecta a Eficacia Clínica, Seguridad y Tolerancia con Amlodipino 5mg/AAS 75mg.



ANEXO No. 2

“A randomized Placebo-Controlled Comparison of Amlodipine and Atenolol in Mild to Moderate Systemic Hypertension” William H. Frishman, Richard Brobyn, Ronald D. Brown, Brian F. Johnson, Robert L. Reeves, and Duane G. Wombolt.

A Randomized Placebo-Controlled Comparison of Amlodipine and Atenolol in Mild to Moderate Systemic Hypertension

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Summary: Amlodipine, a new long-acting dihydropyridine calcium antagonist, was compared with placebo and atenolol in 125 patients with mild to moderate systemic hypertension [supine diastolic blood pressure (DBP) 90–114 mm Hg]. Patients received placebo for 4 weeks, followed by a random allocation to an 8-week double-blind, once-daily treatment with amlodipine ($n = 41$), atenolol ($n = 43$), or placebo ($n = 41$). The changes in 24-h post-dose blood pressure (BP) from baseline to final visit for amlodipine (mean daily dose 8.8 mg, range 5–10 mg) were $-12.8 \pm 2.0/-10.1 \pm 1.2$ mm Hg in supine BP and $-11.5 \pm 2.3/-9.8 \pm 1.1$ mm Hg in standing BP ($p < 0.001$); for atenolol (mean daily dose 83.7 mg, range 50–100 mg), the changes from baseline were $-11.3 \pm 2.3/-11.7 \pm 1.3$ mm Hg in supine BP and $-13.3 \pm 3.1/-12.3 \pm 1.5$ mm Hg in standing BP ($p < 0.001$); for placebo, the

changes from baseline were $-0.9 \pm 2.8/-3.5 \pm 0.9$ mm Hg in supine BP and $-1.6 \pm 2.6/-4.0 \pm 1.0$ mm Hg in standing BP. In the study, goal response was defined as a supine DBP of <90 mm Hg or its decrease by ≥ 10 mm Hg. The response rates were similar for atenolol (65%) and amlodipine (61%). Both active therapies were significantly more effective than placebo. Heart rate was significantly lowered by atenolol only. Both amlodipine and atenolol were well tolerated and neither drug had any significant effects on plasma lipids or lipoproteins. It is concluded that once-daily amlodipine is as effective and well tolerated as atenolol in reducing BP in patients with mild-to-moderate hypertension. **Key Words:** Amlodipine—Atenolol—Hypertension—Calcium blockers—Dihydropyridine— β -blocker.

Calcium antagonists are a distinct group of compounds that interfere with the transmembrane flux of extracellular calcium ions on which vascular tissue depends for contraction (1). The drugs have been successfully used in the management of ischemic heart disease, hypertrophic cardiomyopathy, and certain arrhythmias (2,3). In recent years interest has been focused on the use of calcium antagonists in the management of systemic arterial hypertension (4–8). In this multicenter study, the safety and efficacy of amlodipine, a new once-daily dihydropyridine calcium antagonist, were compared with those of atenolol and placebo in patients with mild to moderate systemic hypertension.

METHODS

Patients with mild to moderate hypertension were enrolled in the multicenter trial after written informed consent was obtained.

Patient selection

All patients who were entered had systemic hypertension with a stable resting diastolic blood pressure (DBP) of 95–114 mm Hg in both the standing and supine positions (Korotkoff phase V). It was a criterion for continuation in the study that the average of three DBP measurements at 24 h (supine and standing) at weeks 2 and 4 of the placebo run-in period could not differ by more than 10 mm Hg. The demographic characteristics of the patients studied are shown in Table 1.

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TABLE 1. Demographic details of patients

	Amlodipine (n = 41)	Atenolol (n = 43)	Placebo (n = 41)
Mean age (yr)	54.9	56.2	60.2
15-44 yr	3	4	3
45-64 yr	32	31	23
≥65 yr	6	8	15
White	37	39	37
Black	4	3	2
Hispanic	0	1	2
Mild hypertensive (90 mm Hg ≤ supine DBP ≤ 104 mm Hg)	36	33	30
Moderate hypertensive (105 mm Hg ≤ supine DBP ≤ 114 mm Hg)	5	10	11

DBP, diastolic blood pressure.

Patients with the following conditions were excluded from the study: significant cardiovascular disease other than essential hypertension, impaired renal function, second- or third-degree heart block or sick sinus syndrome, insulin-dependent diabetes, pregnancy, or known hypersensitivity to β -adrenergic blockers or calcium antagonists.

Experimental design

This was a multicenter study using a common protocol (Fig. 1). It consisted of a 4-week single-blind placebo run-in period, followed by a double-blind parallel 8-week comparison of amlodipine, atenolol, or placebo. Doses were adjusted every 2 weeks for 6 weeks with either amlodipine 2.5, 5.0, and 10.0 mg once daily, placebo, or atenolol 50 and 100 mg once daily until a goal response was obtained. Goal response was defined as either a reduction in supine DBP to <90 mm Hg or at least a 10 mm Hg reduction from baseline. When the goal response was achieved, patients were maintained on this regimen for the duration of the study. Therapy was immediately discontinued or reduced to a previously tolerated dose level if significant adverse effects occurred.

Methods of observation

For all review visits, patients were examined in the morning, 24 h after the previous dose. At the visits of study weeks 0, 4, and 8 (double-blind phase), BPs and pulse rate were measured first, after which patients received their medication under clinic supervision. Supine

and standing BPs and pulse rates were recorded before dosing, hourly for 12 consecutive hours postdose and again at 24 h postdose. BP and pulse rate were measured in triplicate after 5 min in the supine position and after 2 min in the standing position at each review visit.

Lipid and lipoprotein profiles were determined from blood specimens obtained throughout the study. Safety was monitored during the placebo and active treatment phases with adverse reaction profiling, electrocardiograms (ECGs), complete blood counts, blood chemistry, and urinalysis.

Statistical methods

Data are presented as mean $\pm$ SD. All analyses were performed using a two-way analysis of variance.

RESULTS

Patients

A total of 168 patients were recruited for the study: 125 received double-blind treatment (Table 1). Forty-three of the 168 patients who entered the placebo run-in period did not advance to the double-blind phase because they did not fulfill BP entry criteria. Eleven patients did not complete the double-blind phase of the study (three with amlodipine, five with atenolol, and three with placebo).

Compliance

Patient compliance (based on capsule and tablet counts) was good throughout the study. Only one patient was removed from the study because of poor compliance (amlodipine).

Blood pressure and pulse rate

The efficacy analysis was based on measurements made at the end of the placebo run-in period (baseline) and at the end of the double-blind treatment (final). Supine BP was reduced by amlodipine from $153.4 \pm 2.5/100.2 \pm 0.7$ mm Hg to $140.7 \pm 2.4/90.1 \pm 1.5$ mm Hg ($p < 0.001$); atenolol decreased it from $154.8 \pm 2.5/102.0 \pm 0.8$ to $143.5 \pm 2.6/90.2 \pm 1.5$ mm Hg ($p < 0.001$); with placebo, there was a slight change from $155.8 \pm 3.0/100.8 \pm 0.7$ mm Hg to $156.6 \pm 2.3/97.3 \pm 1.0$ mm Hg. The supine pulse rate was reduced 9.1 beats/min by atenolol ($p < 0.001$), 1.2 beats/min by amlodipine, and was practically unchanged by placebo. The standing BP was reduced by amlodipine from $150.6 \pm 2.8/102.1 \pm 0.9$ mm Hg to $139.1 \pm 3.3/92.3 \pm 1.6$ mm Hg ($p < 0.001$); atenolol reduced it from $154.5 \pm 3.1/103.4 \pm 0.8$ mm Hg to $141.1 \pm 2.6/91.1 \pm 1.5$ mm Hg ($p < 0.001$); with placebo it was reduced from $152.3 \pm 2.8/102.0 \pm 0.8$ mm Hg to $150.8 \pm 2.4/98.0 \pm 1.3$ mm Hg. The standing pulse rate was decreased by 13.0 beats/min by atenolol ($p < 0.001$), and was virtually unchanged by amlodipine and placebo.

The mean BP value throughout the study are shown in Fig. 2. The BP curves for amlodipine and atenolol are superimposable and are clearly apart from that of placebo.

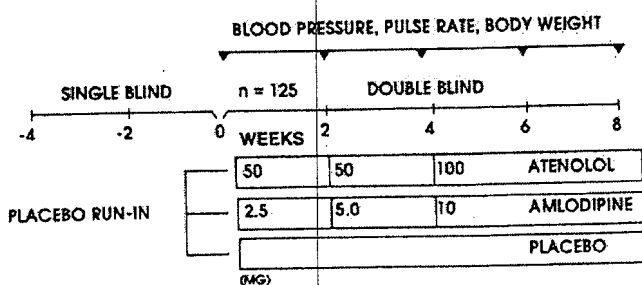


FIG. 1. Study protocol.

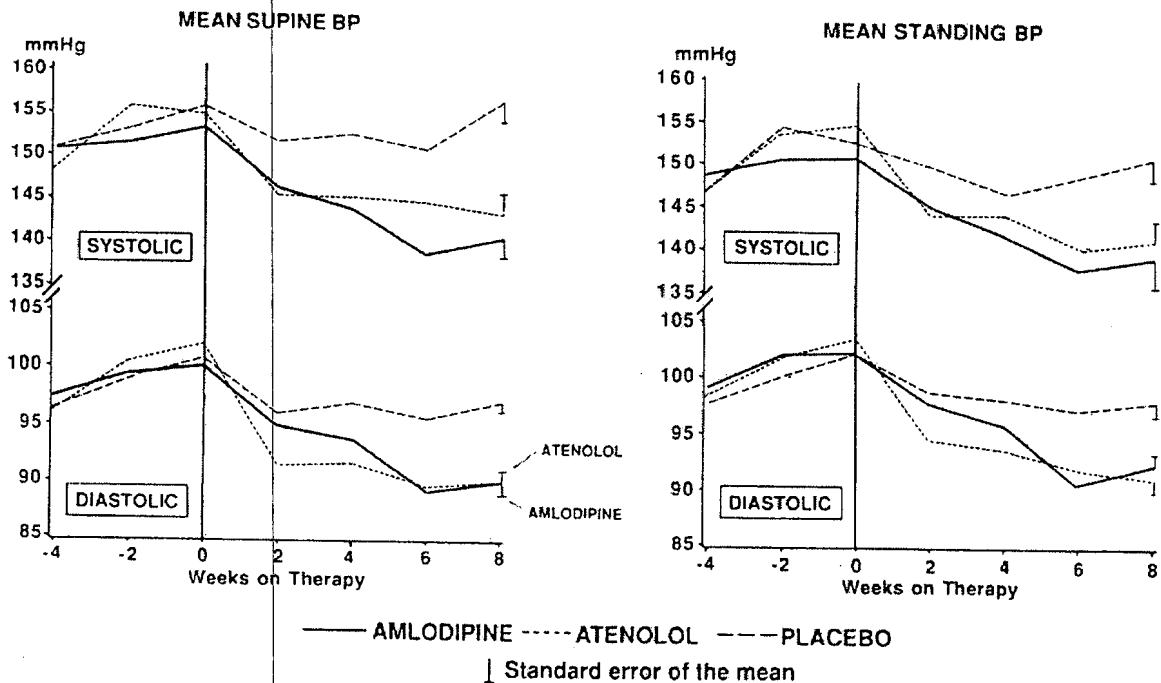


FIG. 2. Effects of placebo, atenolol, and amlodipine on mean supine and standing blood pressure. Mean changes in supine blood pressure from placebo baseline values to week 8 of therapy for amlodipine were $-12.8/-10.1$ mm Hg ($p < 0.001$); for atenolol, $-11.3/-11.7$ mm Hg ($p < 0.001$); and for placebo, $-0.9/-3.5$ mm Hg. The corresponding changes for standing blood pressure were $-11.5/-9.8$ mm Hg ($p < 0.001$); $-13.3/-12.3$ mm Hg ($p < 0.001$); and $-1.6/-4.0$ mm Hg, respectively.

Goal BP was attained in 61.1% of patients (23/36) receiving amlodipine; 64.9% of patients (24/37) receiving atenolol; and 11.1% of patients (4/36) receiving placebo.

Blood lipids

There was an increase of 22.2 mg/dl in serum triglycerides in the atenolol group ($p = \text{NS}$). The levels of total cholesterol and low-density lipoprotein (LDL) cholesterol were not elevated by amlodipine, atenolol, or placebo. High-density lipoprotein (HDL)-cholesterol, LDL-cholesterol, and the ratio HDL/LDL were virtually unchanged by the treatments.

Safety

The side effects (considered by the investigators to be possibly or definitely related to double-blind

treatment) are shown in Table 2. Peripheral edema was more prevalent in the amlodipine group; insomnia and fatigue were more prevalent with atenolol than with amlodipine or placebo. Only one patient was withdrawn because of side effects. The patient had received amlodipine for 17 days when he developed generalized fatigue, gastric reflux, swelling of the hands, and arthralgia. The dosage of amlodipine was 5 mg/day.

Laboratory abnormalities were few and transient. Atenolol was associated with more bradycardia than amlodipine on the ECG. ECG intervals were not prolonged by either atenolol or amlodipine. There was no increase in body weight in any of the treatment groups, or clinically significant postural hypotension.

DISCUSSION

Calcium antagonists are safe and effective drugs for treatment of systemic hypertension (4-9) and hypertensive emergencies (10,11). In this study, once-daily amlodipine was as effective as atenolol in reducing BP. Both drugs were well tolerated, with no alterations in plasma lipids or lipoproteins observed. Atenolol therapy was associated with a significant reduction in heart rate, a recognized effect of β -adrenoceptor blockade.

The time-effect curves for both atenolol and amlodipine revealed that both drugs maintained the average BP below the hypertensive range, whereas with placebo, BP was in the hypertensive range. A

TABLE 2. Most frequent side effects

	Amlodipine	Atenolol	Placebo
No. of patients evaluable	41	43	41
Total with side effects (withdrawn)	19 (1)	14 (0)	10 (0)
Edema	7	0	0
Headache	3	4	2
Fatigue	1	3	0
Insomnia	0	3	0
Flushing	2	0	1
Micturition frequency	1	0	2

Only one patient taking amlodipine was withdrawn because of side effects.

similar time-course of the antihypertensive effect of amlodipine and atenolol was observed in the standing position.

This study demonstrates that once-daily administration of amlodipine (2.5–10.0 mg daily) or atenolol (50–100 mg daily) to mild-to-moderate hypertensive patients is both safe and effective. The safety and efficacy of amlodipine in comparison with other calcium antagonists for antihypertensive treatment needs to be determined.

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ANEXO No. 3

“Amlodipine and captopril in moderate-severe Essentials hipertensión” D. Maclean, E.T. Mitchell, R.G. Wilcox, P. Walker and H.M. Tyler. Department of Pharmacology, Ninewells Hospital, Dundee, DD1 9 SY, Queen’s Medical Center, Nottingham, and Pfizer Central Research, Sandwich, Kent, UK



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Amlodipine and captopril in moderate-severe essential hypertension

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Summary: The therapeutic usefulness of adding once-daily amlodipine (10 mg) for four weeks in moderate-severe hypertensive patients uncontrolled on low dose captopril (25 mg twice daily) alone was studied in 29 patients in a double-blind, placebo-controlled two-way crossover comparison. Once daily amlodipine was shown to be an effective antihypertensive drug when combined with captopril. The amlodipine minus placebo differences in mean changes from captopril baseline values were: -18/-12 mmHg and -20/-12 mmHg for supine and standing systolic/diastolic pressures ($P < 0.001$ for all four pressure variables). The combination was well tolerated, and no patient discontinued therapy. Five patients experienced ankle oedema and four patients reported flushing while receiving amlodipine/captopril.

Introduction

Various drugs, either alone or in combination, may effectively control moderate to severe hypertension, but clinically unacceptable side-effects are common and often mitigate against their successful use. Thus, there remains a need to find effective low-dose drug combinations with low side-effect profiles.

Captopril may be effective in low dose (25 mg twice daily)¹⁻³ and may also be useful when used in combination with the dihydropyridines,^{4,5} which are likewise now being widely used in moderate to severe hypertension.⁶

Amlodipine is a novel dihydropyridine calcium antagonist which, in animals, selectively dilates arterial resistance vessels.⁷ It has pronounced antihypertensive effects in animals⁸ and in man,⁹ but no formal comparison of its potency with nifedipine has yet been published. Amlodipine has a longer elimination half-life (amlodipine, 45 hours;¹⁰ nifedipine, ~6 hours¹¹) in steady state and is effective throughout the 24-hour dosing period when given once daily. It has no negative inotropic activity at therapeutic plasma concentrations.¹² This study compared the therapeutic usefulness of adding amlodipine for four weeks in hypertensive patients uncontrolled on low dose captopril alone.

Patients and methods

Males and females aged 18-65 years attending the hypertension outpatient clinic of Ninewells Hospital, Dundee, were studied if their mean DBP both sitting and standing (WHO grades I-III) was 100-119 mmHg (Phase V) after four weeks on placebo.

Patients were either newly presenting, uncontrolled on previous monotherapy, or taking antihypertensive drugs with unacceptable side effects; only six were cigarette smokers. Patients were excluded if they had clinically significant impairment of renal or hepatic function (serum creatinine $> 120 \mu\text{mol/l}$ or serum levels of liver enzymes more than 10% above the upper limit of normal), myocardial infarction or stroke within the preceding six months, severe angina pectoris, a history of allergy to or intolerance of ACE-inhibitor drugs or calcium antagonists, intermittent, unstable or accelerated hypertension, a history of poor attendance or compliance, or were of child-bearing potential. Concurrent therapy with drugs likely to interfere with the test drugs, e.g. cimetidine or indomethacin, also led to exclusion. The standard contra-indications for both ACE-inhibitors and dihydropyridine calcium antagonists were observed.

Blood pressure (systolic and diastolic Phase V) was measured, using the same arm on all occasions, three times in the supine position (after five minutes) and three times with the patient standing (after two minutes) using a Hawksley Random Zero sphygmomanometer with the arm supported

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at heart level. BP was recorded by the same individual on each occasion. The radial pulse was measured over 30 seconds in each position immediately after each BP measurement. Mean values of each measure were used for the analyses. Body weight was also measured at each visit.

Study design

After a two- to four-week single-blind placebo run-in phase, those patients whose DBP was 100–119 mmHg entered the open captopril phase. Of the original 41 patients who completed the placebo run-in period, 33 entered the open captopril phase and eight were excluded because they did not meet the BP criteria. One further patient (already on captopril therapy) entered the open captopril phase directly. A total of 34 patients received open captopril, 25 mg twice daily, plus placebo capsules matching amlodipine for four weeks. Twenty-nine of these patients proved to be inadequately controlled (i.e. their average DBP, both supine and standing was >95 mmHg), and they then entered the study proper which was a computer randomised, double-blind, two-way crossover comparison of either amlodipine 10 mg once daily or matching placebo added to continuing background therapy with captopril 25 mg twice daily for four weeks. Subsequently, all patients then received for a further four weeks the alternative amlodipine/placebo treatment plus background captopril, irrespective of their BP at the time of the change over (i.e. each patient acting as their own control).

BP was measured approximately 12 hours after the previous dose of captopril and approximately 24 hours after the previous dose of amlodipine. The four week assessment periods were chosen so as to permit each combined treatment to exhibit its maximum antihypertensive effect without the need to incorporate a washout period at the crossover.^{9,12,14}

The study was conducted according to the principles of the Declaration of Helsinki and the Tokyo amendments. All patients gave their written informed consent to participation in this study, after approval of the protocol by the Committee on Medical Ethics of the Tayside Health Board.

Captopril was dispensed as commercially available tablets 25 mg ('Capoten'®—E. R. Squibb and Sons) and amlodipine as capsules of the maleate salt containing the equivalent of amlodipine 10 mg as base. Placebo capsules matched the active drug. Returned tablets and capsules were counted at each visit.

Routine biochemical (AST, γ -GT, bilirubin, alkaline phosphatase; total protein and albumin;

random blood glucose; urea, creatinine; Na^+ , K^+ , total Ca^{2+}) and haematological (haemoglobin, red blood cell count, total and differential white blood cell count, platelet count and haematocrit) screening, together with an ECG and urinalysis, were performed at baseline and at each subsequent visit.

Volunteered and observed side effects were recorded at each visit throughout the study. No leading questions were asked. Side effects were classified as either mild, moderate or severe and their likely relationship to the blinded therapy was judged by the investigator. Details of intercurrent illnesses were also recorded.

Statistical methods

Efficacy was assessed statistically by analysing the change from baseline BPs and heart rates to the values recorded at the end of each period of double-blind therapy. Baseline values were taken to be the means of the triplicate measurements obtained at the end of captopril monotherapy, immediately prior to the commencement of double-blind therapy. These baseline means were subtracted from the means of the triplicate measurements recorded at the end of each period of double-blind therapy and the resulting changes from baseline were subjected to an analysis of variance.

A standard analysis of variance model appropriate for a two-period two-treatment crossover design was fitted, permitting tests of the treatment, period, and treatment by period interaction effects. Data on body weight were subjected to an analysis of similar structure.

Tests of BP data featured one-sided hypothesis testing, in which the null hypothesis of no treatment difference was tested against the alternative hypothesis of a greater reduction in pressure from baseline values during captopril and amlodipine combined therapy compared with the reduction during captopril and double-blind placebo combined therapy. Tests of heart rates and of body weight featured two-sided hypothesis testing.

