SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
HUMBERTO RUBIO CAMACHO

ASUNTO	Radicación	08-115511
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	12142
	Folios	17

Patente de Invención ☐ Patente de Modelo de Utilidad ☐
Vía Nacional
Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐

No. Solicitud Internacional PCT/EP2007/003631
Fecha de Presentación Internacional 25/Abril/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 30 a 51	29/Octubre/2008
Reivindicaciones:	Folios 51 a 58	29/Octubre/2008
Oposiciones:	Folios 64 a 156	Procaps 01/Julio/2009
	Folios 157 a 168	Lafrancol 02/Julio/2009
Prioridad:	EU 06008850.7	28/Abril/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: "Combinación farmacéutica que comprende 3-(3-dimetilamino-1-etil-2-metilpropil) fenol y un NSAID"

El problema planteado en esta solicitud consiste en la necesidad de suministrar una combinación farmacéutica alternativa para el tratamiento del dolor, con un menor efecto secundario indeseable.

Para resolver este problema técnico la solicitud en estudio proporciona una combinación farmacéutica de 3-(3-dimetilamino-1-etil-2-metil-propil) fenol y un agente AINES para el tratamiento del dolor.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/137, A61K31/192, A61K31/196, A61P29/00.

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

El objeto de las reivindicaciones 32 a 34 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso (Art 14 D 486)

El uso de la reivindicación 30 y 31 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

Titulo

El título no corresponde con el objeto de la solicitud, por lo tanto se sugiere cambiar el título a "composiciones de tapentadol y un AINES como ibuprofeno o ketoprofeno".

Reivindicaciones (Art 30 D 486, Art 22 PCT)

- Las reivindicaciones no están redactadas con la siguiente estructura: preámbulo-conector-parte característica. La redacción de estas reivindicaciones no cumple con la estructura porque se encabezan así: lo reivindicado es, a continuación sigue un conector con problemas de traducción, en seguida una palabra que corresponde a la característica intrínseca o categoría de la invención, por ejemplo combinación; luego un segundo conector: que comprende y por último la definición de la materia.

  De acuerdo a lo anterior, se sugiere que el solicitante aporte un nuevo juego de reivindicaciones que no tenga problemas de traducción o errores de digitación y que se ajuste a la estructura preámbulo-conector- parte característica. El preámbulo es lo que identifica la categoría de invención (producto o procedimiento), el conector es por ejemplo "que comprende" y la parte característica es la que define el objeto de la invención en términos de sus elementos esenciales.

- Las reivindicaciones 1 y 12 no son claras porque el término "droga antiinflamatoria no esferoidal", para la abreviatura NSAID es incorrecto. Se sugiere corregir el significado de la sigla y la traducción porque en español es AINES, no NSAID.

- Los términos "CARACTIRIZADO" y "aniotica" en las reivindicaciones 1 y 12 y "acurdo" en la reivindicación 24 corresponden a errores en la traducción y en la digitación. Se sugiere corregir la escritura, redacción y la traducción del capítulo reivindicatorio para darle claridad.

- Las reivindicaciones 1 y 12 corresponden a una combinación, la cual no asegura un único sistema de entrega, dado que la reivindicación 1 no se encabeza como composición, además no hay sustento en el capítulo descriptivo de un sistema de entrega con dos fármacos. Por lo tanto se deduce que la invención es una asociación de los 2 principios activos

durante la administración al mismo tiempo, tal como se describe el folio 41, página 20. Se sugiere modificar las reivindicaciones y la descripción para que concuerden.

- El segundo ingrediente de la composición de las reivindicaciones 1 y 12, se define en términos de función (antiinflamatorio no esteroideo) y esto no es admisible. Es posible incluir la función que cumple el agente pero hay que definir los compuestos combinados por su denominación común internacional o por su nombre IUPAC.

- El termino "opcionalmente" reivindicaciones 1,12, 19, 25 y 26 es impreciso, lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso

- La reivindicación 1, 12 y 19 hacen referencia a un enantiómero y diasteroisómeros pero no se caracterizan dichos isómeros y tampoco están soportados en la descripción.

- Los términos "teniendo un grupo que es capaz de formar una sal con el componente a" en la reivindicación 12 y "fragmento" en la reivindicación 19 que hacen relación a la unión química entre 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol y un NSAID no son claros además no tienen soporte en la descripción.

- La reivindicación 29 abarca adicionalmente cafeína pero este fármaco no está soportado en la descripción. Se sugiere que se encabece la reivindicación en forma de composición que se relaciona a un solo sistema de entrega y no a la administración de una dosis. Adicionalmente se sugiere corregir la inconsistencia entre la descripción y la reivindicación porque solo hay sustento para combinaciones binarias, no para ternarias y de las binarias solo las que se combinan efectivamente.

- La selección del segundo componente para las combinaciones definidas en las reivindicaciones 5, 6, 7, 8 y 9 no se encuentran totalmente soportadas en la descripción, dado que los ejemplos de preparación solo incluyen AINES como el ketoprofeno y el ibuprofeno.

7. Análisis de las Oposiciones

Oposición de Procaps

Afirma el opositor que esta solicitud no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

De acuerdo con el señor opositor la solicitud carece de nivel inventivo porque el documento ES2304659 divulga en la página 8, línea 19 el compuesto 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para el tratamiento del dolor.

Frente al documento MX9701477 el señor opositor agrega que revela la combinación de agentes activos con AINES para el tratamiento del dolor, de hecho, asegura que a partir de la publicación se deriva la asociación de un AINES

con el compuesto 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para el tratamiento del dolor.

Oposición de Lafrancol

Dice el opositor que esta solicitud incumple los requisitos materiales de patentabilidad, porque la solicitud no cumple con la novedad y el nivel inventivo.

Respuestas del Solicitante

El solicitante no se pronunció frente a las oposiciones de Lafrancol y Procaps.

Respuesta del Examinador Técnico

Los documentos presentados en las oposiciones no desvirtúan la novedad y el nivel inventivo del objeto de esta solicitud ya que estos no dan a conocer la asociación de 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol y un AINES, además no se puede derivar de ellos la eventual combinación de un AINES con el agente 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol, por lo tanto no se utilizaran en el Examen de Patentabilidad.

