

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
ALICIA LLOREDA RICAURTE

ASUNTO Radicación 09 020 350
 Trámite 011
 Evento 378
 Actuación 519
 Oficio
 Folios 016

E 13985

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒		
Vía PCT (Fase Nacional)	☒	Capítulo I	☒
		Capítulo II	☐
No. Solicitud Internacional	PCT/US2007/074997		
Fecha de Presentación Internacional	01/Agosto/2007		

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 83 a 110	27/Febrero/2009
Reivindicaciones:	Folios 111 a 113	27/Febrero/2009
	Folios 136 a 138	08/Junio/2009
	Folios 142 a 144	10/ Junio/2009
Dibujos (figuras):	Folios 115 a 116	27/Febrero/2009
Oposiciones:	Folios 147 a 163	Lafrancol 19/Julio/2010
Prioridad:	US 60 823,868	29/Agosto/2006

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "USO DE TENECTEPLASA PARA TRATAR UN ICTUS ISQUÉMICO AGUDO".

El problema planteado en esta solicitud consiste en la necesidad de suministrar un método para mejorar la respuesta clínica en el ictus isquémico agudo, por ejemplo aumentando el flujo sanguíneo agudo cerebral y/o reduciendo el tamaño del infarto, con tenecteplasa (FI.90, pág. 8).

Para resolver este problema técnico la solicitud en estudio proporciona un proceso para preparar un medicamento y un producto de acuerdo a las reivindicaciones (FIs. 142 a 144).

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 38/16, A 61 P 9/10.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 1 – 16 no es patentable de acuerdo con el Art citado, porque se refiere a métodos terapéuticos, aunque las reivindicaciones se encabecen con la expresión "El proceso..." estas se caracterizan por la administración de dosis de tenecteplasa, principio activo que ya es conocido en el estado de la técnica en el documento: "TENECTEPLASA informe para la comisión de Farmacia y Terapéutica, Francesc Puigventós, Ana Escrivá, Pere Ventayol, 30-9-2001" y en el artículo "A pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke", E. Clarke Haley et al., Febrero de 2005; en donde se divulgan las mismas dosis usadas en la presente invención para ser administradas durante un tratamiento terapéutico en un tiempo determinado.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La Reivindicación 1 y sus dependientes 2 a 16, se refieren a un proceso para preparar un medicamento pero dicho proceso se caracteriza por la administración de la tenecteplasa en diferentes dosis en un tiempo de 50 a 90 minutos y no por las etapas, reactivos y condiciones (como tiempo de reacción, temperatura, agitación etc.) a las cuales se debe realizar; además en la descripción no existe evidencia de un proceso para preparar un medicamento sino lo que se observa son protocolos de métodos terapéuticos (págs.8, 9, 15) y de administración de dosis (pág. 22 y 25), del tenecteplasa solo así como de éste y otro activo, por ejemplo un agente antitrombótico, un anticuerpo antiCD18 (págs. 14 y 15), administrado antes, después o al mismo tiempo que la Tenecteplasa.

La reivindicación 25 se refiere a un producto de acuerdo con las reivindicaciones 17 a 24 (composición), que comprende un segundo fármaco que es un agente antitrombótico, un antagonista de la glicoproteína IIb/IIIa o un anticuerpo antiCD18, pero de esta composición no existe soporte porque lo que se observa en la descripción es la administración del tenecteplasa y otro principio activo como los mencionados (págs. 14 y 15) administrado antes, después o al mismo tiempo que el tenecteplasa.

6. Análisis de la Oposición

Argumentaciones de Lafranco

Afirma el oponente que esta solicitud pretende obtener patente para composiciones
Expediente 09 020 350 1er Art 45

farmacéuticas y los métodos de tratamiento, sin perjuicio de que no puedan ser protegidos, que ya son conocidos mundialmente en el sector farmacéutico desde hace un tiempo considerable en el documento WO9324635 (FI.155).

Respuesta del Examinador Técnico

El documento presentado en la Oposición sí desvirtúa la Novedad del objeto de esta solicitud; por lo cual si se considerará dentro del Examen de Patentabilidad.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la Solicitud de Prioridad: Agosto 29 de 2006 y se encontró el siguiente documento que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	WO9324635	Tissue plasminogen activator glycosylation variants with improved Therapeutic properties	Diciembre 9 de 1993

D1 divulga el compuesto Tenecteplasa t-PA TNK y sus composiciones.

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 17 consiste en un producto que comprende:

- a) un envase que contiene tenecteplasa;
- b) instrucciones para usar la tenecteplasa para tratar el ictus isquémico agudo en humanos mediante la administración de tenecteplasa al humano en una dosis total de aproximadamente 0,05 a 0,5mg/Kg, que se administra mediante (a) administración en embolada de una dosis inicial de aproximadamente 0,005 a 0,15mg/kg, seguida de la infusión de una cantidad igual la dosis total menos la dosis inicial durante un período de tiempo de aproximadamente 50 a 90 minutos, o b) mediante administración en embolada.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
un producto que comprende	Composiciones que comprenden
un envase que contiene tenecteplasa	un envase que contiene tenecteplasa

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual enseña composiciones en forma de soluciones estériles o polvos estériles, tal como proteína liofilizada, que contienen tenecteplasa (pág. 27, líneas 15 a 20).

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

Adicionalmente, se recuerda que la solicitud de protección mediante patente de un kit de partes, como lo es esta reivindicación, sólo puede ser considerada cuando el centro de la invención es una composición o combinación nueva de dos o más compuestos conocidos para una finalidad terapéutica específica y el producto será comercializado en forma de kit (denominado también como envase médico, estuche o empaque).

Las reivindicaciones dependientes 18 – 24 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9324635	17-24	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

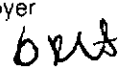
Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

17/4 AGO. 2012

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

Elaborado por: Lyna del Carmen Mordecay Dunoyer
Revisado Por: Gloria Jacqueline Alfonso Rozo
Aprobado por: José Luis Salazar López. 

TENECTEPLASA

Informe para la Comisión de Farmacia y Terapéutica
 Francesc Puigventós, Ana Escrivà, Pere Ventayol
 30-9-2001

SOLICITUD: Dr. Miquel Fiol (UCI). 5-07-01.

PRESENTACIONES: Metalyse vial 40 mg (8000 unidades), Metalyse vial 50 mg (10000 unidades). Lab Boehringer Ingelheim

Coste para el hospital (P.V.L -2% descuento+4 % de IVA). Metalyse 40 mg: 175.302 pts, Metalyse 50 mg: 180.398 pts.