Results

Thirty-four patients (mean BP $171 \pm 3/107 \pm 1$ mmHg supine and $169 \pm 3/111 \pm 1$ mmHg standing) entered the captopril run-in phase of the study. At the end of this phase, 29 patients (mean BP $167 \pm 3/104 \pm 1$ mmHg supine and $168 \pm 4/110 \pm 1$ mmHg standing), were randomised to the double-blind cross-over part of the study; 15 patients received amlodipine first. The mean age of

Table I Previous antihypertensive therapy

Previous therapy	Amlodipine then placebo n = 12
None	6
Ace inhibitor	3
Dihydropyridine calcium antagonist	4
Diuretic	0
β -blocker	6

the 29 patients was 53.6 years, all had a supine and standing BP >160/95 mmHg despite four weeks' treatment in addition to placebo. Compliance was judged by the investigator to be 'good' in 21 of the 29 patients; only nine out of the 29 patients completed the 'days' study therapy during the crossover period.

Previous antihypertensive therapy in the 29 patients who completed the crossover phase is detailed in Table I. Three patients were excluded from the crossover phase because BP measurements were outside the appropriate 'window' (i.e. >160/95 mmHg dose of captopril), and this occurred in both double-blind phases.

For those patients included in the crossover phase, analysis of variance showed that mean changes from captopril baseline values were: -13.3 mmHg on amlodipine vs. -0.4 mmHg on placebo (supine) and -1.1 mmHg on amlodipine vs. -0.4 mmHg on placebo (standing). Mean changes in standing SBP were: -13.5 mmHg on amlodipine vs. -2.5 mmHg on placebo (supine) and -1.6 mmHg on amlodipine vs. -0.4 mmHg on placebo (standing). Thus, amlodipine minus placebo (mean $\pm$ SE) in mean changes from baseline values were: -18.0 mmHg (supine) and -20.4 mmHg (standing) ($P < 0.001$), for supine and standing SBP (Tables II and III). Supine DBP was achieved by 19 patients on placebo but only 3 patients on placebo had a BP <90 mmHg in nine on amlodipine and only one on placebo/captopril. In only one on placebo/captopril patients showed a fall in SBP and 16 showed a fall in DBP when amlodipine was added.

No clinically important differences in body weight or in the side effect profile were seen between the two treatments.

An 'intention to treat' analysis (including all data from the crossover phase) here) including all data from the crossover phase did not show important differences in results.

rea, creatinine; Na⁺, K⁺, ological (haemoglobin, red d differential white blood and haematocrit) screen- OG and urinalysis, were at each subsequent visit. erved side effects were roughout the study. No asked. Side effects were moderate or severe and the blinded therapy was r. Details of intercurrent ed.

istically by analysing the s and heart rates to the end of each period of seline values were taken triplicate measurements aptopril monotherapy, mmencement of dou- baseline means were sub- of the triplicate measure- end of each period of d the resulting changes ected to an analysis of

nce model appropri- -treatment crossover deg tests of the treatment, by period interaction ght were subjected to an ire. ed one-sided hypothesis hypothesis of no treat- d against the alternative duction in pressure from uptopril and amlodipine are with the reduction ble-blind placebo com- heart rates and of body l hypothesis testing.

mean BP 171±3/107 169±3/111±1 mmHg opril run-in phase of the phase. 29 patients (mean upine and 168±4/ were randomised to the part of the study; 15 ne first. The mean age of

Table I Previous antihypertensive therapy

Previous therapy	Amlodipine then placebo n=15	Placebo then amlodipine n=14
None	6	5
Ace inhibitor	3	1
Dihydropyridine calcium antagonist	4	5
Diuretic	0	1
β-blocker	6	9

the 29 patients was 53.6 years (range 36–65 y) and all had a supine and standing DBP ≥95 mmHg despite four weeks' treatment with captopril in addition to placebo. Compliance was judged by the investigator to be 'good' throughout the study; only nine out of the 29 patients missed one or two days' study therapy during the 16 week trial period.

Previous antihypertensive therapy received by the 29 patients who completed the double-blind phase is detailed in Table I. Two of the 29 patients were excluded from the primary efficacy analysis because BP measurements were made at a time outside the appropriate 'window', (9–15 hrs post-dose of captopril), and this occurred at the end of both double-blind phases.

For those patients included in the primary efficacy analysis, mean changes in supine SBP/DPB from captopril baseline values were –18.4/–13.3 mmHg on amlodipine with captopril and –0.4/–1.1 mmHg on placebo with captopril; mean changes in standing SBP/DBP were –22.9/–13.5 mmHg on amlodipine with captopril and –2.5/–1.6 mmHg on placebo with captopril. Thus, amlodipine minus placebo differences (±SE) in mean changes from captopril baseline values were : –18.0(±4)/–12.2(±2) mmHg (P<0.001) and –20.4(±4)/–11.9(±2) mmHg (P<0.001), for supine and standing BPs (Figure 1, Tables II and III). Supine DBP <95 mmHg was achieved by 19 patients on amlodipine/captopril but only 3 patients on placebo/captopril; and <90 mmHg in nine on amlodipine/captopril and in only one on placebo/captopril. Eleven of the 27 patients showed a fall in SBP of 20 mmHg or more and 16 showed a fall in DBP of at least 10 mmHg when amlodipine was added to the captopril.

No clinically important differences in pulse rate, body weight or in the serial ECGs occurred between the two treatments.

An 'intention to treat' analysis (not reported here) including all data from all 29 patients, did not show important differences from the above results.

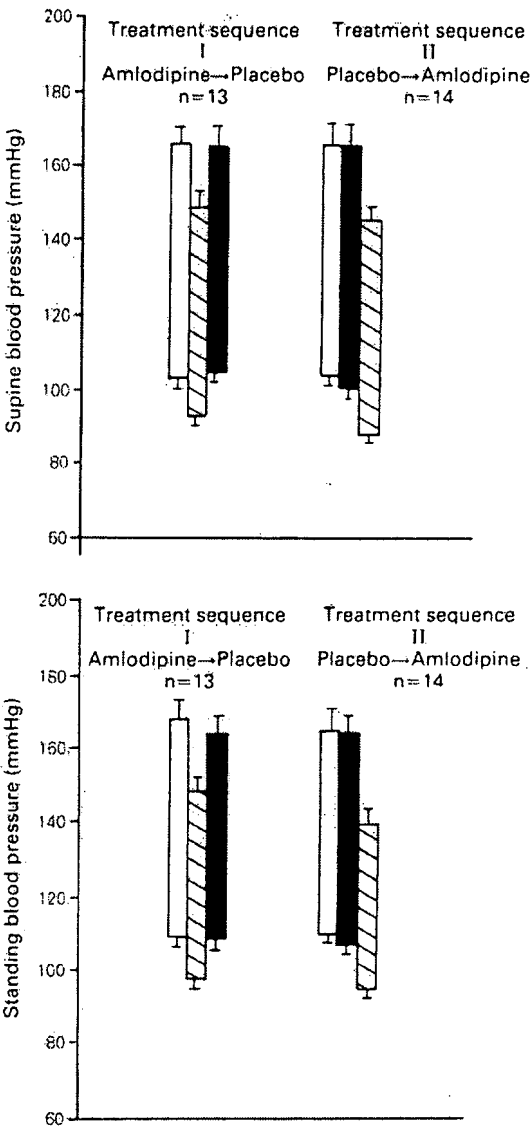


Figure 1 Supine and standing blood pressures (mean±SE) for treatment sequences I and II: baseline captopril plus single-blind placebo □ compared with double-blind amlodipine plus captopril ▨ and/or double-blind placebo plus captopril ■ at randomisation, at the end of the first treatment period and at the end of the study.

Unwanted effects, withdrawals and deaths

The most frequently reported unwanted effects associated with this dose of captopril and the

Table II Supine blood pressures and heart rates—changes from baseline to end of each period of double-blind therapy

Variable	Period	Treatment	n	Baseline mean	End of period mean	Mean difference (95% CI) in changes between treatment groups (amlodipine–placebo)	Significance of comparisons P
Supine Systolic mmHg	1st Period	amlodipine	13	166.3	149.2	-18.0 (-25.5, -10.3)	P<0.001
		placebo	14	167.2	167.2		
	2nd Period	amlodipine	14	167.2	147.5		
		placebo	13	166.3	165.4		
Supine Diastolic mmHg	1st Period	amlodipine	13	104.0	93.2	-12.2 (-15.9, -8.5)	P<0.001
		placebo	14	105.9	102.4		
	2nd Period	amlodipine	14	105.9	90.3		
		placebo	13	104.0	105.4		
Supine Heart Rate (bpm)	1st Period	amlodipine	13	83.1	85.0	2.9 (-0.1, 6.1)	P=0.0477
		placebo	14	84.2	85.7		
	2nd Period	amlodipine	14	84.2	86.5		
		placebo	13	83.1	79.7		

Table III Standing blood pressures and heart rate—changes from baseline to end of each period of double-blind therapy

Variable	Period	Treatment	n	Baseline mean	End of period mean	Mean difference (95% CI) in changes between treatment groups (amlodipine–placebo)	Significance of comparisons P
Standing Systolic mmHg	1st Period	amlodipine	13	168.0	148.5	-20.4 (-28.0, -12.4)	P<0.001
		placebo	14	165.7	164.9		
	2nd Period	amlodipine	14	165.7	139.6		
		placebo	13	168.0	163.7		
Standing Diastolic mmHg	1st Period	amlodipine	13	109.4	97.9	-11.9 (-15.8, -8.0)	P<0.001
		placebo	14	110.9	108.0		
	2nd Period	amlodipine	14	110.9	95.5		
		placebo	13	109.4	109.2		
Standing Heart Rate (bpm)	1st Period	amlodipine	13	86.7	88.3	3.2 (-0.8, 7.4)	P=0.1121
		placebo	14	88.2	91.2		
	2nd Period	amlodipine	14	88.2	90.9		
		placebo	13	86.7	81.4		

combined therapy are shown in Table IV. Ankle swelling (5 patients) and flushing (4 patients) were the two most frequent amlodipine-related side effects but the ankle swelling was not associated with weight gain. In all but one patient these effects were mild-moderate and none of the patients discontinued therapy because of them during the double-blind crossover part of the study. No patients died during the study, but one patient died from acute myocardial infarction two

days after completing the final four weeks on captopril/placebo. There were no other deaths during the six months following the study.

Laboratory variables

Overall no clinically significant differences were seen in body weight, serum urea or creatinine, or glucose levels. One patient had a low serum potassium level (3.2 mmol/l) at the end of the double-

Table IV All reported unwanted possibly treatment-related occurred during double-blind therapy

Unwanted effect	Captopril + Double-blind amlodipine (n=29)
Ankle swelling	5
Flushing/hot flushes	4
Fatigue	3
Dizziness	2
Headache	1
Palpitations	1
Nausea	0
Nervousness	1
Insomnia	1
Itchy eyes	0

Adverse effects not treatment related
Only two other adverse events occurred during the double-blind phase, namely tinnitus and dizziness, both were related to treatment.
One patient died from acute myocardial infarction two days after completing the final four weeks on captopril/placebo.

blind placebo plus captopril returned to within the normal range. The amlodipine plus captopril group showed minor elevations in the liver enzymes seen from time to time but these were not related to the study drugs, a reflection of the degree and duration of the patients' ethanol intake. No changes in haematological indices were seen. Qualitative urinary protein output was normal throughout.

Discussion

This is the first completed double-blind study of amlodipine added to low-dose captopril and compared with captopril alone in moderate-severe essential hypertension. Combined treatment with a diuretic, calcium antagonist and an ACE inhibitor has been shown to be effective antihypertensive therapy. Captopril was chosen as the reference drug because of its widespread use in the treatment of hypertension, and especially in the elderly, both in Europe and in the United States. The dose of captopril used in this study was the same as because of its claimed efficacy in Caucasians.¹

each period of double-blind

(95% CI) Significance of com-
en treat- parisons P
-londipine-

- 10.3) P<0.001

- 8.5) P<0.001

1) P=0.0477

each period of double-blind

(95% CI) Significance of com-
en treat- parisons P
-londipine-

- 12.4) P<0.001

- 8.0) P<0.001

P=0.1121

he final four weeks on
were no other deaths
llowing the study.

icant differences were
im urea or creatinine, or
t had a low serum potas-
t the end of the double-

Table IV All reported unwanted effects defined as possibly treatment-related occurring during double-blind therapy

Unwanted effect	Captopril + Double-blind amlodipine (n=29)	Captopril + Double-blind placebo (n=29)
Ankle swelling	5	0
Flushing/hot flushes	4	0
Fatigue	3	0
Dizziness	2	2
Headache	1	1
Palpitations	1	1
Nausea	0	1
Nervousness	1	0
Insomnia	1	0
Itchy eyes	0	1

Adverse effects not treatment related
Only two other adverse events were recorded during the double-blind phase, namely back pain and Raynaud's phenomenon, both were considered unrelated to treatment.
One patient died from acute myocardial infraction two days after completing the final four weeks of the study while on captopril/placebo.

blind placebo plus captopril period but this returned to within the normal range by the end of the amlodipine plus captopril phase. Transient minor elevations in the liver enzyme levels were seen from time to time but these bore no apparent relationship to the study drugs and were probably a reflection of the degree and variability of the patients' ethanol intake. No clinically significant changes in haematological indices were noted. Qualitative urinary protein output remained constant throughout.

Discussion

This is the first completed double-blind comparative study of amlodipine added as second drug to low-dose captopril and compared with captopril alone in moderate-severe essential hypertension. Combined treatment with a dihydropyridine calcium antagonist and an ACE-inhibitor has been shown to be effective antihypertensive therapy.^{4,5}

Captopril was chosen as baseline therapy because of its widespread use in all grades of hypertension, and especially the moderate-severe forms, both in Europe and in the USA. The low dose of captopril used in this study was chosen because of its claimed efficacy and lack of toxicity in Caucasians.³

Although one potential disadvantage of captopril is its relatively short antihypertensive efficacy so that dosing three times daily has been considered necessary in order to achieve continuous and adequate BP control, twice daily dosage is increasingly popular in the United Kingdom and it was considered likely that the addition of the long-acting drug amlodipine was likely to maintain adequate BP control at the times of trough captopril effects.

Amlodipine was prescribed at 10 mg daily because preliminary data had shown this dose to have a consistently useful antihypertensive effect in moderate hypertension and that it was likely to be well tolerated by most patients.

The four week periods were chosen in order that assessments of efficacy would be made after an interval well in excess of five times the known elimination half-life of both amlodipine (45 hours)¹⁰ and the very much shorter half-life of captopril (<2 hrs)^{15,16}, so that each drug would have expressed its full antihypertensive potential. Captopril therapy was unchanged throughout all active treatment periods but carry-over amlodipine-related adverse effects were still possible in the early days of the final treatment phase in those who were randomised to amlodipine before placebo.

The addition of once daily amlodipine to the twice daily low-dose captopril regimen reduced BP much more effectively than did this dose of captopril alone, both in terms of the change in BP over the four week period and the number of patients achieving target supine DBP (<90 mmHg). The reduction in BP induced by captopril-amlodipine was not associated with significant change in mean heart rate. It should be noted that this study did not assess the effects of the addition of amlodipine in captopril 'non-responders', as some patients may well have responded to higher doses of captopril alone. Similarly, our study design did not include an amlodipine only phase so it remains speculative as to how much of the antihypertensive benefit on the combination might have been achieved by amlodipine alone.

We did not measure BP at peak captopril activity. No patients complained of dizziness especially 1-2 hours after taking captopril, so that unsuspected more pronounced hypotensive effects at that time are unlikely.

The two treatment regimens were associated with a low overall incidence of unwanted effects but amlodipine caused a few mainly vasodilator-related effects characteristic of the use of dihydropyridines. Ankle swelling and flushing occurred only in those patients treated with the combination but the incidence of dizziness and headache

Supra-normal creatinine clearance in hypertensive patients

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was identical between the two regimens. No concomitant increase in weight was observed in patients reporting ankle swelling, supporting the theory that such dihydropyridine-related oedema may result from pre-capillary vasodilation rather than fluid retention.¹⁷ Unpublished data indicate that these amlodipine-induced effects are dose-related. It is possible that a lower dose of amlodipine could have been used equally successfully together with the low dose of captopril but with an even smaller side-effect burden.

We conclude that in these patients once daily amlodipine (10 mg), at least in the short term, was an effective 'second-line' antihypertensive drug when combined with captopril 25 mg twice daily and generally the combination was well tolerated. Longer-term studies of the efficacy and acceptability of amlodipine/captopril combinations are warranted, especially as there is some evidence that tolerance may develop to both the antihypertensive benefits and the mainly vasodilator-mediated side-effects^{17,18} of dihydropyridines, as well as tolerance to the efficacy of captopril¹⁹ in some patients. Preferably, each drug used should be dose ranged separately in each individual in order to optimise the therapeutic benefit of the combination.

Acknowledgements

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Summary: Glomerular filtration rate (GFR) in 104 mildly hypertensive, 104 moderately hypertensive and 167 severely hypertensive patients was prebiopsies were performed. The mean values were 154.5 ± 15.0 , 83.1 ± 14.3 and 13.0 (female) respectively recorded in all patients with mild and functional renal damage.

Introduction

Many hypertensive patients, especially in Nigeria, have no evidence of renal disease. Their blood pressures are severely elevated. The purpose of this study was to evaluate the glomerular filtration rate in black hypertensive patients in relation to the severity of their hypertension.

Patients and methods

Creatinine clearance (Cr.Cl) as an estimate of glomerular filtration rate (GFR) was measured in 35 mildly hypertensive, 104 moderately hypertensive and 167 severely hypertensive patients selected from the outpatient clinic of the University Teaching Hospital. The patients were from 16 to 65 years and the duration of hypertension was 0.5 to 5 years. All patients had no evidence of renal disease. The cause of hypertension was idiopathic in all but 13 severe patients in whom renal biopsies were performed. The criteria for inclusion in the study were sustained hypertension in the absence of diabetes mellitus, cardiac failure or a history of features of cerebro-vascular disease.

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ANEXO No. 4

“A dose-response study of amlodipine in mild to moderate hipertensión” M. Heikki Frick, D. McGibney & H.M. Tyler From the First Department of Medicine, University Central Hospital, Helsinki, Finland and the Pfizer Central Research, Kent, UK.



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A dose-response study of amlodipine in mild to moderate hypertension

M. HEIKKI FRICK, D. MCGIBNEY† & H. M. TYLER†

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Abstract. Frick MH, McGibney D, Tyler HM and other members of the study group (First Department of Medicine, University Central Hospital, and Pfizer Central Research, Kent, UK). A dose-response study of amlodipine in mild to moderate hypertension. *Journal of Internal Medicine* 1989; 225: 101-105.

The antihypertensive efficacy and suitability for once daily dosing of amlodipine, a new calcium antagonist, was studied in a series of 205 patients with mild to moderate hypertension. The study was conducted double-blind in 13 centres. The starting doses of amlodipine were 1.25, 2.5 and 5 mg, respectively, which were doubled after 4 weeks if normotension or a preset target blood pressure was not reached. Target blood pressure was reached in 25% of patients with placebo, 41% with 2.5 mg of amlodipine, 56% with 5 mg of amlodipine and 73% with 10 mg of amlodipine once daily. The drug was well tolerated at all dose levels and no changes occurred in heart rate, body weight or electrocardiogram during treatment. Amlodipine is a useful new calcium antagonist for the treatment of hypertension producing smooth, dose-dependent blood pressure reductions with convenient once daily dosing.

Keywords: amlodipine, calcium antagonists, hypertension.

Growing awareness of the significance of adverse metabolic effects, especially on lipoprotein profiles, caused by antihypertensive therapy with diuretics [1-3] and β -blocking agents [4-6] has evoked interest in other forms of therapy, notably α -blocking agents and calcium antagonists which do not adversely change blood lipids [5-9].

The present study addresses itself to evaluate the antihypertensive efficacy and suitability for once daily dosing of amlodipine, a new calcium channel blocker structurally related to nifedipine [10,11]. Preliminary clinical studies indicate that amlodipine has antihypertensive and antianginal activity [12,13].

Study population and methods

Patients

Thirteen centres throughout Finland studied 205 hypertensive patients aged 18-75 years. Any antihypertensive medications were withdrawn for 2

weeks before entry into a 4-week single-blind run-in placebo after which supine and standing diastolic blood pressure had to be 95-114 mmHg or 100-114 mmHg if aged 60 years or older. Failure to meet these criteria led to exclusion. Other exclusion criteria were: child-bearing potential, concomitant use of any hypertensive or investigational medication, oral anticoagulants, intermittent, severe or malignant hypertension, any major renal, hepatic, cardiac, gastrointestinal, endocrine or metabolic diseases. The use of any concomitant medication was maintained without change throughout the trial. The patients who satisfied the above-mentioned criteria were randomly assigned in four groups (Table 1).

Study design

The randomly assigned groups represent placebo and three starting dose levels of amlodipine: 1.25, 2.5 and 5 mg daily. These initial dosages were doubled to 2.5, 5 and 10 mg daily if after a 4-week double-blind period a target blood pressure was not reached. This

target was defined as supine and standing diastolic blood pressure < 90 mmHg and a reduction from baseline > 10 mmHg. The study was then run for additional 4 weeks. Amlodipine and the placebo were administered as identically appearing capsules once daily on awakening each morning, except on the day before the clinical assessment when the dose was taken 24 hours before the clinical visit.

Clinical assessments were made every 2 weeks during the placebo run-in and double-blind periods. Blood pressure and heart rate were recorded 24 h after the previous dose, and the average of three recordings were taken after a 5-min supine rest and after 2 min of standing. A standard mercury sphygmomanometer was used to measure blood pressure, and diastolic phase V was recorded. Routine haematological tests and urine analysis were performed at each visit, and body weight was recorded. A standard 12-lead electrocardiogram (ECG) was performed at entry to the placebo run-in and at the end of the study. Side-effects were recorded when observed by the physician or spontaneously volunteered by the patient. The side-effects were classified as definitely, probably or not drug-related and graded as mild, moderate or severe in intensity.

