

Clarke, Modet & C
COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-052072- -00003-0000

Fecha: 2009-02-27 16:08.42 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E.S.D.

REF: EXPEDIENTE No. 07.052.072
SOLICITANTE: ROXRO PHARMAN, INC.

ASUNTO: SOLICITUD EXAMEN DE PATENTABILIDAD

DILIA RODRÍGUEZ D'ALEMAN identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad solicitante, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 09-13,342, por la suma de \$452.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

DILIA RODRIGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.

P-939

181

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-052072- -00003-0000

RECIBO OFICIAL DE CAJA : 9 - 13,342
FECHA : FEBRERO 18 DE 2009

Fecha: 2009-02-27 16:08:42 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eje: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	107996851	18/02/2009	58,595,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	452,000.00
		TOTAL :	\$ 452,000.00

SON: CUATROCIENTOS CINCUENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL ASUNTO No.

P-939

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-52072

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **596** DE

FECHA **30 DE SEPTIEMBRE DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **30 DE DICIEMBRE DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

Supplement to
WHO Chronicle, 1984
Vol. 38, No. 2 (April)

International Nonproprietary Names for Pharmaceutical Substances

In accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances,¹ notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in the *WHO Chronicle*, e.g., for List 51 Prop. INN not later than 31 August 1984.

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

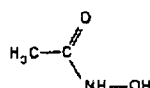
Proposed International Nonproprietary Names (Prop. INN): List 51²

Proposed International
Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number

acidum acetohydroxamicum
acetohydroxamic acid

acetohydroxamic acid
C₂H₃NO₂ 546-88-3



Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (*Nonproprietary Names for Pharmaceutical Substances*, Twentieth Report of the WHO Expert Committee), ISBN 92 4 120581 4 (price: Sw. fr. 6.-), an account of this publication will be found on page 21 of this Supplement (Annex 2). All names from Lists 1-47 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in: *International Nonproprietary Names (INN) for Pharmaceutical Substances Cumulative List No. 6, 1982*, World Health Organization, Geneva (ISBN 92 4 056013 0) (price: Sw. fr. 55.-). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to April 1982. The printout also indicates in which of the 47 individual lists of proposed names and 21 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of the *WHO Chronicle*. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland.

¹ See Annex 1, p. 19.

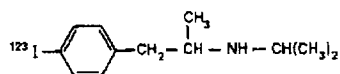
² Other lists of proposed and recommended international nonproprietary names can be found in *Cumulative List No. 6, 1982*.

Proposed International
Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number

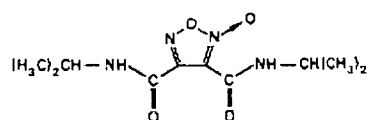
iofetamium (^{123}I)
iofetamine (^{123}I)

($\pm$)-*p*-iodo- ^{123}I -*N*-isopropyl- α -methylphenethylamine
 $\text{C}_{12}\text{H}_{15}^{123}\text{I}\text{N}$ 75917-92-9



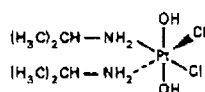
ipramidilum
ipramidil

N,N-diisopropyl-3,4-furazandicarboxamide 2-oxide
 $\text{C}_{10}\text{H}_{18}\text{N}_4\text{O}_4$ 83656-38-6



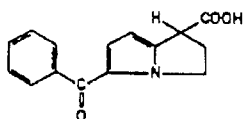
iproplatinum
iproplatin

ab-dichloro-*ce*-dihydroxy-*df*-bis(isopropylamine)platinum
 $\text{C}_6\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2\text{Pt}$ 62928-11-4



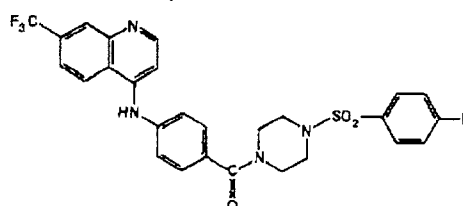
ketorolacum
ketorolac

($\pm$)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid
 $\text{C}_{15}\text{H}_{15}\text{NO}_3$ 74103-06-3



losulazinum
losulazine

1-[(*p*-fluorophenyl)sulfonyl]-4-[*p*-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperazine
 $\text{C}_{27}\text{H}_{22}\text{F}_4\text{N}_4\text{O}_2\text{S}$ 72141-57-2





US006333044B1

185
D₁(12) **United States Patent**
Santus et al.(10) **Patent No.:** US 6,333,044 B1(45) **Date of Patent:** Dec. 25, 2001(54) **THERAPEUTIC COMPOSITIONS FOR
INTRANASAL ADMINISTRATION WHICH
INCLUDE KETOROLAC®**(75) **Inventors:** Giancarlo Santus, Milan; Giuseppe
Bottoni, Bergamo; Ettore Bilato,
Padua, all of (IT)(73) **Assignee:** Recordati, S.A. Chemical and
Pharmaceutical Company, Chiasso
(CH)(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) **Appl. No.:** 08/383,707(22) **Filed:** Feb. 1, 1995**Related U.S. Application Data**(63) Continuation of application No. 07/875,700, filed on Apr.
29, 1992, now abandoned.(30) **Foreign Application Priority Data**