8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de prioridad (28/Abril/2006) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health. Lauren E. Ta, Raymond A. Dionne. Pain, Volume 111, Issues 1–2, Pages 13-21	Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen	19/Abril/2004
D2	The Journal of Pain. Volume 7, Issue4, Supplement. Pages S26. T. Tzschentke, J. De Vry, T. Christoph.	Tapentadol HCl: Analgesic profile of a novel centrally active analgesic with a dual mode of action in animal models of nociception, inflammatory, and neuropathic pain	18/Abril/2006

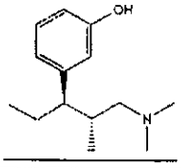
D1 Divulga la administración de celecoxib como COX -2 y naproxeno o acetaminofen como NSAID. La combinación fue bien tolerada para el tratamiento de dolor mandibular. (Pág. 13,14 y 20) http://www.sinab.unal.edu.co:2053/science/article/pii/S0304395904002210 .
D2 Divulga la asociación de Tapentadol HCl o clorhidrato de (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol con otros analgésicos como el tramadol, para mejorar el perfil analgésico en un modelo de nocicepción e inflamación animal.(Pág. S26)
http://www.sinab.unal.edu.co:2053/science/article/pii/S1526590006001040

9. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La **reivindicación 1** está caracterizada por una combinación que comprende como componentes: (folios 51 y 52, Pág. 30 y 31, línea 1).

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

Características esenciales	**D1**	**D2**
Combinación que comprende	Combinación que comprende	Combinación que comprende
3-(3-dimetilamino-1-etil-2-metil-propil)-fenol. Comunmente denominado Tapentadol 	Celecoxib	3-(3-dimetilamino-1-etil-2-metil-propil)-fenol. Comunmente denominado Tapentadol 
Uno o más AINES	Naproxeno o Acetaminofen	Tramadol u otro analgésico

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan un AINES (naproxeno o acetaminofen) asociado a un inhibidor de COX-2 selectivo (celecoxib) para el tratamiento de dolor mandibular y la asociación de Tapentadol HCl o clorhidrato de (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol con otro analgésico (tramadol) para mejorar el efecto analgésico.

D1 da a conocer una asociación de celecoxib como inhibidor de COX-2 selectivo con un AINES (naproxeno o acetaminofen) para el tratamiento del dolor mandibular, demostrando una mejora significativa en los síntomas clínicos y con pocos efectos adversos. (Pág. 484)

D2 menciona que el (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol exhibe efecto analgésico y además divulga que puede administrarse con otros analgésicos como el tramadol para el tratamiento del dolor crónico. (Pág. S26)

La diferencia entre la invención, definida en la reivindicación 1 y la combinación de D1 consiste en que el AINES se combina con un inhibidor de COX-2 selectivo como el 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol.

La diferencia entre la invención, definida en la reivindicación 1 y la combinación de D2 consiste en que el 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol se combina con uno o más AINES y esto no se encuentra en D2.

El efecto que logra incluir esta combinación de principios activos es mejorar el tratamiento del dolor, no obstante la información suministrada en esta solicitud no lo demuestra.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el efecto analgésico del 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol conocido en D2 para aumentar el efecto nociceptivo y tener una alternativa al tratamiento del dolor".

Sin embargo, el AINES para aumentar la eficacia analgésica de los inhibidores de COX-2, ya está divulgada en el documento D1 que se refiere a la asociación de naproxeno y celecoxib en el tratamiento farmacológico. (Pág. 484)

En consecuencia, la persona del oficio normalmente versada en la materia, combinaría el 3-(3-dimetilamino-1-etil-2-metil-propil)-fenol que es un COX-2 (folio 22, página 1) de D2 con un AINES de D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Conclusión:

La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 2 a 28 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health. Lauren E. Ta, Raymond A. Dionne. Pain, Volume 111, Issues 1–2, Pages 13-21	1 a 28	Nivel inventivo
D2	The Journal of Pain. Volume 7,	1 a 28	Nivel inventivo

	Issue4, Supplement. Pages S26. T. Tzschentke, J. De Vry, T. Christoph		

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.

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.

JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 JUL. 2012

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PAIN

Pain 111 (2004) 13–21

www.elsevier.com/locate/pain

Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen

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Received 4 August 2003; received in revised form 8 April 2004; accepted 19 April 2004

Abstract

To compare the efficacy and adverse effects of celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, with naproxen, a non-steroidal anti-inflammatory drug, and placebo in the treatment of painful temporomandibular joints (TMJs). In this randomized, double-blind, placebo-controlled trial, 68 subjects with painful TMJs secondary to disc-displacement with reduction, received celecoxib 100 mg twice a day; naproxen, 500 mg twice a day; or placebo for 6 weeks. Subjects were evaluated with standard measures of efficacy: pain intensity measured by visual analogue scale, maximal comfortable mandibular opening, and quality of life (SF-36), at baseline (1 week after discontinuing previous analgesic therapy) and again after 6 weeks of drug treatment. Naproxen significantly reduced the symptoms of painful temporomandibular joint disc-displacement (TMJ DD) with reduction as determined by most efficacy measures. Significant improvement in pain intensity occurred within 3 weeks of treatment, and was sustained throughout the 6-week study. Clinically significant improvement in mandibular range of motion was observed for naproxen compared to celecoxib and placebo. Celecoxib showed slightly better pain reduction than placebo, but was not significantly effective for temporomandibular disorder pain. Celecoxib and naproxen were well tolerated, with similar number of reported adverse effects. Dual COX-1 and COX-2 inhibition with naproxen was demonstrated to be effective for the treatment of painful TMJs, as seen by significant improvement in clinical signs and symptoms of TMJ DD with reduction compared to celecoxib and placebo. Inhibition of both COX isozymes is needed to achieve effective analgesia for this type of musculoskeletal pain.

Keywords: Non-steroidal anti-inflammatory drug; Coxibs; Temporomandibular disorder; Chronic pain; Clinical trial

1. Introduction

Temporomandibular disorders (TMDs) represent a group of chronic painful conditions involving the muscles of mastication and the temporomandibular joint (TMJ) with a prevalence in the general population up to 12% (Carlsson and LeResche, 1995; Dworkin et al., 1990; Von Korff et al., 1988). For TMD involving joint disorders, TMJ disc-displacement (TMJ DD) refers to any abnormality within the TMJ that denotes an abnormal position of the articular disc relative to the mandibular condyle and the articular eminence. Early stage TMJ DD, often referred to as TMJ DD with reduction, is quite common and characterized by joint noise or clicking of the joint on opening and closing due to the impaired gliding function of the articular disc. Pain can be present at any stage of TMD and is a significant part of the symptoms that prompt patients to seek treatment (Rugh and Solberg, 1985).

Anti-inflammatory or analgesic medications are often prescribed in an attempt to decrease the pain associated with TMD. Non-steroidal anti-inflammatory drugs (NSAIDs), as non-selective COX inhibitors, are thought to exert their analgesic and anti-inflammatory effects through both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition (DeWitt et al., 1993; Vane, 1971). To improve the safety of NSAIDs, therapeutic agents were

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inhibition of COX-2 (Masferrer et al., 1994; Siebert et al., 1994).