For each variable analysed, a two-way analysis of variance model was fitted, permitting tests of treatment, centre and treatment by centre interaction. Each variable was analysed as change from baseline using the means of triplicate observations. Tests between each dose group and placebo were implemented from the analysis of variance as contrasts between means, leading to a *t*-test.

Results

There was no significant difference between the groups' demographic data (Table 1). Concomitant diseases and concomitant medications (most commonly antibacterial, analgesic and anti-inflammatory drugs) were those normally expected in an age-matched population. The four groups were homogenous for supine and standing blood pressure, and heart rate at entry.

All the patients who entered were evaluated for tolerability. The number of patients completing the study, those finally evaluated for efficacy and reasons for the withdrawals are shown in Table 2. After 4 weeks the dose was increased in most patients since the target blood pressure was not reached: 94%, 89% and 78% of patients in 1.25, 2.5, and 5 mg groups had their dosage doubled.

Table 3 shows the changes in supine and standing blood pressure and heart rate during treatment. There was no clinically significant change in supine or standing heart rate during treatment in any group. Supine and standing blood pressures decreased progressively and in a dose-dependent manner with amlodipine (Fig. 1). After 4 weeks of therapy supine blood pressures were significantly reduced in the 2.5 and 5 mg groups as compared to placebo. After 8 weeks of therapy both supine and standing blood pressures (with the exception of standing diastolic in low dose group) were reduced significantly (*P* < 0.05–0.001) in all groups compared with placebo. For the groups receiving placebo and amlodipine up to 2.5, 5 and 10 mg, respectively,

Table 1. Patient characteristics at entry

Characteristic	Amlodipine (mg)						
	1.25-2.5		2.5-5		5-10		Placebo
No. of patients entering*	55	(36:19)	50	(29:21)	49	(27:22)	51 (30:21)
Mean age (years)†	48.0	(30-72)	50.3	(29-72)	50.5	(23-72)	52.2 (30-74)
Mean weight (kg)†	82.8	(49-120)	83.7	(60-129)	77.6	(42-109)	80.3 (58-115)
Mean duration of hypertension (yrs)†	7.3	(8-25)	6.7	(0-32)	7.1	(1-25)	7.4 (0-20)
Severity of hypertension (mild:moderate‡)	39:16		34:16		32:17		44:7
No. of smokers	6		4		13		5
No. of patients with concomitant disease	13		12		14		18
No. of patients receiving concomitant medication	16		18		14		13

* The ratio of males: females is given in parentheses.

† The range is given in parentheses.

‡ Supine diastolic blood pressure: 90–< 105 mmHg (mild) and 105–< 115 mmHg (moderate).

Table 2. Number of patients completing the study, reasons for withdrawals and final dosages received

Characteristic	Amlodipine (mg)			Placebo
	1.25-2.5	2.5-5	5-10	
No. of patients completing 8 weeks therapy	49	47	47	47
No. of patients withdrawing due to:	6	3	2	4
Side-effects	0	1	2	2
Laboratory data	1	0	0	0
Protocol violation	2	1	0	1
Laboratory data (not drug-related)	3	1	0	1
No. of patients evaluated for efficacy*	47	44	45	42
No. of patients increasing dosage	44 (94%)	39 (89%)	35 (79%)	38 (80%)
Mean daily dosage at week 8 (mg d ⁻¹)	2.4	4.7	8.9	—

* Efficacy data missing on the report cards of some patients.

Table 3. Supine and standing blood pressure and heart rate changes during treatment with amlodipine and placebo (mean)

Treatment and parameter	Time (weeks)					
	0	4	n	0	8	n
Supine systolic (mmHg)						
Placebo	159.6	155.5	46	158.5	154.5	42
Amlodipine 1.25-2.5 mg	159.1	155.0	48	159.0	149.2*	47
Amlodipine 2.5-5 mg	159.8	149.7*	46	160.7	147.8**	44
Amlodipine 5-10 mg	165.4	148.3***	48	166.4	142.7***	45
Supine diastolic (mmHg)						
Placebo	101.1	97.5	46	100.9	96.2	42
Amlodipine 1.25-2.5 mg	101.7	97.3	48	101.8	93.5*	47
Amlodipine 2.5-5 mg	101.7	95.3*	46	102.0	91.8***	44
Amlodipine 5-10 mg	103.0	93.9***	48	103.1	89.9***	45
Supine heart rate (beats/min)						
Placebo	71.9	72.4	45	71.2	71.5	42
Amlodipine 1.25-2.5 mg	69.7	69.7	47	69.9	69.0	46
Amlodipine 2.5-5 mg	73.5	71.1	46	73.4	70.3	44
Amlodipine 5-10 mg	70.3	70.3	48	70.8	70.9	45
Standing systolic (mmHg)						
Placebo	157.0	150.9	45	156.2	149.9	42
Amlodipine 1.25-2.5 mg	156.5	150.9	48	156.1	144.1*	47
Amlodipine 2.5-5 mg	154.8	146.1	46	156.6	142.5**	44
Amlodipine 5-10 mg	161.1	142.4***	48	162.0	137.7***	45
Standing diastolic (mmHg)						
Placebo	106.0	101.5	45	106.0	100.6	42
Amlodipine 1.25-2.5 mg	105.6	101.6	48	105.4	97.8	47
Amlodipine 2.5-5 mg	106.3	100.4	46	106.3	96.3**	44
Amlodipine 5-10 mg	106.4	98.3**	48	106.3	93.5***	45
Standing heart rate (beats/min)						
Placebo	77.3	77.9	44	77.4	77.7	42
Amlodipine 1.25-2.5 mg	78.0	76.4	47	78.0	75.8	46
Amlodipine 2.5-5 mg	78.3	77.6	45	77.7	76.1	44
Amlodipine 5-10 mg	75.9	76.5	48	76.4	77.9	45

Statistically significant compared with mean change on placebo: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

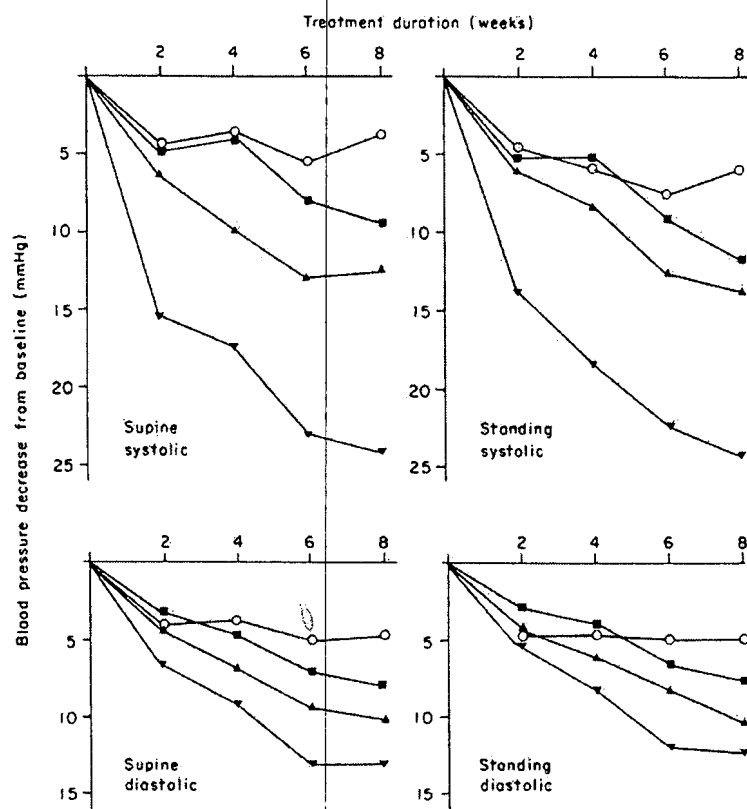


Fig. 1. Mean decrease in blood pressure compared with baseline in hypertensive patients treated with amlodipine up to 2.5 mg (■), 5.0 mg (▲) and 10.0 mg (▼) once daily, and the placebo (○).

target blood pressure was achieved at 8 weeks in 25, 41, 56 and 73% of patients. A marked or moderate clinical improvement took place in 35, 42, 59 and 82% of patients as assessed by the physicians global opinion at the end of the treatment. Side-effects were generally mild to moderate and often transient. Five patients (three amlodipine and two placebo) withdrew from the study because of treatment-related side-effects. There was a trend towards more cardiovascular side-effects with amlodipine (nine cases with oedema), but body weight was not significantly different in any amlodipine group as compared to placebo. There was no clinically significant change in laboratory test values and no significant change in the recorded ECGs (PR, QRS and QT intervals).

Discussion

An ideal blood pressure reducing drug should have a smooth pressure-lowering effect without marked postural pressure drops, dose-related blood pressure response, convenient dosage regime and no significant biochemical or other side-effects. None of the compounds currently available fulfil these require-

ments. Amlodipine produced a dose-related reduction in supine and standing blood pressures. The data suggest that the optimum effect on blood pressure may not have been reached at 4 weeks when the dose was doubled for most patients. However, amlodipine, 2.5 mg once daily, appears to be the minimum effective dose. In the majority of the patients a dose range of 5–10 mg once daily was effective. This is consistent with earlier observations [12].

All measurements were made 24-h postdose and the data suggest that amlodipine can conveniently be used once daily which is consistent with the long half-life of the compound. Once daily dosing presumably increases compliance, although very little formal research has been conducted on dose-regime-compliance interactions.

Amlodipine was well tolerated in this short-term study as determined by clinical signs and laboratory test values. Some incidence of peripheral oedema is not unexpected with compounds related to nifedipine, but the virtual absence of flushing and an incidence of headache no greater than for placebo suggest amlodipine is particularly well tolerated. No

detailed metabolic laboratory analyses were done in the present study. The possible effect on lipid profiles will be studied separately, but it is highly unlikely that amlodipine would adversely change the lipids as this class of compounds have been neutral in this respect [8].

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ANEXO No. 5

“Double-blind evaluation of the dose-response relationship of amlodipine in Essentials hipertensión” Jawahar L. Mehta, MD, PhD, Larry M. Lopez, PharmD, Nicholas D. Vlachakis, MD, Alan H. Gradman, MD, David T. Nash, MD, Mark T. O’Connell, MD, W. Thomas Garland, MD, and Bryant I. Pickering, MD Gainesville, Flu., Los Angeles, Calif., West Haven, Conn., Syracuse, NY., Miami, Flu., New Orleans, La., and Phoenix, Ark. From the University of Florida, Gainesville; University of Southern California, Los Angeles; Cardiology Section, Veterans Administration Medical Center, West Haven; D.T.N. Clinical and Research Laboratory, Syracuse; Department of Medicine, Jackson Memorial Hospital, and University of Miami Medical Center. Supported by funds from Pfizer Research, Groton, Conn. Received for publication Aug. 10, 1992; accepted Dec. 1, 1992. Reprint requests: Jawahar L. Mehta, MD, University of Florida, Division of Cardiology, Box 100277 JHMHC, Gainesville, FL 32610. 1993 by Mosby-Year Book.

Double-blind evaluation of the dose-response relationship of amlodipine in essential hypertension

To determine the dose-response efficacy of once-daily administration of placebo or a new long-acting calcium channel blocker amlodipine in patients with mild to moderate hypertension, a randomized, multicenter, placebo-controlled, double-blind trial was conducted. The study included 210 patients with diastolic hypertension (blood pressure 95 to 114 mm Hg) without major hematologic, renal, hepatic, cardiac, or endocrine abnormalities. After a 4-week single-blind placebo run-in period, patients were given placebo or amlodipine (1.25, 2.5, 5, or 10 mg) daily for 4 weeks. To assess the antihypertensive effect of amlodipine over a 24-hour period, blood pressure and pulse rate at weeks 0 and 4 were recorded for 12 hours after the dose and then again at 24 hours. At the end of the study patients treated with all doses of amlodipine greater than 1.25 mg daily had significantly reduced diastolic blood pressure in both supine and standing positions. Amlodipine, 1.25 mg daily, was also associated with a decrease in standing diastolic blood pressure. Response to treatment was greater in all amlodipine-treated patients than in those receiving placebo. Pulse rate in both the supine and standing positions was not significantly affected by amlodipine. At doses of 2.5, 5.0, or 10.0 mg daily, amlodipine maintained blood pressure below values obtained with placebo throughout the 24-hour period. Treatment with amlodipine was well tolerated and the incidence of side effects was low. Once-daily dosing with amlodipine is effective in the 24-hour control of blood pressure in patients with mild to moderate hypertension. Because of its efficacy as monotherapy given once a day and its low side effect profile, amlodipine may be well suited in the treatment of hypertension. (AM HEART J 1993;125:1704.)

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Calcium antagonists are frequently used in the treatment of hypertension,¹ mainly because of their ability to relax vascular smooth muscle and to decrease peripheral vascular resistance. However, the high clearance rate of these agents from the body² has necessitated repeated daily dosing to maintain blood pressure at a reduced level, although controlled

release preparations of many of the calcium blockers are currently available. Many of the presently available calcium antagonists have unacceptable side effects; for example, verapamil and diltiazem exert negative inotropic and chronotropic effects, especially in patients with underlying cardiac dysfunction, and nifedipine capsules often cause reflex tachycardia and edema.³ Amlodipine is a novel dihydropyridine calcium antagonist that has an extended elimination half-life (45 hours)⁴ and therefore has the potential for blood pressure control on a once-daily dosing regimen. In previous studies,⁵⁻⁹ this agent has been shown to lower blood pressure in patients with mild to moderate hypertension. Its efficacy is similar to that of atenolol,¹⁰ and it exerts cumulative antihypertensive effects when combined with captopril¹¹ or hydrochlorothiazide.¹² We now report the dose-response relationship of once-daily dosing of amlo-

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Table 1. Pretreatment patient data

	Placebo	Amlodipine (mg per day)			
		1.25	2.5	5.0	10.0
Number of patients					
Male	23	19	22	24	24
Female	17	22	20	20	19
Mean age (yr)	51	52.5	52.9	54.2	53.3
Mean weight (kg)					
Male	83.4	83.6	91.1	88.2	88.1
Female	74.3	75.8	78.3	77.3	73.3
Race					
White	28	29	23	28	22
Black	7	8	14	10	14
Hispanic	5	4	5	6	5
Other	0	0	0	0	2
Severity of hypertension*					
Mild	34	32	38	41	38
Moderate	6	9	4	3	5

*Severity of hypertension defined in terms of baseline supine diastolic blood pressure: mild-90 to 104 mm Hg; moderate-105 to 114 mm Hg.

dipine in a large number of patients with mild to moderate hypertension. We assessed the effects of this agent on blood pressure over a 24-hour postdos- ing period in a multicenter trial.

METHODS

Subjects. Two hundred ten patients, 112 men and 98 women, 18 to 75 years of age, with diastolic blood pressure (phase V) between 95 and 114 mm Hg (supine and stand- ing) were included (Table I). Patients in any of the follow- ing categories were excluded: pregnant women and those of child-bearing potential; concomitant therapy with other antihypertensive agent, use of an investigational or antico- agulant drug; major hematologic, renal, hepatic, or endo- crine disease; unstable or malignant hypertension; and any clinically significant cardiac abnormality. Written consent was obtained from all patients. The study was approved by the appropriate institutional review boards.

Study design. This study was a multicenter, double- blind, randomized, parallel, placebo-controlled evaluation of four doses of amlodipine in patients with mild to mod- erate hypertension. Following a 4-week single-blind pla- cebo run-in period, patients were randomly assigned to one of five treatment groups; placebo (*n* = 40) or amlodipine 1.25 (*n* = 41), 2.5 (*n* = 42), 5.0 (*n* = 44), and 10.0 mg of drug daily (*n* = 43). Treatment was administered once daily upon awakening, except on the days of review visits when doses were given after examination. Blood pressure and pulse rate were recorded at the start of the trial (week -4) and then every 2 weeks throughout the study. Side effects (observed and volunteered) were monitored at weeks -2, 0, 2, and 4, and a global assessment of the patient's condition was made on the final visit. Standard biochemical, hema- tologic, and urinalysis laboratory tests were performed at weeks -4, 0, 2, and 4. A 12-lead electrocardiogram (ECG) was obtained at the beginning and end of the trial, and body

weight was recorded at each visit. In addition, to assess the antihypertensive effect of amlodipine over a 24-hour pe- riod, blood pressure and pulse rate at weeks 0 and 4 were recorded hourly for 12 hours postdose, and then again at 24 hours.

Measurements. Blood pressure and pulse rate record- ings were made in triplicate after the patients had been 5 minutes in the supine position and then after 2 minutes in the standing position, and a mean value was obtained. Di- astolic pressure was measured in the dominant arm to the nearest 2 mm Hg using a standard mercury sphygmoma- nometer. Hypertension was subdivided into two degrees of severity, defined in terms of baseline supine diastolic blood pressure: mild = 90 to 104 mm Hg and moderate = 105 to 114 mm Hg.

Data analysis. The efficacy analysis was based on mea- surements made at the end of the placebo run-in (baseline) and at the end of double-blind treatment (final). The effects of amlodipine on blood pressure and pulse rate were compared with the corresponding placebo effects. Re- sponse to treatment was defined as a supine diastolic pres- sure of less than 90 mm Hg, or its reduction by 10 mm Hg or more from baseline at the final visit.

Statistical analysis. Statistical analysis of between- treatment group differences in changes from baseline to the final visit for the 24-hour postdose blood pressures, heart rates, body weight, and ECG parameters was performed by a two-way analysis of variance (ANOVA). Whenever the treatment by center interaction was not statistically sig- nificant (*p* < 0.1), an additive model was used to test the main effect. Type III sum of squares was used in the der- ivation of the F statistics. Fisher's least significant differ- ence (LSD) multiple comparison procedure was used to compare each dose of amlodipine with placebo. One-tailed tests were used in the analysis of blood pressure recordings, and two-tailed tests were used for pulse rate, body weight,

Table II. Baseline/Final blood pressures

Blood pressure	Treatment group	n	Baseline mean (mm Hg)	Final mean (mm Hg)	p (comparison with placebo)
Supine systolic	10.00 mg	40	155.1	141.0	0.0008
	5.00 mg	44	149.2	141.4	NS
	2.50 mg	40	151.8	140.4	0.0128
	1.25 mg	40	149.2	141.3	NS
	Placebo	39	153.3	148.6	—
Supine diastolic	10.00 mg	40	99.8	89.1	0.0025
	5.00 mg	44	99.1	90.2	0.0332
	2.50 mg	40	99.3	89.0	0.0043
	1.25 mg	40	99.9	92.0	NS
	Placebo	39	100.0	93.8	—
Standing systolic	10.00 mg	40	152.8	139.4	0.0003
	5.00 mg	44	151.0	142.7	0.0374
	2.50 mg	40	150.7	143.4	NS
	1.25 mg	40	147.3	139.4	NS
	Placebo	39	153.4	150.0	—
Standing diastolic	10.00 mg	40	101.9	91.1	0.0001
	5.00 mg	44	101.6	94.2	0.0159
	2.50 mg	40	102.2	93.7	0.0029
	1.25 mg	40	101.6	94.1	0.0144
	Placebo	39	102.0	97.8	—

NS, Not significant.

and ECG parameters. The effect of a decreasing blood pressure with an increasing dose was assessed using a non-parametric testing procedure.¹³

RESULTS

Seven of 210 patients were discontinued from double-blind therapy, but only two because of amlodipine-related side effects; one was discontinued because of edema and one other because of headache. The remaining five patients were withdrawn because of no show (*n* = 1), refusal to continue participation (*n* = 2), inadequate response (*n* = 1), or intercurrent illness (*n* = 1). Thus 203 patients were available for final analysis. At the start of double-blind therapy, supine and standing mean blood pressures were comparable for all treatment groups. The average baseline/final blood pressures can be seen in Table II and the changes in baseline/final values are illustrated in Fig. 1. Treatment with placebo lowered supine diastolic pressure by 6.1 mm Hg by the end of week 4. After the same time, amlodipine therapy (in doses of 2.5, 5.0, and 10.0 mg daily) was associated with significant reductions in diastolic pressure of 10.3, 8.9, and 10.7 mm Hg, respectively (*p* < 0.05). The lowest dose of amlodipine (1.25 mg daily) caused an 8 mm Hg decrease in diastolic blood pressure, but the decrease was not significant. Standing diastolic

pressure was also lowered, but with significant results being obtained with all doses of amlodipine (*p* < 0.05). Supine systolic pressure was significantly lowered with 2.5 and 10.0 mg daily doses of amlodipine (*p* < 0.05), and reductions in standing systolic pressure were achieved with amlodipine, 5.0 and 10.0 mg daily (*p* < 0.05).

Changes in mean supine and standing pulse rates for placebo and amlodipine, 1.25, 2.5, 5.0, and 10.0 mg daily, were: supine—0.4, -1.6, 0.6, -1.4, and 1.9 beats/min, respectively; and standing—0.7, -1.5, -0.3, -1.8, and 1.9 beats/min, respectively. Neither standing nor supine pulse rates were significantly affected by treatment. The response (responder) rates (decrease in supine diastolic pressure by ≥ 10 mm Hg or to 90 mm Hg at the final visit) were: amlodipine 47.5% (1.25 mg), 52.5% (2.5 mg), 47.7% (5 mg), and 62.5% (10 mg); placebo 33.3%.