Jul. 22, 1991 (IT) MI91A2024

(51) **Int. Cl.⁷** A61K 9/14; A61K 9/12;
A61K 31/40; A01N 43/38(52) **U.S. Cl.** 424/434; 514/947; 514/413(58) **Field of Search** 424/434; 514/947,
514/413(56) **References Cited****U.S. PATENT DOCUMENTS**

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90/1322 * 2/1990 (WO) .
WO 90/07333 7/1990 (WO) A61K/31/445**OTHER PUBLICATIONS**

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 Ketorolac Tromethamine and Aspirin in the Treatment of
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 106S-110S.*

* cited by examiner

Primary Examiner—Diana Dudash*Assistant Examiner*—Clinton Ostrup(74) *Attorney, Agent, or Firm*—Darby & Darby(57) **ABSTRACT**

An analgesic/anti-inflammatory pharmaceutical dosage
 form which comprises an effective amount of an active
 ingredient selected from the group consisting of racemic
 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid,
 optically active forms thereof and pharmaceutically accept-
 able salts thereof, in combination with a pharmaceutically
 acceptable excipient or diluent, said dosage form being an
 intranasally administrable dosage form.

51 Claims, No Drawings

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THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION WHICH INCLUDE KETOROLAC®

This is a continuation of application Ser. No. 07/875,700, filed Apr. 29, 1992 abandoned.

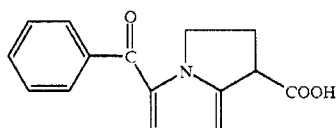
FIELD OF THE INVENTION

This invention relates to therapeutic compositions with analgesic and anti-inflammatory activity, suitable for intranasal administration, which include KETOROLAC® or its pharmaceutically acceptable salts as the active ingredient.

This invention also relates to a therapeutic method which provides for the administration of KETOROLAC® or its salts by the intranasal route.

BACKGROUND OF THE INVENTION

KETOROLAC® or 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, the formula of which is:



has been known for several years (U.S. Pat. No. 4,089,969) and is used in human therapy as an analgesic and an anti-inflammatory.

Both the racemic form and each of the dextro and levo isomers of this compound are known. Many pharmaceutically acceptable salts, the most commonly used of which is the tromethamine(2-amino-2-hydroxymethyl-1,3-propanediol) salt, are also known. Hereinafter, the name KETOROLAC® shall encompass individually or collectively the racemic mixture or either optically active compound and shall encompass the free acid as well as the tromethamine salt or any other pharmaceutically acceptable salt of any one of the foregoing.

Ample literature is available on KETOROLAC® (for instance, "KETOROLAC®—A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", *Drugs* 39(1): 86-109, 1990. It is described as a drug with considerably higher analgesic and anti-inflammatory activity than many other non-steroid anti-inflammatory drugs. Most significantly, it has higher analgesic activity than morphine, without the well-known side effects of the latter.

In the several pharmacological and clinical trials involving KETOROLAC® that have been conducted, this drug was administered both by the oral route and by injection (in turn, both intravenous and intramuscular). Regardless of the administration route, KETOROLAC® proved active and was found comparatively more active than the better known non-steroid drugs with analgesic and anti-inflammatory activity. However, about 10% of the patients treated (20 doses of 30 mg each administered over five days) by the intramuscular route suffered from one or more undesirable side effects such as somnolence, local (injection site) pain, sweating, nausea, headache, dizziness, vomiting, pruritus, and vasodilation.

The incidence of side effects was even higher (around 32%) in the patients treated with KETOROLAC® by the oral route for a few days. In the case of oral administration, gastrointestinal disorders (nausea, g.i. pain, dyspepsia,

diarrhea, flatulence, g.i. fullness, vomiting) were noted in up to 50% of the patients in addition to side effects incident to i.m. administration.

Intravenous administration is inconvenient and is limited to the treatment of acute conditions.

On the whole, the data available to date clearly describe a drug which is very active, but still unsatisfactory from the point of view of convenience of administration and/or side effects.

SUMMARY OF THE INVENTION

We have now found that it is possible to prepare Analgesic/anti-inflammatory formulations containing KETOROLAC® as an active ingredient, which are suitable for intranasal administration and that KETOROLAC® so administered is rapidly and thoroughly absorbed, giving therapeutic effects equivalent to those obtained by the intravenous route (acute treatments) or the intramuscular or oral routes (extended or chronic treatments), without inducing severe side effects. Most important, any possibility of gastrointestinal disorders is excluded, while disorders caused by CNS stimulation are considerably reduced both in incidence (e.g. number of patients affected) and intensity.

Another aspect of the present invention is directed to a therapeutic method for the treatment of inflammatory processes and for the therapy of pain of a traumatic or pathologic origin, which method comprises administering by the intranasal route an analgesic/anti-inflammatory amount of KETOROLAC® along with an absorption promoter and pharmaceutically acceptable diluents and/or excipients.

The new method provides for the intranasal administration of KETOROLAC® doses ranging between 0.5 and 40 mg, preferably between 5 and 30 mg, and is particularly effective in acute therapies, where a very rapid systemic delivery is required especially one not accompanied by the drawbacks of i.v. delivery (hospitalization, cost, etc.).

