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DIRECCIÓN DE NUEVAS CREACIONES

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CARLOS R. OLARTE

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Patente de Invención ☒ Patente de Modelo de Utilidad

Vía Nacional

Vía PCT (Fase Nacional) ☒ Capítulo I ☒ Capítulo II

No. Solicitud Internacional PCT/US2007/025808

Fecha de Presentación Internacional 18/Diciembre/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 44 a 73	17/Junio/2009
Reivindicaciones:	Folios 74 a 79	17/Junio/2009
	Folios 106 a 109	14/Octubre/2009
Dibujos:	Folios 81 a 85	17/Junio/2009
Prioridad:	US 60 870 907	20/Diciembre/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: "COMPOSICIONES FARMACEUTICAS Y METODO PARA EL TRATAMIENTO DE LA INFLAMACION EN EL GANADO Y EN OTROS ANIMALES".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una formulación farmacéutica transdérmica estable y de fácil administración para uso en ganado y en otros animales.

Para resolver este problema técnico la solicitud en estudio proporciona una preparación líquida transdérmica que contiene:

- a) flunixinina o una sal farmacéuticamente aceptable de la misma;
- b) un primer y un segundo mejorador de la penetración dérmica; y
- c) uno o más solventes primarios apróticos

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 9/00

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

El objeto de la reivindicación 21 no es patentable de acuerdo con el Art citado.

5. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque no define las características técnicas de la invención por cuanto las composiciones farmacéuticas para el tratamiento de inflamación en el ganado ya son conocidas en el estado de la técnica y además se refiere a un método de tratamiento el cual no es patentable según la legislación aplicable (Art 20 D 486 literal (d)), por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capítulo reivindicatorio no es claro puesto que las reivindicaciones 3 a 6 reclaman proporciones del primer y segundo mejorador de la penetración dérmica en términos de porcentaje peso/volumen; Sin embargo dichas proporciones son reclamadas en la reivindicación 20 en términos de porcentaje en peso. Se requiere hacer las aclaraciones necesarias.

La reivindicación 1 no es concisa cuando reclama un primer y segundo mejorador de la penetración dérmica y un solvente primario aprótico; sin embargo esta definición genérica y funcional no establece o define un componente como tal, lo que da origen a un gran número de composiciones. Se recuerda al solicitante que las composiciones se deben definir por características técnicas esenciales como son los ingredientes activos y auxiliares de formulación específicos. Igualmente no es claro cuantos componentes presenta la formulación dado que solventes apróticos como es el caso de dimetilsulfóxido y pirrolidona pueden actuar como mejoradores o promotores de la penetración dérmica con lo cual no es claro si una formulación que contenga estos solventes presenta tres o cuatro componentes. Se requiere hacer las aclaraciones necesarias.

Las reivindicaciones 3 a 6 no son concisas por cuanto los términos "primer mejorador de la penetración dérmica" y "segundo mejorador de la penetración dérmica" no establecen o definen un componente como tal, lo que da origen a un gran número de composiciones. Se recuerda al solicitante que las composiciones se deben definir por características técnicas esenciales como son los ingredientes activos y auxiliares de formulación específicos.

La reivindicación 6 no está sustentada en la descripción puesto que en los ejemplos no se especifica la cantidad del segundo mejorador de la penetración dérmica de manera que no es posible definir la relación reclamada en esta reivindicación. Se requiere hacer las aclaraciones necesarias.

La reivindicación 7 no es concisa dado que al revisar la descripción en los ejemplos se muestra que el primer mejorador de la penetración dérmica corresponde a mentol. Se sugiere restringir la solicitud a las preparaciones sustentadas en la descripción.

La reivindicación 10 no es clara cuando utiliza el término: "aproximadamente", el cual no es preciso ni limitativo, por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto (igual observación aplica para las reivindicaciones 14, 15, 20 y 21).

Las reivindicaciones 11, 12 y 13 no son concisas dado que al revisar la descripción en los ejemplos se muestra que el solvente primario aprótico corresponde a 2-pirrolidona. Se sugiere restringir la solicitud a las preparaciones sustentadas en la descripción.

La reivindicación 14 no es clara puesto que no especifica el valor inferior del rango de proporciones en que se encuentra el solvente primario aprótico en la preparación. Se requiere hacer las aclaraciones necesarias.

La reivindicación 18 no es clara ni concisa cuando reclama la preparación líquida transdérmica de la reivindicación 1, que comprende además un segundo compuesto farmacéuticamente activo. Esta manera de definir el segundo componente de la preparación no es aceptable, puesto que no se define ningún ingrediente activo como tal, lo que da origen a un número indefinido de composiciones por la utilización de este término genérico. Por tal motivo se sugiere eliminar esta reivindicación del alcance del pliego reivindicatorio.

La reivindicación 19 no es clara ni concisa cuando reclama la preparación líquida transdérmica de la reivindicación 18, en donde el segundo compuesto farmacéuticamente activo está seleccionado del grupo integrado por antimicrobianos, agentes anti-inflamatorios, oxitocina, hormonas para la reproducción, compuestos para el mejoramiento del crecimiento, compuestos de intervención fisiológica, compuestos ansiolíticos, antihistaminas, estimulantes inmunes y vacunas. Esta manera de definir el segundo componente de la preparación no es aceptable, puesto que no se define ningún ingrediente activo como tal, lo que da origen a un número indefinido de composiciones por la utilización de este término genérico. Por

tal motivo se sugiere eliminar esta reivindicación del alcance del pliego reivindicatorio.

La reivindicación 21 se refiere a un método de tratamiento aunque la reivindicación esté encabezada en términos de una preparación líquida transdérmica, la materia objeto de la reivindicación 21 ya se encuentra contemplada en la reivindicación 20. Se sugiere eliminar esta reivindicación del pliego reivindicatorio.

6. 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: Diciembre 20 de 2006, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO0135883	Transdermal Delivery System for Alkaloids of Aconitum Species	25/Mayo/2001
D2	WO2005009510A	Penetration Enhancer Combinations for Transdermal Delivery	03/Febrero/2005
D3	US20030175331A1	Analgesic/Anti-inflammatory Patches for Topical Use	18/Septiembre/2003
D4	JP11222443	Percutaneous Absorption-Promoting Composition and Percutaneous Absorption Preparation	17/Agosto/1999

D1

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=0135883A1&KC=A1&FT=D&ND=3&date=20010525&DB=worldwide.espacenet.com&locale=en_EP divulga (página 2 línea 10 a página 7 línea 15) una formulación transdérmica antiinflamatoria

D2

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005009510A2&KC=A2&FT=D&ND=3&date=20050203&DB=worldwide.espacenet.com&locale=en_EP divulga (página 9 párrafo 0022, página 112 reivindicación 44) una formulación farmacéutica que comprende una combinación de potenciadores de penetración química