The time course of the reduction in supine and standing diastolic and systolic blood pressures with placebo and amlodipine, 2.5, 5.0, and 10.0 mg daily, during the 24-hour dosing interval at the final visit can be seen in Figs. 2 and 3. At the start of the recording session, blood pressures of patients receiving amlodipine were lower than those of placebo-treated subjects. Treatment with placebo resulted in a maximum reduction in mean supine diastolic and

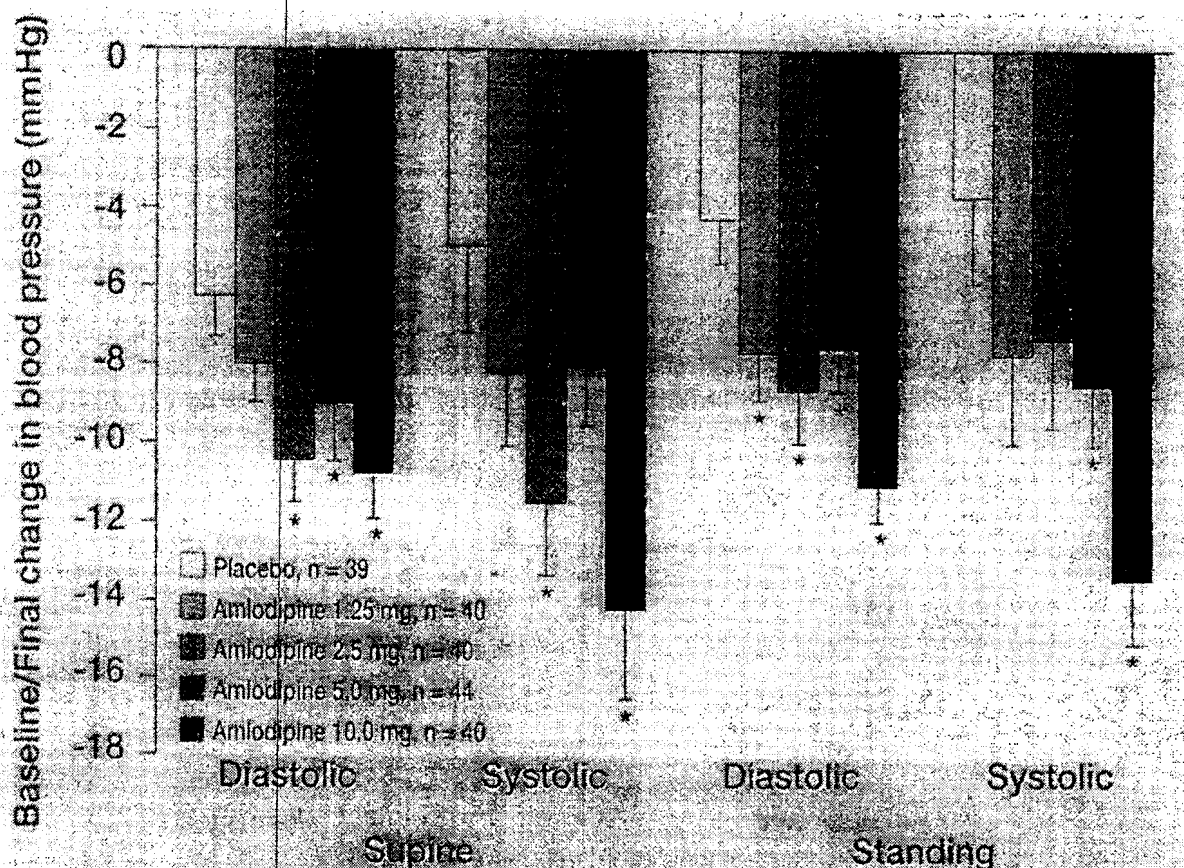


Fig. 1. Baseline/final changes in blood pressure in patients receiving placebo or amlodipine as indicated. Values are mean $\pm$ SEM. * $p < 0.05$ compared with placebo.

systolic pressures to 89.8 and 143.2 mm Hg, respectively (Fig. 2). At 0 hours, supine diastolic pressure in the amlodipine-treated patients was below 90 mm Hg, and was maintained below this level for the entire 24-hour period. Amlodipine, 1.25 mg daily (not shown), also maintained pressure around 90 mm Hg except at the 10-hour reading, when it rose to levels above those seen with placebo. Maximum reductions of supine systolic pressure to 137.1, 137.5, and 138.0 mm Hg occurred 2 to 6 hours after treatment with amlodipine, 2.5, 5.0, and 10.0 mg daily, respectively. A similar pattern of results was obtained for standing blood pressures (Fig. 3). Amlodipine therapy, 2.5, 5.0, and 10.0 mg daily, resulted in a peak standing diastolic effect of 90.3, 89.8, and 87.9 mm Hg, respectively, 2 to 8 hours post dose, and a peak systolic effect of 139.3, 137.3, and 138.8 mm Hg, respectively, 2 to 6 hours post dose. The corresponding effects for placebo were 94.2 mm Hg (diastolic) and 145.5 mm Hg (systolic). Effects of amlodipine, 1.25 mg daily, on supine and standing systolic and standing diastolic

pressures were similar to but less marked than those observed at higher doses. At the end of the 24-hour observation period, both systolic and diastolic blood pressures in amlodipine-treated patients were reduced ($p < 0.05$) compared with the placebo effect. There was no significant change in the standing or supine pulse rates during the dosing interval.

After 4 weeks of double-blind therapy, there was a dose-dependent increase in the number of patients attaining normotension (supine diastolic blood pressure > 90 mm Hg), reaching 58% for amlodipine, 10.0 mg daily. Only 28% of placebo-treated patients attained normotension. Amlodipine was associated with a similar, but more marked, dose-dependent effect on investigator global evaluation at the end of the study. An overall therapeutic improvement was detected in 84% of patients given amlodipine, 10.0 mg daily, but in only 53% of those receiving placebo.

There was a low occurrence of side effects throughout all the groups and only two patients treated with amlodipine (one receiving 2.5 mg, the other, 10.0 mg

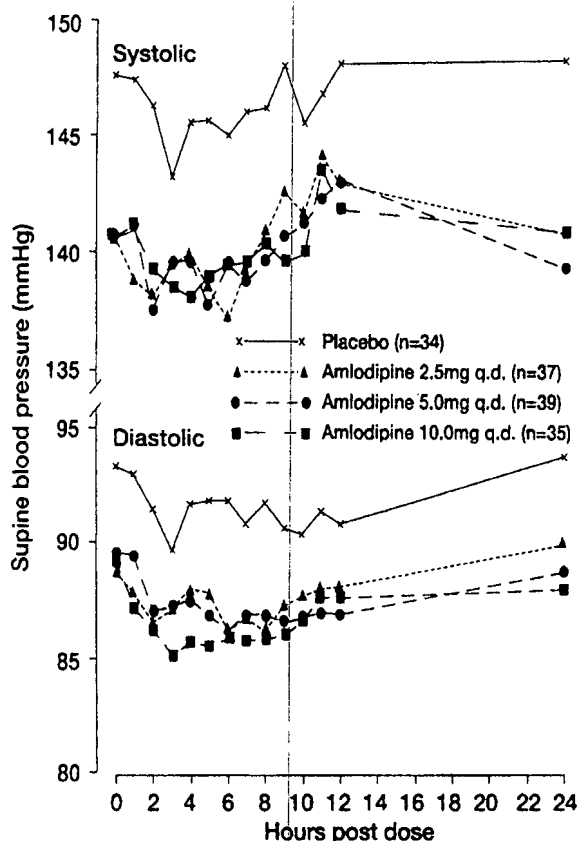


Fig. 2. Mean supine blood pressures recorded at the final visit over a 24-hour period following administration of placebo or amlodipine.

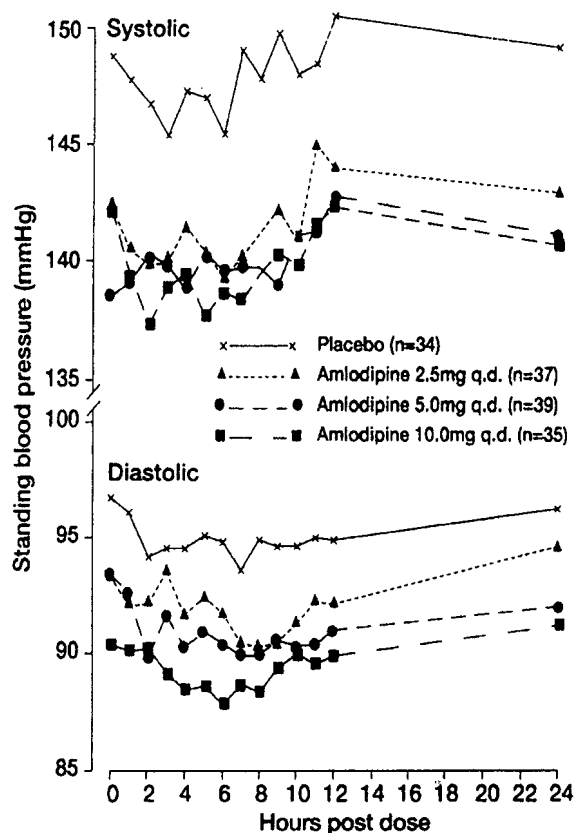


Fig. 3. Mean standing blood pressures recorded at the final visit over a 24-hour period following administration of placebo or amlodipine.

daily) had the drug discontinued as a result of treatment. No patients receiving placebo were discontinued from treatment because of side effects. Side effects included peripheral edema, headaches, and nausea. The overall incidence of side effects was the same as with placebo. For example, edema occurred in 4 of 170 amlodipine-treated patients (1.2%) and in 1 of 40 placebo-treated patients (2.5%). Headache was reported by 10 amlodipine-treated patients (5.9%) and by three placebo-treated patients (7.5%). Laboratory abnormalities were few and occurred at a similar incidence in all treatment groups. No changes in QRS duration, PR interval, or QT_c interval were observed in the ECGs of patients given either amlodipine or placebo. Neither amlodipine nor placebo caused significant changes in body weight.

DISCUSSION

Dihydropyridine calcium antagonists are potent peripheral arterial dilators and thus are beneficial in the management of hypertension. Amlodipine has

previously been shown to be effective in the treatment of hypertensive patients.⁵⁻¹² Of the calcium antagonists currently available and under development, amlodipine has the longest elimination half-life,¹⁴ giving it a true potential for blood pressure management on a once-daily dosing basis. In this multicenter study in a large number of patients with essential hypertension, amlodipine given once daily reduced diastolic pressure in both the supine and standing positions. Amlodipine in doses of 2.5 to 10 mg produced a significant antihypertensive effect in most instances (when compared with placebo), in accordance with the findings of previous reports.⁵⁻⁸ The smallest dose of amlodipine (1.25 mg) also lowered standing diastolic blood pressure. Changes in systolic blood pressure were slightly more variable, but significant effects were observed at 2.5 and 10.0 mg daily in the supine position and at 5.0 and 10.0 mg daily in the standing position.

Although the systolic blood pressure was not significantly lowered at other doses, there was a clear

trend toward a decrease. These observations are similar to those made previously in smaller number of patients.⁵⁻⁸ Importantly, the reduction in blood pressure was not associated with an increase in pulse rate and was effective throughout a 24-hour postdosing period. Twenty-four-hour effective control of hypertension with a single dose of amlodipine is in keeping with the results of previous reports.^{5,6} The absence of a change in heart rate differentiates this calcium antagonist from other currently available dihydropyridine calcium antagonists. Nifedipine capsules in particular can cause profound tachycardia and often require concomitant use of β -blockers.³ Absence of reflex tachycardia with amlodipine accounts for the lack of side effects such as palpitations in our patients.

The number of patients responding to monotherapy with amlodipine was greater than in the placebo group, and there was an increase in the number of patients achieving normotension. Although blood pressure reduction was significantly different with different doses of amlodipine, the most marked changes in blood pressure were seen with the 10.0 mg daily dose of amlodipine, and 84% of patients receiving this dose experienced therapeutic improvement. Amlodipine treatment was well tolerated, with only two patients being withdrawn from therapy because of side effects. None of our patients experienced myocardial ischemia, which is sometimes seen with nifedipine capsules.^{15,16} It is noteworthy that the side effect profile of amlodipine was quite favorable, with 11.7% of patients having one or more side effects (vs 10% of placebo-treated patients with one or more side effects). Incidence of headache, dizziness, and edema was similar whether patients received amlodipine or placebo. Laboratory abnormalities were few and transient and there were no significant changes in ECG parameters or body weight. Thus amlodipine effectively reduced blood pressure and was well tolerated when administered once-daily to patients with uncomplicated mild to moderate hypertension.

Although left ventricular function was not measured in these patients, there was no clinical evidence of left ventricular function deterioration, as seen by fatigue or shortness of breath, over 4 weeks of therapy with amlodipine. Whether left ventricular function will remain unaltered with prolonged use of amlodipine, particularly if patients have underlying left ventricular function defect, remains to be determined. However, a preliminary report of a multicenter study shows that amlodipine may be quite safe in patients with mild left ventricular dysfunction.¹⁷ This aspect of safety clearly differentiates this cal-

cium blocker from verapamil and diltiazem, which can precipitate left ventricular dysfunction in susceptible individuals. One of the major therapeutic problems in the long-term treatment of hypertension continues to be patient compliance, related to the requirement for multiple dosing and the occurrence of side effects from drugs. The results of this multicenter trial in large numbers of patients clearly suggest that amlodipine may be a suitable therapeutic agent for a majority of patients with mild to moderate hypertension.

One of the common accompaniments of essential hypertension is angina pectoris. Amlodipine has been found to be efficacious in patients with different forms of angina pectoris.¹⁸ The doses of amlodipine effective in the management of angina pectoris are 5 to 10 mg daily, similar to the doses required for monotherapy of hypertension. Other calcium blockers such as verapamil and diltiazem are also effective in the management of angina pectoris. In a study comparing the hemodynamic profile of verapamil, diltiazem, and amlodipine,¹⁹ Silke et al. observed that pulmonary capillary wedge pressure and systemic vascular resistance declined in response to amlodipine, but increased or remained unchanged after verapamil and diltiazem. As such, amlodipine therapy may be considered at least safe in most patients with coronary artery disease. The usefulness of monotherapy with the once-daily administration of amlodipine, with its very low incidence of side effects and its efficacy in ischemic heart disease, often associated with hypertension, makes this agent a very attractive candidate for the therapy of such patients.

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Impaired left ventricular filling in borderline hypertensive patients without cardiac structural changes

To determine the effect of borderline hypertension on left ventricular diastolic performance, 16 patients with borderline hypertension who did not have left ventricular hypertrophy and 16 age-sex-matched patients with normotension of similar age and body mass index were investigated. Pulsed Doppler echocardiography was used to record left ventricular filling signals at rest and immediately after supine ergometer exercise. All subjects had normal left ventricular structure and systolic function. At rest the borderline hypertension group in comparison with the normotension group had a depressed peak velocity of early filling (E) (44 ± 7 vs 54 ± 10 cm/sec; $p < 0.01$), no enhanced peak velocity of late filling (A) (52 ± 8 vs 50 ± 11 cm/sec; not significant), and a reduced E/A ratio (0.9 ± 0.2 vs 1.1 ± 0.3 ; $p < 0.05$). Atrial filling time and preejection period were similar in the two groups. The effect of exercise on left ventricular filling velocity in patients with borderline hypertensive resembled that in those with normotension. Percentage changes in E ($+14\% \pm 12\%$ vs $+14\% \pm 13\%$) and A ($+13\% \pm 8\%$ vs $11\% \pm 12\%$) were equivalent, suggesting a preserved diastolic reserve for exercise in the borderline hypertension group. In conclusion, borderline hypertension appears to be predictive of early filling impairment, and a late filling compensative mechanism is not yet apparent. These findings in borderline hypertension without apparent cardiac damage call for clinical attention to prevent further deterioration in cardiac function. (*AM HEART J* 1993;125:1710.)

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Considerable advances in our understanding of the role of diastolic function in hypertensive disease have marked the past decade. Emerging evidence suggests that left ventricular diastolic dysfunction is one of the earliest expressions of cardiac malfunction and may lead to congestive heart failure.¹⁻⁴ Damages of diastolic function are also likely to be present in pa-

ANEXO No. 6

“Valsartan, a new angiotensina II antagonista for the treatment of Essentials hipertensión: A comparative study of the efficacy and safety against amlodipine”
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Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: A comparative study of the efficacy and safety against amlodipine

Objective: To compare the antihypertensive efficacy of a new angiotensin II antagonist, valsartan, with a reference therapy, amlodipine.

Methods: One hundred sixty-eight adult outpatients with mild to moderate hypertension were randomly allocated in double-blind fashion and equal number to receive 80 mg valsartan or 5 mg amlodipine for 12 weeks. After 8 weeks of therapy, in patients whose blood pressure remained uncontrolled, 5 mg amlodipine was added to the initial therapy. Patients were assessed at 4, 8, and 12 weeks. The primary efficacy variable was change from baseline in mean sitting diastolic blood pressure at 8 weeks. Secondary variables included change in sitting systolic blood pressure and responder rates.

Results: Both valsartan and amlodipine were effective at lowering blood pressure at 4, 8, and 12 weeks. Similar decreases were observed in both groups, with no statistically significant differences between the groups for any variable analyzed. For the primary variable the difference was 0.5 mm Hg in favor of valsartan ($p = 0.68$; 95% confidence interval, -2.7 to 1.7). Responder rates at 8 weeks were 66.7% for valsartan and 60.2% for amlodipine ($p = 0.39$). Both treatments were well tolerated. The incidence of drug-related dependent edema was somewhat higher in the amlodipine group, particularly at a dose of 10 mg per day (2.4% for 80 mg valsartan; 3.6% for 5 mg amlodipine; 0% for valsartan plus 5 mg amlodipine; 14.3% for 10 mg amlodipine).

Conclusions: The data show that valsartan is at least as effective as amlodipine in the treatment of mild to moderate hypertension. The results also show valsartan to be well tolerated and suggest that it is not associated with side effects characteristic of this comparator class, dihydropyridine calcium antagonists. (Clin Pharmacol Ther 1996;60:341-6.)

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Several classes of antihypertensive agents with proven efficacy are currently recommended for first-line monotherapy in the treatment of mild to

moderate hypertension.¹⁻³ However, unwanted effects associated with the relatively nonspecific action of established classes of drugs may limit their use.

Angiotensin II receptor antagonists represent a new class of antihypertensive agent. These agents selectively and specifically antagonize the action of angiotensin II at its receptor, the last step in the renin-angiotensin-aldosterone cascade.⁴ The highly selective and specific mechanism of action of angiotensin II receptor antagonists would be anticipated to result in antihypertensive agents that are equal in efficacy to existing treatments but that have a superior safety profile.

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Valsartan is a new orally active specific angiotensin II receptor antagonist.^{5,6} The efficacy and tolerability of valsartan, compared to placebo, has been established in several well-controlled studies (unpublished data, Ciba-Geigy, 1996). Data have shown daily doses of 80 mg valsartan and above to produce clinically relevant and statistically significant decreases in blood pressure compared to placebo. Data from a dose-finding study showed decreases in sitting diastolic blood pressure after 4 weeks of therapy minus placebo effect of 0.5, 2.1, 3.9, and 4.7 mm Hg for 10, 40, 80, and 160 mg valsartan, respectively. Other phase II data have also supported 80 mg as the appropriate starting dose for valsartan. Further large phase III studies have shown 80 mg valsartan, as a single daily dose, to be a highly effective, well-tolerated antihypertensive agent irrespective of age, sex, or race. Data on the efficacy of valsartan compared to existing therapies, such as calcium antagonists, have not been previously reported. Calcium antagonists are currently widely used in the treatment of hypertension. Adverse reactions have been reported with some calcium antagonists in up to 20% to 50% of patients, although newer agents have been introduced in an attempt to reduce the incidence of drug related side effects. Amlodipine is one of the newer calcium antagonists. It has well-established efficacy and is widely used in the treatment of essential hypertension.⁷⁻⁹ The starting dose of amlodipine is generally 5 mg once daily.

This study compares the efficacy and tolerability of a new angiotensin II antagonist, valsartan, with a reference therapy, the calcium antagonist amlodipine, in the treatment of mild to moderate essential hypertension.

PATIENTS AND METHODS

Patients. Male and female outpatients with mild to moderate essential hypertension who were between the ages of 18 and 80 years were eligible to participate in the study. Mild to moderate hypertension was defined as sitting diastolic blood pressure (SDBP) of >95 mm Hg and <120 mm Hg after a 2-week single-blind placebo run-in period. The most important exclusion criteria were presence of overt heart failure; a history of heart failure or myocardial infarction in the preceding 3 months; second- or third-degree heart block; malignant hypertension; evidence of significant hepatic, renal, or gastrointestinal disease; pregnancy; and use of estrogen-progestogen preparations.

Patients were withdrawn from the trial in cases of

intolerable adverse events, lack of therapeutic response resulting in mean SDBP of >120 mm Hg, major violation of the trial protocol, or withdrawal of consent. All patients gave written consent to participate in the study, which was approved by the relevant local ethical review boards. The study was conducted according to Good Clinical Practice requirements.

Study design. The study was a multicenter (seven centers), randomized, double-blind comparative trial conducted in Italy. After a run-in period, patients who met the inclusion criteria were randomized in equal numbers within a center to receive either 80 mg valsartan or 5 mg amlodipine once daily. After 8 weeks of therapy, patients in either group whose blood pressure was not adequately controlled (SDBP >95 mm Hg) received, in addition to their initial therapy, 5 mg amlodipine daily in an open fashion for a further 4 weeks. Therefore nonresponders at 8 weeks took either 80 mg valsartan and 5 mg amlodipine daily or 10 mg amlodipine daily for the last 4 weeks of the study. Patients whose SDBP was controlled at 8 weeks continued to receive their initial therapy for a further 4 weeks.

Patients were assessed at 4 and 8 weeks of monotherapy and at 12 weeks (with additional therapy for 4 weeks in uncontrolled patients). Weight, pulse rate, systolic blood pressure, and diastolic blood pressure were recorded at each visit. Measurements were carried out at each visit at the same time of day before daily dosing to provide consistent trough measurements. For each patient, blood pressure was measured by the same clinician with use of the same mercury sphygmomanometer in the dominant arm of the subject. Systolic and diastolic blood pressures were measured in the sitting position according to World Health Organization guidelines (two measurements in the sitting position after 5 minutes of rest, followed by one measurement in the standing position after at least 2 minutes of equilibration).¹⁰ All measurements were rounded to the nearest 2 mm Hg. Phase V (disappearance of the Korotkoff sound) was used for measurement of diastolic blood pressure.