COX-1 can be induced in human chronic bursitis (Gretzer et al., 1998), in human synovium of acute and chronic arthritis (Iniguez et al., 1998) and in inflamed synovial membrane of patients with TMD joint disorders (Yoshida et al., 2001). COX-2 is constitutively expressed in many tissues including the central nervous system and the kidney (O'Banion, 1999; Vanegas and Schaible, 2001). These findings suggest that the inhibition of both isozymes may be necessary to obtain maximal prostanoid reduction and, conversely, that inhibition of either COX-1 or COX-2 will induce unwanted side effects (Wallace, 1999a,b). Variable observations have been made on the analgesic actions of selective COX-2 inhibitors, ranging from no advantage over conventional, non-selective NSAIDs in the treatment of acute pain (Doyle et al., 2002; Morrison et al., 1999; Salo et al., 2003) or arthritis (Hochberg, 2002; Matheson and Figgitt, 2001), to claims of greater coxib efficacy for arthritis treatments (Cannon et al., 2000; Kivitz et al., 2001.

Although NSAIDs and coxibs are frequently used for TMD pain, there have been no controlled trials establishing their effectiveness for these applications (Antczak-Bouckoms, 1995; Dionne, 1997; List et al., 2003). Given the prevalence of TMD, safety concerns with chronic NSAID administration, and the controversial nature of non-pharmacologic therapy (TMJ surgery, splints, occlusal alteration), we tested clinically the hypothesis that celecoxib has anti-inflammatory and analgesic properties for TMD that can be differentiated from placebo. In addition, comparison was made to naproxen to determine if selective COX-2 inhibition reduces the signs and symptoms of TMD to the same extent as inhibition of both COX-1 and COX-2.

2. Methods

2.1. Study population

Seventy-eight subjects were recruited by newspaper advertisement and through recruitment letter sent to local dentists. Male and female subjects aged 18–65 years were eligible for inclusion if they had clinical diagnoses of TMJ DD with reduction and arthralgia or painful disc-displacement of the TMJ. The TMD diagnosis was classified using axis I of the research diagnostic criteria (RDC) for TMDs (Dworkin and LeResche, 1992). The RDC diagnoses consist of joint pain at rest (spontaneous pain) and evoked pain (hyperalgesia) on palpation of the TMJ. TMJ reduction consists of reciprocal clicking or joint noise with mandibular movement examination. For joint pain complaint, subjects were required to have a self-report of at least 1 month of daily or near-daily pain. Subjects with myogenic pain were included if they met inclusion and exclusion criteria since patients with TMJ DD are known to exhibit muscle pain secondary to their joint dysfunction.

Exclusion criteria for the study were subjects with infectious arthritis, crystal induced arthropathies, musculoskeletal disorders, subjects with a primary diagnosis of myofascial pain based on the RDC (Dworkin and LeResche, 1992), kidney or liver dysfunctions, GI tract, hematologic, unstable cardiovascular disorders or malignancy. Subjects with untreated depressive disorder or not on stable antidepressant medication for more than 6 months were not included. Subjects with dental diseases that required ongoing treatment, which would confound the evaluation of orofacial pain, were also excluded. Further exclusion criteria for the study were subjects with known hypersensitivity to celecoxib, naproxen, allergy to sulfonamides, or demonstrated allergic-type reactions after taking aspirin or other NSAIDs. Subjects who were pregnant, lactating, or not following an effective birth control regimen were also excluded from the study.

2.2. Study protocol

This randomized, double-blind, placebo-controlled trial was conducted at the Clinical Center of the National Institute of Dental and Craniofacial Research (NIDCR) over a 40 months period (January 2000 to April 2003). The protocol was approved by the NIDCR's Institutional Review Board. All subjects were required to provide a written informed consent prior to undergoing evaluation and treatment as outpatients at the Clinical Center. Screening by medical history, clinical evaluation, and laboratory tests were done during the screening visit and up to 5 days before the first dose of the study medication. All subjects were evaluated by an investigator who is a dentist (LET) trained in orofacial pain. This evaluation consisted of medical and dental history review, a head and neck examination, assessment of TMJ function, palpation of the TMJ and masticatory muscles, and a dental examination. Laboratory evaluation included a complete blood count, blood chemistry and hematology profile, thyroid panel, complements, liver and kidney function tests, sedimentation rate, C-reactive protein, and rheumatoid factor. A panoramic radiograph and MRI of the TMJs were also obtained. MRI of the TMJ of each subject was completed and interpreted by a radiologist using diagnostic criteria of disc-displacement with reduction (Drace and Enzmann, 1990). Although MRI is not required under the RDC diagnosis of TMJ DD with reduction, we used this diagnostic screening process to confirm disc-displacement with reduction.

The Minnesota multiphasic personality inventory-2 (MMPI-2) (Hathaway, 1967) was administered as part of a general psychological screening process to exclude subjects with severe personality or psychosis disorders. After being screened for study enrollment, eligible subjects who were taking NSAID or analgesic treatment were told to withhold NSAIDs for 5–7 days before study entry. Subjects were also instructed to discontinue all intraoral appliances, jaw exercises, or self-application of moist heat or ice prior

and during study participation. Study progress was monitored with a weekly telephone call by the investigator or the study nurse, and medication intake was assessed by tablet count. Subjects were withdrawn from the study for protocol violation or non-compliance, adverse sign or symptom, or if they were lost to follow-up. Use of anti-coagulants, NSAIDs (including low-dose aspirin) other than the study drug, muscle relaxants or chronic use of an analgesic or anti-ulcer drug was prohibited during the study.

2.3. Drug treatment

Subjects who satisfied the entry criteria were randomly assigned to receive 6-week treatment of either celecoxib 100 mg BID, naproxen 500 mg BID, or placebo BID. The doses of the active drugs are the maximum recommended daily doses for osteoarthritis for each drug (USP Drug Information, 2003). Subjects were also given acetaminophen 325 mg as rescue medication, with a maximum dose of 3900 mg/day, and all medication was taken with food. Treatment randomization was stratified using a block size of 9 or 6 by National Institutes of Health Pharmaceutical Development Service.

2.4. Clinical assessment

Clinical assessments were performed for each subject at screening, at baseline prior to study drug administration, and at 6-week post-drug. Safety was evaluated according to the incidence and type of adverse reactions and the rate of withdrawal because of adverse reactions. Subjects were also monitored for laboratory abnormality at the initial and 6-week visits.

2.5. Primary outcome

The primary outcome was efficacy in the treatment of TMD pain as measured by a visual analogue scale (VAS). Subjects completed once daily in the evening for 7 days a baseline diary of pain, and daily thereafter for 6 weeks of dosing with study medication. Subjects were asked to rate their overall average daily joint pain using VAS. The VAS consisted of a 100 mm line, anchored with the extremes of pain intensity represented as 'no pain' and 'worst pain possible'. VAS has shown to provide a robust, sensitive, and reproducible method of measuring pain (Huskisson, 1982).

2.6. Secondary outcomes

To assess for the mandibular function, the maximal comfortable mandibular opening was measured in millimeters at the subject's maximum incisor to incisor mouth opening using a ruler. This measure of mandibular movement is defined as the maximal inter-incisal distance a subject can open without experiencing evoked pain. This measure has previously been shown to be valid and reliable (Goulet and Clark, 1990; Okeson et al., 1983; Wright and Schiffman, 1995).