D3

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2003175331A1&KC=A1&FT=D&ND=3&date=20030918&DB=worldwide.espacenet.com&locale=en_EP divulga (página 1 párrafo 0007, páginas 2 y 3 tablas 1 y 2, ejemplos 1 a 4) una formulación farmacéutica antiinflamatoria para uso tópico

D4 divulga una preparación farmacéutica de absorción percutánea comprendiendo dos potenciadores de penetración dérmica (Ver folios 124 a 128)

7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una preparación líquida transdérmica que comprende:

- a) un primer y segundo mejorador de la penetración dérmica;
- b) un solvente aprótico; y
- c) una cantidad terapéuticamente efectiva de flunixina o una sal farmacéuticamente aceptable de la misma.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D1
Preparación líquida transdérmica que comprende	Formulación farmacéutica transdérmica (correspondientes a soluciones, lociones, cremas, ungüentos, geles, pastas, aerosoles, etc.) (página 3 líneas 1 a 14, página 14 líneas 14 y 15, páginas 30 a 43, ejemplos IV a VI) que comprende
Un primer y segundo mejorador de la penetración dérmica	Una mezcla de potenciadores de permeación(página 14 línea 20)
Un solvente aprótico	Pirrolidonas (página 15 líneas 24 a 26)
flunixina	Flunixina meglumina(página 4 líneas 22 y 23)

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual da a conocer una formulación farmacéutica transdérmica que comprende una mezcla de potenciadores de permeación (página 14 línea 20), un solvente aprótico (pirrolidonas, página 15 líneas 24 a 26) y flunixina (página 4 líneas 22 y 23).

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 2, 7 – 9, 11, 18 - 19 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D2
Preparación líquida transdérmica que comprende	Formulación para administración tópica o transdérmica de un fármaco (página 112 reivindicación 44),correspondiente a una loción en forma líquida o semilíquida (página 77 parágrafo 00297, página 78 parágrafo 00300)
Un primer y segundo mejorador de la penetración dérmica	Un primer y segundo potenciadores de penetración química (página 112 reivindicación 44)
Un solvente aprótico	Un vehículo farmacéuticamente aceptable(página 112 reivindicación 44) Solventes que incluyen acetona, dimetil formamida, polietilenglicol, etoxi di glicol (página 17 parágrafo 0062)
N,N dimetilformamida, acetona, éteres de glicol (folio 57)	
flunixina	Una cantidad efectiva de un fármaco (página 112 reivindicación 44), flunixina, flunixina meglumina (página 21 parágrafo 0078)

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D2, el cual da a conocer una formulación farmacéutica comprendiendo una combinación de potenciadores de penetración química (página 9 parágrafo 0022, página 112 reivindicación 44)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D2.

Puesto que las reivindicaciones 2, 7 - 9 y 11 no presentan características nuevas adicionales tampoco se pueden considerar nuevas.

En consecuencia las reivindicaciones 1, 2, 7 – 9, 11, 18-19 carecen de novedad.

Nivel Inventivo (Art18 D486)

La reivindicación 3 consiste en la preparación líquida transdérmica de la reivindicación 1, en donde el primer mejorador de la penetración dérmica comprende desde aproximadamente 2 hasta aproximadamente 20% p/v de la preparación líquida transdérmica

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

SOLICITUD	D1	D2	D3	D4
Preparación líquida transdérmica que comprende	Formulación farmacéutica transdérmica (correspondientes a soluciones, lociones, cremas, ungüentos, geles, pastas, aerosoles, etc.) (página 3 líneas 1 a 14, página 14 líneas 14 y 15, páginas 30 a 43, ejemplos IV a VI) que comprende	Formulación para administración tópica o transdérmica de un fármaco (página 112 reivindicación 44), correspondiente a una loción en forma líquida o semilíquida (página 77 parágrafo 00297, página 78 parágrafo 00300)	Formulación farmacéutica antiinflamatoria para uso tópico (página 1 parágrafo 0007) Los componentes son disueltos en una solución líquida (página 2 parágrafo 0022)	Preparación de absorción percutánea (página 2 parágrafo 0001) correspondiente a preparaciones líquidas, lociones, soluciones (página 5 parágrafo 0023)
Un primer y segundo mejorador de la penetración dérmica	Una mezcla de potenciadores de permeación (página 14 línea 20)	Un primer y segundo potenciadores de penetración química (página 112 reivindicación 44)	Un primer y segundo mejorador de la penetración dérmica (mentol y un éster de ácido graso de glicerol (páginas 2 y 3, parágrafo 0022, tabla 1, ejemplos 1 a 4)	1- mentol y pirrolidona o sus derivados (página 3 parágrafo 0007)

Un solvente aprótico	Pirrolidonas (página 15 líneas 24 a 26)	Un vehículo farmacéuticamente aceptable (página 112 reivindicación 44) Solventes que incluyen acetona, dimetil formamida, polietilenglicol, etoxi di glicol (página 17 parágrafo 0062)	2-pirrolidona (páginas 2 y 3, parágrafo 0022, tabla 1, ejemplos 1 a 4)	Pirrolidona o sus derivados (página 3 parágrafos 0007 y 0009)
flunixinina	Flunixinina meglumina(página 4 líneas 22 y 23)	Una cantidad efectiva de un fármaco (página 112 reivindicación 44), flunixinina, flunixinina meglumina (página 21 parágrafo 0078)	No se menciona	NSAIDs No divulga específicamente flunixinina
El primer mejorador de la penetración dérmica comprende desde aproximadamente 2 hasta aproximadamente 20% p/v de la preparación líquida transdérmica	No se menciona	No se menciona	Mentol (porcentajes en peso 2%, 3%, 1%) (páginas 2 y 3, parágrafo 0022, tabla 1, ejemplos 1 a 4)	1-mentol 0,1 a 30% (prefiriéndose porcentajes de 0,2 a 15% y 0,5 a 5%) (página 3 parágrafo 0008)

El documento D1 divulga una formulación farmacéutica transdérmica que comprende una mezcla de potenciadores de permeación (página 14 línea 20), un solvente aprótico (pirrolidonas, página 15 líneas 24 a 26) y flunixinina (página 4 líneas 22 y 23).

La diferencia entre la invención, definida en la reivindicación 3 y la formulación de D1 consiste en que D1 no divulga las proporciones de cada uno de los potenciadores de penetración dérmica

El documento D2 divulga una formulación farmacéutica comprendiendo una combinación de potenciadores de penetración química (página 9 parágrafo 0022, página 112 reivindicación 44)

La diferencia entre la invención, definida en la reivindicación 3 y la formulación de D2 consiste en que D2 no divulga las proporciones de cada uno de los potenciadores de penetración dérmica

El documento D3 divulga una formulación farmacéutica antiinflamatoria para uso tópico (página 1 parágrafo 0007, páginas 2 y 3 tablas 1 y 2, ejemplos 1 a 4)

La diferencia entre la invención, definida en la reivindicación 3 y la formulación de D3 consiste en que D3 no divulga específicamente el porcentaje de 2 a 20% del primer

potenciador de penetración dérmica y no divulga la flunixinina como principio activo de la formulación.