DETAILED DESCRIPTION OF THE INVENTION

All cited patents and literature are incorporated by reference in their entirety.

Although nasal administration to mammals (especially humans) of certain therapeutic agents is known, it is not to be presumed that all therapeutic agents can be effectively administered by this route. To the contrary, many therapeutic agents cannot be nasally administered. At present, the molecules which have proved suitable for this route of administration are still very few and consist essentially of only small peptide or hormone molecules (such as calcitonin, cerulean, β -endorphin, glucagon, horseradish peroxidase, B-interferon, oxytocin and insulin) in special formulations. The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes. In fact, mucous membrane irritation caused by the drug and/or excipient is the most common reason for which intranasal administration has not gained wider acceptance.

The new compositions according to the invention include the active ingredient in quantities ranging from 0.5 to 40 mg per dose, preferably 5 to 30 mg per dose, diluted in excipients such as humectants, isotoning agents, antioxidants, buffers and preservatives. A calcium chelating agent is also preferably included.

The intranasal formulations of the invention contain KETOROLAC® concentrations ranging from 5 to 20%,

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preferably about 15% weight/volume. Of course, the selection of the particular excipients depends on the desired formulation dosage form, i.e. on whether a solution to be used in drops or as a spray (aerosol) is desired or a suspension, ointment or gel to be applied in the nasal cavity are desired. In any case, the invention make it possible to have single-dose dosage forms, which ensure application of an optimum quantity of drug.

Administration of the present intranasal formulations provides very good absolute bioavailability of KETOROLAC®, as demonstrated in tests involving rabbits. The predictive value of the rabbit model with respect to bioavailability of nasally administered KETOROLAC® in humans is art-recognized (Mroszczak, E. J. et al., *Drug Metab. Dispos.*, 15:618-626, 1987, especially Tables 1 and 3). According to the results of the rabbit tests set forth below it is extrapolated that in humans intranasal administration of a composition according to the invention in amounts ranging between 0.5 mg/kg/day and 4 mg/kg/day will generate plasma levels of KETOROLAC® within the range of 0.3-5 mg/liter of plasma.

Suitable vehicles for the formulations according to the invention include aqueous solutions containing an appropriate isotoning agent selected among those commonly used in pharmaceuticals. Substances used for this purpose are, for instance, sodium chloride and glucose. The quantity of isotoning agent should impart to the vehicle (taking into account the osmotic effect of the active ingredient), an osmotic pressure similar to that of biological fluids, i.e. generally from about 150 to about 850 milliOsmoles (mOsm) preferably from about 270 to about 330 mOsm.

However, it is known that nasal mucous membranes are also capable of tolerating slightly hypertonic solutions. Should a suspension or gel be desired instead of a solution, appropriate oily or gel vehicles may be used or one or more polymeric materials may be included, which desirably should be capable of conferring bioadhesive characteristics to the vehicle.

Several polymers are used in pharmaceuticals for the preparation of a gel; the following can be mentioned as nonlimiting examples: hydroxypropyl cellulose (KLUCEL®), hydroxypropyl methyl cellulose (METHOCEL®), hydroxyethyl cellulose (NATROSOL®), sodium carboxymethyl cellulose (BLANOSE®), acrylic polymers (CARBOPOL®, POLYCARBOPHIL®), gum xanthan, gum tragacanth, alginates and agar-agar.

Some of them, such as sodium carboxymethyl cellulose and acrylic polymers, have marked bioadhesive properties and are preferred if bioadhesiveness is desired.

Other formulations suitable for intranasal administration of KETOROLAC® can be obtained by adding to the aqueous vehicle polymers capable of changing the rheologic behavior of the composition in relation to the temperature. These polymers make it possible to obtain low viscosity solutions at room temperature, which can be applied for instance by nasal spray and which increase in viscosity at body temperature, yielding a viscous fluid which ensures a better and longer contact with the nasal mucous membrane. Polymers of this class include without limitation polyoxyethylene-polyoxypropylene block copolymers (POLOXAMER®).

In addition to aqueous, oil or gel vehicles, other vehicles which may be used in the compositions according to the invention comprise solvent systems containing ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol, mixtures thereof or mixtures of one or more of the foregoing with water.

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In any case, a pharmaceutically acceptable buffer should be present in order to create optimum pH conditions for both product stability and tolerance (pH range about 4 to about 8; preferably about 5.5 to 7.5). Suitable buffers include without limitation tris (tromethamine) buffer, phosphate buffer, etc.

Other excipients include chemical enhancers such as absorption promoters. These include chelating agents, fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxylic acids (ascorbic acid, amino acids), glycyrrhetic acid, o-acetylcarnitine. Preferred promoters are diisopropyladipate, POE(9) lauryl alcohol, sodium glycocholate and lysophosphatidyl-choline which proved to be particularly active. Finally, the new compositions according to the invention preferably contain preservatives which ensure the microbiological stability of the active ingredient. Suitable preservatives include without limitation, methyl paraoxybenzoate, propyl paraoxybenzoate, sodium benzoate, benzyl alcohol, benzalkonium chloride and chlorbutanol.