To assess the chronic TMD pain impact on daily life functioning, usual daily activities, and general well-being, the rand health status measure (SF-36) (Ware, 1987) was administered. The SF-36 is a standardized questionnaire measure of health that consists of following eight health domains: physical functioning, social functioning, role physical, role emotional, bodily pain, mental health, vitality, and general health perception. The SF-36 has been shown to be comprehensive, reliable, and valid (Ware, 1987).

2.7. Tolerability and safety

Vital signs were monitored at every visit. Laboratory evaluations were performed at the initial visit, and the final visit. Spontaneously reported adverse events were recorded throughout the study.

2.8. Statistical analysis

The data were analyzed using SPSS standard statistical package (SPSS Statistical Software, Chicago, IL). Homogeneity of treatment for gender, primary job status, educational level and types of past and current treatments were analyzed by χ^2 test. One way analysis of variance (ANOVA) was used to examine the differences in age and pain duration across treatment groups. As measure of overall pain outcomes, pain diaries collected daily by VAS for 6 weeks were assessed by ANOVA with repeated measures. To account for baseline differences, analysis of covariance (ANCOVA) was used, with VAS at baseline as covariate. To determine the onset of treatment effects, each week's mean VAS was analyzed with ANOVA. Maximum mandibular comfortable opening was also analyzed with ANOVA, followed by post hoc testing with Bonferroni correction. Values are reported as mean ± 1 standard deviation (SD). To assess for the relationship between treatment groups and treatment response (responders vs non-responders) a χ^2 analysis was used. All tests were considered statistically significant at $\alpha = 0.05$.

The determination of sample size for this study was based on a postulated improvement treatment effect 50% of the active treatment group compared to the placebo group (Simon et al., 1998). A sample size of 22 per treatment group was calculated a priori as sufficient to detect this difference with 80% power with an α level of 0.05.

3. Results

Five hundred and twenty subjects were referred to Clinical Center for study participation from the NIH Patient Recruitment and Referral Center. Following questionnaire and telephone interview, 145 subjects were invited for screening evaluation. At the completion of the screening

evaluation, 78 subjects were recruited and with a total 68 subjects completing the study. Of the 10 subjects who did not complete the study, four were non-compliant, three withdrew from study due to time constraint, and three failed to return for follow-up.

3.1. Subject characteristics

No significant differences between the three treatments groups were detected with respect to demographic characteristics or measures of TMD disease activity at baseline (Table 1). Close to half of all subjects had a history of using occlusal splints as treatment for their TMD pain. At the time of the initial screening visit, four subjects were actively using the occlusal appliances. Close to 80% of all subjects reported history for the use of various NSAIDs for their TMD pain. The results of the MRI were used as screening criterion such that all subjects randomized were confirmed to have disc-displacement with reduction. A total of 53 subjects had bilateral joint complaints; 15 reported unilateral pain. The MMPI-2 for most subjects had slightly elevated scores for the depression and anxiety scales, which is consistent with chronic pain populations (data not shown). Subjects with elevated scores for scale 4 (psychopathic deviate), scale 6 (paranoia) or scale 8 (schizophrenia) that reflected severe personality disorders or psychosis were excluded at the initial screening prior to randomization.

Compliance assessment showed that 76% of the subjects reported taking 80–84 tablets over 6 weeks, 95% took at least 78 out of 84 tablets, and no subject took fewer than 70 tablets. During the 6-week study, 47 subjects (70%) did not take rescue medication (celecoxib = 18 subjects, naproxen = 14, placebo = 15). Twelve subjects (17%) took less than a total of eight tablets of acetaminophen (celecoxib = 4, naproxen = 5, placebo = 3). Three subjects (4%) took more than a total of 14 tablets of rescue medication (celecoxib = 0, naproxen = 0, placebo = 3).

3.2. Efficacy

Naproxen reduced significant symptoms in painful TMD disc-displacement with reduction as shown in the subject's pain severity score (Fig. 1, Table 2). ANOVA with repeated measure showed that naproxen was significantly superior to

Table 1
Subject baseline characteristics (mean ± SD)

Characteristics	Celecoxib (n = 24)	Naproxen (n = 22)	Placebo (n = 22)
Demography			
Mean age in years	34.5 ± 10.2	33.6 ± 9.3	34.7 ± 10.7
Median age in years	31	31	31
Range in years	21–52	22–52	20–52
Female/male	17/7	16/6	13/9
% Female/male	70/30	73/27	60/40
Primary job status (%)			
Full time	17 (70.8)	17 (77.3)	16 (72.7)
Part time	2 (8.3)	2 (9.1)	5 (22.7)
Unemployed	3 (12.5)	0 (0)	0 (0)
Retired	1 (4.2)	0 (0)	0 (0)
Homemaker	0 (0)	1 (4.5)	0 (0)
Full time/part time student	1 (4.2)	2 (9.1)	1 (4.5)
Education level (%)			
High school	1 (4.2)	1 (4.5)	1 (4.5)
Some college	5 (20.8)	4 (18.2)	4 (18.2)
College graduate	9 (37.5)	10 (45.5)	7 (31.8)
Professional school	3 (12.5)	3 (13.6)	2 (9.1)
Postgraduate school	6 (25)	4 (18.2)	8 (36.4)
TMD pain duration			
Mean (years ± SD)	3.1 ± 3.3	4.0 ± 3.2	4.0 ± 4.7
Median in years	1.5	3.7	2.0
Range in months	3.6–144	3.6–120	2.4–180
History of pain treatment (%)[a]			
Subjects with previous use of splint	14 (58)	10 (45)	13 (60)
Subjects with current use of splint	1 (4)	1 (4)	2 (9)
Subjects with previous treatment with physical therapy	1 (4)	0 (0)	1 (4.5)
Subjects with current psychotropic medication	1 (4)	1 (4)	2 (9)
Subjects had used different NSAIDs before study entry[b]	19 (80)	17 (77)	17 (77)

[a] These treatments are not mutually exclusive.
[b] Types of NSAIDs varied, most commonly ibuprofen, sodium naproxen, diclofenac, meloxicam, rofecoxib, and some with no known medication.