El documento D4 divulga una preparación farmacéutica de absorción percutánea comprendiendo dos potenciadores de penetración dérmica (página 2 párrafo 0001, página 3 párrafos 0007 a 0010)

La diferencia entre la invención, definida en la reivindicación 3 y la formulación de D4 consiste en que D4 no divulga la flunixinina como principio activo de la formulación.

El efecto que logra el incluir el primer potenciador de penetración dérmica en un porcentaje entre 2 y 20% es facilitar la administración de la preparación de flunixinina en animales

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar las formulaciones divulgadas en D1 y D2 para facilitar la administración de flunixinina en animales.

Sin embargo, D3 revela las proporciones en las que se encuentran los dos potenciadores de penetración dérmica (mentol en porcentajes correspondientes a 2%, 1%, 3% y 2,5%) en la administración transdérmica de un fármaco antiinflamatorio (páginas 2 y 3, párrafo 0022, tabla 1, ejemplos 1 a 4) y D4 divulga una preparación transdérmica conteniendo diversos agentes antiinflamatorios no esteroideos utilizando porcentajes de 1-mentol de 0,1 a 30% (prefiriéndose porcentajes de 0,2 a 15% y 0,5 a 5%) y pirrolidona o sus derivados en porcentaje de 0,1 a 60% (prefiriéndose porcentajes de 0,2 a 40% y 0,5 a 20%) (página 3 párrafos 0008 y 0009) en donde la relación de mentol a pirrolidona esta entre 0,15:1,0 y 1,0:1,0 (página 3 párrafo 0010)

En consecuencia, la persona del oficio normalmente versada en la materia, modificaría los porcentajes de los potenciadores mencionados en D3 según se sugiere en D4 en las formulaciones dérmicas mencionadas en D1 y D2 utilizando flunixinina como principio activo como se divulga en D1 y D2 teniendo en cuenta que el fármaco flunixinina es uno de los fármacos antiinflamatorios no esteroideos utilizados eficazmente en el tratamiento de inflamación en animales según se conoce en el estado de la técnica¹ para llegar así al objeto de la reivindicación 3 de la solicitud. Por lo cual se considera obvia a la luz de D1 con D3 o D1 con D4 o D2 con D3 o D2 con D4

Puesto que las reivindicaciones 4 - 6, 10, 12 - 17 y 20 no presentan características inventivas adicionales tampoco se pueden considerar inventivas.

En conclusión las reivindicaciones 3 - 6, 10, 12 - 17 y 20 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

1 Kamerling Steven G. "Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Affect Pain and Inflammation". Louisiana State University Equine Veterinary Research Program. Newsletter. 1997 (Ver folios 129 a 134)
Expediente 09-62884 1er Art 45

8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO0135883	1, 2, 7 – 9, 11, 18, 19	Novedad
		3 - 6, 10, 12 – 17, 20	Nivel Inventivo
D2	WO2005009510A	1, 2, 7 – 9, 11	Novedad
		3 - 6, 10, 12 – 17, 20	Nivel Inventivo
D3	US20030175331A1	3 - 6, 10, 12 – 17, 20	Nivel Inventivo
D4	JP11222443	3 - 6, 10, 12 – 17, 20	Nivel Inventivo

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.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
14 AGO. 2012

Elaborado por: Rodolfo Cadena Amaya. *ok*
Revisado por: Gloria Jacqueline Alfonso.

PATENT ABSTRACTS OF JAPAN

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(43)Date of publication of application : 17.08.1999

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(21)Application number : 10-317368 (71)Applicant : SAITAMA DAIICHI SEIYAKU KK
(22)Date of filing : 09.11.1998 (72)Inventor : NAGAI TAKESHI KUSUNOKI AKIHIKO YAMAUCHI HITOSHI

(30)Priority

Priority number : 09325489 Priority date : 11.11.1997 Priority country : JP

* NOTICES *

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- 1. This document has been translated by computer. So the translation may not reflect the original precisely.
- 2. *** shows the word which can not be translated.
- 3. In the drawings, any words are not translated.

(54) PERCUTANEOUS ABSORPTION-PROMOTING COMPOSITION AND PERCUTANEOUS ABSORPTION PREPARATION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject composition exhibiting excellent skin-permeating property of a physiologically active substance and remarkably increasing skin permeating rate and capable of providing a percutaneous absorption preparation extremely excellent in percutaneous absorption property of medicine by including 1-menthol, pyrrolidone, etc.
SOLUTION: This composition comprises at least one kind of (A) 1-menthol and (B)

pyrrolidone or its derivative (preferably 2-pyrrolidone or N-methyl-2- pyrrolidone). The composition preferably contains the components A and B at a weight ratio of (0.15-1.0) to 1. The component A is used also for essential oil component, etc. such as peppermint oil containing the component A as a main component and the compounding amount of the component A is 0.1-30 wt.%, preferably 0.5-5 wt. % based on the composition. The compounding amount of the component B is 0.1-60 wt.%, preferably 0.5-20 wt. %.

TECHNICAL FIELD

[Field of the Invention]This invention relates to a new percutaneous absorption promotion constituent and percutaneous absorption preparation. If it says in more detail, this invention relates to the percutaneous absorption promotion constituent and percutaneous absorption preparation which promote the percutaneous absorption of the substance (drug) which has physiology activity, and make send promptly the whole body through a partial part or the circulatory system and in which it deals.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention]This invention relates to a new percutaneous absorption promotion constituent and percutaneous absorption preparation. If it says in more detail, this invention relates to the percutaneous absorption promotion constituent and percutaneous absorption preparation which promote the percutaneous absorption of the substance (drug) which has physiology activity, and make send promptly the whole body through a partial part or the circulatory system and in which it deals.

[0002]

[Description of the Prior Art]Endermic drug delivery (Transdermal Drug Delivery, TDD) is the method of controlling the concentration of drug in a general circulation system or a part in the useful range on Medical Science Division, by making a drug absorb from the skin. The medication method of the drug which makes the skin a route of administration can avoid the first-pass effect in internal use, and also. In administration by the conventional taking orally or injection of there being no possibility of causing an alimentary canal obstacle, and not giving a patient a shock of pain or a drug unlike administration by injection, since it has some advantages which are not acquired, attention is attracted.

[0003]However, in order that the skin may work as a barrier to a foreign matter, generally, the skin permeability of a drug is low and there is a limit in TDD of a drug. For this reason, in order to carry out percutaneous absorption of the drug effectively, it is indispensable to promote the percutaneous absorption of a drug by a certain method. Although the formation of pro Drac of a drug, complex formation, iontophoresis, etc. are

tried as a method of promoting this percutaneous absorption, methods currently performed most include use of penetration enhancer.