The liquid KETOROLAC® formulations, preferably in the form of solutions, may be administered in the form of drops or spray, using atomizers equipped with a mechanical valve and possibly including a propellant of a type commercially available, such as butane, N₂, Ar, CO₂, nitrous oxide, propane, dimethyl ether, chlorofluorocarbons (e.g. FREON) etc. Vehicles suitable for spray administration are water, alcohol, glycol and propylene glycol, used alone or in a mixture of two or more.

Generally, illustrative formulations will contain the following ingredients and amounts (weight/volume):

Ingredient	Broad Range (%)	Preferred Range (%)
Na ₂ EDTA	0.001-1	0.05-0.1
Nipagin	0.01-2	0.05-0.25
POE (9) Lauryl alcohol	0.1-10	1-10
NaCMC (Blanose 7m8 sfd)	0.1-5	0.3-3
Carbopol 940	0.05-2	0.1-1.5
Glycerol	1-99	
Sodium glycocholate	0.05-5	0.1-1

It will be appreciated by those of ordinary skill that ingredients such as sodium carboxymethyl cellulose and Carbopol exist in many types differing in viscosity. Their amounts are to be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others. It is thus not possible to give an all-encompassing amount range for each ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

Another, although not preferred, alternative for the intranasal administration of the KETOROLAC®-based compositions comprises a suspension of finely micronized active ingredient (generally from 1 to 200 micrometers, preferably from 5 to 100 micrometers) in a propellant or in an oily vehicle or in another vehicle in which the drug is not soluble. The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and diluents suitable for use in pharmaceuticals are added to these vehicles. Surfactants include without limitation sorbitan sesquioleate, sorbitanmonooleate, sorbitan trioleate (amount: between about 0.25 and about 1%); suspending agents include with-

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out limitation isopropylmyristate (amount: between about 0.5 and about 1%) and colloidal silica (amount: between about 0.1 and about 0.5%); and diluents include without limitation zinc stearate (about 0.6 to about 1%).

The following examples of formulations for the intranasal administration of KETOROLAC® serve to illustrate the invention without limiting its scope.

EXAMPLE 1

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
EDTA disodium (chelating agent)	0.01	1 g
NIPAGIN (preservative)	0.1	10 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

The isotonicity of this composition was 190 mOsm but can be adjusted e.g. to 270 mOsm by the addition of 0.3% NaCl or 2.03% of glucose.

EXAMPLE 2

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
POE (9) lauryl alcohol (enhancer/promoter)	5	500 g
NIPAGIN	0.1	10 g
EDTA disodium	0.01	1 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution, of the components.

Cool the obtained solution to room temperature.

Add POE (9) lauryl alcohol and stir to complete dissolution.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

EXAMPLE 3

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
Sodium carboxymethyl cellulose	1	100 g
Tromethamine, q.s. to pH = 6		
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

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Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® and continue stirring to complete dissolution of the drug.

Disperse sodium carboxymethyl cellulose in the solution stirring vigorously.

Continue stirring to complete hydration of the polymer.

Adjust the pH to the required value by suitably adding tromethamine dissolved in water.

Bring to volume with water.

EXAMPLE 4

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
NIPAGIN	0.1	10 g
EDTA disodium	0.01	1 g
CARBOPOL 940	0.1	10 g
Tromethamine, q.s. to pH = 7-7.4		
Glycerol	2	200 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA.

Cool the solution to room temperature.

Dissolve KETOROLAC® tromethamine.

Complete the dissolution of the active ingredient and adjust the pH to a value of 7.1-7.4 by adding a 5% tromethamine solution.

In a separate vessel equipped with mixer, introduce the quantity of glycerol called for in the formulation.

Introduce CARBOPOL and mix until a homogeneous dispersion in the glycerol is obtained.

Add 4 liters of purified water with vigorous stirring and continue stirring the solution to complete hydration of the polymer.

Combine the solution containing the active ingredient and the polymer solution with stirring.

If necessary, adjust the pH to the required value with the tromethamine solution.

Bring to volume with water.

EXAMPLE 5

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
LUTROL F127	17	1.7 Kg
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Cool the solution to 4° C. and then, maintaining it between 4 and 6° C. throughout the operation, gradually add Lutrol F127 with stirring.

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Continue stirring to complete hydration of the polymer.
Bring the solution to room temperature.
Dissolve KETOROLAC® tromethamine.
Bring to volume with water.

EXAMPLE 6

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
Sodium carboxymethyl cellulose	2	200 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

The procedure of Example 3 was used to make the above formulation except that no buffer was added.

EXAMPLE 7

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
LUTROL F127	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified Water, q.s. to	100	10 L

The procedure of Example 5 was used to make the above formulation.

EXAMPLE 8

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Sodium glycocholate	0.3	30 g
Purified water, q.s. to	100	10 L

The procedure of Example 1 was used except that sodium glycocholate was dissolved with the nipagin and disodium EDTA at 80° C. in water. The isotonicity of this composition was 190 mOsm; it can be adjusted e.g. to 330 mOsm by the addition of 0.44% NaCl or 3.05% glucose.

EXAMPLE 9

Composition	%	For 10 liters
KETOROLAC® tromethamine	5	500 g
Lutrol F127	15	1500 g
Sodium glycocholate	0.3	30 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

The procedure of Example 5 was used except that sodium glycocholate was dissolved along with nipagin and disodium EDTA at 80° C.