At each visit the occurrence of any adverse events was recorded. Measurements of basic hematologic, biochemical, and urinary parameters were carried out at baseline and at 8- and 12-week visits. The use of any concomitant treatment that could interfere with evaluation of efficacy, safety, or tolerability was prohibited during the study, with the exception of the use of acetaminophen for pain relief.

The primary efficacy variable was the change from baseline in mean SDBP at the end point of monotherapy (8 weeks). Secondary variables analyzed included change from baseline at the end point of monotherapy in mean sitting systolic blood pressure (SSBP) and responder rates (defined as the percentage of patients at end point with SDBP <90 mm Hg or decrease in SDBP ≥ 10 mm Hg compared to baseline).

Statistical methods. A sample size of at least 80 evaluable patients per group was calculated to be required for a treatment difference to be estimated with precision in terms of a 95% confidence interval (CI) ± 2.5 mm Hg, assuming the standard deviation of SDBP measurement to be 8 mm Hg.¹¹

Two data sets were used for the analysis of efficacy parameters. The primary analysis was based on the "intent-to-treat" data set, which included all randomized patients who had a baseline measurement and at least one postrandomization measurement for the variable to be analyzed. A secondary analysis was performed for the "acceptable patient" data set. This excluded major protocol violators (blood pressure measurements <12 or >30 hours from last dose, mean SDBP ≤ 95 mm Hg at baseline, excessive delay between visits, trial treatment for <25 days, and use of forbidden concomitant medication). For both analyses the end point measurement was after 8 weeks of monotherapy or, in the case of premature discontinuation, the last post-baseline observation carried forward.

The primary efficacy variable (change in baseline SDBP) and secondary efficacy variables (change in baseline SSBP, standing systolic blood pressure, and diastolic blood pressure) were analyzed by analysis of covariance, fitting treatment, baseline, treatment-by-baseline interaction, center, and treatment-by-center interaction. Because all centers were of adequate size, there was no pooling of small centers. The estimated mean treatment difference and CI were calculated from the model. All statistical tests were carried out at the two-sided 5% level. Responder rates were analyzed by means of a χ^2 test. Efficacy data after possible titration at 12 weeks were summarized.

All randomized patients were included in the safety evaluation, which was descriptive. All data analyses were performed by the Department of Biometrics, Ciba-Geigy, Basel, Switzerland.

RESULTS

Patients. A total of 168 patients were randomized. All were white and in the age range from 26 to 74

years. Of the randomized patients, only six patients quit the study prematurely, with 162 completing the 8-week double-blind monotherapy period. In the valsartan group two patients discontinued prematurely because they did not meet the protocol criteria and one patient discontinued because of an adverse experience. In the amlodipine group one patient discontinued because of unsatisfactory therapeutic effect, one because of an adverse experience, and one withdrew consent.

Table I shows that there were no important differences between the amlodipine and valsartan treatment groups with respect to demographics and baseline measurements. One patient randomized to amlodipine was excluded from the intent-to-treat analysis because the patient withdrew consent at the week 4 visit and therefore had no postbaseline measurements. Five patients in total were excluded from the "acceptable patient" analysis because of major protocol violations (two in the valsartan group and three in the amlodipine group).

After 8 weeks of monotherapy 24 (28.6%) of patients receiving valsartan and 28 (33.7%) of patients receiving amlodipine required the addition of 5 mg amlodipine for blood pressure control.

Efficacy. Both treatments were effective at lowering SDBP and SSBP (Table II). Similar mean changes from baseline were observed in both groups after 8 weeks of monotherapy (SDBP: -11.5 mm Hg for valsartan and -11.1 mm Hg for amlodipine; SSBP: -13.1 mm Hg for valsartan and -14.8 mm Hg for amlodipine). Blood pressure reduction was also comparable between the groups at 12 weeks after additional therapy in patients whose blood pressure was uncontrolled (SDBP: -13.5 for valsartan and -14.8 for amlodipine; SSBP: -16.5 for valsartan and -19.3 for amlodipine). For the primary analysis of SDBP reduction after 8 weeks of monotherapy, a nonstatistically significant estimated mean difference of -0.5 mm Hg (95% CI, -2.7, 1.7) in favor of valsartan was observed ($p = 0.68$). There was also no statistically significant difference between the two groups for change in SSBP after 8 weeks of monotherapy ($p = 0.82$). For both variables the differences between treatment groups were small and fell well within relatively narrow CI values, supporting the hypothesis that valsartan is at least as effective as amlodipine. Results from the secondary analysis with the acceptable patient data set were comparable to those observed for the intent-to-treat data set.

Similar decreases in SDBP and SSBP were ob-

Table I. Patient demographics and baseline characteristics

	Valsartan (n = 84)	Amlodipine (n = 84)
Sex (% female)	41.7%	42.9%
Age (yr)*	52.8 ± 10.5	52.9 ± 8.9
Weight (kg)*	73.5 ± 9.6	74.0 ± 11.5
Height (cm)*	169.0 ± 7.7	167.5 ± 7.7
Duration of hypertension (yr)	5.1 ± 5.0	6.1 ± 6.1
Antihypertensive treatment during previous 3 months (%)	54.8%	60.7%
Significant medical history (%)	34.5%	58.3%
Baseline BP (mm Hg)		
Sitting diastolic BP*	101.1 ± 3.7	101.8 ± 4.5
Sitting systolic BP*	157.5 ± 13.3	161.8 ± 12.8
Pulse (beats/min)*	72.6 ± 7.2	73.3 ± 9.6

BP, Blood pressure.
*Data are mean values ± SD.

Table II. Mean ± SD sitting diastolic and systolic blood pressures (intent-to-treat data set; n = 167)

	Diastolic blood pressure (mm Hg)		Systolic blood pressure (mm Hg)	
	Valsartan	Amlodipine	Valsartan	Amlodipine
Baseline	101.1 ± 3.7	101.8 ± 4.5	157.5 ± 13.3	161.8 ± 12.8
4 weeks	92.0 ± 8.2	91.7 ± 7.6	147.5 ± 14.2	148.5 ± 14.3
8 weeks	89.5 ± 7.9	90.8 ± 8.2	143.9 ± 15.9	147.5 ± 14.3
12 weeks*	87.4 ± 7.1	86.8 ± 6.9	140.4 ± 14.5	142.6 ± 11.7

*After additional therapy in patients whose blood pressure was uncontrolled at 8 weeks.

served in both men and women for the two treatment groups. Similar decreases in mean SDBP were also observed in the two groups for patients aged <65 years and those ≥65 years. For SSBP, the mean change was similar in patients <65 years for both groups, but the SSBP decreased more in the amlodipine group for patients aged ≥65 years. However, the number of patients in this age group was small (12 who were receiving valsartan and eight who were receiving amlodipine), which does not allow any conclusion to be drawn from this result.

After 8 weeks of monotherapy, the responder rate was 66.7% in the valsartan group and 60.2% in the amlodipine group. This difference in favor of valsartan did not reach statistical significance (*p* = 0.39). The responder rates also support valsartan as being at least as effective as amlodipine.

Tolerability and safety. Both trial medications were generally well tolerated both during the monotherapy phase and also in nonresponders receiving additional therapy. Of the 168 patients randomized, a total of 31 (18.5%) reported one or more adverse experiences, regardless of relationship to trial medication. Of these, 13 were taking valsartan monotherapy, one was taking valsartan and 5 mg amlo-

dipine, 13 were taking amlodipine monotherapy, and four were taking 5 mg amlodipine plus 5 mg amlodipine daily. Only two patients discontinued therapy because of adverse experiences, one patient experienced a headache and tachycardia after the first dose of valsartan and the other experienced a headache of moderate severity after the first dose of amlodipine.

A total of 19 patients (10.2%) reported adverse experiences that were considered to be related to trial medication. The most frequently occurring drug-related adverse experiences were edema and headache in both groups (Table III). Edema was observed more frequently in the amlodipine group, particularly in those patients receiving a total dose of 10 mg per day.

The majority of trial drug-related adverse experiences were mild to moderate in severity with the exception of one patient on amlodipine who experienced a severe headache. Only one patient reported a dry cough, and this occurred in the amlodipine group.

The number of patients with a detectable drop in blood pressure on standing was small in both groups at 8 weeks and also at 12 weeks, when patients may

Table III. Incidence of most frequently reported ($\geq 3\%$) adverse experiences considered to be drug related

	Valsartan, 80 mg		Amlodipine, 5 mg	
	Monotherapy	With 5 mg amlodipine	Monotherapy	With 5 mg amlodipine
Total patients	n = 84	n = 24	n = 84	n = 28
Total patients with an adverse experience				
n	6	1	8	4
%	7.1%	4.2%	9.5%	14.3%
Edema dependent				
n	2	0	3	4
%	2.4%		3.6%	14.3%
Dizziness				
n	0	1	0	0
%		4.2%		
Headache				
n	2	1	3	0
%	2.4%	4.2%	3.6%	

have been on additional therapy. More patients receiving amlodipine (seven patients) experienced postural decreases in diastolic blood pressure ≥ 20 mm Hg compared to valsartan (one patient). However no patients at any time point in either treatment group experienced symptoms associated with a postural blood pressure change. These data suggest that neither 80 mg valsartan or 5 mg amlodipine produce clinically significant changes in diastolic blood pressure on rising from sitting.

No clinically significant changes in sitting or standing pulse rates from baseline were observed during the study in either group. No significant effect on body weight was observed for either treatment. Furthermore, no clinically relevant changes in laboratory parameters were observed during the study for either treatment group. There were no deaths or serious adverse experiences related to study medication reported during the study.

DISCUSSION

This study confirms that both 80 mg valsartan once daily and 5 mg amlodipine once daily are effective antihypertensive agents in patients with mild to moderate essential hypertension. The study shows no significant differences in efficacy between the two agents.

Amlodipine is a well recognized antihypertensive agent that belongs to the dihydropyridine group within the calcium antagonist class. It is generally given at doses between 2.5 mg and 10 mg daily, with 2.5 mg being regarded as the minimal effective dose and 10 mg being used if the desired therapeutic effect has not been achieved with 5 mg. The efficacy

of 5 mg amlodipine is well documented, and the drug is widely used at this dose in the treatment of essential hypertension.

The data show reductions in SDBP and SSBP of similar magnitude produced by valsartan and amlodipine. Comparison of two antihypertensive agents shows that the range of clinical equivalence can be considered to be 2 mm Hg. For the primary efficacy variable (change in SDBP from baseline) the CI for the difference between valsartan and amlodipine was -2.7 to 1.7 mm Hg (negative number in favor of valsartan). Although the study was not designed to demonstrate equivalence between the two therapies, the data show that valsartan is as least as effective as amlodipine in the treatment of mild to moderate essential hypertension.

Both medications were well tolerated during both the monotherapy and possible titration phase. Postural changes in SDBP and SSBP were noted in some patients in both treatment groups, although decreases ≥ 20 mm Hg were observed more commonly with amlodipine. However, no cases were associated with any concomitant symptoms. A somewhat higher incidence of drug-related edema in the amlodipine group, particularly at a daily dose of 10 mg, is in keeping with this well-recognized side effect of calcium antagonists, related to peripheral vasoconstriction, that may also cause dizziness, headache, and flushing.⁴ No cases of cough occurred with valsartan treatment, confirming previous findings that angiotensin II receptor antagonists, as a result of their mechanism of action at the last step in the renin-angiotensin-aldosterone pathway, do not have the unwanted effects associated with agents

such as angiotensin converting enzyme inhibitors, which interfere with the pathway at a more proximal point.¹² The efficacy data from the current study are in keeping with those reported for another angiotensin II antagonist, which has been shown to have approximately equal efficacy to established agents, including calcium antagonists.¹³

In summary, these data show that valsartan, a novel angiotensin II receptor antagonist, is at least as effective as a well-established calcium antagonist, amlodipine. The data also suggest that valsartan is not associated with the side effects characteristic of the comparator class used in this study, calcium antagonists.

We acknowledge the collaboration and commitment of all the local investigators and their staff, without whom this study would not have been possible.

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ANEXO No. 7

“Efficacy, safety, and effects on hipertensión-associated symptoms of losartan, alone or in combination with hydrochlorothiazide versus amlodipine in patients with mild to moderate hipertensión” Renate Tiebel, Arnold Valhbruch, and Manfred Stapff. MSD Sharp & Dhme GmbH, Haar bei Muenchen, and Private Practice, Liccstandt, Germany.

EFFICACY, SAFETY, AND EFFECTS ON
HYPERTENSION-ASSOCIATED SYMPTOMS OF LOSARTAN, ALONE
OR IN COMBINATION WITH HYDROCHLOROTHIAZIDE, VERSUS
AMLODIPINE IN PATIENTS WITH
MILD-TO-MODERATE HYPERTENSION

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ABSTRACT

This randomized, double-masked, multicenter, clinical study with three parallel treatment groups was conducted to compare the efficacy and tolerability of losartan potassium (losartan), alone or combined with hydrochlorothiazide (HCTZ), and amlodipine in patients with mild-to-moderate hypertension. A 4-week placebo period was followed by a 12-week treatment period. A total of 935 patients were randomized to 3 treatment regimens: losartan 50 mg once daily with a possible increase to 100 mg once daily (L 50/100, n = 308), losartan 50 mg once daily with a possible addition of HCTZ 12.5 mg once daily (L/HCTZ, n = 313), or amlodipine 5 mg once daily with a possible increase to 10 mg once daily (A 5/10, n = 314) at week 6. Approximately 50% of the patients in each treatment group required a dose adjustment because of inadequate response. At the end of the study the reductions in mean trough sitting diastolic blood pressure (SiDBP) were -11.4 mm Hg, -13.2 mm Hg, and -13.6 mm Hg in the L 50/100, L/HCTZ, and A 5/10 treatment groups, respectively. Reductions in mean trough sitting systolic blood pressure (SiSBP) were similar in all treatment groups. Blood pressure reductions (SiSBP/SiDBP) were comparable in the two subgroups without dose adjustment (-18.6 mm Hg/-14.2 mm Hg for losartan 50 mg and -19.0 mm Hg/-14.8 mm Hg for amlodipine 5 mg) during the 12-week treatment period. Differences between the treatment groups in patient-reported symptoms were significant, with a higher rate of swelling and edema reported with amlodipine (10%) than with losartan (3%). In this study, losartan appeared to be as effective as amlodipine and to have fewer drug-related side effects. *Key words:* losartan, amlodipine, hydrochlorothiazide, hypertension.

INTRODUCTION

In industrialized European countries the prevalence of arterial hypertension ranges from 9% to 20% in the general adult population and from 44%

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to 60% in those 65 years of age or older.¹ This represents a major risk factor for the development of cardiovascular and cerebrovascular diseases (eg, stroke), which are responsible for almost 50% of all deaths among the population aged 35 to 64 years.²⁻⁴ To help avoid this risk, the World Health Organization recommends reducing systolic blood pressure to <140 mm Hg and diastolic blood pressure to <90 mm Hg by means of antihypertensive therapy.⁵ Unfortunately, even in controlled clinical studies, adequate blood pressure reduction has been achieved in approximately 50% of the patients with the usual dose of a single drug. These unsatisfactory results are due not only to the inadequate efficacy of antihypertensive drugs but also to poor patient compliance. The tolerability profile of an antihypertensive drug has a direct effect on patient compliance because hypertension is often asymptomatic and patients are reluctant to accept the adverse effects associated with treatment. The aim in developing new antihypertensive medications is, therefore, to improve both efficacy and compliance. The objective of taking two drugs concomitantly is to achieve better control of blood pressure while maintaining tolerability compared with the usual doses of the drugs when taken as monotherapy.⁶

The renin-angiotensin-aldosterone system has a key function in the pathogenesis of hypertension, making blockade of this system an ideal target for antihypertensive therapy. All known clinical effects of angiotensin II, including vasoconstriction, aldosterone release, and augmented catecholamine release, are mediated by the AT₁-type angiotensin II receptor.^{7,8} Losartan potassium (hereafter referred to as losartan) is the first orally active, nonpeptide antagonist of the angiotensin II subtype 1 receptor.⁹ Losartan selectively and specifically blocks the binding of angiotensin II to the AT₁ receptor found in many tissues. This selective activity has been extensively demonstrated to be effective and well tolerated in clinical studies of losartan.¹⁰⁻²⁰

The antihypertensive activity of amlodipine, a dihydropyridine calcium channel blocker, relies on blockade of calcium ion influx into vascular smooth muscle cells. Arterial blood pressure is lowered systemically by means of peripheral vasodilation, which also accounts for the adverse reactions typical of calcium channel blockers (eg, peripheral edema and flushing).²¹

Determination of the clinical efficacy of antihypertensive medications is relatively straightforward compared with the assessment of tolerability or the patient's perception of a change in hypertension-associated symptoms in response to antihypertensive drugs. In recent years considerable efforts have been undertaken to design instruments capable of measuring the effects of antihypertensive therapy on symptoms and detecting differences in these variables between various classes of antihypertensive agents.^{22,23}

The aim of this study was to compare losartan (alone or combined with

hydrochlorothiazide [HCTZ]) and amlodipine in terms of tolerability (assessed by symptom questionnaires) and antihypertensive efficacy in the treatment of mild-to-moderate hypertension.

PATIENTS AND METHODS

The study protocol was approved by the institutional review board at each of the 98 clinical centers included in the study. All patients gave their written informed consent in accordance with the Declaration of Helsinki. The execution and monitoring of the study were conducted in accordance with the requirements of good clinical practice. Fifteen percent of the centers were audited by an independent organization to ensure that the study was conducted properly and was in compliance with all regulations and guidelines.

Patients

Male and female patients at least 18 years of age with mild-to-moderate hypertension and without known hypersensitivity to losartan, amlodipine, other calcium channel blockers, or diuretics were eligible for inclusion. Exclusion criteria included a history of malignant or secondary hypertension; congestive heart failure; cardiovascular, cerebrovascular, hepatic, or renal disease; recent myocardial infarction; or angina pectoris. Pregnant and nursing women were excluded, as were patients with clinically significant abnormalities in laboratory findings. Diabetic patients were allowed to enroll if their condition was stable (ie, their glucose levels were controlled).

Study Design

This prospective, double-masked, multicenter study with three randomized, parallel treatment groups was designed to assess the tolerability, therapeutic efficacy, and safety of losartan 50 mg once daily with a possible increase to 100 mg once daily (L 50/100 group) or losartan 50 mg with a possible addition of HCTZ 12.5 mg once daily (L/HCTZ group) compared with amlodipine 5 mg once daily with a possible increase to 10 mg once daily (A 5/10 group). The study design and blood pressure entrance criteria are outlined in Figure 1.

The study consisted of a 4-week placebo period followed by a 12-week treatment period. Eight clinical visits were planned during the study: three visits during the placebo run-in period at weeks -4, -2, and 0 (baseline), and five visits during the treatment period at weeks 1, 3, 6, 9, and 12. Following a 7-day washout of current antihypertensive drugs, patients with a pre-placebo mean sitting diastolic blood pressure (SiDBP) of 90 to 115 mm Hg were enrolled. At the time of randomization (week 0), the mean

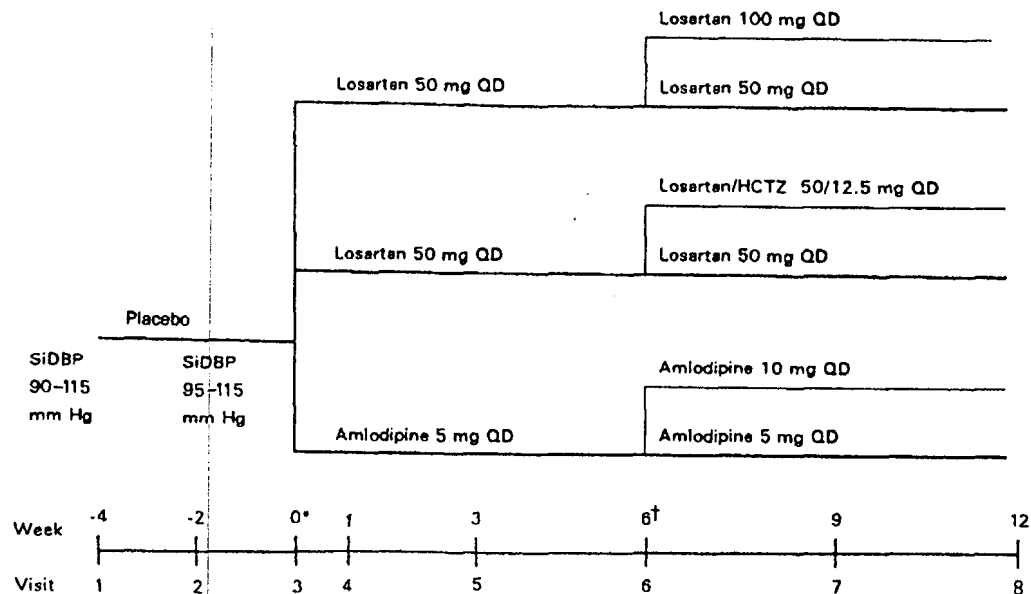


Figure 1. Study design and blood pressure entrance criteria. QD = once daily; HCTZ = hydrochlorothiazide; SiDBP = sitting diastolic blood pressure. * Baseline randomization. † Increase in dosage if SiDBP ≥ 90 mm Hg.