GRUPO TERAPEUTICO: B01AD. Agentes antitrombóticos.

AREA DE ACCION FARMACOLOGICA

Indicaciones clínicas: Tratamiento trombolítico de sospecha de infarto de miocardio con elevación ST persistente o bloqueo reciente del haz de rama izquierda, en las 6 horas siguientes a la aparición de síntomas de infarto de miocardio (IAM).

Mecanismo de acción: Tenecteplasa (TNK-tPA) es un agente fibrinolítico, activador tisular del plasminógeno, de estructura polipeptídica similar a Alteplasa (tPA), de la que se diferencia estructuralmente en tres posiciones de los aminoácidos. Se obtiene de células de ovario de hamster chino mediante técnicas de DNA recombinante. Respecto a alteplasa presenta mayor duración de acción, mayor especificidad a la fibrina y mayor resistencia al inhibidor del activador del plasminógeno.

Posología: Se administra en vía intravenosa directa en bolus de 10 segundos, en dosis única y lo antes posible después del inicio de los síntomas. En función del peso corporal se indica:

Peso corporal (Kg)	Dosis
<60	30 mg (6000 U)
>=60 a < 70	35 mg (7000 U)
>=70 a < 80	40 mg (8000 U)
>=80 a < 90	45 mg (9000 U)
> 90	50 mg (10000 U)

Farmacocinética

	tPA	TNK-tPA
Semivida	3,5 h	17 h
Aclaramiento plasm.	572 ml/min	151 ml/min
Excreción	hepática	hepática

EVALUACION DE LA EFICACIA:

El ensayo clínico ASSENT-II (Lancet 1999, Llevadot JAMA 2001) se diseñó para establecer la equivalencia de eficacia y evaluar la seguridad entre alteplasa y tenecteplasa. Es un ensayo doble ciego aleatorizado. Participaron 16949 pacientes de 1021 hospitales y 29 países. Se midió la mortalidad a los 30 días, y las complicaciones hemorrágicas.

Los resultados globales de eficacia muestran **equivalencia** de ambos tratamientos, la mortalidad a los 30 días fue de 6,15 % en los que recibieron tPA y de 6,18 % en los que recibieron TNK-tPA. (tabla 1)

Tabla 1. Estudio ASSENT-II: 16.949 pacientes de 1021 hospitales y 29 países

Eficacia				
	tPA	TNK-tPA	p	NNT
Mortalidad 30 días	6,18 %	6,15 %	(*)	--
Mortalidad o AVC no mortal	7,05 %	7,11 %	ns	--
Mortalidad subgrupo que se inicia tto pasadas más de 4 h	9,2 %	7,0 %	0,018	45,4

*no diferencias con p=0.006 para test de equivalencia

En el análisis de subgrupos del ASSENT-II se observa que tenecteplasa es más eficaz que alteplasa en los pacientes en que la administración se realiza después de las 4h: En este subgrupo, la mortalidad valorada a los 30 días es de 7,0 % con tenecteplasa vs 9,2 % con alteplasa (p: 0,018). El NNT es de 45.4 (tabla 1).

-Recientemente se ha publicado el estudio ASSENT-3 (Lancet 2001) en que participan 6095 pacientes. En el estudio TNK.tPA asociada a heparina no fraccionada se presentó una mortalidad a los 30 días de 6,0 % y TNK.tPA asociada a enoxaparina del 5,4 % , datos similares a los del estudio ASSENT-2. El avance de resultados del estudio ENTIRE (resultados preliminares 2001), el TNK-tPA también asociado a enoxaparina presenta una mortalidad a los 30 días es de 2,5 % comparado con 4,1 % con heparina no fraccionada. (tabla 2)

Tabla 2. Eficacia, medida como mortalidad a los 30 días. Resultados en la ramas de los EECC con heparina no fraccionada.			
	Estreptokinasa	tPA	TNK-tPA
GUSTO-1 (1993)	7,4 %	6,3%	--
GISSI-2 (1992)	9,2 %	9,3%	--
ISIS-3 (1992)	10,6%	10,3%	--
ASSENT-2 (1999)	--	6,15	6,18 %
ASSENT-3 (2001)	--	--	6,0 %

EVALUACIÓN DE LA SEGURIDAD

El punto básico es la evaluación del aumento de riesgo de hemorragias asociado a la terapia trombolítica. Se consideran las hemorragias intracraneales y las hemorragias no cerebrales (mayores y menores).

-El estudio ASSENT-II (Lancet 1999) muestra que no hay diferencias significativas entre tPA y TNK-tPA en la presentación de hemorragias intracraneales, ni en hemorragias no cerebrales menores. El perfil es favorable a TNK-tPA en hemorragias no cerebrales mayores y en este caso el NNH (número necesario a tratar para evitar un daño) es de 78,1. (tabla 3)

Tabla 3. ASSENT-II. 16949 pacientes de 1021 hospitales y 29 países				
Seguridad				
	tPA	TNK-tPA	p	NNH
Hemorragia intracraneal	0,94 %	0,93 %	ns	--
Complicaciones hemorrágicas no cerebrales totales	28,95 %	26,43 %	0,0003	39,7
-Complicaciones hemorrágicas no cerebrales mayores	5,94%	4,66 %	0,0002	78,1
-Complicaciones hemorrágicas no cerebrales menores	22,99 %	21,76%	ns*	--

*P=0,0553

-Recientemente se ha publicado el estudio Assent-3 (Lancet 2001). En dicho estudio TNK-tPA asociada a heparina no fraccionada produjo hemorragia intracraneal en el 0,93 % y TNK-tPA asociada a enoxaparina en el 0,88% de los pacientes, datos similares a los del estudio ASSENT-2. Las complicaciones hemorrágicas mayores no cerebrales en ASSENT-3 fueron de 2,2 %, es decir menores que el 4,7 % del ASSENT-2 . (ver tabla 3 y 4)

-El estudio TIMI-10B (Circulation 1998) mostró que a la dosis de 50 mg, TNK-tPA se asoció a mayores hemorragias intracraneales severas que tPA. De aquí la importancia de dosificar de forma ajustada al peso del paciente, tal como indica el informe técnico, así como ajustar la dosis de heparina.