EXAMPLE 10

We studied the stability of the preparations described in the Examples 1, 2, 6, 7, 8 and 9. The storing conditions were

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4° C., 22° C., 45° C. and 55° C. We analyzed the preparations at the beginning of the storing period and after 1, 2, 3 and 6 months. We used UV and HPLC analysis.

The parameters tested were:

- content of active compound (UV and HPLC)
 - content of keto and hydroxy degradation products (UV and HPLC)
 - appearance and color (visual examination)
 - pH (digital pH meter)
- The results are summarized in Table 1.

TABLE 1

Ex- am- ple	Temp. ° C.	Months	KTM (mg/ ml)	Keto %	Hy- droxy %	Appearance of solution	pH
1	22	0	50.1	0.8	0.3	light yellow	6.2
	45	2	50.8	0.2	0.0	yellow	6.5
	45	3	49.6	0.2	0.0	opalescent yellow	6.5
2	45	6	51.4	0.4	0.0	yellow with deposit	6.5
	22	0	49.0	0.1	0.3	light yellow	6.4
	45	2	47.7	0.4	0.0	yellow	6.8
6	45	3	46.7	0.2	0.0	yellow	6.9
	45	6	47.3	1.0	0.0	yellow	7.0
	22	0	49.6	0.1	0.4	yellow	6.0
25	45	1	47.0	0.1	0.1	yellow	6.5
	45	3	48.8	0.2	0.0	yellow	6.5
	45	6	50.1	0.9	0.0	yellow with deposit	5.5
7	22	0	48.5	0.0	0.5	light yellow	6.7
	55	1	49.0	0.8	0.0	yellow gel	6.8
	55	3	47.1	1.4	1.9	orange gel	6.6
8	22	0	52.3	0.0	0.0	light yellow	6.2
	45	1	53.2	0.0	0.0	yellow	6.4
	45	3	54.3	0.5	0.0	yellow	6.5
9	22	0	48.7	0.0	0.0	light yellow	6.7
	45	1	51.7	0.0	0.0	yellow	6.8

EXAMPLE 11

We tested in vitro the thermosetting properties of some preparations (Examples 1, 2, 7, 9). We sprayed a standardized amount of every preparation to a 37° C. constant-temperature, vertical glass surface and we measured the time that the drops of preparation spent to cover 10 cm. The speed of solution in moving on the constant-temperature surface is an indicator of the thermosetting properties of the dosage form. Examples 7 and 9 gave the best results in terms of thermosetting properties.

The results are reported in Table 2.

TABLE 2

Preparation Time to Cover 10 cm		
H ₂ O		3 sec.
Example 1		3 sec.
Example 2		3 sec.
Example 7		12 sec.
Example 9		15 sec.

EXAMPLE 12

We studied the nasal absorption and the local tolerance of four preparations (Examples 1, 6, 8, 9) in White New Zealand rabbits (three rabbits for each experimental group plus three controls). Each rabbit received a active preparation in one nostril and its placebo in the other. Each animal received 2 mg/kg of KETOROLAC® tromethamine (KTM), twice a day for seven days and once on the eighth day. The control rabbits were treated, after seven days of nasal

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administration of physiologic solution, with 2 mg/kg of KTM by intravenous route once. After the last treatment plasma samples were collected at several times and KTM plasma levels were investigated by HPLC. After the last blood sample was drawn all the animals were killed by excision of femoral arteries, after having been completely anaesthetized. Nasal turbinates, larynx and pharynx were removed and subjected to histological examinations.

Pharmacokinetic parameters are reported in Tables 3, 4, 5, 6, 7 and in FIG. 1. The local (nasal mucous) tolerance data showed good tolerance of the KETOROLAC-containing intranasal preparations with the formulation of Example 1 being the best tolerated followed by that of Example 6, Example 9 and Example 8 in that order.

TABLE 3

Control Absorption of KTM Composition: Example 9 Route of Administration: Intravenous Administered Dose: 2 mg/kg Plasma Concentration of KTM as ng/ml		
Sampling Time (hours)	Mean	± S.D.
Basal	0	0
0.083	14510	1999
0.25	7682	2887
0.5	3884	1891
1	1703	792
2	403	167
3	120	67
5	20	7

TABLE 4

Nasal Absorption of KTM Composition: Example 1 Route of Administration: Intranasal Administered Dose: 2 mg/kg/administration		
Sampling Time (hours)	Mean	± S.D.
Basal	18	16
0.25	2363	1035
0.5	1875	726
1	1103	490
2	593	217
3	267	55
5	121	52

TABLE 5

Nasal Absorption of KTM Composition: Example 8 Route of Administration: Intranasal Administered Dose: 2 mg/kg/administration		
Sampling Time (hours)	Mean	± S.D.
Basal	29	22
0.25	2973	1258
0.5	2654	880
1	2246	1145
2	1121	832
3	665	444
5	427	194

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TABLE 6

Nasal Absorption of KTM Composition: Example 9 Route of Administration: Intranasal Administered Dose: 2 mg/kg/administration		
Sampling Time (hours)	Mean	± S.D.
Basal	35	17
0.25	2036	572
0.5	1663	778
1	1009	345
2	325	103
3	184	22
5	198	52