SiDBP must have been between 95 and 115 mm Hg. The difference between the mean trough SiDBP (measured 24 ± 2 h after the last morning dose) at weeks -2 and 0 had to be ≤ 7 mm Hg. In patients with SiDBP < 90 mm Hg at week 6, treatment was continued to week 12 with losartan 50 mg or amlodipine 5 mg once daily. If the trough SiDBP was ≥ 90 mm Hg at week 6, treatment was changed to losartan 100 mg, losartan 50 mg + HCTZ 12.5 mg, or amlodipine 10 mg once daily.

Before admission to the study, patients underwent a complete physical examination and their medical history was taken. At each visit, trough systolic and diastolic blood pressures and heart rate were measured both sitting and standing, and adverse events were recorded. Laboratory tests, including hematology, blood chemistry, and urinalysis, were conducted at weeks -2, 6, and 12. Electrocardiography was performed at week -2 and at the end of the 12-week treatment period. A complete physical examination was again performed at the end of the study. At weeks -2, 0, 1, 3, 6, 9, and 12, the investigators completed a questionnaire regarding the occurrence of 24 symptoms (the specific symptoms questionnaire). At weeks 0, 6, and 12, a 32-question symptoms inventory was completed by the patient.

Blood pressure was measured in accordance with the guidelines of the American Heart Association using a standard mercury sphygmomanometer. Systolic and diastolic blood pressures were determined by averaging at least three replicate measurements obtained 1 minute apart until stability was obtained.

Statistical Analysis

The efficacy, safety, and tolerability analyses were performed on an intent-to-treat (all patients treated) and per-protocol basis. Comparability of the treatment groups with respect to patient characteristics was tested by means of the chi-square test for dichotomous variables and the Kruskal-Wallis test for ordered categoric variables. Analysis of variance was performed to assess changes in efficacy variables, which were measured repeatedly throughout the study with respect to baseline. These included systolic and diastolic blood pressures, clinical and laboratory test results, symptoms, and the change from baseline in the global symptom score. The analysis of variance models included treatment groups and investigators as factors.

The primary end point used to address the tolerability objective was the day-adjusted area under the concentration–time curve (AUC/day) for the change from baseline in the global symptom score, as calculated from the specific symptoms questionnaire. The global symptom score represents the total number of the 24 listed symptoms that the patient had experienced since the last visit and was calculated by assigning 0 points when a symptom was absent and 1 point when present and then adding the points. Fisher's exact test was used to compare proportions of patients in the three treatment groups with adverse events, discontinuations, and changes from baseline in laboratory measurements outside predefined limits.

The sample-size calculation was based on the assumption that a between-group difference in the change from baseline in the total symptom score would be 0.77, with a standard deviation of 2.8. A total sample size of 840 patients (280 per treatment group) was needed to achieve a power of 90% with a type 1 error of 0.05.

RESULTS

Patients

The study was conducted at 98 clinical centers in Germany from May 1995 to July 1996. A total of 935 patients were randomized and available for safety analysis: 308 in the L 50/100 group, 313 in the L/HCTZ group, and 314 in the A 5/10 group. Data on systolic and diastolic blood pressures were available for 928 patients for efficacy analysis: 304 in the L 50/100 group, 310 in the L/HCTZ group, and 314 in the A 5/10 group. A summary of patient characteristics and baseline SiDBP is given in Table I. The differences in the demographic characteristics between the three treatment groups were not significant. Mean patient age ranged from 55.3 to 56.0 years, and mean body weight ranged from 81.2 to 82.3 kg.

Table I. Patient characteristics at entry.

Characteristics	L 50/100 (n = 308*)	L/HCTZ (n = 313*)	A 5/10 (n = 314*)
Sex, n (%)			
Male	165 (54)	167 (53)	157 (50)
Female	143 (46)	146 (47)	157 (50)
Age (y), n (%)			
<35	18 (6)	19 (6)	16 (5)
35-44	40 (13)	33 (11)	41 (13)
45-54	73 (24)	76 (24)	84 (27)
55-64	105 (34)	114 (36)	102 (32)
≥65	72 (23)	71 (23)	71 (23)
Mean age (y)	55.3	56.0	55.6
Range	18-90	18-87	25-87
Body weight (kg)	81.7	81.2	82.3
Severity of hypertension (mm Hg), n (%)			
Low (<95)	4 (1)	5 (2)	6 (2)
Mild (95-105)	234 (76)	214 (68)	230 (73)
Moderate (106-115)	68 (22)	89 (28)	77 (25)
Severe (>115)	2 (1)	5 (2)	1 (<1)
Sitting diastolic blood pressure (mm Hg)			
Mean ± SD	101.8 ± 5.6	103.0 ± 5.9†	101.8 ± 5.2
Range	83-130	90-120	90-117

L 50/100 = losartan 50 mg once daily (QD), possibly increased to 100 mg QD; L/HCTZ = losartan 50 mg QD, with the possible addition of hydrochlorothiazide 12.5 mg QD; A 5/10 = amlodipine 5 mg QD, possibly increased to 10 mg QD.

* Number of randomized patients.

† $P = 0.020$.

At entry, 15 patients (2%) had low blood pressure (<95 mm Hg), 678 patients (73%) had mild hypertension (95 to 105 mm Hg), 234 patients (25%) had moderate hypertension (106 to 115 mm Hg), and 8 patients (1%) had severe hypertension (>115 mm Hg). At 103 mm Hg, the mean SiDBP in the L/HCTZ group was higher than in the other two groups. The difference was statistically significant ($P = 0.020$). A total of 819 patients (88%) had concurrent diseases. Metabolic diseases such as hyperlipidemia with obesity were most common, affecting approximately 50% of the patients. Other common conditions, in descending order of frequency, were cardiovascular diseases, diseases of the locomotor and nervous systems, and psychiatric diseases, each accounting for approximately one third of the patients, while approximately 12% of the patients had diabetes mellitus.

Tolerability

Tolerability of the three treatment regimens was determined by means of two different symptom questionnaires—the specific symptoms questionnaire and the symptoms inventory. The global symptom score was regarded as the more important tolerability criterion and represents the total score from the specific symptoms questionnaire.

In the 6 weeks following randomization, the symptom score improved by 0.2 point ($P = 0.008$) during treatment with losartan 50 mg. With amlodipine 5 mg the change from baseline values was not significant. After the 12-week treatment period the symptom score in all three groups improved approximately 0.3 point (L 50/100, $P = 0.010$; L/HCTZ, $P = 0.011$; A 5/10, $P = 0.015$) (Figure 2). With amlodipine the symptom score improved only during the second half of the study, whereas with losartan the symptom score improved steadily throughout the treatment period. Similar improvements in patient well-being were seen with all three treatment regimens.

Except for the poor tolerability of amlodipine in terms of swelling and edema, comparable improvements in well-being occurred in all three treatment groups. The only significant deterioration ($P < 0.001$) was an 8% increase in swelling and edema in the A 5/10 group. In all three treatment groups a statistically significant decrease of 6.3% (L 50/100, $P = 0.014$), 7.1% (L/HCTZ, $P < 0.001$), and 7.7% (A 5/10, $P < 0.001$) was found in the incidence of dizziness. In the L/HCTZ and A 5/10 groups, the incidence of headache also decreased significantly by 7% ($P = 0.006$) and 9% ($P < 0.001$), respectively.

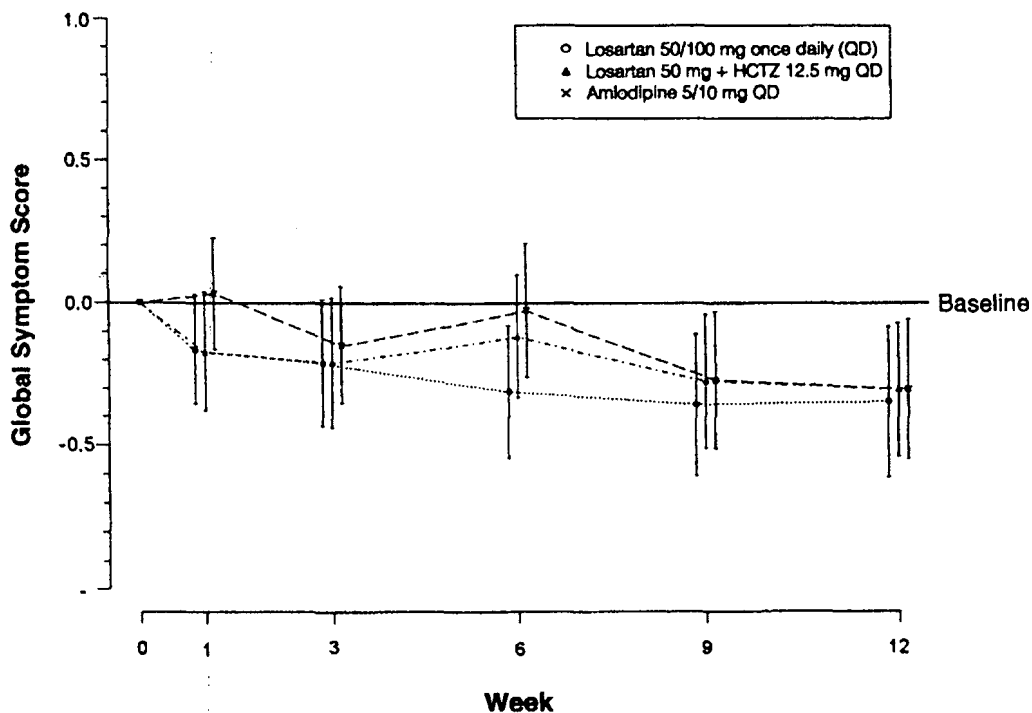


Figure 2. Mean change in the global symptom score from baseline and 95% confidence interval, by week. The global symptom score represents the total score from the specific symptoms questionnaire.

Analysis of the change in the symptoms inventory score from baseline to week 12 confirmed many of the findings from the specific symptoms questionnaire (eg, the significantly lower incidence of headache [L 50/100, -7.2%, $P < 0.005$; L/HCTZ, -8.8%, $P < 0.001$; A 5/10, -5.8%, $P = 0.009$] and the significantly greater incidence of swelling and edema in the A 5/10 group [+8.0%, $P < 0.001$]). Figure 3 shows the differences in the incidences

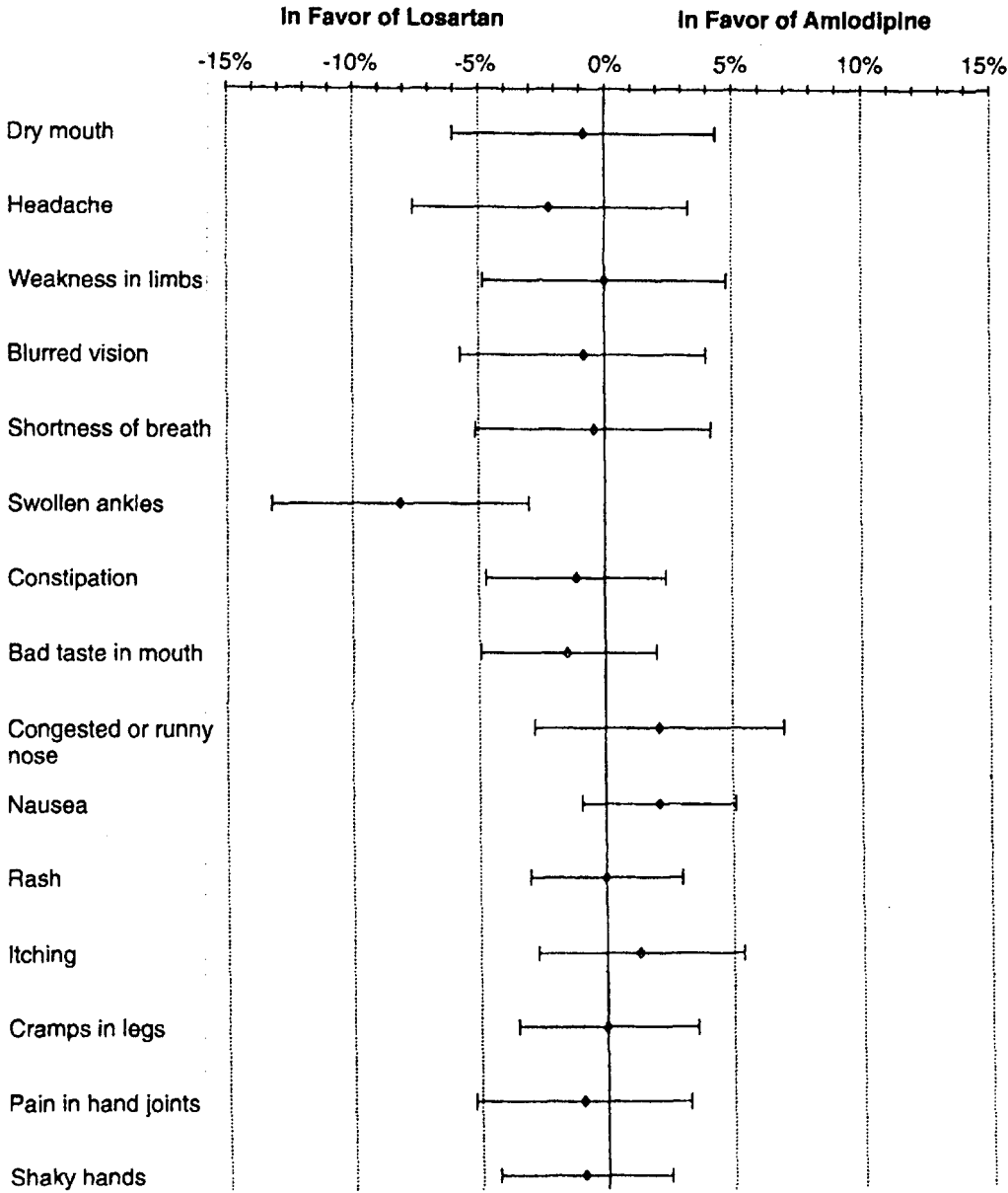


Figure 3. Estimate and 95% confidence interval for the differences between the losartan regimen and the amlodipine regimen with respect to the change from baseline to week 12 in the incidence (%) of the symptoms listed in the symptoms inventory.

of symptoms, as determined by the symptoms inventory, from baseline to week 12 between the losartan and amlodipine treatment groups.

Antihypertensive Efficacy

In all three treatment groups the trough sitting systolic and diastolic blood pressures decreased significantly during the study (Table II). The mean changes in SiDBP from baseline through week 12 are shown in Figure 4.

In the L/HCTZ group and the A 5/10 group the reductions in mean

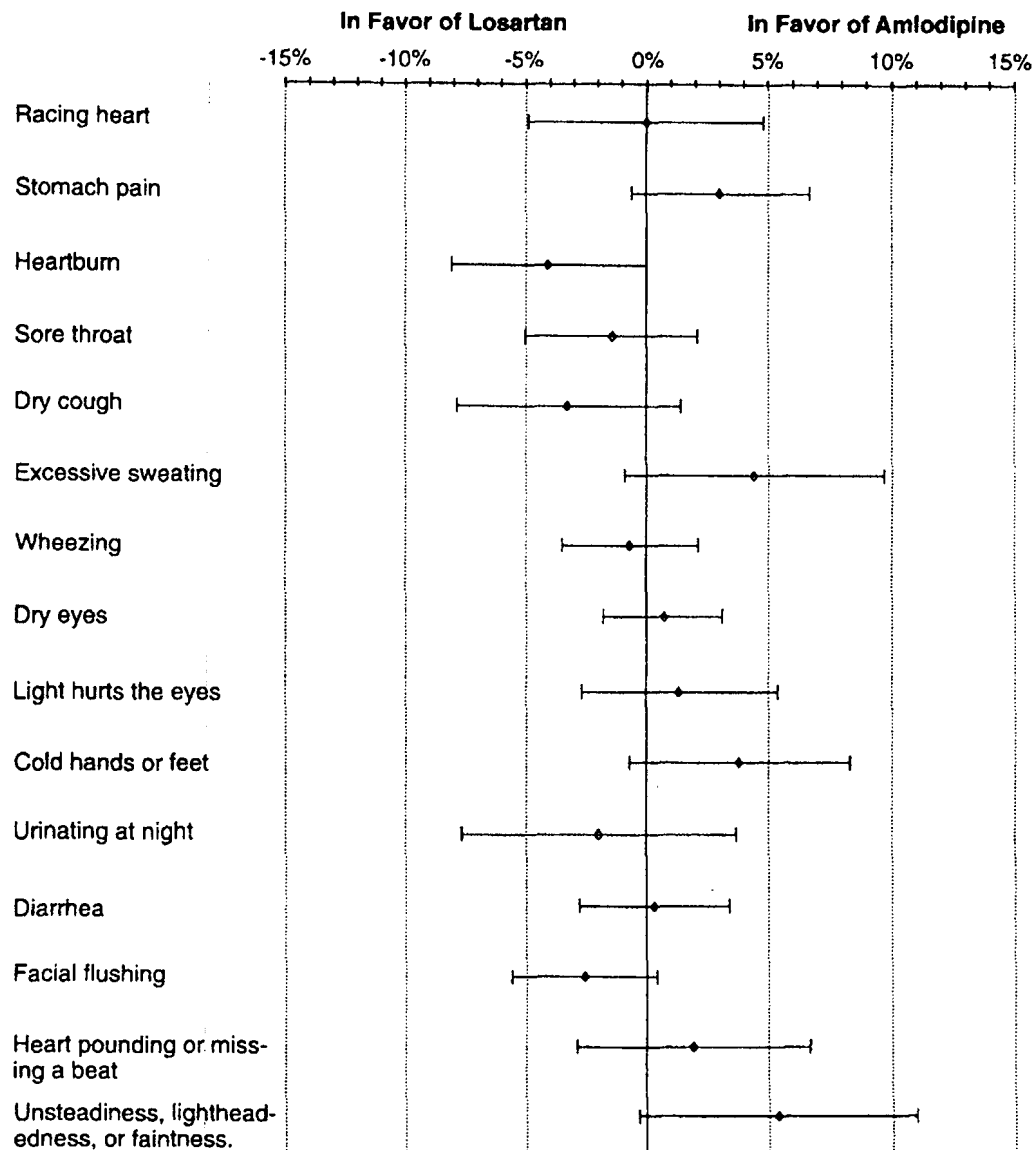


Figure 3. Continued.

Table II. Change from baseline in mean ($\pm$ SD) systolic and diastolic sitting blood pressures in the three treatment groups through week 12.

Blood Pressure	L 50/100 (n = 304*)	L/HCTZ (n = 310*)	A 5/10 (n = 314*)
Mean systolic blood pressure			
Baseline	164.0 $\pm$ 16.8	164.2 $\pm$ 16.5	162.9 $\pm$ 16.5
Week 12	147.1 $\pm$ 17.3	145.8 $\pm$ 14.3	144.4 $\pm$ 14.1
Change from baseline	-16.9 $\pm$ 16.2	-18.4 $\pm$ 16.0	-18.5 $\pm$ 13.7
P	<0.001	<0.001	<0.001
Mean diastolic blood pressure			
Baseline	101.8 $\pm$ 5.6	103.0 $\pm$ 5.9	101.8 $\pm$ 5.2
Week 12	90.4 $\pm$ 9.9	89.8 $\pm$ 8.1	88.2 $\pm$ 8.0
Change from baseline	-11.4 $\pm$ 9.5	-13.2 $\pm$ 7.7	-13.6 $\pm$ 7.4
P	<0.001	<0.001	<0.001

L 50/100 = losartan 50 mg once daily (QD), possibly increased to 100 mg QD; L/HCTZ = losartan 50 mg QD, with the possible addition of hydrochlorothiazide 12.5 mg QD; A 5/10 = amlodipine 5 mg QD, possibly increased to 10 mg QD.

* Number of patients with data for systolic and diastolic blood pressures.

SiDBP were comparable (-13.2 mm Hg and -13.6 mm Hg, respectively), whereas the reduction was lower in the L 50/100 group (-11.4 mm Hg). Fifty-eight percent of patients responded to monotherapy with losartan 50 mg and 57% of patients to amlodipine 5 mg; 53% of the patients in the L/HCTZ group responded to losartan monotherapy without the addition of HCTZ (Table III). The reductions in sitting blood pressure were compa-

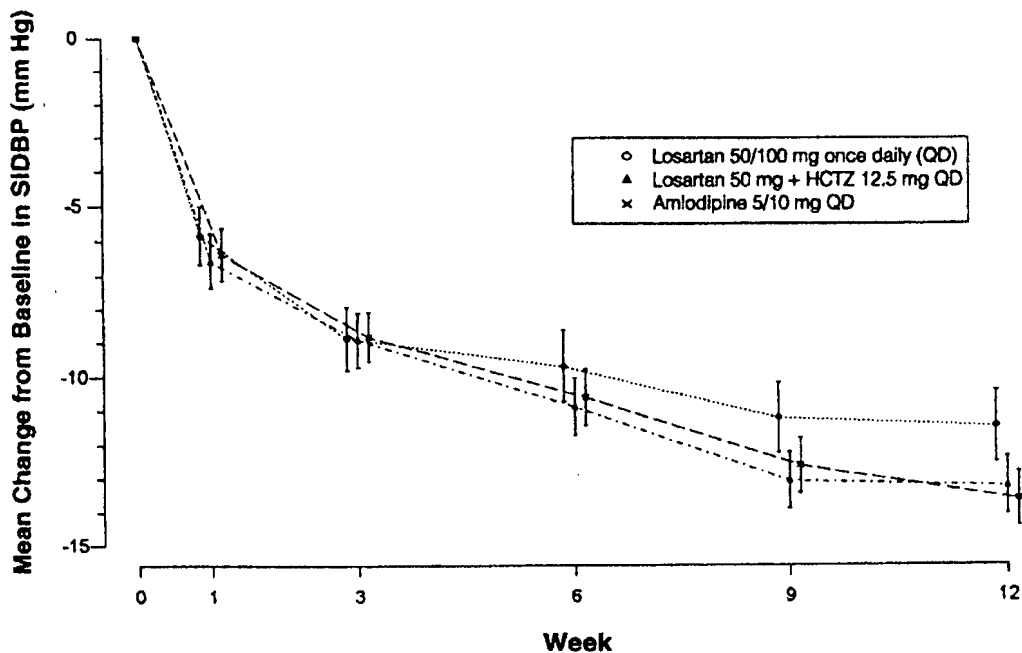


Figure 4. Mean change from baseline and 95% confidence interval by week (through week 12) in sitting diastolic blood pressure (SiDBP) (mm Hg).

table in the two subgroups without dosage adjustment (-18.6 mm Hg/ -14.2 mm Hg in 345 patients receiving L 50/50 and -19.0 mm Hg/ -14.8 mm Hg in 178 patients receiving A 5/5) during the 12-week treatment period.