Tabla 4. Seguridad. Hemorragias intracraneales. Resultados en las ramas de los EECC con heparina no fraccionada.			
	Estreptokinasa	tPA	TNK-tPA
GUSTO-1 (1993)	(0,5 %)	(0,9%)	--
GISSI-2 (1992)	(0,3%)	(0,4%)	--
ISIS-3 (1992)	(0,25%)	(0,72%)	--
ASSENT-2 (1999)	--	(0,94%)	(0,93%)
ASSENT-3 (2001)	--	--	(0,93%)

-Un metanálisis de 7 ensayos clínicos publicados (Mehta, Lancet 2000) evalúa el riesgo de hemorragia intracraneal de distintos trombolíticos, concluyendo que hay un aumento de riesgo cuando se administra en bolus respecto a cuando se administra en infusión: 0,8 % vs 0,6 % con una OR de 1,25 (p: 0.003). Otro metaanálisis publicado recientemente muestra resultados similares, con mayor riesgo para la terapia trombolítica en bolus (Eikelboom JW, JAMA 2001)

-Por subgrupos, los pacientes con mayor riesgo de hemorragia intracraneal por trombolíticos son (Braunwald 2001): edad: 65-74 años (OR=2,71); edad >75 años (OR=4,34), sexo mujer (OR=1,59), historia de ACV (OR=1,79) y hipertensión sistólica (OR=1,48).

En relación con lo anterior, Ohman (Chest 2001) señala que en los pacientes de más de 75 años hay una tendencia a reducción de la hemorragia intracraneal con TNK-tPA (1,7 %) vs tPA (2,6%), y también en otro grupo de alto riesgo, es decir las mujeres ancianas de menos de 67 Kg : TNK-tPA (1,1%) vs tPA (3%) (Ohman Chest 2001), sin embargo estos estudios no están completamente publicados.

Por otro lado no hay estudios comparativos con estreptokinasa, cuyo riesgo de hemorragia intracraneal es menor en comparación a tPA (GUSTO 1, tabla 4). Todo ello hace que en pacientes ancianos y otros de alto riesgo deban considerarse los riesgos potenciales del TNK-tPA.

Recomendaciones de elección de fibrinolítico:

-Magnum Ohman (Chest 2001) en una revisión sistemática que incluye niveles de evidencia y grados de recomendación propone en los pacientes con IAM candidatos a fibrinolítico:

- menos o igual 6h desde inicio de síntomas: alteplasa o tenecteplasa (1A)
- menos o igual 12 h desde inicio de síntomas: estreptokinasa, anistreplasa o alteplasa (1A)
- pacientes con alergia o sensibilidad a estreptokinasa: alteplasa o tenecteplasa (1C)

-Braunwald 2001, valora el riesgo de muerte y de hemorragia intracraneal en cada grupo de pacientes y propone:

- menos o igual a 4 horas desde inicio síntomas: Alteplasa o Tenecteplasa
- menos o igual a 4 horas desde inicio síntomas en pacientes jóvenes, con IM inferior menor y hipertensión: estreptokinasa o alteplasa
- de 4 a 12 horas desde inicio de los síntomas en ancianos con IM inferior y hipertensión y frecuencia cardíaca <100: estreptokinasa

EVALUACION ECONOMICA:

Coste tratamiento. Comparación entre tPA y TNK-tPA

La dosis de Tenecteplasa se ajusta al peso del paciente. El coste de un paciente medio de 70-75 Kg es de 175.302 ptas, lo que significa un incremento de 3058 ptas por paciente respecto a la terapia actual con tPA. Si consideramos que en el caso de alteplasa se precisa de sueros y equipo para su administración se deberían incrementar unas 300 ptas aprox. por paciente.

Peso corporal (Kg)	Tenecteplasa (Metalyse)			Alteplasa (Actylise)			Diferencia
	Dosis	Viales	Coste	Dosis	Viales	Coste	
<60	30 mg (6000 U)	1 de 40 mg	175.302	15-45-30 (90 mg)	2	172.244	3058
>=60 a < 70	35 mg (7000 U)	1 de 40 mg	175.302	15-50-35 (100 mg)	2	172.244	3058
>=70 a < 80	40 mg (8000 U)	1 de 40 mg	175.302	15-50-35 (100 mg)	2	172.244	3058
>=80 a < 90	45 mg (9000 U)	1 de 50 mg	180.398	15-50-35 (100 mg)	2	172.244	8154
> 90	50 mg (10000 U)	1 de 50 mg	180.398	15-50-35 (100 mg)	2	172.244	8154

Coste-eficacia incremental.

La eficacia es similar, pero TNK-tPA presenta menos hemorragias no cerebrales mayores, así como menor necesidad de transfusión de sangre. Para evitar una complicación hemorrágica mayor el NNH es de 78,1 y el coste incremental para evitar que un paciente una complicación hemorrágica mayor no intracraneal es del orden de 238.906 ptas.

Peso del paciente (kg)	Coste TNK-tPA	Coste tPA	NNH	Coste incremental para evitar una hemorragia no cerebral mayor
70 Kg	175.302	172.244	78.1	238.906

En los pacientes que se inicia tratamiento de Tenecteplasa después de 4 horas, la eficacia es mayor que con alteplasa, con un NNT de 45.4. Para conseguir una unidad de eficacia adicional (una muerte menos) en este subgrupo de pacientes el coste incremental es del orden de 138.833 ptas.

Peso del paciente (kg)	Coste TNK-tPA	Coste tPA	NNT	Coste incremental para evitar una muerte *
70 Kg	175.302	172.244	45.4	138.833

*Nota: el coste incremental respecto a estreptokinasa, según datos de eficacia del GUSTO-1 que compara con tPA y del que resulta un NNT de 91, es de aproximadamente de 14.800.000 ptas.

Estimación del número de pacientes año candidatos al tratamiento en H. Son Dureta y coste estimado anual. Estimación del impacto económico global para el hospital.

Nº de pacientes. En base al consumo de Actylise de los últimos 12 meses (Agosto 2000 a Julio 2001) que es de 119 viales, se puede estimar que se tratan unos 60 pacientes anuales con terapia trombolítica del IAM. aproximadamente 15.000.000 ptas con pocas diferencias de coste adicional respecto a tPA.

Nº de pacientes estimado	Coste aprox por paciente (65-75 Kg)	Coste anual
60 + 25 (procedentes de EECC) = 85 pacientes	175.302	14.900.670

* Gasto año 2000: ptas

Nº de pacientes estimado año 2002	Coste adicional por paciente (65-75 Kg)	Coste adicional anual global de los 85 pacientes
60 + 25 (procedentes de EECC)	3.058 ptas	260.000 ptas

RESUMEN:

Medicamento equivalente terapeutico de tPA, con eficacia, seguridad y coste similares, y que presenta mayor facilidad y rapidez de administración:

-Eficacia: Similar a Alteplasa: No hay aumento de eficacia, ya que la mortalidad a los 30 días pasa de 6,18% a 6,15 % sin diferencias estadísticas significativas.