TABLE 7

Nasal Absorption of KTM Composition: Example 6 Route of Administration: Intranasal Dose Administered: 2 mg/kg/administration		
Sampling Time (hours)	Mean	± S.D.
Basal	23	20
0.25	1872	1228
0.5	1772	1027
1	1213	619
2	616	293
3	269	96
5	133	23

From the foregoing data, the following bioavailability parameters were calculated:

TABLE 8

Formulation	i.v.	Example 1 (A)	Example 8 (B)	Example 9 (C)	Example 6 (D)
<u>AUC₀₋₅ (h.ng/ml)</u>					
average	7355	3237	5972	2692	3197
± S.D.	2405	1129	2973	571	976
CV (%)	32.7	34.9	49.8	21.2	30.5
<u>T_{max} (hours)</u>					
average	0.25	0.42	0.33	0.33	0.33
± S.D.	0	0.14	0.14	0.14	0.14
CV (%)	0	34.6	43.3	43.3	43.3
<u>C_{max} (ng/ml)</u>					
average	2363	3226	2229	1895	1895
± S.D.	1035	1079	335	1203	1203
CV (%)	43.8	33.4	15.0	63.5	63.5
<u>AUC i.n./AUC i.v.</u>					
average	0.44	0.81	0.36	0.43	0.43

i.n. = intranasal
i.v. = intravenous

Each value is the mean of the data obtained from three animals.

The foregoing results indicate that intranasal formulations of KETOROLAC® according to the invention compare favorably with intravenous formulations in terms of absorption (Formulation B from Example 8 being the best absorbed), time to maximum plasma concentration, and maximum plasma concentration and exhibit good absolute bioavailability (especially formulation B).

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EXAMPLE 13

Composition	%	For 10 Liters
KETOROLAC® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

EXAMPLE 14

Composition	%	For 10 Liters
KETOROLAC® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Glycocholic acid	0.3	30 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine and glycocholic acid by stirring.

Bring to volume with water.

EXAMPLE 15

Composition	%	For 10 Liters
KETOROLAC® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Glycocholic acid	0.3	30 g
Lutrol F 127	15	1500 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 8 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution to 4° C. and then, maintaining it between 4° and 6° C. throughout the operation, gradually add Lutrol F127

Continue stirring to complete hydration of the polymer.

Bring the solution to room temperature.

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Dissolve KETOROLAC® tromethamine and glycocholic acid.

Bring to volume with water.

APPENDIX OF PRODUCT NAMES AND
EXAMPLES OF COMMERCIAL SOURCES

KETOROLAC TROMETHAMINE: SYNTEX IRELAND, CLARECASTLE, IRELAND

10 HYDROXYPROPYLCELLULOSE (KLUCEL) DOW CHEMICAL CO, MIDLAND Mich. USA

HYDROXYPROPYLMETHYLCELLULOSE (METHOCEL) DOW CHEM. CO, MIDLAND Mich.

15 HYDROXYETHYLCELLULOSE (NATROSOL) HERCULES INC, WILMINGTON Del. USA

SODIUM CARBOXYMETHYLCELLULOSE (BLANOSE) HERCULES INC, WILMINGTON Del.

CARBOPOL: BF GOODRICH CHEMICAL CO., CLEVELAND, Ohio, USA

20 POLYCARBOPHIL: BF GOODRICH CHEMICAL CO., CLEVELAND, Ohio, USA

GUM TRAGACANTH: COLONY IP. & EXP. CO., NEW YORK, N.Y., USA

25 GUM XANTHAN: ALDRICH CHEMIE, STANHEIM, GERMANY

SODIUM ALGINATE: EDWARD MANDELL CO., CARMEL, NEW YORK, USA

AGAR AGAR: ALDRICH CHEMIE, STANHEIM, GERMANY

30 POLOXAMER (LUTROL f127): BASF WYNDOTTE CORP., PARSIPPANY, N.J., USA

ETHYL ALCOHOL: EASTMAN CHEMICAL PRODUCTS INC., KINGSFORD, Tenn., USA

35 ISOPROPYL ALCOHOL: BAKER CHEMICAL CO., NEW YORK, N.Y., USA

PROPYLENE GLYCOL: DOW CHEMICAL CO., MIDLAND, Mich., USA

POLYETHYLENE GLYCOL: BASF WYNDOTTE CORP., PARSIPPANY, N.J., USA

40 DIISOPROPYLADIPATE: CRODA, GOOLE, NORTH HUMERSIDE, UK

SODIUM GLYCOCHOLATE: SIGMA CHEMICAL COMPANY, ST. LOUIS, Mo., USA

45 LYSOPHOSPHATIDYLCHOLINE: AMERICAN LECITHIN, LONG ISLAND, N.Y., USA

METHYLPARAOXYBENZOATE (NIPAGIN): BDH CHEMICAL LTD, POOLE, DORSET, UK

PROPYLPARAOXYBENZOATE: BDH CHEMICAL LTD, POOLE, DORSET, UK

50 SODIUM BENZOATE: PFIZER INC., NEW YORK, N.Y., USA.

BENZYL ALCOHOL: BDH CHEMICAL LTD, POOLE DORSET, UK

BENZALCONIUM CHLORIDE: ION PHARMACEUTICALS, COVINA, Calif., USA

55 CHLOROBUTANOL: EASTERN CHEMICAL PRODUCTS, SMITHTOWN, N.Y. USA

EDTA DISODIUM: GRACE AND CO., LONDON, UK.