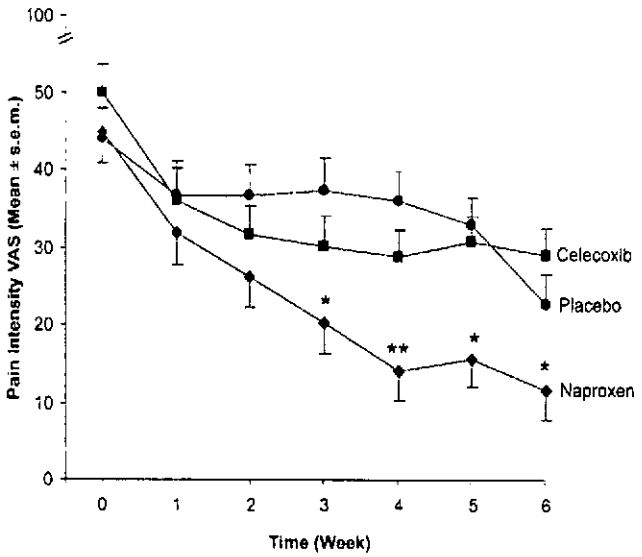

Fig. 1. Drug effects on TMD pain intensity. Pain intensity weekly time-effect curve as measured on a 100 mm visual analogue scale for placebo, 200 mg BID celecoxib, 500 mg BID naproxen. Data are expressed as mean values ± SEM. Naproxen had significant analgesic effect on spontaneous pain compared with placebo in week 3 ($P < 0.01$), week 4 ($P < 0.001$), week 5 ($P < 0.01$), and week 6 ($P < 0.01$). Naproxen also showed significant analgesic effect compared to celecoxib only in week 4 ($P < 0.01$). Although there was trend in decreasing pain severity in celecoxib group, no significant difference detected in this decrease in pain reduction compared to placebo over time. *$P < 0.01$ vs placebo, **$P < 0.01$ vs placebo and celecoxib.

placebo throughout the 6-week study ($P < 0.05$). Although celecoxib showed a gradual decrease in pain from baseline, the mean results did not differ from placebo. Similar findings in statistical values were observed when the mean baseline pain intensity of three treatment groups were considered in ANCOVA for repeated measure.

The treatment effect was evident starting at the third week for the naproxen group and was sustained throughout the study. A significant difference in mean pain reduction was observed between naproxen and placebo group in week 3 ($P < 0.01$), week 4 ($P < 0.001$), week 5 ($P < 0.01$) and in week 6 ($P < 0.01$). Although naproxen had better analgesic effect than celecoxib, a significant difference between drugs was only seen in week 4 ($P < 0.01$). No significant difference was found between celecoxib and the placebo group in any week.

Treatment responders were defined as subjects whose baseline pain rating decreased by 50% during the treatment period (Turk et al., 1993). When 50% pain reduction was used as the difference in pain intensity from baseline to week 6, a significantly greater number of subjects in the naproxen group ($P < 0.01$) responded to treatment than either celecoxib or placebo group (Fig. 2). Similarly, higher number of responders was observed in the naproxen group compared to celecoxib or placebo group when 33% of pain reduction was used as the responder criteria (Farrar et al., 2001). Although there was a trend for drug effect between celecoxib and placebo for 50% pain reduction ($P = 0.055$), this effect was not apparent for 33% pain reduction ($P = 0.739$).

3.3. Mandibular range of motion

Subjects in all three treatment groups had an increased mandibular range of motion at the final visit as reflected in their greater scores with their maximal comfortable mouth opening compared to baseline scores ($P < 0.01$) (Fig. 3). A between subject comparison analysis showed that subjects in the naproxen group (12.6 mm) had a significant change in mandibular opening relative to celecoxib group (8.2 mm) and the placebo group (7.3 mm) ($P < 0.01$). However, there was no significant difference found between celecoxib and placebo group.

3.4. Quality of life

The SF-36 baseline scores from all study participants were within the normal range (data not shown) compared to published normative data from US population (Ware, 1987). Although all subjects had slight improved scores following study participation, there is no significant difference detected for three treatment groups (data not shown). Naproxen did slighter better in three health domains of role

Table 2
Primary outcome measure with pain intensity (mean ± SD)

Week	Mean VAS score			Mean change VAS score from baseline		
	Celecoxib ($n = 24$)	Naproxen ($n = 22$)	Placebo ($n = 22$)	Celecoxib ($n = 24$)	Naproxen ($n = 22$)	Placebo ($n = 22$)
Baseline	49.99 ± 7.42	44.76 ± 7.74	44.00 ± 7.79			
Week 1	36.14 ± 8.26	31.93 ± 8.63	36.68 ± 8.83	13.85 ± 6.11	12.82 ± 6.39	7.31 ± 6.54
Week 2	31.59 ± 7.56	26.14 ± 7.90	36.70 ± 8.08	18.41 ± 7.39	18.63 ± 7.72	7.30 ± 7.9
Week 3	30.18 ± 7.78	20.31 ± 8.12[a]	37.34 ± 8.31	19.82 ± 8.03	24.46 ± 8.38	6.66 ± 8.59
Week 4	28.70 ± 7.11	14.06 ± 7.43[a,b]	35.98 ± 7.60	21.30 ± 8.13	30.70 ± 8.49	8.02 ± 8.69
Week 5	30.70 ± 6.58	15.50 ± 6.68[a]	33.02 ± 7.03	19.30 ± 8.11	29.27 ± 8.47	10.98 ± 8.66
Week 6	28.92 ± 7.13	11.71 ± 7.45[a]	28.66 ± 7.63	21.08 ± 8.89	33.05 ± 9.28	15.34 ± 9.51

[a] Significant difference observed between naproxen and placebo in week 3 ($P < 0.01$), week 4 ($P < 0.001$), week 5 ($P < 0.01$), and week 6 ($P < 0.01$). One-way ANOVA with post hoc test with Bonferroni correction was used for analysis to detect differences across treatment groups for each week.

[b] Significant difference detected between naproxen and celecoxib in week 4 ($P < 0.01$).

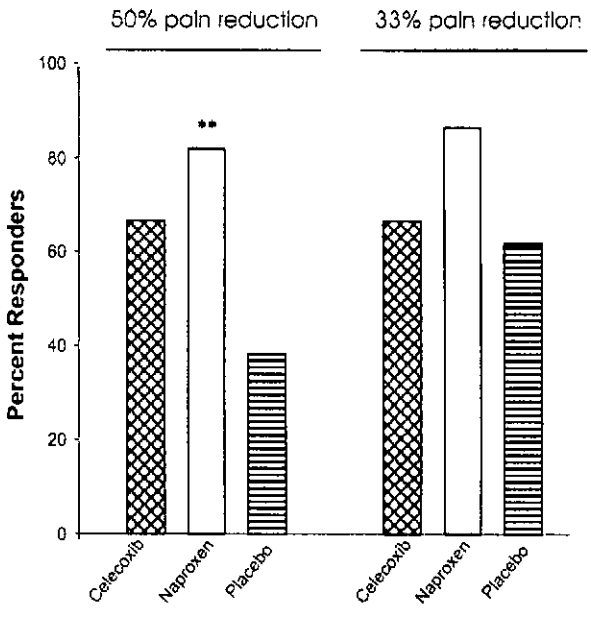

Fig. 2. Treatment responders following 6-week study. Pain reduction is tabulated using number of subjects demonstrating either 50% reduction from baseline to week 6 (left hand side of panel) or 33% pain reduction (right hand side of panel). A greater number of subjects in naproxen group (82%) responded to treatment than either celecoxib (67%) or placebo (36%) using the 50% pain reduction. $^{**}P < 0.01$ vs placebo and celecoxib.