-Seguridad: Menor producción de hemorragias mayores 4,7 % vs 5,9 %. Igual riesgo de hemorragias intracraneales y hemorragias menores. Un metanálisis indica un mayor riesgo de hemorragias intracraneales de los fibrinolíticos administrados en bolus, no confirmado por el estudio comparativo directo entre tPA y TNK-tPA. En todo caso habrá que tener, igual que con tPA, precaución en pacientes de riesgo de hemorragia intracraneal, básicamente los mayores 75 años.

-Comodidad de Administración: Su administración en bolus facilita su correcto uso y su administración precoz respecto a Alteplasa. No precisa de bomba de infusión y supone un consumo menor en horas de enfermería. Facilita la reperfusión y el tratamiento posterior en pacientes con infarto agudo de miocardio

-Coste: El coste de Tecneplasa y Alteplasa es similar. Impacto económico menor. El coste para el hospital del uso de tenecteplasa se estima en 175.302 pts por tratamiento, aproximadamente 3.058 ptas más que con alteplasa convencional.

-Esquema propuesto:

-Tenecteplasa: pacientes con IAM en que este indicado tratamiento trombolítico con menos de 6 horas desde inicio de síntomas. Considerar tenecteplasa o estreptokinasa en pacientes con menos de 12 horas desde el inicio de los síntomas.

-Estreptoquinasa: Pacientes con IAM en que este indicado tratamiento trombolítico de más de 6 y 12 horas desde inicio de síntomas. Pacientes con más de 12 horas desde inicio de síntomas.

CONCLUSIONES:

- Valorar Incluir Tenecteplasa como terapia de elección en todos los pacientes con IAM en que este indicado tratamiento trombolítico, de menos de 75 años y 6 horas desde inicio de los síntomas.
- Considerar la administración de estreptoquinasa en aquellos pacientes entre 6 y 12 horas desde inicio de síntomas, y en mayores de 75 años.

- Solicitar adaptar el protocolo de IAM, con criterios de inclusión, exclusión inicial en función de la edad (>75 años) y si son pacientes con más de 6/12 horas desde inicio de síntomas.
- Mantener Alteplasa para tratamiento de la embolia pulmonar, indicación no aprobada hasta el momento de tenecteplasa

BIBLIOGRAFIA:

- Varios autores (Cartas): Intracranial haemorrhage with thrombolytic agents. Lancet , 2000, 356: 1848-1850
- Cannon CP et al: TNK-Tissue plasminogen activator compared with front-loaded alteplase in AMI. Results of TIMI 10B trial. Circulation 1998; 98: 2805-2814.
- ASSENT-2 investigators: Single-bolus tenecteplase compared with front-loaded alteplase in AMI, the ASSENT-2 double-blind randomised trial. Lancet 1999; 354: 716-22
- Mehta S et al: Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. Lancet 2000; 356: 449-54
- LLevadot J et al: Bolus fibrinolytic therapy in acute myocardial infarction. JAMA 2001, 286:442-449.
- Informe tecnico Lab Boehringer Ingelheim
- Assent-3 investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001; 356:605-13
- Magnus Ohman E: Intravenous thrombolysis in acute myocardial infarction. Chest 2001; 119: 253S-277S
- Micromedex Drug Dex 2001
- Eikelboom JW Safety outcomes in meta-analyses of phase 2 vs phase 3 randomized trials. intracranial hemorrhage in trials of bolus thrombolytic therapy. JAMA 2001, 285:444-450
- Baunwald : Heart disease, a textbook of cardiovascular medicine 6 ed 2001 (disponible en Md-consult)

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



A Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke E. Clarke Haley, Jr, Patrick D. Lyden, Karen C. Johnston, Thomas M. Hemmen and the TNK in Stroke Investigators

Stroke. 2005;36:607-612; originally published online February 3, 2005;

doi: 10.1161/01.STR.0000154872.73240.e9

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2005 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/36/3/607>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

A Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke

E. Clarke Haley Jr, MD; Patrick D. Lyden, MD; Karen C. Johnston, MD; Thomas M. Hemmen, MD; the TNK in Stroke Investigators*

Background and Purpose—Recombinant tissue-type plasminogen activator (rtPA) is the only approved treatment in acute ischemic stroke. However, intracerebral hemorrhage (ICH) occurs in 6.4% of patients treated with rtPA and limits its use. Tenecteplase (TNK) is a modified form of rtPA, with longer half-life and greater fibrin specificity. Patients after myocardial infarction had fewer systemic hemorrhages when treated with TNK compared with rtPA. This open-label, dose-escalation safety study was conducted to develop initial experience with TNK in the treatment of ischemic stroke.

Methods—Eligible patients were treated with an intravenous bolus infusion of TNK within 3 hours of stroke onset. The dose escalation was conducted in tiers of 25 patients, starting at 0.1 mg/kg, to a planned maximum of 0.6 mg/kg. The primary endpoint was symptomatic intracranial hemorrhage within 36 hours of treatment. All patients were followed-up for 3 months.

Results—Eighty-eight (88) patients were treated in 4 dosing tiers. In the first 3 tiers (0.1, 0.2, 0.4 mg/kg) of 25 patients each, no symptomatic and 2 (8%), 8 (32%), and 7 (28%) asymptomatic ICHs occurred. Enrollment into the fourth tier at 0.5 mg/kg was closed after 2 of 13 patients (15%) had symptomatic and 3 (23%) had asymptomatic ICHs. Overall, modified Rankin scores at 3 months were similar to those of historical controls treated with rtPA and not significantly different between treatment groups.

Conclusions—TNK doses of 0.1 to 0.4 mg/kg are safe in ischemic stroke. Future trials are needed to compare the effect of TNK on neurological outcome and safety as compared with rtPA. (*Stroke*. 2005;36:607-612.)

Key Words: ischemic stroke ■ tenecteplase ■ tissue plasminogen activator ■ thrombolytic therapy

Ischemic stroke remains a major public health problem in the United States and the world.¹ Despite approval of recombinant tissue-type plasminogen activator (rtPA) for treatment of patients with acute ischemic stroke within 3 hours of onset, use of this therapy remains limited, even among patients who reach medical attention within the time window, largely because of concerns regarding associated hemorrhagic complications.² Moreover, even with timely treatment, up to 40% of patients may remain severely disabled or die,³ leaving substantial room for improvement.