[0004]Until now, as penetration enhancer of a drug, ethanol, dimethyl sulfoxide, 1-dodecylazacycloheptane-2-one (trade name Azone), terpenes, a surface-active agent, etc. are independent, or combine, and are examined. For example, the facilitatory effect [in / in JP 1-81693,A / in the facilitatory effect in the mixed stock of 1-menthol, ethanol, and water / the mixed stock of oleic acid and ethanol] is shown in JP 4-217926.A to the narcotics painkiller and the nonnarcotic painkiller. It is known that d-limonene shows a Tsuguaki facilitatory effect to the percutaneous absorption of a lipophilicity drug like indomethacin or ketoprofen (JP 2-207024,A). However, in the absorption enhancers reported conventionally, it was not able to be said that the proabsorptive effect of drugs (for example, indomethacin, ethenzamide, etc.) was still enough.

[0005]

[Problem to be solved by the invention]An object of this invention is to provide the percutaneous absorption promotion constituent and percutaneous absorption preparation in which the skin permeability which was excellent in the physiological active substance (drug) is shown.

[0006]

[Means for solving problem]As a result of this invention persons' repeating research variously in view of an above-mentioned situation, the constituent containing 1-menthol and a pyrrolidone compound increases the skin transmission rate of a drug remarkably. The percutaneous absorption preparation which furthermore blended the drug with this constituent finds out excelling in the percutaneous absorption of a drug extremely, and came to complete this invention.

[0007]Provide a percutaneous absorption promotion constituent, wherein this invention contains (a) 1-menthol and at least one sort of the (b) pyrrolidone or its derivative, and further Namely, (a) 1-menthol, (b) Provide the percutaneous absorption preparation containing at least one sort of a pyrrolidone or its derivative, and the (c) physiological active substance.

[0008]In this invention, an essential oil ingredient [not only like a pure article but the mentha oil in which this is made into the main ingredients] etc. whose above-mentioned (a) 1-menthol is are used. although the loadings in particular of such 1-menthol are not limited -- general -- a constituent -- it blends in 0.5 to 5weight % of the range preferably especially 0.2 to 1.5weight % 0.1 to 30weight %.

[0009]As the above-mentioned (b) pyrrolidone or its derivative, Pyrrolidone carboxylic acid, pyrrolidone-carboxylic-acid sodium, pyrrolidone-carboxylic-acid triethanolamine, Although pyrrolidone-carboxylic-acid ethyl, pyrrolidone-carboxylic-acid octyl, N-pyrrolidone-carboxylic-acid ethyl, 2-pyrrolidone, N-methyl-2-pyrrolidone, an N-ethyl-2-pyrrolidone, an N-dimethyl-2-pyrrolidone, etc. can be used. It is preferred to use 2-pyrrolidone and N-methyl-2-pyrrolidone especially. although the loadings in particular of these pyrrolidone compounds are not limited -- general -- a constituent -- it blends in 0.5 to 20% of range preferably especially 0.2 to 40% 0.1 to 60%.

[0010]This invention contains the above-mentioned ingredient (a) 1-menthol, the (b) pyrrolidone, or at least one sort of the derivative of (a) -(b) both ingredients. Although a content ratio in particular of both ingredients is not limited, when an ingredient (b) is set to 1, it is preferred that an ingredient (a) is a rate of 0.15-1.0 (weight ratio) to an

ingredient (b).

[0011]By combining the two above-mentioned ingredients which are the penetration enhancer known conventionally, if this invention is unexpectedly independent, it finds out a percutaneous absorption facilitatory effect which obtained and was excellent. Although details of the mechanism of action which a constituent of this invention makes promote percutaneous absorption are not solved, they are presumed to be what percutaneous absorption promotes remarkably by a synergistic effect of an operation which reduces skin horny layer barrier ability by 1-menthol, and a drug solvent action by a pyrrolidone compound.

[0012]Arbitrary things can be conventionally chosen and used for a physiological active substance (drug) used for this invention out of a publicly known drug. When these drugs are illustrated, it is as follows, but it is not limited to these.

[0013]Aspirin, diflunisal, mefenamic acid, tolfenamic acid, diclofenac, Sulindac, indomethacin, indomethacin fancy roller flannel, acetaminophen, Pro gourmet TASHIN, nabumetone, ibuprofen, flurbiprofen, Ketoprofen, naproxen, pranoprofen, fenoprofen, Nonsteroidal resolution analgesics, such as thia pro FEN, oxaprozin, loxoprofen sodium, aluminoprofen, phenylbutazon, piroxicam, tialamide, eprizole, ibufenac, hyaluronic acid, salicylic acid, and etheznazamide.

[0014]Steroid system antiinflammatory drugs, such as hydrocortisone, prednisolone, and triamcinolone.

[0015]Estradiol, ethinylestradiol, estriol, estramustine, Progesterone, hydroxyprogesterone, medroxyprogesterone, Chlormadinone, allyltrenol, a dimethylsterone, norethisterone, Hormonal drugs, such as testosterone, dehydroepiandrosterone, fluoxymesterone, oxymetholone, methenolone. GONADOREN, pre Tire Lynn.

SOMATORERIN, corticorelin, oxytocin, vasopressin, desmopressin, a bromocriptine, and octreotide.

[0016]Antiviral drugs, such as BITARABIN, aciclovir, and ganciclovir. Antifungal drugs, such as a GURISEO flavin, fluconazole, and miconazole. Anticancer drugs, such as cyclophosphamide and fluorouracil. Immunosuppressive agents, such as cyclophosphamide and methotrexate tacrolimus hydrate. Antirheumatic drugs, such as golden thiomalic acid.

[0017]Arthrfuge, such as colchicine and allopurinol. Resolution enzymes, such as pro meline and lysozyme chloride. Antihistaminic agents, such as diphenhydramine, diphenylpyraline, dimenhydrinate, and chlorpheniramine. Antiallergic drugs, such as cromoglycic acid, tranilast, and ketotifen. Diabetic medicine, such as an insulin.

[0018]Antithyroid drugs, such as propylthiouracil and thiamazole. The stomach and calcium metabolism medicine, such as alfacalcidol, calcitriol, calcitonin, an ERUKARUSHI tonin, and calcitonin salmon. Hemostatics, such as adrenochrome, tranexamic acid, and thrombin. Antithrombotic drugs, such as heparin and wafarin. Hyperlipemia medicine, such as clofibrate, simvastatin, and cholestyramine.

[0019]Angina pectoris remedies, such as nitroglycerine, isosorbide, nifedipine, diltiazem, verapamil, nisoldipine, nitrendipine, and nicorandil. Vasodilators, such as alprostadil, caronium chloride, and minoxidil. Hypotensive agents, such as nilvadipine, nifedipine, a PUPURANO roll, nifedipine, clonidine, methyldopa, hydralazine, tobradipine, and budralazine. Bronchodilators, such as theophylline, salbutamol, tulobuterol, formoterol, and clenbuterol.