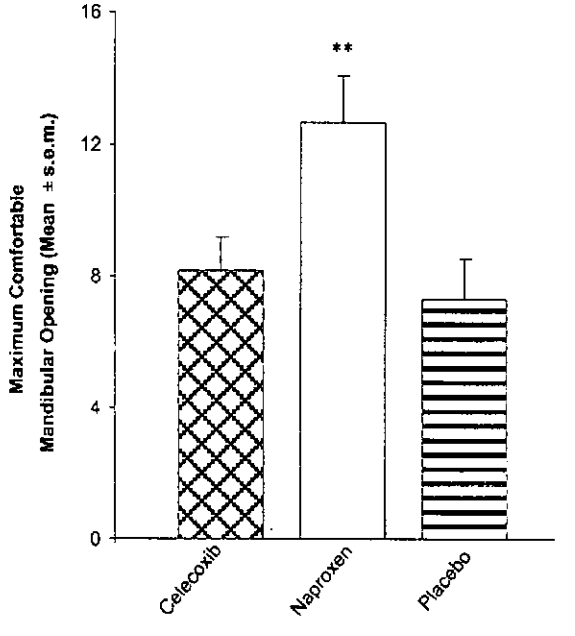

Fig. 3. Drug effects on maximum comfortable mandibular opening. The effectiveness of therapeutic intervention was evaluated by assessing the change in maximum comfortable mandibular opening following 6 weeks treatment. Analgesic effect on evoked pain or hyperalgesia was observed for three treatment groups as all subjects showed increase in mandibular mobility. Data are expressed as mean values ± SEM. However, only naproxen group (12.6 mm) had significant improvement with greater change in mandibular movement ($P < 0.01$) compared to celecoxib (8.2 mm) and placebo groups (7.3 mm). No significant difference detected between celecoxib and placebo groups. $^{**}P < 0.01$ vs placebo and

physical, vitality, and general health perception relative to celecoxib and placebo. For bodily pain, both naproxen and celecoxib group had similar improvement, and both did better than placebo.

3.5. Adverse effects

All the reported adverse events were mild to moderate in severity. There were no severe adverse events, hospitalizations, or subject dropout due to adverse events. Thirty six subjects experienced a total of 61 adverse events during the course of the study (Table 3). Headache was among the most commonly reported, with the highest incidence observed in the celecoxib group. Of the four common GI related adverse events (dyspepsia, abdominal pain, flatulence, diarrhea and constipation), 40% more reported incidences were observed in the naproxen group (13) compared to celecoxib (8) and placebo (7) group. Peripheral edema was observed for one subject in the naproxen group. Subjects in the naproxen and celecoxib groups both experienced a higher numbers of total adverse events (23) compared to placebo group (15).

Throughout the study, no significant change from the mean creatinine values, liver-function enzymes alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were detected for three treatment groups (data not

Table 3
Incidence of adverse events reported during the 6-week study

	Celecoxib ($n = 24$)	Naproxen ($n = 22$)	Placebo ($n = 22$)
Reported adverse events			
Headache	9	6	4
Dyspepsia	2	5	2
Abdominal pain	3	3	1
Flatulence	3	2	3
Nausea	3	1	1
Upper respiratory tract infection	2	1	1
Diarrhea	0	1	1
Constipation	0	2	0
Fatigue	1	1	0
Dizziness	0	0	1
Gastrointestinal tract adverse events			
Total	8	13	7
Renal adverse events			
Peripheral edema	0	1	0
Increased creatinine level	0	0	0
Hepatic adverse events			
Elevated serum ALT, AST	0	0	0
Cutaneous adverse events			
Rash	0	0	1
All adverse events			
Total incidences	23	23	15
Total subjects affected	12	13	11

shown). No subject had values out of normal range for creatinine, ALT, and AST tests.

4. Discussion

To our knowledge, this is the first controlled study that evaluates the effects of an NSAID or a selective COX-2 inhibitor on clinical TMD with joint pain (List et al., 2003). The results of this randomized, double-blind, placebo-controlled trial shows the clinical efficacy of naproxen, a non-selective COX-1 and COX-2 inhibition, at therapeutic doses in subjects with painful TMJ DD with reduction. The magnitude of pain improvement observed with therapeutic doses of naproxen is significantly greater than those observed in placebo; however, there was also a greater incidence of gastrointestinal adverse events associated with naproxen relative to celecoxib and placebo. Results tabulated as a responder index utilizing either the criterion suggested by Turk et al. (50% pain reduction), or Farrar et al. (33% pain reduction), demonstrated greater numbers of responders in the naproxen group compared to celecoxib and placebo group. Although we did not detect a significant drug effect between celecoxib and placebo, given the observation of a trend ($P = 0.055$) in the number of patients experiencing a 50% pain reduction, a significant drug effect is likely to occur with a larger number of subjects. Nevertheless, these data suggest that inhibition of both COX isozymes is an effective approach to the treatment of painful TMD with joint disorders.

The observation that celecoxib, at the doses used in this trial, did not result in significant amelioration of TMD pain suggests that selective inhibition of COX-2 does not produce analgesic effects comparable to those achieved with combined COX-1/COX-2 inhibition. This is consistent with a previous study (Khan et al., 2002) comparing two doses of 200 mg celecoxib to the non-selective NSAID ibuprofen demonstrating greater analgesia for acute pain and suppression of PGE_2 production by ibuprofen in comparison to both celecoxib and placebo. Though indirect, the results of these two studies argue for an important role of COX-1 derived prostaglandins in human inflammatory hyperalgesia. Several lines of evidence support this conclusion. The association of COX-1 with inflammation is shown by studies in COX-1 deficient mice (Ballou et al., 2000; Mahler et al., 1996; Wallace et al., 1998), and is further confirmed with data from anti-inflammatory effects of drugs selective for COX-1 in various rat models of acute inflammation (Gilroy et al., 1998; Kusuhara et al., 1997). These findings suggest that COX-1 is also involved in pain and inflammatory responses (Lawrence et al., 2002; Parente and Perretti, 2003; Wallace, 2002).