Tenecteplase (TNK) is a genetically engineered mutant tissue plasminogen activator that has a longer half-life, is more fibrin-specific, and is more resistant to plasminogen activator-1 than rtPA.⁴ In patients with myocardial infarction, doses of ~0.5 mg/kg administered as an intravenous bolus resulted in similar mortality rates but with less systemic bleeding than in patients treated with front-loaded rtPA.⁵ Symptomatic intracranial hemorrhage rates were similar in the 2 groups. These findings led to Food and Drug Administration approval of TNK for treatment of patients with acute

myocardial infarction. In animal models of acute ischemic stroke, hemorrhagic conversion of experimental infarcts was less frequent with TNK than equipotent doses of rtPA, although the differences did not reach statistical significance.^{6,7} Peripheral bleeding was less with TNK.

In December 1999, an initial pilot dose-escalation safety study of TNK in patients with acute ischemic stroke was funded. This open-label, single-arm trial was designed to test the hypothesis that TNK could be administered safely to patients with acute ischemic stroke within 3 hours of onset at doses that may be associated with improvement in clinical neurological outcome.

Patient Selection and Study Design

The inclusion and exclusion criteria for this study are summarized in Table 1 and were designed to be nearly identical to those used for the National Institutes of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial.¹ All patients underwent pretreatment head computerized tomography (CT) scanning to exclude hemorrhage. The protocol and

Received August 11, 2001; final revision received October 25, 2001; accepted November 10, 2001.

From the Department of Neurology (E.C.H., K.C.J.), University of Virginia Health System, Charlottesville, Va, and the Department of Neuroscience (P.D.L., T.M.H.), University of California at San Diego.

* See Appendix 2 online at <http://www.strokeaha.org> for list of participating investigators.

Correspondence to Dr E. Clarke Haley, Jr., Department of Neurology, Box 800394, University of Virginia Health System, Charlottesville, VA 22908. Ph: 434-924-8041, Fax: 434-982-1726. E-mail: ech@virginia.edu

© 2005 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000154872.73240.e9

TABLE 1. Inclusion and Exclusion Criteria**Inclusion criteria**

- Ischemic stroke with serious measurable deficit on NIH Stroke Scale
- Treatment within 3 hours of stroke onset
- Age 18 years or older

Exclusion criteria

- Minor stroke symptoms, or major symptoms rapidly improving
- Intracranial hemorrhage on pretreatment head CT scan
- Clinical presentation suggesting subarachnoid hemorrhage
- Pregnancy
- Known bleeding diathesis and/or platelet count $<100\,000$, or taking oral anticoagulants. Patients who have received heparin within 48 hours must have a normal partial thromboplastin time.
- Major surgery or serious trauma within 14 days; serious head trauma within 3 months
- Gastrointestinal or urinary tract hemorrhage within 21 days
- Arterial puncture at a noncompressible site or lumbar puncture within 7 days
- Systolic blood pressure >185 mm Hg, diastolic blood pressure >110 mm Hg
- Clinical stroke within 3 months or history of intracranial hemorrhage
- Other serious medical illness likely to interfere with treatment or treatment might adversely affect that illness
- Concomitant myocardial infarction or postmyocardial infarction pericarditis
- Seizure at stroke onset
- Confounding pre-existent neurological or psychiatric disease
- Any other investigational drug within 14 days
- Large areas (greater than one lobe) of obvious low density on baseline head CT scan
- Unlikely to complete the protocol follow-up
- Patients for whom informed consent cannot be obtained

consent form used for this study were reviewed and approved by each participating hospital's institutional review board. Eligible patients were offered alternative treatment with intravenous tPA in every case.

The initial dose of TNK chosen for study was 0.1 mg/kg to be administered as a bolus. This dose was chosen to be bio-equivalent to the approved dose of tPA used for acute ischemic stroke based on lytic bio-equivalence studies conducted in a rabbit embolic stroke model.⁶ The planned number of patients to be enrolled in each dosage tier was 25. This number was chosen to provide 80% power of observing at least 1 symptomatic intracranial hemorrhage if the true symptomatic intracranial hemorrhage rate for TNK was 6.4% (the rate reported for tPA in the NINDS tPA Stroke Trial) or greater. No patient in any dosage tier was to receive more than that dose calculated for a 100-kg person. At the outset of the study, the maximum dose planned to be studied was 0.6 mg/kg, because doses above that level were associated with excessive bleeding in patients with myocardial infarction.⁸

After informed consent was obtained, a baseline National Institutes of Health Stroke Scale (NIH Stroke Scale) examination⁹ was performed, and patients were treated with TNK at the assigned dose calculated for their estimated body weight. After treatment, patients were monitored closely in either an

intensive care unit or an acute stroke care and monitoring unit where frequent blood pressure and neurological checks could be performed. Post-treatment elevations in blood pressure were managed as per guidelines developed in the NINDS tPA Stroke Trial.¹⁰ Antiplatelet and anticoagulant therapy were prohibited for 24 hours after treatment.

Patients were closely monitored for adverse events, particularly bleeding. Minor systemic bleeding (eg, gum bleeding, bleeding from shaving cuts or venipuncture sites) not requiring treatment beyond direct compression were distinguished from major bleeding (ie, causing hypotension, resulting in surgery, or requiring blood transfusion). Intracranial bleeding was classified as either asymptomatic or symptomatic (ie, associated with neurological worsening judged to be caused by the hemorrhage). All patients with clinically important neurological worsening underwent emergency head CT scanning and repeat NIH Stroke Scale examination. Additionally, all patients, whether they had neurological worsening, underwent follow-up head CT scanning at 48–6 hours after treatment to detect asymptomatic bleeding. All baseline and head CT scans were read by a central neuroradiologist, and hemorrhages were classified as either asymptomatic or symptomatic by consensus of the investigators (E.C.H. and P.D.L.) and an independent National Institutes of Health Data and Safety Monitoring Board (NIH DSMB).

Fibrinogen levels were obtained at baseline before treatment and at 2 and 24 hours. The assays were performed locally and are reported here as a percent change from baseline. Additionally, a TNK blood level was obtained at 1 hour after treatment. These specimens were immediately spun, separated, and frozen for shipment on ice to Genentech, Inc, where the assays were performed.