60 POE(9)LAURYL ALCOHOL: BASF WYNDOTTE CORP., PARSIPPANY, N.J., USA

TROMETHAMINE: FARMITALIA, MILAN, ITALY

GLYCEROL: DOW CHEMICAL CO., MIDLAND, Mich., USA

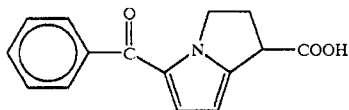
65 SODIUM CHLORIDE: ALDRICH CHEMIE, STANHEIM, GERMANY

GLUCOSE: ROQUETTE LTD, TUNBRIDGE WELLS, KENT, UK

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What is claimed is:

1. An analgesic/anti-inflammatory pharmaceutical liquid dosage form which comprises a systemically effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being a non-thermosetting intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration.

2. The dosage form of claim 1 comprising 0.5–40 mg of said active ingredient.

3. The dosage form of claim 1 comprising 2–20 mg of said active ingredient.

4. The dosage form of claim 1 in a single-dose form.

5. The dosage form of claim 1 comprising 5–20% of said active ingredient (weight/volume).

6. The dosage form of claim 1 in the form of a solution or suspension.

7. The dosage form of claim 1 containing 15% of said active ingredient.

8. The dosage form of claim 1 wherein said excipient comprises a bioadhesive.

9. The dosage form of claim 1 further comprising as an excipient an intranasal absorption promoter.

10. The dosage form of claim 8 wherein said promoter is selected from the group consisting of POE (9) lauryl alcohol and sodium glycocholate and lysophosphatidyl choline.

11. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin which comprises the administration by the intranasal route of a dosage form according to claim 1.

12. A method according to claim 11 wherein said mammal is a human and wherein said effective amount is sufficient to generate a plasma concentration of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid within the range between 0.3 and 5 mg/liter of plasma.

13. The dosage form of claim 1 comprising a mucosal absorption promoter that is not a mucosal irritant.

14. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin, which comprises the administration by the intranasal route of a dosage form comprising a systemically effective amount of the active ingredient 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, in a racemic or optically active form or in the form of a pharmaceutically acceptable salt, said dosage form being a non-thermosetting intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels for said active ingredient effective for analgesic or anti-inflammatory use after intranasal administration.

15. A method according to claim 14 wherein said effective amount is within the range of 0.5–40 mg.

16. A method according to claim 14 wherein said effective amount is within the range of 5–30 mg.

17. A method according to claim 14 wherein said effective amount is within the range of 5–20% (weight/volume).

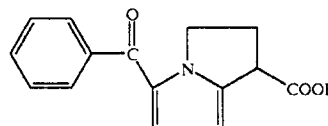
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18. A method according to claim 14 wherein said effective amount is within the range of 15% (weight/volume).

19. A method according to claim 18 wherein said dosage form comprises said active ingredient is dissolved in an aqueous liquid carrier.

20. A method according to claim 18 wherein said dosage form also comprises a mucosal adsorption promoter that is not a mucosal irritant.

21. An analgesic/anti-inflammatory pharmaceutical liquid dosage form which comprises a systemically effective amount for a human of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being an intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration, wherein the dosage form is free of polymers providing a low viscosity composition at room temperature but an increased viscosity composition at body temperature.

22. The dosage form of claim 21 in the form of a solution.

23. The dosage form of claim 21 in combination with a container suitable for delivering a spray of the liquid dosage form.

24. The dosage form of claim 21 comprising about 5–20% of said active ingredient (weight/volume).

25. The dosage form of claim 24 containing about 15% of said active ingredient (weight/volume).

26. The liquid dosage form of claim 21, wherein the active ingredient is a pharmaceutically acceptable salt.

27. The liquid dosage form of claim 26, wherein the active ingredient is ketorolac tromethamine and the diluent is water.

28. The dosage form of claim 27 in the form of a solution.

29. The dosage form of claim 28 comprising about 5–20% of ketorolac tromethamine (weight/volume).

30. The dosage form of claim 29 containing about 15% of ketorolac tromethamine (weight/volume).

31. The dosage form of claim 27 consisting essentially of an aqueous solution of ketorolac tromethamine optionally containing at least one additive chosen from a humectant, isotoning agent, antioxidant, buffer, preservative, and chelating agent.

32. The dosage form of claim 31 consisting essentially of an aqueous solution of ketorolac tromethamine that optionally contains a chelating agent and optionally a preservative.

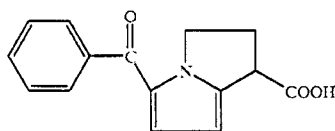
33. The dosage form of claim 27, wherein said amount of ketorolac tromethamine is sufficient to generate, upon administration of said dosage form to a human subject, a plasma concentration of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid within said subject between about 0.3 and 5 mg/liter of plasma.