[0020]Narcotic analgesics, such as morphine. Nonnarcotic analgesics, such as pentazocine, buprenorphine, EPUTAZOSHIN, butorphanol, opioid, peptide, and dihydroetorphine. Antipyretic analgesics, such as sulpyrine, acetaminophen, phenacetin, and dimetofiazine.

[0021]Brain metabolism improvement medicine, such as adenosine mirin acid disodium, ifenprodil, gamma-aminobutyric acid, gamma amino beta hydroxybutyric acid, ANIRASETAMU, and nicardipine. Neuromuscular junction blocking drugs, such as dantrolene sodium. Muscle relaxants, such as pridinol mesilate, baclofen, eperisone, CHIZANJIN, an alcuronium chloride, suxamethonium chloride, tubocurarine chloride, dantrolene sodium, pancuronium bromide, and bromination BEMARONIUMU. Local anesthetics, such as procaine, cocaine, a tetracaine, lidocaine, dibucaine, and prillocaine etc. These salts permitted pharmacologically.

[0022]They are a nonsteroidal resolution analgesic and a drug above all with most preferred indomethacin and ethebamide especially among the above-mentioned drugs. If needed, one sort of these drugs may be used, they may be used in two or more sorts of combination, and the loadings should just be sufficient quantity to demonstrate drug effect.

[0023]Although the pharmaceutical form in particular of percutaneous absorption type pharmaceutical preparation is not limited, for example, an ointment, cream pharmaceuticals, liquids and solutions, loions, liniments, plaster (plaster agent), cataplasms, a patch agent, gel, or a tape can be mentioned in this invention. Especially gel, liquids and solutions, plaster (plaster agent), and cataplasms show the outstanding effect, and are preferred. These pharmaceutical preparation can be manufactured with a conventional method by combining an adjuvant, the constituent by this invention, and components of the drug product required for the pharmaceutical form to manufacture, i.e., a base, an additive agent, etc. if needed.

[0024]For example, as a base used for gel, alcohols (an example: ethanol, propanol, 8 acetylation cane-sugar denatured alcohol, etc.), gelling agents (an example: a carboxy vinyl polymerization object, ethyl cellulose, etc.), water, etc. are mentioned. moreover -- as the base used for liquids and solutions -- alcohols (example: -- ethanol.) Glycols, vegetable oil (an example: a butylene glycol, propylene glycol, etc.) (an example: olive oil, soybean oil, etc.) and liquefied higher fatty acid groups (an example: oleic acid, linolic acid, etc.), such as propanol, higher alcohol, water (an example: octyl alcohol etc.), etc. are mentioned. As a base used for plaster (plaster agent), A binder (an example: an ethylene vinyl acetate system binder, acrylic pressure sensitive adhesive, styrene isoprene styrene block copolymer, etc.). As a base which tackifiers (an example: a rosin system, a terpene series, a synthetic petroleum resin system, etc.) etc. are mentioned, and is used for cataplasms, Binders (an example: polyacrylic acid, a polyacrylic acid partial neutralized substance, sodium polyacrylate, a carboxyvinyl polymer, gelatin, a maleic anhydride copolymer, etc.) etc. are mentioned.

[0025]As an adjuvant used for gel, liquids and solutions, plaster (plaster agent), or cataplasms, or an additive agent. A surface-active agent (an example: polyoxyethylene sorbitan fatty acid ester etc.), PH adjusters (an example: diisopropanolamine etc.), an antiseptic (an example: paraoxybenzoic acid etc.), Things generally used for external preparations, such as an anti-oxidant (an example: butylhydroxytoluene), a softener (an example: liquid paraffin), extenders (an example: kaolin, titanium oxide, light anhydrous

silicic acid, etc.), and moisturizers (an example: glycerin, propylene glycol, etc.), are mentioned.

[0026]

[Working example]Hereafter, although this invention is explained still in detail using working example, this invention is not limited to these working example.

[0027]To solvent 100 weight section which consists of 5:95 (weight ratio), the "working example 1" N-methyl-2-pyrrolidone and water. Indomethacin 1 weight section, l-menthol 3 weight section, and polyoxyethylene-sorbitan-fatty-acid-ester (made in [Nikko Chemicals], tangent line-10) 0.1 weight section were added, respectively, it agitated on a 42 ** water bath for 12 hours, and the suspension which distributed indomethacin uniformly was obtained.

[0028]The suspension which distributed indomethacin uniformly like working example 1 was obtained except having set the weight ratio of the "working example 2" N-methyl-2-pyrrolidone and water to 10:90.

[0029]The suspension which distributed indomethacin uniformly like working example 1 was obtained except having set the weight ratio of the "working example 3" N-methyl-2-pyrrolidone and water to 20:80.

[0030]The weight ratio of the "comparative example 1" N-methyl-2-pyrrolidone and water was set to 0:100, and the suspension (namely, aqueous suspension which does not contain N-methyl-2-pyrrolidone and l-menthol at all) which distributed indomethacin uniformly like working example 1 was obtained except not adding l-menthol.

[0031]The suspension which distributed indomethacin uniformly like working example 1 was obtained except having set the weight ratio of the "comparative example 2" N-methyl-2-pyrrolidone and water to 0:100 (that is, N-methyl-2-pyrrolidone is not included at all).

[0032]The suspension which distributed indomethacin uniformly like working example 1 was obtained except not adding "comparative example 3" l-menthol 3 weight section.

[0033]The horizontal-type diffusion cell (applied-surface product: 0.95 cm2) which circulated 37 ** water pinches the abdomen extraction skin (depilation on the extraction previous day) of an experiment 1Wistar system male rat (eight weeks old), 3 ml of 1/15 mol / l phosphate buffer solutions were put into the receiver (dormis) side, and it agitated with the magnetic stirrer. 3 ml of suspension prepared by working example 1-3 and the comparative examples 1-3 was applied to the donor (keratin) side, respectively. The solution in a receiver was extracted temporally, the concentration of drug in it was measured with high performance chromatography, and the quantity of the drug which penetrated the rat skin was calculated.

[0034]The accumulation volume of the indomethacin which penetrated the rat skin from each suspension of working example 1-3 and the comparative examples 1-3 is shown in drawing 1. Working example 1-3 which used together l-menthol and N-methyl-2-pyrrolidone so that clearly from drawing 1, Skin permeability higher than any of the comparative example 1 which does not use l-menthol and N-methyl-2-pyrrolidone, the comparative example 2 used by a l-menthol independent, and the comparative example 3 used by a N-methyl-2-pyrrolidone independent is accepted.

[0035]Suspension which distributed indomethacin uniformly like working example 1 was obtained except having made "working example 4" N-methyl-2-pyrrolidone into 2-pyrrolidone.

[0036]Using each suspension of experiment 2 working example 4 and the comparative examples 1 and 2, the experiment 1 and the same experiment were conducted and accumulation volume of indomethacin which penetrated the rat skin from each suspension was calculated. The result is shown in drawing 2.