NIH Stroke Scale examinations were performed at baseline, 24 hours after stroke onset, at 7 to 10 days, and at 3 months. The Barthel Index,¹¹ modified Rankin Scale,¹² and Glasgow Outcome Scale¹³ were performed at 7 to 10 days and at 3 months. Ischemic stroke subtype, using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria,¹⁴ was assessed at day 7 to 10 using all clinical diagnostic studies available to date. Additionally, major neurological improvement, defined prospectively as an improvement of ≥ 8 points or a score of 0 on the NIH Stroke Scale at 24 hours, was monitored as a surrogate for drug activity.¹⁵

The cumulative safety experience from each dosage tier, including each case in which hemorrhage was detected on a follow-up head CT scan, was reviewed with the NIH DSMB before escalation to the next highest dose. The primary outcome of the study was the occurrence of symptomatic intracranial hemorrhage within 36 hours of treatment. Sequential alerting rules were in place to halt enrollment if observed symptomatic intracranial hemorrhage rates were inconsistent with a true rate of $\leq 6.4\%$.

Results

From July 8, 2000 to April 16, 2003, 88 patients were treated in 4 escalating dosage tiers: 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, and 0.5 mg/kg. The study was closed when 2 of 13 patients in the fourth tier sustained symptomatic intracranial hemorrhages within 36 hours of treatment.

TABLE 2. Baseline Characteristics

Variable	TNK Dose			
	0.1 mg/kg n = 25	0.2 mg/kg n = 25	0.4 mg/kg n = 25	0.5 mg/kg n = 13
Age, mean ± SD	67 ± 14	69 ± 11	72 ± 13	68 ± 13
Gender, no. (% female)	15 (60)	11 (44)	12 (48)	7 (54)
Race, no. (% non-white)	3 (12)	6 (24)	2 (8)	1 (8)
Baseline NIH Stroke Scale score, median (interquartile range, minimum-maximum)	12 (8–17, 4–28)	14 (9–20, 2–27)	10 (6–15, 3–28)	8 (6–15, 5–23)
Time from stroke onset to treatment, median in minutes (median, interquartile range)	145 (135–165)	150 (130–170)	158 (121–168)	154 (135–161)
Ischemic stroke subtype, no. (%)				
Large vessel atherosclerosis	1 (4)	6 (24)	3 (12)	1 (8)
Cardioembolic	10 (40)	7 (28)	12 (48)	4 (31)
Lacunar	4 (16)	2 (8)	1 (4)	2 (15)
Other	0 (0)	1 (4)	1 (4)	0 (0)
Unknown	10 (40)	9 (36)	8 (32)	6 (46)

Table 2 displays the baseline characteristics and day 7 to 10 ischemic stroke subtypes of the enrolled patients. The median baseline NIH Stroke Scale score varied from 8 to 14 across dosage tiers, and most patients were treated between 91 and 180 minutes from stroke onset.

Table 3 summarizes the bleeding complications encountered in the trial. No symptomatic intracranial hemorrhages were observed within 36 hours of treatment among any of the first 75 patients treated with 0.1 mg/kg, 0.2 mg/kg, or 0.4 mg/kg. As noted, 2 patients among the first 13 treated with 0.5 mg/kg sustained symptomatic hemorrhagic conversions (Figure) of their large cerebral infarctions within 36 hours of treatment. Both patients subsequently died: one after support was withdrawn per his pre-expressed wishes, and the other from presumed aspiration pneumonia at a local nursing home. The rate of asymptomatic intracranial hemorrhage detected on the protocol-required head CT scan at 48 hours ranged from 8% to 32%. Whereas the 8% were observed with the lowest dose, no dose-response trend was observed across the remaining dose tiers for asymptomatic hemorrhage alone. Many of the asymptomatic hemorrhagic changes noted were trivial (Figure). None occurred outside the area of the

clinically relevant infarct. One patient treated with 0.1 mg/kg and who had an asymptomatic hemorrhage noted on the 48-hour scan had a transient neurological worsening on day 5 after treatment. A repeat head CT scan at that time showed a small amount of subarachnoid extension of the blood into the insular cistern not present on the 48-hour scan. The relationship of the subarachnoid extension seen on the follow-up scan to the transient neurological worsening was not clear, nor was the extension clearly attributable to TNK treatment. When the incidence of symptomatic and asymptomatic intracranial hemorrhage within 48 hours is combined (ie, all intracranial hemorrhage), a trend toward increasing intracranial hemorrhage with increasing dose is noted. This trend was not seen with minor systemic bleeding. No major systemic bleeding was reported.

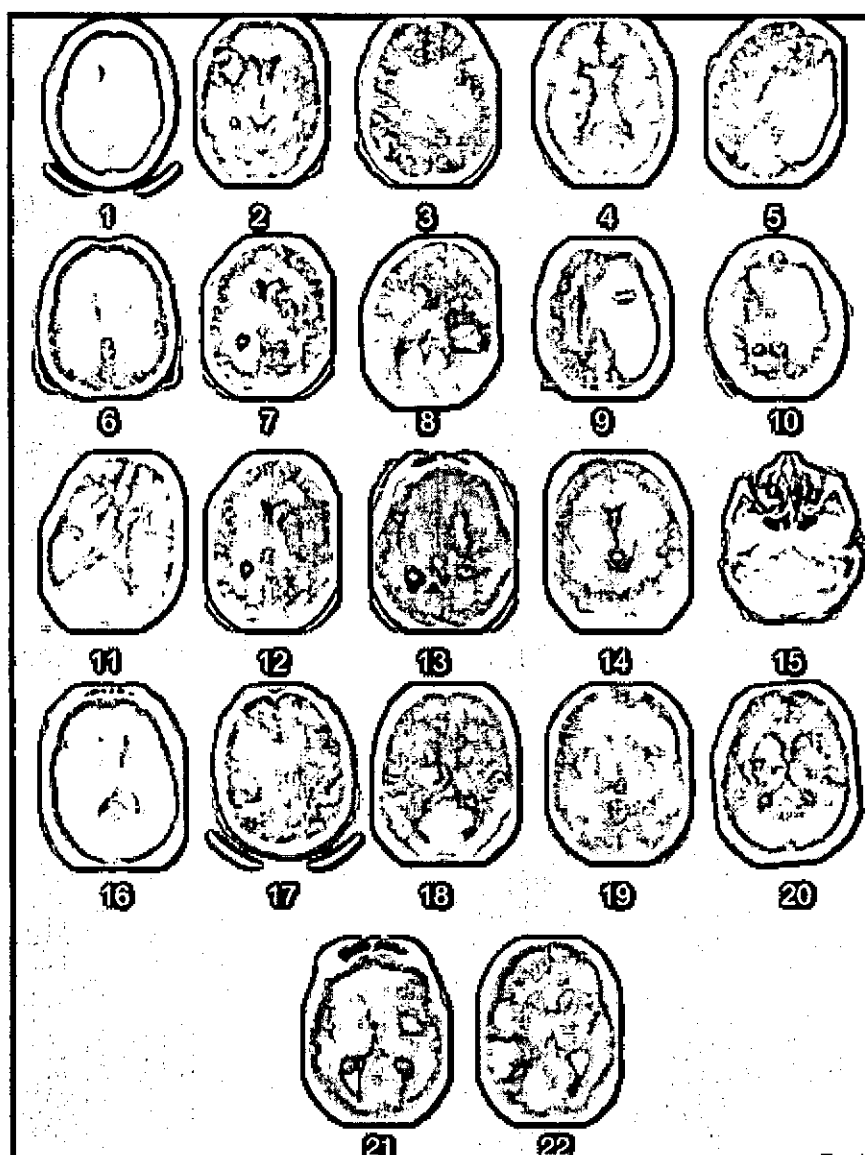
Fifteen patients (17%) died during the 3-month follow-up period of the study. Except for the 2 patients in tier 4 who died after their symptomatic intracranial hemorrhages, none of the deaths was attributable to TNK administration.