The results of this study suggest that both the induction of COX-2 and the continuing production by COX-1 isozymes are important pathophysiologic components of painful TMJ DD. COX-1 and COX-2 have shown to be markedly expressed in inflamed synovial tissue in several forms of arthritis patients (Iniguez et al., 1998) as well as TMJ DD patients (Yoshida et al., 2001, 2002). The production of prostaglandins from COX-2 is known to contribute to local sensitization of nociceptors as well as mediating nociceptive effects of other pro-inflammatory agents including bradykinin, histamine, cytokines such as IL-1β, IL-6, and TNFα, and nitric oxide in the brain and spinal cord (Funk, 2001; Samad et al., 2002). While current evidence has emphasized the relevance of the spinal COX-2 in pain, basal levels of both COX-1/COX-2 exist in the spinal cord (Beiche et al., 1998). Their relative distribution and increased expression following injury may lead to varied neural responses in different types of pain (Svensson and Yaksh, 2002). The integration process involved in spinal systems mediating hyperalgesia is complex, furthermore, the surprise lack of effect for intrathecal administration of NSAIDs and COX-2 inhibitors in recent pre-clinical studies implies that yet other systems might also be contributing to hypersensitivity after peripheral and central inflammation (Dirig et al., 1998; Samad et al., 2001).

We have demonstrated the analgesic activity of a dual COX-1/COX-2 inhibitor for clinical TMD pain. Our results are consistent with recent findings in human study of dental pain (Doyle et al., 2002; Khan et al., 2002) and animal study of inflammatory and arthritis pain (Martinez et al., 2002). In contrast, others have failed to indicate any marked difference in efficacy between COX-1/COX-2 and COX-2 inhibitors in clinical arthritis studies (Cannon et al., 2000; Kivitz et al., 2001). Systematic review of clinical trials for TMD, atypical facial pain and burning mouth syndrome failed to identify any previous clinical trials demonstrating an effect for an NSAID for TMD (List et al., 2003). Possible explanation for these discrepant findings includes differences in maximum effective doses and characteristics of the populations studied. Based on findings from models of acute inflammation, it has been suggested that the degree to which each COX isoform contributes depends on the inflammatory stimulus, the time point examined, the tissue or organ in which the insults occurs, and other factors (Tilley et al., 2001).

Movement-evoked pain in mouth opening is a common measure in TMD pain and also used in recent study of clinical acute pain following post-surgical extraction since this measure directly reflects patient's jaw functions as well as change in symptoms or rehabilitative efforts (Gilron et al., 2000; Goulet and Clark, 1990). For painful TMD conditions, a minimum of 9 mm increase in mandibular range of motion is considered to be clinically significant improvement following a therapeutic intervention (Kropmans et al., 1999, 2000). In our finding, subjects in the naproxen group had significantly greater change (12.6 mm) in the mandibular mobility relative to celecoxib (8.2 mm) and placebo (7.3 mm) groups. The improved mandibular mobility observed also correlated with those seen in daily reported pain intensity at rest. This finding

indicates that naproxen had a clinically significant analgesic effect on evoked pain or hyperalgesia that closely reflect those on pain at rest or spontaneous pain.

In this 6-week study, celecoxib and naproxen were safe and well tolerated at the maximal recommended doses for osteoarthritis. No significant hepatic or renal toxicity was observed in this study although this was a short term study. A higher overall incidence of adverse effects was observed with both naproxen and celecoxib, as compared to placebo in our study. Although subjects in the celecoxib group experienced less incidences of gastrointestinal adverse event, if given higher doses to achieve the desired anti-analgesic effects, toxicity associated with inhibition of COX-1 is likely to be encountered.

Biological actions of prostanoids formed by the COX isozymes are much more diverse and inter-related than previously appreciated. Emerging evidence supports that full analgesic response to prostaglandin metabolites may require inhibition of both isozymes. Due to the present lack of a selective COX-1 antagonist for human use, it remains unclear as to the differential effects of COX-1 and COX-2 within the central nervous system in post-injury hyperalgesia. While demonstrating the efficacy of 6 weeks of naproxen treatment, our study did not evaluate whether pain relief is maintained over the months to years over which TMJ joint pain may persist. Further studies are warranted to determine the role of both selective COX-2 and COX-1/2 inhibitors in chronic TMD joint pain.

Acknowledgements

The authors would like to thank Nicholas Patronas, MD and Suvimol Hill, MD for the MRI interpretations, George Parsons, PhD for the psychological interpretations of the MMPI-2 instruments, Gloria Lee, BS for her exceptional nursing assistance. We also would like to thank James Witter, MD, PhD, Stanley Pillermer, MD, and Mitchell Max, MD for their comments on the manuscript. This study was supported by the Division of Intramural Research, NIDCR.

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The Journal of Pain

Volume 7, Issue 4, Supplement, April 2006, Pages S23

B. system (physiology, anatomy, animal model)

(687): Tapentadol HCl: Analgesic profile of a novel centrally active analgesic with a dual mode of action in animal models of nociception, inflammatory, and neuropathic pain

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Available online

http://dx.doi.org/10.1016/j.jpain.2006.01.687

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Tapentadol HCl [(-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride] is a novel dual mode μ-opioid receptor (MOR) agonist and norepinephrine (NE) reuptake inhibitor. The present study tested the effects of tapentadol HCl in models of acute pain (hot plate, tail flick, writhing, chemically and mechanically induced visceral pain), and chronic neuropathic and inflammatory pain (formalin; yeast; chronic constriction injury [CCI] and spinal nerve ligation [SNL] vincristine-induced and diabetic neuropathy) in rats and mice, using various routes of administration (IV, IP, and PO). In most models, the potency of tapentadol HCl was between that of the reference compounds morphine and tramadol. After IV administration, the ED50 values of tapentadol HCl, morphine, and tramadol ranged from 0.7, 0.4, and 3.5 mg/kg, respectively (phenylquinone writhing, mouse) to 5.5, 3.5, and 18 mg/kg, respectively (colorectal distension-induced visceral pain, rat), and after IP administration from 3.8, 0.8, and 5.9 mg/kg, respectively (formalin test, rat) to 13, 14, and 7.1 mg/kg, respectively (CCI model of neuropathic pain, rat). Tolerance development to the analgesic effects of equianalgesic doses of tapentadol HCl and morphine was investigated in an acute (tail-flick) and a chronic (CCI) pain model in rats. In both models, morphine tolerance developed at least twice as fast (complete tolerance on day 22 and 10 for morphine, and on day 51 and 23 for tapentadol HCl, in the tail flick and CCI model, respectively). The main metabolite, the glucuronide of tapentadol, which does not bind to the MOR and does not inhibit NE uptake, was devoid of any analgesic activity. It is concluded that tapentadol HCl is a novel analgesic drug with a dual mode of action, resulting in a broad analgesic profile that might be more resistant to the development of tolerance than classical opiates such as morphine.