[0037]In a passage clear from drawing 2, working example 4 which used l-menthol and 2-pyrrolidone together shows permeability higher than the comparative example 2 used by the comparative example 1 and the l-menthol independent which do not use l-menthol and 2-pyrrolidone.

[0038]A solution (A) in which 8 acetylation cane-sugar denatured alcohol 40 weight section was made to dissolve "working example 5" indomethacin 1 weight section and l-menthol 3 weight section, A solution (B) in which mixed liquor of water 43 weight section and N-methyl-2-pyrrolidone 10 weight section was made to dissolve the amount part of carboxyvinyl polymer duplex is each prepared, After adding A to B and agitating it, it harmonized into one weight section, diisopropanolamine was agitated for 10 minutes, and uniform hydrophilic gel ointment was prepared.

[0039]The solution (C) in which 8 acetylation cane-sugar denatured alcohol 40 weight section was made to dissolve "comparative example 4" indomethacin 1 weight section, The solution (D) in which water 56 weight section was made to dissolve the amount part of carboxyvinyl polymer duplex was each prepared, after adding C to D and agitating it, it harmonized into one weight section, diisopropanolamine was agitated for 10 minutes, and uniform hydrophilic gel ointment was prepared.

[0040]The vertical mold diffusion cell (applied-surface product: 3.14 cm²) which circulated 37 ** water pinches the abdomen extraction skin (depilation on the extraction previous day) of an experiment 3Wistar system male rat (seven weeks old), 19 ml of 1/15 mol / 1 phosphate buffer solutions were put into the receiver (dermis) side, and it agitated with the magnetic stirrer. It applied each 0.5g of gel prepared by working example 5 and the comparative example 4 to the donor (keratin) side. The solution in a receiver was extracted temporally, the concentration of drug in it was measured with high performance chromatography, and the quantity of the drug which penetrated the rat skin was calculated.

[0041]The accumulation volume of the indomethacin which penetrated the rat skin from working example 5 and the comparative example 4 is shown in drawing 3. In the gel using indomethacin, it turns out that working example 5 which used together l-menthol and N-methyl-2-pyrrolidone shows permeability higher than the comparative example 4 which does not use l-menthol and N-methyl-2-pyrrolidone so that clearly from drawing 3.

[0042]The solution (E) in which 8 acetylation cane-sugar denatured alcohol 40 weight section was made to dissolve the amount part of "working example 6" ethenzamide duplex, and l-menthol 3 weight section, The solution (F) in which the mixed liquor of water 42 weight section and N-methyl-2-pyrrolidone 10 weight section was made to dissolve the amount part of carboxyvinyl polymer duplex is each prepared, After adding E to F and agitating it, it harmonized into one weight section, diisopropanolamine was agitated for 10 minutes, and uniform hydrophilic gel ointment was prepared.

[0043]The solution (G) in which 8 acetylation cane-sugar denatured alcohol 40 weight section was made to dissolve the amount part of "comparative example 5" ethenzamide duplex, The solution (H) in which water 55 weight section was made to dissolve the amount part of carboxyvinyl polymer duplex was each prepared, after adding G to H and

agitating it, it harmonized into one weight section, diisopropanolamine was agitated for 10 minutes, and uniform hydrophilic gel ointment was prepared.

[0044]Using experiment 4 working example 6 and the comparative example 5, the experiment 3 and the same experiment were conducted and the accumulation volume of the ethenzamide which penetrated the rat skin from working example 6 and the comparative example 5 was calculated. The result is shown in drawing 4.

[0045]In the gel using ethenzamide, working example 6 which used together l-menthol and N-methyl-2-pyrrolidone shows skin permeability higher than the comparative example 5 which does not use l-menthol and N-methyl-2-pyrrolidone so that clearly from drawing 4.

[0046]After making it dissolve, adding and stirring ethylene-vinyl acetate copolymer resin (LEVAPREN 450; made by a Beyer company), and a rosin system tackifier (rosin ester; made by Arakawa Chemical Industries, Ltd.) in the "working example 7" toluene, Indomethacin, l-menthol (made by TAKASAGO INTERNATIONAL CORP.), and N-methyl-2-pyrrolidone (made by Wako Pure Chemical Industries, Ltd.) were added, and it stirred enough. After coating this solution uniformly on a PET (polyethylene terephthalate) film, desiccation for 10 minutes was performed 70 degrees, and it covered with the PET film which carried out siliconizing, it judged to 10 cm x 7 cm, and uniform plaster was prepared.

The formula of working example 7 (presentation weight section after toluene removal) Indomethacin 9.0-copy N-methyl-2-pyrrolidone 3.0-copy l-menthol 3.0-copy ethylene-vinyl acetate copolymer resin 50.0 copy rosin system tackifier 35.0 copies

[0047]"Comparative example 6" natural-rubber-latex 40 weight section, liquid paraffin 9.5 weight section, For the base ingredient which consists of rosin system tackifier (rosin ester) 35 weight section, Beforehand Indomethacin 9 weight section, l-menthol 3 weight section, monooleic acid polyoxyethylene sorbitan 3 weight section, After carrying out addition mixing and coating uniformly the constituent which mixed dibutylhydroxytoluene 0.5 weight section on a PET (polyethylene terephthalate) film, it covered with the PET film which carried out siliconizing, it judged to 10 cm x 7 cm, and uniform plaster was prepared.

[0048]Using experiment 5 working example 7 and the comparative example 6, the experiment 3 and the same experiment were conducted and the accumulation volume of the indomethacin which penetrated the rat skin from working example 7 and the comparative example 6 was calculated. The result is shown in drawing 5.

[0049]In indomethacin content plaster, working example 7 which used together l-menthol and N-methyl-2-pyrrolidone shows skin permeability higher than the comparative example 6 which does not use N-methyl-2-pyrrolidone so that clearly from drawing 5.

[0050]Gelatin was added and it dissolved, after adding the liquid which distributed carboxymethylcellulose sodium in glycerin to the "working example 8" purified water. Subsequently, the liquid which distributed a polyacrylic acid partial neutralized substance, dried aluminium hydroxide gel, and polyoxyethylene hydrogenated castor oil in glycerin was added, and it kneaded enough. After adding the liquid which dissolved indomethacin and l-menthol in N-methyl-2-pyrrolidone beforehand, After spreading the mixture obtained by adding lactic acid and kneading enough to a nonwoven fabric, it covered with the polypropylene film, and judged to 10 cm x 14 cm, and indomethacin content cataplasms were obtained.

formula (presentation weight section) of working example 8
Indomethacin 0.3-copy N-methyl-2-pyrrolidone . 2.5-copy l-menthol 0.4-copy
polyacrylic acid partial neutralized substance . 6.5-copy carboxymethylcellulose sodium
1.0-copy gelatin 3.0-copy glycerin 29.7-copy dried-aluminium-hydroxide-gel 0.08-copy
polyoxyethylene hydrogenated-castor-oil 0.5-copy lactic acid 1.0-copy water 55.02
copies [0051]
[Effect of the Invention]According to this invention, the skin permeability of a drug can
be promoted remarkably and sufficient absorbed amount is obtained also with the drug
with which skin permeability sufficient in a Prior art was not acquired so that clearly also
from the above result. It becomes possible according to this invention to carry out dermal
administration of the drug of remedially sufficient quantity. When injection
administration of the drug is carried out, QOL (quality of life) can be improved by
removing a mental uneasy and corporal pain which a patient receives, and an
advantageous effect is acquired on clinical.