Serious adverse events (life-threatening or resulting in prolonged or recurrent hospitalization) were reported at rates similar to those of other ischemic stroke populations.¹⁶ Aside from the 2 symptomatic intracranial hemorrhages reported, only 1 additional serious adverse event was attributable to TNK administration. Serious oral-lingual angioedema developed requiring endotracheal intubation for airway protection within 1 hour of treatment with 0.5 mg/kg of TNK. The swelling subsided within 4 hours, and the patient was safely extubated without sequelae. This was presumed to be reaction to the medication. Most of the observed serious adverse events were events commonly seen in an ischemic stroke population.¹⁶

Table 4 summarizes the fibrinogen data and TNK blood levels. Because the measurements were made at the individual sites, as opposed to a central laboratory, the results are expressed as a percent change from baseline. Negative percent changes represent a decrease from baseline.

TABLE 3. Hemorrhage

	TNK Dose			
	0.1 mg/kg n = 25	0.2 mg/kg n = 25	0.4 mg/kg n = 25	0.5 mg/kg n = 13
Symptomatic ICH				
< 36 hours, no. (%)	0 (0)	0 (0)	0 (0)	2 (15)
Asymptomatic ICH				
< 48 hours, no. (%)	2 (8)	8 (32)	7 (28)	3 (23)
All ICH				
< 48 hours, no. (%)	2 (8)	8 (32)	7 (28)	5 (38)
Minor bleeding				
< 36 hours, no. (%)	4 (16)	10 (40)	9 (36)	3 (23)



Head CT scans from the 22 patients with intracranial hemorrhage observed within 48 hours of treatment with TNK. Scans 21 and 22 are from the 2 patients with neurological worsening attributed to the intracranial bleeding. Scans 1 and 2 are from tier 1; scans 3 to 10 are from tier 2; scans 11 to 17 are from tier 3; and scans 18 to 22 are from tier 4.

whereas positive percentages represent an increase. The data suggest a modest reduction of fibrinogen concentration at 2 hours that largely recovered by 24 hours. The mean percent decrease in 2-hour fibrinogen level increased with increasing dose and peaked at $16 \pm 17\%$ in the

0.4-mg/kg dose. Severe hypofibrinogenemia defined by a fibrinogen < 100 mg/dL did not develop. TNK blood levels at 1 hour after treatment ranged from a mean of 359 ± 146 ng/mL with 0.1 mg/kg to 1647 ± 732 ng/mL with 0.5 mg/kg. The 2 patients with symptomatic intracranial hem-

TABLE 4. Fibrinogen Changes and TNK Blood Levels

	TNK Dose			
	0.1 mg/kg n=25	0.2 mg/kg n=25	0.4 mg/kg n=25	0.5 mg/kg n=13
Percent Change in Fibrinogen at 2 Hours				
Mean $\pm$ SD	$-3 \pm 25\%$	$5 \pm 8\%$	$-16 \pm 17\%$	$-12 \pm 14\%$
No. (% reporting)	22 (88)	24 (96)	19 (76)	13 (100)
Percent Change in Fibrinogen at 24 Hours				
Mean $\pm$ SD	$3 \pm 35\%$	$3 \pm 25\%$	$-10 \pm 29\%$	$-11 \pm 17\%$
No. (% reporting)	24 (96)	23 (92)	20 (80)	13 (100)
TNK Blood Level at 1 Hour				
(ng/mL, mean $\pm$ SD)	389 ± 146	641 ± 240	$1,227 \pm 491$	1647 ± 732
No. (% reporting)	18 (72)	24 (96)	20 (80)	13 (100)

TABLE 5. Major Neurological Improvement at 24 Hours and Outcome at 3 Months

	TNK Dose				NINDS Trial	
	0.1 mg/kg n=25	0.2 mg/kg n=25	0.4 mg/kg n=25	0.5 mg/kg n=13	Placebo n=155	rtPA n=167
Major neurological improvement at 24 hours	9 (36)	6 (24)	4 (16)	3 (23)	26 (17)	45 (27)
Modified Rankin Scale score						
0 or 1 (minimal disability)	9 (36)	8 (32)	8 (32)	6 (46)	41 (26)	65 (36)
2 or 3 (mild to moderate disability)	9 (36)	8 (32)	6 (24)	4 (31)	39 (25)	35 (21)
4 or 5 (severe disability)	4 (16)	3 (12)	7 (28)	1 (8)	42 (27)	39 (23)
6 (death)	3 (12)	6 (24)	4 (16)	2 (15)	33 (21)	28 (17)

orrhage in tier 4 had 1-hour blood levels of 2000 and 2010 ng/mL, respectively.

Table 5 summarizes early major neurological improvement measured by the NIH Stroke Scale at 24 hours, as well as the 3-month clinical outcomes as measured by the modified Rankin Scale. No patients were lost to follow-up. In terms of early activity, there did not appear to be a dose response with major neurological improvement within 24 hours of treatment. The best results were observed with the 0.1-mg/kg dose (36%). In general, the 3-month outcomes followed the same trends as the early neurological improvement data, ie, that the best outcomes were observed with the 0.1-mg/kg dose, although none of the distributions was statistically significantly different across the 5-fold dose escalation. The Glasgow Outcome Scale, Barthel Index, and NIH Stroke Scale scores at 3 months showed similar trends (Appendix 1, available online only at <http://www.strokeaha.org>).