Withdrawals and Clinical, Laboratory, and Other Adverse Events

A total of 859 (92%) randomized patients completed the study; 76 patients (8%) withdrew from the study prematurely because of clinical adverse events or lack of cooperation (41 [13%] of 308 patients in the L 50/100 group [most during treatment with losartan 100 mg], 16 [5%] of 313 in the L/HCTZ group, and 19 [6%] of 314 patients in the A 5/10 group). Table IV lists all drug-related clinical adverse events that occurred with an incidence of $\geq 4\%$, serious adverse events, and withdrawals because of adverse events.

During the placebo period, clinical adverse events occurred in 274 (29%) of the 935 patients in the study. The incidences of clinical adverse events were similar to each other with respect to the number of patients in the three treatment groups. In 4 patients the clinical adverse events that started in the placebo period persisted, resulting in withdrawal from the study during the double-masked phase. Before randomization 3 patients experienced serious clinical adverse events.

Four hundred eighty patients had at least one clinical adverse event that began during the 12-week treatment period, with a similar frequency (50% to 52%) in the three treatment groups. The 11 serious clinical adverse events during the treatment period were similarly distributed among the three treatment groups. The most common clinical adverse events in all three treatment groups were swelling and edema, headache, dizziness, bronchitis, cough, and upper respiratory tract infections.

A total of 196 patients (21%) had clinical adverse events that were possibly, probably, or definitely related to the study drugs during the treatment phase. The incidence of drug-related clinical adverse events was significantly higher in the A 5/10 group (26%) than in the two losartan treatment groups (19% [$P = 0.021$] and 18% [$P = 0.012$]). This was due

Table III. Number (%) of patients requiring dosage increases.

Dosage	Losartan 50 mg to 100 mg (n = 308*)	Losartan 50 mg to Losartan 50 mg + HCTZ 12.5 mg (n = 313*)	Amlodipine 5 mg to 10 mg (n = 314*)
Increased	128 (42)	148 (47)	136 (43)
Not increased	180 (58)	165 (53)	178 (57)

HCTZ = hydrochlorothiazide.

* Number of randomized patients.

Table IV. Clinical adverse events with an incidence of $\geq 4\%$, serious adverse events, and withdrawals because of adverse events reported during the treatment phase.

Adverse Events	A L 50/100 (n = 308*)	B L/HCTZ (n = 313*)	C A 5/10 (n = 314*)
Total no. (%) of patients with clinical adverse events regardless of relationship to the study drugs	160 (52)	156 (50)	164 (52)
No. (%) of drug-related clinical adverse events (possibly, probably, or definitely related to the study drugs)	57 (19)†	56 (18)‡	83 (26)
Swelling and edema	8 (3)	10 (3)	30 (10)
Headache	12 (4)	12 (4)	17 (5)
Dizziness	14 (5)	9 (3)	6 (2)
No. (%) of patients with serious clinical adverse events	2 (1)	5 (2)	4 (1)
No. (%) of patients who withdrew because of adverse events	41 (13)§	16 (5)	19 (6)

L 50/100 = losartan 50 mg once daily (QD), possibly increased to 100 mg QD; L/HCTZ = losartan 50 mg QD, with the possible addition of hydrochlorothiazide 12.5 mg QD; A 5/10 = amlodipine 5 mg QD, possibly increased to 10 mg QD.

* Number of randomized patients.

† $P = 0.021$, A versus C.

‡ $P = 0.012$, B versus C.

§ $P < 0.001$, A versus B.

¶ $P < 0.001$, A versus C.

primarily to the significantly higher rate of swelling and edema with amlodipine (10%) than with losartan (3%).

Abnormal laboratory findings were reported for 27 patients (3%) during the double-masked treatment period; however, none of the abnormal findings were considered to be serious. Furthermore, in only 3 of these patients—2 in the L 50/100 group and 1 in the A 5/10 group—were the abnormal findings regarded by the investigator to be possibly, probably, or definitely drug related.

No metabolic changes (eg, hyperlipidemia, obesity, diabetes mellitus) occurred in any of the enrolled patients during the 12-week treatment period.

DISCUSSION AND CONCLUSION

In the present study, as in the studies by Oparil et al¹¹ and Weir et al,¹³ tolerability was analyzed by evaluating questionnaires. This study used the specific symptoms questionnaire (completed by the physician) and the symptoms inventory (completed by the patients); queries regarding many symptoms appeared on both questionnaires. These questionnaires showed that the incidences of headache, sweating, and dizziness decreased significantly in all three treatment groups. It is likely that pharmacologic control of blood pressure led to the reductions in symptoms, which were mainly hypertension related. These results may be regarded as sound in view of

the large number of patients in our treatment groups and the findings by Oparil et al.¹¹ and Weir et al.¹³ Similarly, the results of both questionnaires regarding the increased incidence of swelling and edema with amlodipine agree with the findings of these two studies.^{11,13}

Where significant differences between treatment groups are lacking, the reliability, validity, and sensitivity of the instruments used for detecting changes, as well as the sample size, should be considered. The number of patients in this study was sufficiently large to confirm the findings of Oparil et al.¹¹ and Weir et al.¹³ concerning swelling and edema. Tolerability of the three treatment regimens was similar with regard to many of the other symptoms examined.

Blood pressure reductions were similar in all three treatment groups. Analysis of the two subgroups comprising comparable patients without dosage adjustment (L 50/50 and A 5/5) shows comparable efficacy of monotherapy with losartan 50 mg once daily and amlodipine 5 mg once daily.

Treatment had to be adjusted in approximately 50% of the patients in each treatment group because of inadequate response. Failure of both study drugs to reduce diastolic blood pressure to <90 mm Hg in half the patients at the initial doses suggests that a stepped increase in dose will likely remain necessary in the future.

Combination therapy with two or more antihypertensive drugs is presently regarded as good practice if increasing the dose of the initial drug is not expected to result in additional improvement and if the drugs have different modes of action but similar pharmacokinetic characteristics. These prerequisites are met by the combination of losartan and HCTZ. Losartan has a shorter half-life than HCTZ but is converted to its active metabolite E-3174, which has a longer half-life.²⁴ Hence, the pharmacokinetics of the two antihypertensive components are comparable. Losartan given concomitantly with HCTZ leads to a further marked reduction in blood pressure that is related to the dose of HCTZ administered.¹⁵ The requirement that adverse events with the individual drugs be reduced or neutralized by the combination therapy to achieve better compliance is also met. The typical diuretic-induced changes—a decrease in serum potassium and an increase in blood uric acid—are neutralized by the concomitant administration of losartan and HCTZ.¹⁴ The low daily dosage of HCTZ (12.5 mg) improves the adverse-effect profile of the diuretic in combination with losartan 50 mg.²⁵ Previous studies have shown combinations of losartan 50 mg with HCTZ 12.5 mg^{11,13-15} or 25 mg^{11,13,14} to be effective and well tolerated.

At the onset of antihypertensive monotherapy, consideration should be given as to which regimen will be the most effective and best tolerated; if the response to the initial therapy is unsatisfactory, the decision must be made to increase the dose of the original drug or to initiate combination therapy. In such cases losartan in combination with HCTZ proved to be as

effective as but better tolerated than amlodipine. Increasing the dose of amlodipine was associated with an increased incidence of edema.

The incidences of drug-related clinical adverse events with losartan in this study and in other studies^{11,12,14-18,26} were either comparable to or lower than those of comparative drugs such as amlodipine,¹¹ felodipine,^{12,20} enalapril,^{10,18} nifedipine,¹³ captopril,¹⁷ and atenolol.^{16,20} The incidences of drug-related clinical adverse events in the amlodipine group (26%) were significantly higher than in the losartan groups (19% and 18%) because of the higher incidence of swelling and edema in patients treated with amlodipine.

The most common clinical adverse events in our three treatment groups, as in other clinical trials,¹⁰⁻¹⁷ were swelling and edema, headache, and dizziness (Table IV). Of all clinical adverse events, only the incidence of dizziness was higher in the L 50/100 group (5%) than in the other two treatment groups (3% and 2% in the L/HCTZ group and A 5/10 group, respectively). The withdrawal rate was higher in the L 50/100 group (13%) than in the other two groups (5% and 6% in the L/HCTZ group and A 5/10 group, respectively), whereas in the study by Dahlöf et al,²⁶ which had the same study design, the withdrawal rate was higher in the amlodipine group than in the two losartan groups.

The efficacy and safety profile of losartan make it a desirable first-line antihypertensive drug. Once-daily dosing, good tolerability, and additive efficacy in combination with HCTZ offer many benefits for hypertensive patients.

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ANEXO No. 8

“Haemodynamic and metabolic effects of rilmenidine in hypertensive patients with metabolic syndrome X. A double-blind parallel study versus amlodipine”
Nicola De Lucaa, Raffaele Izzoa, Dario Fontanaa, Gianluigi Iovinoa, Luigi Argenzianoa, Carmine Vecchioneb and Bruno Trimarco.

Haemodynamic and metabolic effects of rilmenidine in hypertensive patients with metabolic syndrome X. A double-blind parallel study versus amlodipine

Nicola De Luca^a, Raffaele Izzo^a, Dario Fontana^a, Gianluigi Iovino^a, Luigi Argenziano^a, Carmine Vecchione^b and Bruno Trimarco^{a,b}

Objective To compare the effects of rilmenidine with those of amlodipine on blood pressure, glucose metabolism, plasma lipid concentration and fibrinolysis parameters.

Design A four-month randomized double-blind, parallel group study.

Patients and methods Obese hypertensive patients with hypertriglyceridaemia (≥ 2.3 mmol/l) and impaired glucose tolerance (OMS-ADA) were included ($n = 52$). A placebo run-in period of 2 weeks was followed by 4 months of double-blind treatment with either rilmenidine or amlodipine. Blood pressure was recorded using a mercury sphygmomanometer. Glucose metabolism was evaluated by an oral glucose tolerance test.

Results Of the 52 patients recruited, 47 (21 rilmenidine and 26 amlodipine) completed the 4-month treatment period. The intention-to-treat analysis showed a comparable reduction in systolic and diastolic blood pressure (SBP, DBP) with the two anti-hypertensive treatments (rilmenidine $-13.9/-13.5$ mmHg; amlodipine $-17.6/-15.0$ mmHg). Insulin concentrations under basal conditions and 2 h after a standard oral glucose load did not change significantly after treatment in both groups. Plasma glucose under basal conditions and 2 h after a standard oral glucose load as well as the area under the plasma glucose concentration curve tended to decrease in the

rilmenidine group and to increase in the amlodipine group so that the changes in these parameters were significantly different between the two study groups ($P = 0.041$, $P = 0.042$ and $P = 0.015$, respectively). Plasminogen activator inhibitor type 1 (PAI-1) antigen and PAI-1 activity were only decreased in the rilmenidine group (not statistically significant).

Conclusion Our results demonstrate that rilmenidine and amlodipine have a comparable anti-hypertensive effect but only rilmenidine is able to improve glucose metabolism. *J Hypertens* 18:1515–1522 © 2000 Lippincott Williams & Wilkins.

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Keywords: imidazoline receptors, insulin resistance, obesity, plasminogen activator inhibitor type 1, PAI-1

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Introduction

One of the reasons for the marginal efficacy of anti-hypertensive treatment in mild hypertension is its inability to reduce the increased incidence of coronary events in hypertension [1,2]. Epidemiological and clinical evidence documents a close association between hypertension, obesity, impaired glucose tolerance or non-insulin-dependent diabetes mellitus, and dyslipidaemia [3–7]. In particular, Reaven *et al.* [8] have described as 'metabolic syndrome X' the combination of these pathological conditions. Therefore, it has been suggested that the dissociation between blood pressure-lowering and reduction of coronary risk may be due to

the co-existence of these additional coronary risk factors, which are not controlled by anti-hypertensive therapy. Although the pathogenic interactions between metabolic disorders and hypertension are still unclear, it has been hypothesized that an abnormal sympathetic response to physiological stimuli may induce insulin resistance which in turn serves as a common causative mechanism linking these pathological conditions [9,10]. As a consequence, anti-hypertensive treatments that reduce the sympathetic response could also have effects on the metabolic abnormalities of hypertensive patients with metabolic syndrome X.

In order to test this hypothesis, we performed the present study to compare the anti-hypertensive efficacy and the clinical and metabolic effects of rilmenidine, a

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selective I1 imidazoline receptor binding agent, and the calcium channel blocker, amlodipine, in patients with mild to moderate essential hypertension, android obesity, impaired glucose tolerance and hypertriglyceridaemia.

Methods

Study design

This single-centre study was performed according to a randomized double-blind parallel-group protocol with the primary objective of assessing the blood pressure changes over a 4 month treatment period. Secondary end-points were the clinical and metabolic tolerability of the two treatments. The study protocol was approved by the Ethics Committee of the University of Naples, and informed written consent was required from all participants.

Study population

The size of the study population required was estimated in terms of supine diastolic blood pressure (suDBP). Twenty-two patients per group were required to allow detection of a 6 mmHg difference between the treatment groups in the change in suDBP, with a type 1 error of 0.05 and a power of 0.80 (two-tailed test).

Patients of either sex, aged 21–70 years, were eligible for inclusion if they satisfied the following criteria: mild-to-moderate essential hypertension ($95 \leq \text{suDBP} \leq 114$ mmHg, $140 \leq \text{supine systolic blood pressure (suSBP)} \leq 210$ mmHg) at selection and confirmed at the inclusion visit, and with a variation in suDBP ≤ 10 mmHg over the 2 week placebo run-in period, android obesity (body mass index (BMI) ≥ 29

kg/m² and waist-to-hip ratio ≥ 0.85 in men and ≥ 0.75 in women) [10], hypertriglyceridaemia (fasting plasma triglycerides > 2.3 mmol/l) and impaired glucose tolerance (fasting plasma glucose ≥ 6.3 and < 7.8 mmol/l or plasma glucose 2 h after oral glucose tolerance test (OGTT) ≥ 7.7 and < 11.1 mmol/l).

Patients with clinical or laboratory evidence of any of the following conditions were excluded: renal insufficiency (serum creatinine level > 180 $\mu\text{mol/l}$), hepatic disease (transaminase levels $>$ twice the upper normal limit), congestive heart failure (New York Heart Association class II–IV), severe hypertension or secondary hypertension, any severe progressive concomitant disease, or known allergy to rilmenidine or amlodipine.

Study implementation

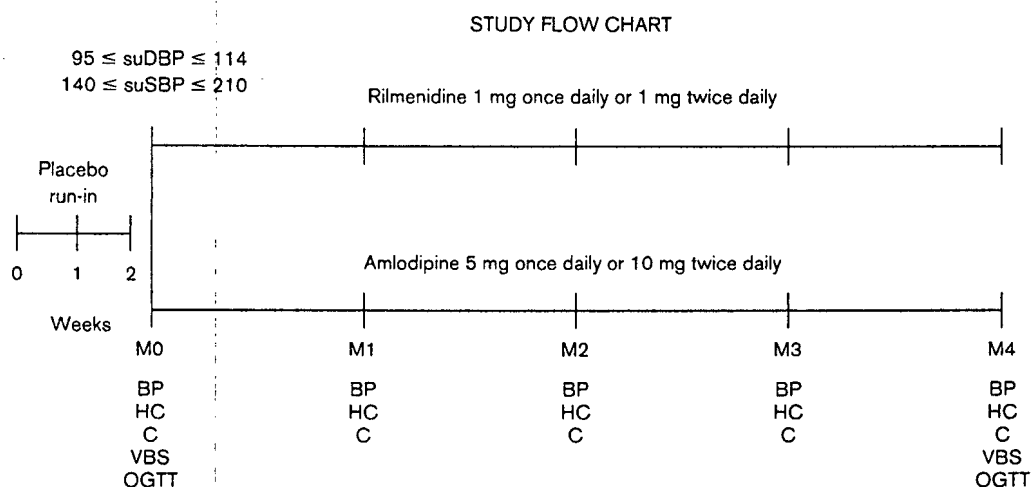
Following a 2 week placebo run-in period, patients were randomly assigned to treatment with either rilmenidine 1 mg once daily or amlodipine 5 mg once daily in a double-blind fashion. The study treatments and placebo were supplied as capsules identical in appearance, smell and taste. Compliance with study medications was monitored by counting returned capsules.

Use of all concomitant anti-hypertensive medications, insulin, oral hypoglycaemic drugs, medications containing phenytoin, monoamine oxidase inhibitors, tricyclic anti-depressants, corticosteroids, oestrogens or thyroid hormones was forbidden during the trial.

Practical conduct of the study (Fig. 1)

All patients were started on placebo, one tablet daily, taken during breakfast. Blood pressure was measured at

Fig. 1



Study flow chart. M0, inclusion visit; M1, visit after treatment for 1 month; M2, visit after treatment for 2 months; M3, visit after treatment for 3 months; M4, visit after treatment for 4 months; BP, blood pressure; HR, heart rate; C, compliance with treatment; VBS, venous blood sample for assessment of glucose, glycosylated haemoglobin, high-density lipoprotein and low-density lipoprotein cholesterol, tryglicerides, apoproteins A₁ and B, insulin; OGTT, oral glucose tolerance test

the end of placebo period. Patients were reviewed at monthly intervals during the active treatment period and blood pressure was measured during each visit and at the end of the treatment period. For blood pressure non-responders (diastolic blood pressure (DBP) > 90 mmHg), dose adjustment was allowed from the M1 visit (to rilmenidine 1 mg twice daily or amlodipine 10 mg once daily). Blindness was maintained by adding one capsule of placebo in the morning in the rilmenidine group and one capsule of placebo in the evening in the amlodipine group.

An suDBP > 114 mmHg or suDBP > 95 mmHg on two consecutive visits were grounds for withdrawal from the study.

At the end of the placebo run-in and after the 4 month treatment period, venous blood was collected for the evaluation of metabolic and fibrinolytic parameters, and an oral glucose tolerance test was carried out.

Blood pressure and heart rate measurements

Systolic blood pressure (SBP) and DBP were defined as Korotkoff phase I and V respectively, and were recorded at each visit, using a mercury sphygmomanometer. Measurements were made in triplicate and in the same arm throughout the study. Blood pressure and heart rate were recorded after 10 min rest in the supine position, and after 2 min standing. The means of the three supine values and the three standing values were used in the efficacy analysis.

Metabolic investigations

An oral glucose tolerance test (OGTT) was carried out at M0 and M4 with patients pre-fasted for 12 h. Venous blood samples were taken at baseline and 30, 60, 90 and 120 min after ingestion of the glucose load (75 g in 250 ml of water in less than 5 min). The following parameters were assessed:

- (1) $T_{\max}$: the times from glucose ingestion (T_0) to maximum plasma levels of glucose and insulin, within 2 h of ingestion (T_{120});
- (2) $C_{\max}$: maximum plasma levels between T_0 and T_{120} ; and
- (3) AUC from T_0 to T_{120} : the area under the concentration-time curve was calculated by the linear trapezoidal rule for plasma glucose and plasma insulin; patients with any missing value (T_0 , T_{30} , T_{60} , T_{90} , T_{120}) were not included in the analysis.

The plasma glucose level was measured in duplicate by the glucose oxidase method on a Beckman Glucose Analyzer (Beckman, Fullerton, California, USA), and insulin level by a radio-immunoassay with a commercial kit (Incstar, Sorin, Saluggia Italy).

Fasting blood samples were taken for glycosylated haemoglobin (HbA_{1c}), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides and apoproteins A₁ and B before performing each OGTT.

Fibrinolytic parameters

Blood samples were obtained by individual venepuncture or via a butterfly device. Samples were placed immediately on ice, and plasma was separated by centrifugation at 3000 g for 30 min. Plasma was stored at -80°C until assayed for tissue plasminogen activator (tPA) antigen, plasminogen activator inhibitor type 1 antigen (PAI-1 antigen) and activity (PAI-1 activity).

The tPA antigen and PAI-1 antigen were measured by enzyme-linked immunosorbent assays from Diagnostica Stago (Asserachrom®, Nantes, France). PAI-1 activity was determined using chromogenic kits from Biopool Laboratories (Spectrolyse®, Stockholm, Sweden).

Statistical analysis

The Statistical Analysis System (SAS Institute Inc., Cary, North Carolina, USA) software was used. All results are expressed as the mean $\pm$ standard deviation for continuous variables and as percentages for dichotomous or polytomous variables. The analyses were performed according to the intention-to-treat (ITT) approach. In this approach, all randomized patients who had taken at least one dose of study medication and who were evaluated at least once under treatment were included in the analysis. Treatment effects on blood pressure throughout the 4 months were compared in the ITT population using a two-tailed Student *t*-test for independent samples. The number of normalized patients (suDBP < 90 mmHg) at the last evaluation under treatment was compared in the ITT population using the χ^2 test.

To take into account baseline values of glucose and insulin parameters, a covariance analysis of the variation (M4 - M0) adjusted on M0 value was performed. A two-tailed Student *t*-test for independent samples was carried out to compare treatment effects on the other metabolic parameters.