CLAIMS

- [Claim(s)]
- [Claim 1](a) A percutaneous absorption promotion constituent containing l-menthol and at least one sort of the (b) pyrrolidone or its derivative.
- [Claim 2](b) The percutaneous absorption promotion constituent according to claim 1 in which a pyrrolidone or its derivative is 2-pyrrolidone or N-methyl-2-pyrrolidone.
- [Claim 3]The percutaneous absorption promotion constituent according to claim 1 or 2 in which a content ratio of an ingredient (a) and an ingredient (b) is characterized by being ingredient (a) 0.15-1.0 to the ingredient (b) 1 by a weight ratio.
- [Claim 4](a) Percutaneous absorption preparation containing l-menthol, at least one sort of the (b) pyrrolidone or its derivative, and the (c) physiological active substance.
- [Claim 5](b) The percutaneous absorption preparation according to claim 4 in which a pyrrolidone or its derivative is 2-pyrrolidone or N-methyl-2-pyrrolidone.
- [Claim 6]The percutaneous absorption preparation according to claim 4 or 5 in which a content ratio of an ingredient (a) and an ingredient (b) is characterized by being ingredient (a) 0.15-1.0 to the ingredient (b) 1 by a weight ratio.
- [Claim 7](c) The percutaneous absorption preparation according to any one of claims 4 to 6 whose physiological active substance is a nonsteroidal resolution analgesic.
- [Claim 8]The percutaneous absorption preparation according to claim 7 whose nonsteroidal resolution analgesic is indomethacin or etheznamide.
- [Claim 9]The percutaneous absorption preparation according to any one of claims 4 to 8 whose pharmaceutical form of pharmaceutical preparation is gel or liquids and solutions.
- [Claim 10]The percutaneous absorption preparation according to any one of claims 4 to 8 whose pharmaceutical form of pharmaceutical preparation is plaster or cataplasms.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: MEADOWS, et al.	Examiner: Gregg Polansky
Serial No.: 11/959,185	Group Art Unit: 1614
Filed: December 18, 2007	Confirmation No.: 2309
For: PHARMACEUTICAL COMPOSITIONS AND METHOD FOR TREATING INFLAMMATION IN CATTLE AND OTHER ANIMALS	Date: February 22, 2011

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Sir:
This responds to the Restriction Requirement notification dated December 23, 2010, for which a response was due January 23, 2011. Applicants herein petition for a one-month extension of time from January 23, 2011 until February 23, 2011. Applicants authorize the Commissioner to charge the one-month extension fee (\$130.00) and any deficiency or credit any excess to Deposit Account No. 19-0365.

Remarks begin on page 2 of this paper.

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Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Affect Pain and Inflammation

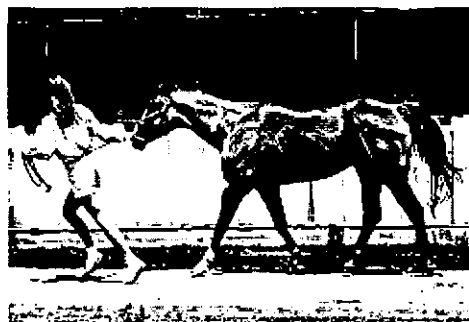
Steven G. Kamerling, RPh, PhD

*Professor of Veterinary Physiology, Pharmacology, &
Toxicology*

Great strides have been made in identifying mediators of inflammation and pain. This has led to new targets for anti-inflammatory drug development. The purpose of this article is: 1) to provide a contemporary overview on mediators of inflammatory pain; 2) to provide information on the comparative efficacy of currently used NSAIDs (nonsteroidal anti-inflammatory drugs) in horses; 3) to introduce the pharmacology of new NSAIDs; and 4) to discuss targets for the development of future NSAIDs with a special discussion of the role of nitric oxide and pain.

The cardinal signs of inflammation are redness, swelling, heat, pain and loss of function. Pain is perhaps one of the most significant manifestations of inflammation which demands our attention and treatment. The expression of pain varies widely among animals. However, stimuli that cause pain are similar. Extremes of heat (e.g., burns) and cold (e.g., frostbite), high concentrations of hydrogen ions (e.g., lactate buildup in muscles), distension of a hollow viscus (e.g., intestinal obstruction and colic), traumatic injury (e.g., bone fractures) and ischemia (e.g., intestinal torsion) can cause pain. Pain elicits protective reflexes and often complex emotional responses. Persistent untreated pain can lead to hormonal, nervous, and psychological abnormalities in animals.

Hyperalgesia refers to an increased sensitivity to pain and typically accompanies inflammation. It is produced by mediator substances in response to tissue injury and repair. Sources of these mediators include damaged tissue, blood vessels, neurons and immune cells.



Horses with musculoskeletal disease, such as laminitis, often demonstrate signs of lameness. Administration of different anti-inflammatory drugs offers variable degrees and duration of pain relief, which are often assessed by gait analysis. Studies evaluating the efficacy and potency of these drugs in horses are ongoing at LSU.

Bradykinin is released from damaged tissue and blood vessels. Substance P is liberated from excited or damaged free nerve endings. Neutrophils release leukotrienes (LTs) and activated macrophages release tumor necrosis factor alpha (TNF α) and interleukins (IL) 1 and 8. Fibroblasts, synoviocytes, and numerous other tissue cells release prostaglandins (PGs). These chemical mediators contribute collectively to hyperalgesia and pain.

Prostaglandins and LTs are produced from arachidonic acid when cell membranes are disrupted. Prostaglandins are formed via the action of cyclooxygenase (COX) which exists in two 'isoforms' (COX-1 and COX-2). Prostaglandins formed from 'constitutive' COX-1 regulate the production of cytoprotective gastric mucus and control renal blood flow. Prostaglandins formed from 'inducible' COX-2 are generated by immune and tissue cells in the presence of inflammation. Leukotrienes are formed via the action of 5-lipoxygenase. Prostaglandin E₂ and LTB₄ products are thought to be important mediators of inflammatory pain or hyperalgesia.

Current NSAIDs are believed to act, at least in part, by inhibiting the COX enzyme. With few exceptions most NSAIDs inhibit both COX-1 and COX-2. Inhibition of COX-1 is thought to underlie the ulcer, hemorrhage, and nephropathy associated with long-term use of NSAIDs. Inhibition of COX-2 is thought to underlie the anti-inflammatory actions. In addition to their actions on COX, current NSAIDs may also inhibit neutrophil production of

destructive superoxide radicals and proteases.