Discussion

This pilot dose-escalation safety study of TNK in patients with acute ischemic stroke demonstrated safety and tolerability of TNK at several doses. No symptomatic intracranial hemorrhages were observed among any of the 75 patients treated with 0.1 mg/kg, 0.2 mg/kg, or 0.4 mg/kg TNK, a 4-fold range of doses begun with a dose calculated to be bio-equivalent to the approved dose of rtPA for stroke. Whereas the upper bound of the 95% confidence interval surrounding 0 of 25 still includes 11%, the observed experience provides encouragement that TNK treatment of acute ischemic stroke at these doses may be safer than rtPA.

Enrollment in the study was stopped after 2 of 13 (15%) patients treated with 0.5 mg/kg sustained symptomatic intracranial hemorrhages within 36 hours of treatment. The decision to stop the study was not based solely on statistical grounds, although 2 of 12 hemorrhages would have crossed 1 of the prespecified statistical boundaries used as a guideline to potentially halt the study. There was concern with the apparent trend toward increasing intracranial hemorrhage (all intracranial hemorrhage) with increasing dose, and it was noted that increasing doses were not clearly associated with increasing clinical benefit, measured either by major neurological improvement at 24 hours or by 3-month outcome.

Moreover, further uncontrolled observations at the 0.5-mg/kg dose up to a total of 25 patients would have little likelihood of providing evidence of a safety advantage over rtPA and would potentially put more patients at risk if the true hemorrhage rate was close to the observed rate.

The incidence of asymptomatic intracranial hemorrhage observed in this study was higher than that reported in the NINDS rtPA Stroke Trial.¹ Two factors may help explain the apparent discrepancy. First, the CT scans checking for asymptomatic bleeding in the TNK study were obtained at 48 hours instead of 24 hours, as in the NINDS study. Previous studies of hemorrhagic conversion in infarction without thrombolysis have demonstrated that the incidence of CT-detectable hemorrhagic change increases over the first 7 to 10 days after the infarct, and may approach 40% if patients are followed-up long enough.¹⁷ Second, this study included so-called hyperdense cerebral infarction (ie, CT findings of a region of intermediate density between gray matter and blood within an area of infarction), as defined by the NINDS Study Group,¹⁸ with frank hemorrhagic changes. The rates from this study are thus more comparable to ECASS¹⁹ than to NINDS.

In terms of clinical benefit, this was an uncontrolled pilot safety study, so inferences regarding potential benefits of treatment compared with rtPA are necessarily limited. Table 5 summarizes reference results from the NINDS rtPA Stroke Trial, parts 1 and 2 combined, in patients treated from 91 to 180 minutes from onset. The results observed with TNK are comparable to those reported in the rtPA group and are generally better than those in the placebo group. These comparisons should be made cautiously, however, because there may be differences in the baseline characteristics of the patients in the 2 studies that may confound any comparisons. Nevertheless, the results from the TNK experience suggest, but do not prove, that doses from 0.1 mg/kg to 0.4 mg/kg may be equally or more effective than rtPA (particularly in reducing combined severe disability and death) and may be safer. A safer alternative to rtPA would be a welcome addition to the clinical armamentarium and would represent a significant medical advance, even within the 3-hour time window. Further studies comparing TNK to rtPA in patients with acute stroke are planned.

Acknowledgments

Supported by a grant (NS37666) from the National Institute for Neurological Disorders and Stroke—National Institutes of Health. Genentech, Inc. supplied tenecteplase and performed the tenecteplase blood level assays for this study. This work was presented, in part, at the 28th International Stroke Conference, February 13 to 15, 2003, Phoenix, Arizona.

References

- Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. *Lancet*. 2003;362:1211–1224.
- Am Academy of Emergency Medicine Work Group on Thrombolytic Therapy in Stroke. Position statement of the Am Academy of Emergency Medicine on the use of intravenous therapy in the treatment of stroke. Available at: www.aacem.org/positionstatements/thrombolytictherapy.shtml. Accessed January 21, 2002.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
- Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet*. 2002;41:1229–1245.
- Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomized trial. *Lancet*. 1999;354:716–722.
- Thomas GR, Thibodeaux H, Erent CJ, Badillo JM, Keyt BA, Refino CJ, Zivin JA, Bennett WF. A long-half-life and fibrin-specific form of tissue plasminogen activator in rabbit models of embolic stroke and peripheral bleeding. *Stroke*. 1994;25:2072–2079.
- Chapman DF, Lyden P, Lapchak PA, Nunez S, Thibodeaux H, Zivin J. Comparison of TNK with wild-type tissue plasminogen activator in a rabbit embolic stroke model. *Stroke*. 2001;32:748–752.
- Cannon CP, Gibson CM, McCabe CH, Adgey AAJ, Schweiger MJ, Sequeira RF, Grolhier G, Giugliano RP, Frey M, Mueller HS, Sleight RM, Weaver WD, Van de Werf F, Braunwald E for the Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction. Results of the TIMI 10B trial. *Circulation*. 1998;98:2805–2814.
- Lyden P, Brott T, Tilley B, Welch KMA, Mascha EJ, Levine S, Haley EC, Grotta J, Marder J, and the NINDS TPA Stroke Study Group. Improved reliability of the NIH Stroke Scale using videotraining. *Stroke*. 1994;25:2220–2226.
- The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. A systems approach to immediate evaluation and management of hyperacute stroke. Experience at eight centers and implications for community practice and patient care. *Stroke*. 1997;28:1530–1540.
- Mahoney FI, Barthel DW. Functional evaluation, the Barthel Index. *MD State Med J*. 1965;14:61–65.
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
- Teasdale G, Knill-Jones R, van der Sande J. Observer variability in assessing impaired consciousness and coma. *J Neurol Neurosurg Psychiatry*. 1978;41:603–610.
- Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke*. 1993;24:35–41.
- Brown DL, Johnston KC, Wagner DP, Haley EC. Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. *Stroke*. 2004;35:147–150.
- Johnston KC, Li JY, Lyden PD, Hanson SK, Feasby TE, Adams RJ, Faight RE, Haley EC for the RANTTAS Investigators. Medical and neurological complications of ischemic stroke. Experience from the RANTTAS Trial. *Stroke*. 1998;29:447–453.
- Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction: a prospective study. *Stroke*. 1986;17:179–185.
- The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997;28:2169–2118.
- Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.