Results

Patient populations

A total of 52 patients (28 men, 24 women) were included. The ITT analysis was performed on 51 patients as one patient in the rilmenidine group (R group) stopped treatment before the M1 evaluation.

Their baseline characteristics were as follows: age = 52.1 ± 8.8 years; weight = 85.2 ± 12.1 kg; body mass index (BMI) = 31.59 ± 2.71 kg/m² (Table 1). Comparison of the two patient populations showed that more

Table 1 Demographic baseline characteristics

	Rilmenidine (n = 25)	Amlodipine (n = 27)
Age (years)	50.8 ± 9.1	53.3 ± 8.5
Weight (kg)	83.4 ± 13.3	86.9 ± 11
Male sex (%)	40.0	66.67
BMI (kg/m ²)	31.33 ± 2.05	31.84 ± 3.23
Waist/hip ratio	1.01 ± 0.01	1.01 ± 0.02
Smoking (%)	36	7.4

Values are means ± standard deviation; BMI, body mass index.

women were included in the rilmenidine group (R: 60%; A: 33.3%). The other baseline clinical characteristics of the groups at randomization were well matched (Tables 2–6).

Table 2 Mean change in blood pressure (mmHg) between M0 and the last evaluation under treatment up to M4: inter-group comparison

Variables	Rilmenidine (n = 24)	Amlodipine (n = 27)
SuDBP (M0)	98.5 ± 4.1	98.5 ± 3.6
ΔsuDBP (M4* – M0)	–13.5 ± 4.4	–15.0 ± 5.0
StDBP (M0)	98.5 ± 3.5	98.5 ± 4.3
ΔstDBP (M4* – M0)	–13.5 ± 4.8	–14.4 ± 6.6
SuSBP (M0)	151.8 ± 11.8	154.1 ± 11.4
ΔsuSBP (M4* – M0)	–13.9 ± 13.7	–17.6 ± 9.7
StSBP (M0)	150.4 ± 11.9	153.1 ± 11.4
ΔstSBP (M4* – M0)	–11.3 ± 14.5	–15.4 ± 10.1

Values are means ± standard deviation; suDBP, supine diastolic blood pressure; stDBP, standing diastolic blood pressure; suSBP, supine systolic blood pressure; stSBP, standing systolic blood pressure; M0, inclusion visit; M4*, last visit up to 4 months of treatment. There were no statistically significant differences between groups.

Table 3 Dose required in ITT population (percentage of the population)

	Rilmenidine (n = 24)		Amlodipine (n = 27)	
	1 mg	2 mg	5 mg	10 mg
M0	100%	0%	100%	0%
M1	50%	50%	63%	37%
M2	46%	54%	63%	37%
M3	38%	62%	50%	50%

M0, inclusion visit; M1, visit after treatment for 1 month; M2, visit after treatment for 2 months; M3, visit after treatment for 3 months.

Table 4 Oral glucose tolerance test; mean change in glucose parameters between M0 and M4. Comparison between groups

Plasma glucose	Rilmenidine		Amlodipine		P values
	M0 (n = 24)	M4 (n = 20)	M0 (n = 27)	M4 (n = 26)	
Fasting glucose (mmol/l) M0	5.51 ± 1.06	5.29 ± 1.37	5.40 ± 0.96	5.70 ± 1.33	0.041
M4 – M0		–0.21 ± 0.75		0.32 ± 0.9	
T ₁₂₀ glucose (mmol/l) M0	9.36 ± 0.85	8.53 ± 1.31	8.91 ± 0.93	8.78 ± 1.38	0.042
M4 – M0		–0.81 ± 0.88		–0.16 ± 1.08	
C _{max} glucose (mmol/l) M0	10.03 ± 1.06	9.31 ± 1.50	9.66 ± 1.16	9.84 ± 1.43	0.009
M4 – M0		–0.72 ± 1.18		0.23 ± 1	
AUC (mmol/l/120 min) M0	1105.4 ± 138.28	1043.66 ± 183.09	1049.33 ± 137.7	1073.79 ± 163.16	0.015
M4 – M0		–67.13 ± 133.57		29.55 ± 100.7	

Values are means ± standard deviation; M0, inclusion visit; M4 – M0, difference after treatment for 4 months.

Forty-seven out of 51 patients completed the 4-month treatment. One patient (R group) was lost to follow-up after M3; three patients (two R group, one A group) left the study for non-medical reasons. One of the 24 patients in the R group was not assessed for technical reasons for the OGTT test at M4.

Blood pressure

The main blood pressure criterion was the change in suDBP between M0 and either M4 or the last recorded value on active treatment. Both rilmenidine and amlodipine reduced blood pressure (supine and standing, systolic as well as diastolic) to a similar degree (Table 2). Rilmenidine reduced suSBP/suDBP respectively from 152 ± 12/98.5 ± 4.1 to 138 ± 10/85 ± 4.9 mmHg and amlodipine from 154 ± 11/98.5 ± 3.6 to 137 ± 8/83.5 ± 4.6 mmHg. Twenty-three of 24 patients on rilmenidine and 25 of 27 patients on amlodipine were normalized (suDBP ≤ 90 mmHg) at M4 or the last visit prior to M4. The required doses of the two study drugs are shown in Table 3.

Metabolic and hormonal parameters

Body weight

Body weight remained stable in both groups (R: before 83.4 ± 13.3/after 83.0 ± 13.5 kg; A: before 86.9 ± 11/after 87.2 ± 10.7 kg).

Glucose and insulin parameters

There was no significant change in fasting glycosylated haemoglobin (HbA_{1c}%) during the study in both groups (R: 5.66 ± 1.13/5.67 ± 1.23%; A: 5.55 ± 1.0/5.55 ± 0.97%).

Figures 2 and 3 show plasma glucose and insulin levels during OGTTs. Fasting plasma glucose concentration was only decreased in the R group (R: –0.21 ± 0.75 mmol/l; A: 0.32 ± 0.9 mmol/l), the mean reduction in the R group was statistically significant in comparison to that in the A group after 4 months of treatment (P = 0.041). Similarly, after 4 months of

Table 5 Oral glucose tolerance test: mean change in insulin parameters between M0 and M4. Comparison between groups

Plasma insulin	Rilmenidine		Amlodipine		P values
	M0 (n = 24)	M4 (n = 20)	M0 (n = 27)	M4 (n = 26)	
Fasting insulin (pmol) M0	68.8 ± 49.3	63.5 ± 42.8	88.4 ± 61.1	92.3 ± 106.1	NS
M4 – M0		–8.2 ± 60		2 ± 124	
T ₁₂₀ insulin (pmol) M0	483.3 ± 272.2	394.6 ± 214.9	381.0 ± 178.5	383.8 ± 158.7	NS
M4 – M0		–103.2 ± 220.8		7.2 ± 228.7	
C _{max} insulin (pmol) M0	542.3 ± 256.4	456.4 ± 224.8	485 ± 158.1	436.6 ± 181.0	NS
M4 – M0		–107.7 ± 168.7		–48.1 ± 180.0	
AUC (pmol/l/120 min) M0	44541.9 ± 22975.2	38604.8 ± 21613.8	40395 ± 12605.9	35411 ± 15165	NS
M4 – M0		–8508 ± 13579		–4977.1 ± 18089.8	

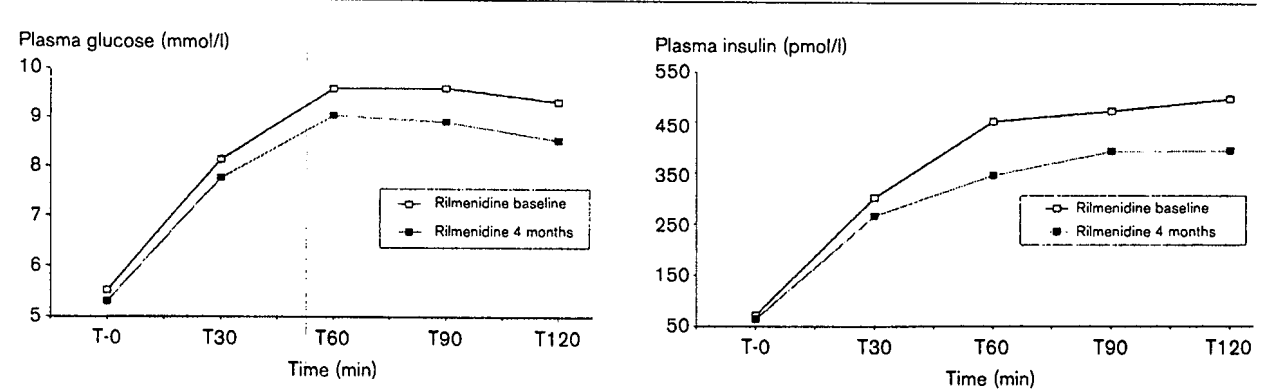
Values are means ± standard deviation; M0, inclusion visit; M4 – M0, difference after treatment for four months. NS, not significant (*P* > 0.05).

Table 6 Fibrinolytic parameters: inter-group comparison of baseline values and treatment effects

Parameters	n	Rilmenidine	n	Amlodipine
Fibrinogen (g/l) M0	23	3.12 ± 0.68	27	3.18 ± 0.61
M4 – M0	20	–0.16 ± 0.43	26	–0.20 ± 0.45
PAI-1 antigen (ng/ml) M0	23	32.03 ± 22.95	27	32.89 ± 34.9
M4 – M0	20	–8.03 ± 15.83	25	–1.07 ± 15.57
PAI-1 activity (IU/ml) M0	23	13.10 ± 10.49	27	11.20 ± 9.79
M4 – M0	20	–4.02 ± 9.29	24	–0.26 ± 8.77
t-PA antigen (ng/ml) M0	23	8.7 ± 2.42	27	8.88 ± 3.31
M4 – M0	20	–0.31 ± 3.47	25	–0.28 ± 2.85

PAI-1, plasminogen activator inhibitor type 1; t-PA, tissue plasminogen activator; M0, inclusion visit; M4 – M0, difference after treatment for 4 months. There were no statistically significant differences between groups.

Fig. 2



Plasma glucose and insulin levels before and during an oral glucose tolerance test (OGTT) at baseline and after 4 months of rilmenidine in 20 hypertensive patients with syndrome X.

treatment, the T₁₂₀ glucose response was significantly (*P* = 0.042) decreased in the R group (–0.8 ± 0.88 mmol/l) compared to the A group (–0.16 ± 1.08 mmol/l).

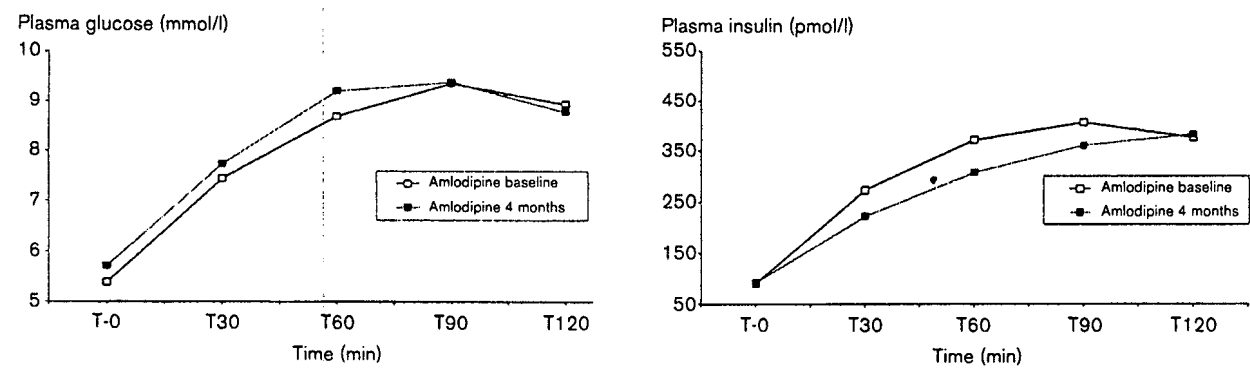
The fasting plasma insulin concentration and the T₁₂₀ plasma insulin concentration only tended to decrease in

the R group. The difference between groups was not statistically significant.

The trends in glucose and insulin responses (AUC, C_{max}) during the OGTTs are shown in Tables 4 and 5.

The plasma glucose AUC and plasma glucose C_{max}

Fig. 3



Plasma glucose and insulin levels before and during an oral glucose tolerance test (OGTT) at baseline and after 4 months of amlodipine in 26 hypertensive patients with syndrome X.

decreased significantly in the R group. A reduction in plasma glucose AUC between M0 and M4 was only observed in the R group compared to the A group (R: -67.13 ± 133.57 mmol/l; A: $+29.55 \pm 100.7$ mmol/l; $P = 0.015$). Similarly, the C_{max} decreased by 0.72 mmol/l in the R group while in the A group it was increased by 0.23 mmol/l.

There was a non-significant decrease in insulin AUC and insulin C_{max} in both groups.

Fibrinolytic parameters

The changes in fibrinogen, PAI-1 antigen, PAI-1 activity and t-PA antigen are detailed in Table 6. PAI-1 antigen was decreased more in the R group than in the A group (R: -25% ; A: -3%) and PAI-1 activity was only decreased in the R group (R: -30% ; A: $+2\%$).

Fibrinogen and t-PA antigen decreased in both groups but without any statistical significance.

Lipid parameters

The changes in lipid parameters were not significantly different between treatment groups (Table 7).

Tolerance

Forty-seven out of 52 patients completed the study. One patient in the R group stopped treatment only 6 days after inclusion because of diarrhoea and dizziness. One patient in the R group developed somnolence after 3 months of treatment. These adverse events were not thought to be drug-related.

In the A group, one patient developed leg oedema from M3, this event was considered possibly drug-related.

Table 7 Lipid parameters: inter-group comparison of baseline values and treatment effects

Parameters	n	Rilmenidine	n	Amlodipine
Serum total cholesterol (mmol/l) M0	24	5.23 ± 0.63	27	5.56 ± 0.74
M4 - M0	21	0.08 ± 0.71	26	0.08 ± 0.67
HDL cholesterol (mmol/l) M0	24	1.24 ± 0.15	27	1.16 ± 0.22
M4 - M0	21	0.02 ± 0.2	26	-0.007 ± 0.26
LDL cholesterol (mmol/l) M0	24	3.26 ± 0.62	27	3.33 ± 0.70
M4 - M0	21	0.18 ± 0.76	26	0.14 ± 0.73
Triglycerides (mmol/l) M0	24	2.50 ± 0.49	27	2.34 ± 0.36
M4 - M0	21	-0.25 ± 0.64	26	-0.11 ± 0.66
Apo A ₁ (g/l) M0	24	1.61 ± 0.272	27	1.56 ± 0.18
M4 - M0	21	-0.03 ± 0.22	26	-0.005 ± 0.26
Apo B (g/l) M0	24	1.24 ± 0.19	27	1.25 ± 0.26
M4 - M0	21	0.06 ± 0.27	26	0.06 ± 0.22

There were no statistically significant differences between groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A₁, apoprotein A₁; Apo B, apoprotein B.

No serious adverse events were reported during the study.

Discussion

The observation that, at the doses used in our study, rilmenidine and amlodipine show comparable anti-hypertensive efficacy is in keeping with the results of previous studies. In hypertensive patients treated with rilmenidine, the reduction in blood pressure was similar in magnitude to that induced by the other main classes of anti-hypertensive drugs [11–14]. However, the ability to reduce blood pressure is the main but not the only parameter that must be taken into account in the choice of the therapeutic regimen. In particular, it has been reported that some anti-hypertensive drugs may exert a negative effect on glucose and lipid metabolism [15], while others have no effect on these parameters [16], or may even improve insulin sensitivity [17,18]. It has been demonstrated that amlodipine does not modify plasma glucose concentration or insulin levels [19]. Our results confirm these previous reports, and show that even taking into account baseline values in glucose and insulin metabolic parameters, there is a statistically significant difference between the changes found, over the 4 month anti-hypertensive treatment, in both fasting and post-glucose load plasma glucose concentrations in the two study groups. This finding seems to suggest a positive effect of rilmenidine on glucose metabolism. The lack of difference in the effects of the two pharmacological treatments on glycosylated haemoglobin may be ascribed to the fact this parameter is characterized by a low sensitivity to changes in plasma glucose concentration.

Our study protocol does not allow any definite conclusion to be made on the mechanisms underlying such a metabolic effect of rilmenidine. In fact, glucose levels are controlled by more factors than insulin alone, so that, at the population level, fasting plasma insulin levels correlate better than post-glucose insulin concentration with the components of the insulin resistance syndrome [20]. However, the finding that both fasting and post-glucose load plasma glucose concentrations are lower in rilmenidine-treated patients as compared to the amlodipine group, in the absence of any increase in plasma insulin level, may support the conclusion that rilmenidine improves insulin sensitivity in hypertensive patients. Such a possibility would be in keeping with the results of studies in an animal model of insulin resistance, the fructose-fed rat, showing a favourable metabolic effect of rilmenidine [21], which may be accounted for by its ability to reduce sympathetic activity [22] or by the capacity to increase the concentration of IRS-1, an intracellular factor essential for insulin-mediated activation of glucose disposal, as shown by another selective imidazoline binding agent [23].

Furthermore, while not statistically different, the decrease in the fibrinolytic parameters PAI-1 antigen and activity was only seen in the rilmenidine group.

Whether or not the theoretical potential positive effect of rilmenidine on this cardiovascular risk factor will translate into tangible long-term clinical advantages for patients with metabolic syndrome X needs to be assessed in specifically designed studies. However, on the available evidence, rilmenidine seems to be a logical choice rather than a calcium channel blocker for the treatment of these at-risk populations.

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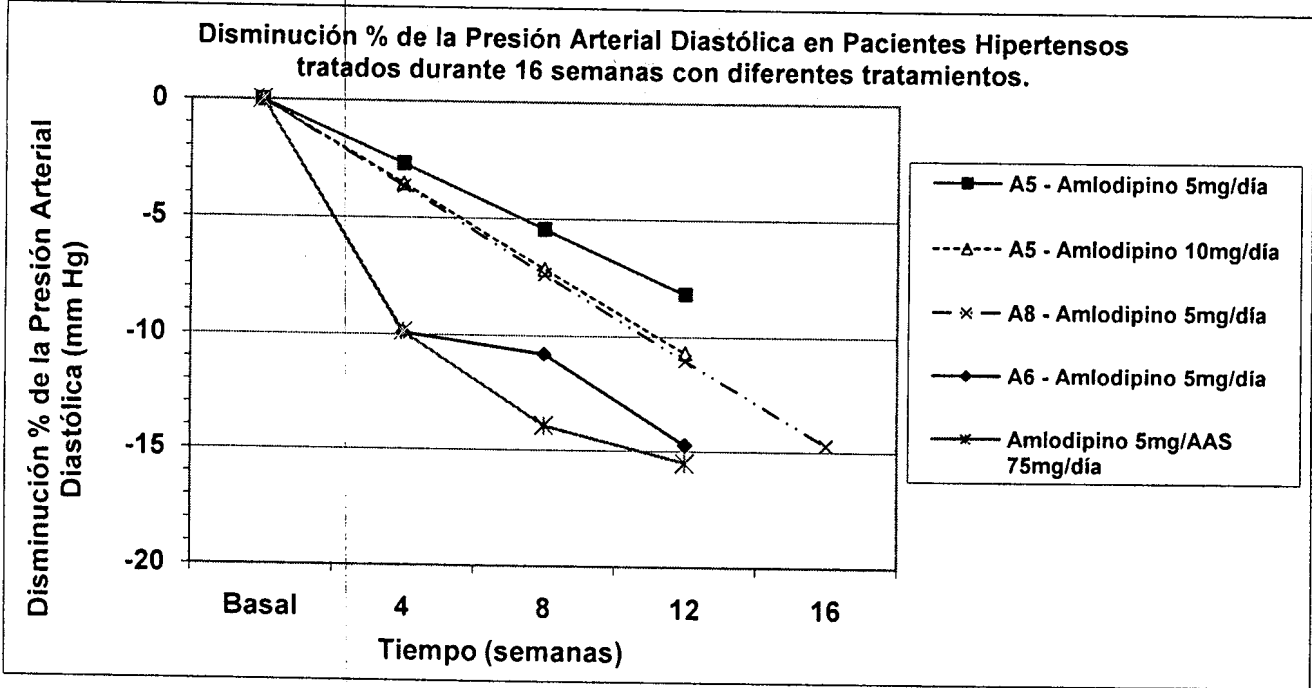
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ANEXO No. 9

Graficas de la PAS y la PAD

Disminución % de la Presión Arterial Diastólica Tratamiento	Semanas de Tratamiento				
	Basal	4	8	12	16
A5 - Amlodipino 5mg/día	0	-2,7	-5,4	-8,17	
A5 - Amlodipino 10mg/día	0	-3,6	-7,1	-10,7	
A8 - Amlodipino 5mg/día	0	-3,7	-7,4	-11,0	-14,7
A6 - Amlodipino 5mg/día	0	-9,92	-10,8	-14,7	
Amlodipino 5mg/AAS 75mg/día	0	-9,89	-13,9	-15,5	



ANEXO No. 10

Gráficas comparativas de la eficacia terapéutica de la combinación de la presente invención comparada con los estudios referidos arriba como anexos 5, 6 y 8.

Efecto Terapéutico (Normalidad en la PAD o disminución de la presión en 10 o mas mm Hg).

PAD - Presión Arterial Diastólica

Tratamiento	Semanas de Tratamiento				
	Basal	4	8	12	16
A5 - Amlodipino 10mg/día	0,0%	58,0%	71,0%	84,0%	
A8 - Amlodipino 5mg/día	0,0%	23,1%	46,3%	69,4%	92,6%
A6 - Amlodipino 5mg/día	0,0%	30,1%	60,2%		
Amlodipino 5mg/AAS 75mg/día	3,3%	76,3%	87,5%	94,4%	