Currently available NSAIDs are indicated for the treatment of mild to moderately severe, acute and chronic pain. Nonsteroidal anti-inflammatory drugs differ widely in potency and therapeutic efficacy. In descending order, the therapeutic efficacy for NSAIDs in horses is flunixin, meclofenamic acid, ketoprofen, phenylbutazone, naproxen, and aspirin. Differences in efficacy can be explained by varying degrees of COX and cytokine inhibition, non-COX mechanisms, differing analgesia versus anti-inflammatory effects, and wide individual variation in response, within and between species.

Recent studies from our laboratory compared the therapeutic efficacy of phenylbutazone and ketoprofen (Ketofen® -- Rhone-Poulenc) in laminitic horses with chronic hoof pain. Four separate measures of analgesia were utilized including responses to an electronic hoof tester and subjective lameness assessment. The electronic hoof tester measured the amount of compressive force required to elicit a withdrawal reaction (i.e., hoof compression threshold or HCT) and the number of regions or 'loci' on the foot that were hyperalgesic. Lameness at a walk and trot were assessed using a modified Obel scale. Recommended therapeutic doses of phenylbutazone (4.4 mg/kg) and ketoprofen (2.2 mg/kg) were roughly equivalent in their ability to increase HCT and decrease lameness. However, a 3.63 mg/kg dose of ketoprofen (a phenylbutazone equimolar dose) produced a greater reduction in lameness and a greater increase in HCT which lasted for 24 hours. These results suggest that ketoprofen is more potent and, at appropriate doses, may be more efficacious than phenylbutazone for the production of analgesia. A similar study was recently performed comparing therapeutic doses of flunixin (Banamine®--Schering Plough Animal Health, Inc) (1.1 mg/kg) and phenylbutazone (4.4 mg/kg). Preliminary results indicate that flunixin (Banamine®): 1) was twice as efficacious as phenylbutazone in elevating HCT and reducing lameness; and 2) had roughly 8 times the analgesic potency (mg/kg) of phenylbutazone. Peak flunixin analgesia was observed 6 to 9 hours after dosing.

Although ketoprofen is the most recently approved NSAID for horses, new NSAIDs have been developed for other species. There is considerable effort on the part of the pharmaceutical industry to identify NSAIDs with

superior anti-inflammatory efficacy, yet minimal gastrointestinal toxicity. Their approach has been to develop NSAIDs that preferentially inhibit COX-2 with minimal effect on COX-1. A member of the oxicam chemical class of NSAIDs, such as meloxicam (Boehringer Ingelheim), has recently undergone extensive testing in Europe. Meloxicam, depending upon the bioassay utilized, has a 1 to 100 fold greater selectivity for COX-2 than COX-1. It is more selective for COX-2 than piroxicam, tenidap, diclofenac and indomethacin. Meloxicam also possesses greater anti-inflammatory potency (2-60 times) than piroxicam, indomethacin, diclofenac, tenidap, naproxen, aspirin and tenoxicam. This NSAID appears to be a potent suppressor of PG production from activated phagocytes. Meloxicam was rated as 'better than good' in human rheumatoid arthritis patients and 'analgesic' in osteoarthritic patients. Compared to piroxicam, diclofenac and naproxen, meloxicam (7.5-15mg/patient for 6 months) was associated with the least number of adverse GI events in arthritic patients. Meloxicam has also been studied in dogs. In a urate-induced canine synovitis model, meloxicam (0.1 and 0.5 mg/kg IV) increased limb loading from 4 to 12 hours. Significant reductions in standing lameness and pain score were also reported from 4-24 hours.

Meloxicam has been studied in horses. A dose of 0.6 mg/kg was administered to ponies, and responses to carrageenan-induced acute inflammation were recorded. Meloxicam reduced heat, protein, lactic dehydrogenase, leukocyte numbers, PGE₂, and thromboxane B₂ in exudates obtained from the site of inflammation. This effect was greatest at 4-8 hours. Meloxicam levels gradually increased over time at the inflamed site. Although the incidence of gastrointestinal side effects in the horse have not been elucidated, meloxicam may be an NSAID worthy of further study.

As greater knowledge of intracellular signaling pathways is gained, new targets for anti-inflammatory drugs are emerging. The intracellular signaling molecule, nitric oxide (NO), has been implicated in the production of pain. Nitric oxide is produced from L-arginine via the action of two enzymes: 'constitutive' NO synthase (cNOS) and 'inducible' NO synthase (iNOS). The constitutive enzyme is found in neurons and endothelial cells where it plays a role in neurotransmission and vasorelaxation, respectively. The inducible enzyme is found in immune cells where it gives rise to NO during inflammation. Nitric

oxide has the beneficial role of being 'microbiocidal' and a natural vasodilator, and the detrimental role of contributing to pain and inflammation.

A number of studies suggest a role for NO in hyperalgesia. For example, intracutaneous injection of NO produces dose-related pain in humans. Inhibitors of NOS, such as L-NAME, produce dose dependent analgesia in hyperalgesic rats. The actions of L-NAME are reversed by L-arginine, the natural substrate for NOS. Nitric oxide synthesis inhibitors such as L-NAME and L-NNA produce analgesia when: 1) administered systemically (e.g., intraperitoneally); 2) administered directly into the cerebral ventricles or spinal cord; or 3) administered directly at the site of inflammation.

L-arginine is the natural substrate for NOS and can increase NO levels in certain tissues. Although it antagonizes the action of the NOS inhibitors, some studies have shown that it produces a moderate degree of analgesia when administered alone. In fact, studies in horses suggest that substances that donate or increase NO may relieve pain. Other studies have shown that a 10% intravenous infusion of L-arginine caused vasodilation and improved the circulation in hooves of ponies with grass-induced acute laminitis. Topical application of nitroglycerine, a potent vasodilator and NO donor, was reported to reduce the bounding pulses, decrease lameness and lower blood pressure in the laminitic ponies. These data suggest that despite the fact that L-arginine and nitroglycerine produce NO (which contributes to pain), their ability to vasodilate, improve pedal circulation and ultimately relieve pain may be more important. Certainly, agents that affect the production of NO are worthy of further study in horses with laminitis and other inflammatory conditions.

In summary, persistent inflammatory pain is a condition that requires treatment. Currently available NSAIDs can be used to treat mild to moderately severe inflammatory pain. Nonsteroidal anti-inflammatory drugs vary in their mechanisms of action and efficacy. Therefore, a number of different NSAIDs should be considered in order to achieve the most efficacious therapy for the equine patient. Nonsteroidal anti-inflammatory drugs which act preferentially on COX-2 may be safer to use, particularly for long-term therapy. Meloxicam is a new NSAID which appears to be efficacious, yet is associated with fewer adverse effects than its predecessors. Nitric oxide appears to play a role in inflammatory pain. Depending

upon the time course of inflammation, suppression or enhancement of NO formation may influence the pain experience.

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