(687) Tapentadol HCl: Analgesic profile of a novel centrally active analgesic with a dual mode of action in animal models of nociception, inflammatory, and neuropathic pain

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Tapentadol HCl [(−)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride] is a novel dual mode μ-opioid receptor (MOR) agonist and norepinephrine (NE) reuptake inhibitor. The compound exhibited analgesic effects in a wide range of animal models of acute pain (hot-plate; tail-flick; writhing; chemically and mechanically induced visceral pain) and chronic neuropathic and inflammatory pain (formalin; yeast; chronic constriction injury [CCI] and spinal nerve ligation [SNL]; vincristine-induced and diabetic neuropathy) in rats and mice, using various routes of administration (IV, IP, and PO). In most models, the potency of tapentadol HCl was between that of the reference compounds morphine and tramadol. After IV administration, the ED50 values of tapentadol HCl, morphine and tramadol ranged from 0.7, 0.4, and 3.6 mg/kg, respectively (phenylquinone writhing, mouse) to 5.5, 3.5, and 18 mg/kg, respectively (colorectal distension-induced visceral pain, rat), and after IP administration from 3.8, 0.8, and 5.9 mg/kg, respectively (formalin test, rat) to 13, 14, and 7.1 mg/kg, respectively (CCI model of neuropathic pain, rat). Tolerance development to the analgesic effects of equianalgesic doses of tapentadol HCl and morphine was investigated in an acute (tail-flick) and a chronic (CCI) pain model in rats. In both models, morphine tolerance developed at least twice as fast (complete tolerance on day 22 and 10 for morphine, and on day 51 and 23 for tapentadol HCl, in the tail-flick and CCI model, respectively). The main metabolite, the glucuronide of tapentadol, which does not bind to the MOR and does not inhibit NE uptake, was devoid of any analgesic activity. It is concluded that tapentadol HCl is a novel analgesic drug with a dual mode of action, resulting in a broad analgesic profile that might to be more resistant to the development of tolerance than classical opiates such as morphine.

(688) Controlled disc stimulation: Pressure compensation for true intradiscal pressure

N Scarborough, J Hamilton, R McNall, M Meyer; Smith & Nephew, Andover, MA

Measurement of pressure within the disc during provocative disc stimulation has been attempted using a variety of pressure manometry devices. Although these devices have provided a quantitative measure of pressure rather than a subjective feel using standard syringes, the pressure measurement is within the syringe rather than the disc. Due to fluid dynamics, this reading is often not indicative of intradiscal pressure, resulting in the potential for errors in the interpretation of the pressure at which pain is elicited with the potential for compromising the specificity of the interpretation. During the development of a novel controlled disc stimulation system, an experiment was conducted to evaluate and quantify the factors that affect fluid dynamics during provocative disc stimulation. A random factorial experiment was designed to assess various levels of factors affecting fluid dynamics. Pressure transducers were placed inside both the syringe and a specially designed disc model. Contrast fluid was injected into the disc model, simulating a discography procedure. Contrast fluid viscocity, flow rate, needle length, needle guage, tubing length, and tubing diameter are the key variables accounting for discrepancies between syringe and intervertebral disc pressure. Incorporating these variables into a pressure compensation algorithm allows for accurate prediction of true intradiscal pressure during provocative disc stimulation. Accurate intradiscal pain readings during controlled disc stimulation procedures offers the potential to improve the interpretation of disc stimulation procedures and may improve the diagnostic value of this procedure.

(689) Pharmacokinetics, excretion, and metabolism of tapentadol HCl, a novel centrally acting analgesic, in healthy subjects

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Tapentadol HCl is a centrally acting oral analgesic with a dual mechanism of action of μ-opioid agonist and norepinephrine reuptake inhibition. Serum pharmacokinetics of tapentadol were determined in healthy subjects after intravenous (IV) infusion of tapentadol HCl 10-80 mg (males, n = 16) and 10-60 mg (females, n = 18), and after oral, buccal, or IV administration of tapentadol HCl 60 mg (males, n = 6). The excretion balance of radiocarbon was determined after administration of a single 100-mg oral dose of ^{14}C-labeled tapentadol HCl (1.867 MBq, 50 μ Ci) to healthy males (n = 4). Following oral and IV administration of tapentadol HCl 60 mg, the AUC was 190 ± 51 h · ng/mL and 588 ± 46 h · ng/mL, respectively; C_{max} was 50.0 ± 23.1 ng/mL and 299.5 ± 48.7 ng/mL, respectively; T_{max} was 0.83 ± 0.13 h and 0.18 ± 0.03 h, respectively; and total clearance after IV administration was 1468 ± 122 mL/min. After buccal administration, individual C_{max} values did not exceed 1.3 ng/mL. The absolute oral bioavailability was 31.9% ± 6.8%; buccal administration yielded no bioavailable tapentadol HCl. The pharmacokinetics of IV tapentadol HCl were linear; after body weight adjustment, no gender-specific differences were observed, except for a higher clearance rate in females at IV doses of 10 and 20 mg. Tapentadol was present in the serum primarily as conjugated glucuronide and sulfate metabolites (conjugated: unconjugated metabolites ≈ 24:1), and no active metabolites contributed to its analgesic activity. Tapentadol HCl was rapidly excreted in the urine (>95% of dose excreted within 24 h). Fecal excretion (1%) and expired CO2 (negligible) accounted for the remainder. The most common adverse events associated with increasing doses of IV tapentadol HCl (10-80 mg) were sleepiness, vertigo, dry mouth, and nausea. Thus, tapentadol HCl was rapidly absorbed and excreted, and was well-tolerated.

(690) Development of an intervertebral disc model for testing a new discography system

J Hamilton, L Manriquez, N Scarborough; Smith & Nephew, Andover, MA

A mechanical disc model was developed for testing a new discography system. The model was designed to simulate axial stiffness behavior of a disc. The literature was reviewed to identify the axial stiffness of normal and degenerated discs, maximum volume injected into a disc and the maximum change in intradiscal pressure. To determine an appropriate size of the test device chamber the relationship between force, stiffness and displacement was used. This relationship is given by the following equations: Force=stiffness*displacement F=k*d, and k=F/d; While, F=Pressure*Cross-Sectional Area d=Volume/Cross-Sectional Area; then, k=F/d= (Pressure*Cross-Sectional Area) (Volume/Cross-Sectional Area). For both normal and degenerated axial stiffness, the cross-sectional area was computed assuming a constant pressure and volume change. From the literature, the range of 0.125 – 0.75MN/m was chosen as the stiffness for a degenerated disc. The maximum volume injected was estimated at 3cc, and the maximum change in intradiscal pressure was approximated to be 90psi. Values for upper and lower end plate areas for Thoracic vertebrae range from 3-10.24cm2 according to White & Panjabi (1990). Since lumbar vertebrae are larger, the values for disc cross-sectional areas were increased up to 15 cm2. The axial stiffness values which led to a computed cross-sectional area within the realistic range included 0.125 & 0.25MN/m. In order to model the lowest stiffness and smallest cross-sectional area, the 1.24in diameter was chosen. The test device was designed so that the disc model consists of a polycarbonate tube of inner diameter 1.25in. The development of a mechanical disc model allows for testing of pressure measurement devices without the use of human or animal models. A pressure transducer and volume measuring device (LVDT)s placed within the model provide accurate measurements which could then be correlated with those recorded by the discography system and allowed for development of compensation algorithms for calculating intradiscal pressure.