34. The dosage form of claim 27 that includes an atomizer that administers the liquid nasally in the form of a spray.

35. The liquid dosage form of claim 21, wherein the active ingredient is the optically active form.

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36. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin in human, which method comprises the administration by the intranasal route of a dosage form comprising a systemically effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, said dosage form being an intranasally-administrable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration, wherein the dosage form is free of polymers providing a low viscosity at room temperature but an increased viscosity composition at body temperature.

37. The method of claim 36, wherein the dosage form is a solution.

38. The method of claim 36, wherein the dosage form is administered in the form of a spray.

39. The method of claim 36, wherein said effective amount is within the range of about 5-20% (weight/volume).

40. The method of claim 39, wherein said effective amount is about 15% (weight/volume).

41. The method of claim 36, wherein the active ingredient is a pharmaceutically acceptable salt.

42. The method of claim 41, wherein the active ingredient is ketorolac tromethamine and the diluent is water.

43. The method of claim 42, wherein the dosage form is a solution.

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44. The method of claim 43, wherein said effective amount is within the range of about 5-20% (weight/volume).

45. The method of claim 44, wherein said effective amount is about 15% (weight/volume).

46. The method of claim 42, wherein the dosage form consists essentially of an aqueous solution of ketorolac tromethamine optionally containing at least one additive chosen from a humectant, isotoning agent, antioxidant, buffer, preservative, and chelating agent.

47. The method of claim 46, wherein the dosage form consists essentially of an aqueous solution of ketorolac tromethamine that optionally comprises a chelating agent and optionally a preservative.

48. The method of claim 42, wherein the active ingredient is ketorolac tromethamine and the effective amount is sufficient to generate a plasma concentration of 5-benzoyl-2,3-dehydro-1H-pyrrolizine-1-carboxylic acid between about 0.3 and 5 mg/liter of plasma.

49. The method of claim 42, wherein the liquid is administered nasally in the form of a spray.

50. The method of claim 36, wherein the active ingredient is the optically-active form.

51. An analgesic/anti-inflammatory aqueous solution as an intranasally administrable pharmaceutical dosage form in a bottle suitable for delivering a spray of the solution, which dosage form comprises about 5% to about 20% (weight/volume) ketorolac tromethamine, optionally less than about 0.1% (weight/volume) sodium ethylenediaminetetraacetic acid, and optionally a preservative, wherein the dosage form is free of any polymer providing a low viscosity composition at room temperature but an increased viscosity composition at body temperature.

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Pain, Analgesia, and Anesthesia

Effect of lidocaine vs ketorolac tromethamine on postoperative laparoscopy pain control: a randomized study

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^a The Union Memorial Hospital, Baltimore, Maryland, USA

Available online 31 May 2000.

Abstract

Objective: To evaluate and compare the effectiveness of intraperitoneal lidocaine and intramuscular ketorolac tromethamine for immediate and delayed postoperative pain management in patients undergoing laparoscopy.

Methods: Design—Seventy-four patients were prospectively randomized into four groups: intraperitoneal lidocaine; intramuscular ketorolac; both drugs; neither drug.

Setting: Community Teaching Hospital Outpatient Surgery Center.

Patients: Private and clinic patients needing operative laparoscopy.

Intervention: One hundred milligrams of lidocaine was instilled into the peritoneal cavity just before the laparoscopy was completed. Sixty milligrams of ketorolac tromethamine was administered intramuscularly approximately 30 minutes before laparoscopy was completed.

Main Outcome Measurements: The amount of analgesic used, the time required in postanesthesia recovery area, and a pain intensity score were used to evaluate the postoperative pain.

Results: Pain intensity scores reported by those women receiving ketorolac and both medications were less than scores of untreated controls. Groups receiving either ketorolac, lidocaine, or both drugs required less morphine postoperatively.

Conclusion: Both intraperitoneal lidocaine or intramuscular ketorolac are effective in reducing the perception of pain and the amount of morphine required postoperatively.

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Effect of lidocaine vs ketorolac tromethamine on postoperative laparoscopy pain control: a randomized study

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Norman H. Dubin, PhD
The Union Memorial Hospital, Baltimore, Maryland

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Conclusion: Both intraperitoneal lidocaine or intramuscular ketorolac are effective in reducing the perception of pain and the amount of morphine required postoperatively.

A randomized, placebo-controlled comparison of EMLATM and dorsal penile nerve block for pain relief during neonatal circumcision

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Karen Fortune, MD, Patricia Generelli, MD,
Denniz Zolnoun, MD, Cynthia tenHooen, NP
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Objective: To evaluate the relative efficacies of eutetic mixture of local anesthetics (EMLATM) cream and dorsal penile nerve block (DPNB) for pain relief during neonatal circumcision.

Methods: After parental informed consent, appropriate-for-gestational age, term, healthy newborns were randomized to receive either EMLA cream and placebo saline DPNB or placebo cream and 1% lidocaine DPNB. Placebo and EMLA cream were prepared by the pharmacy and applied by study nurses. Preloaded syringes of saline or 1% lidocaine were also prepared by the pharmacy for the DPNB injections. This ensured blinding of the surgeons and assistants at the time of circumcisions. Circumcisions were performed with the Gomco clamp technique by one of three obstetrics and gynecology residents. Pain levels were assessed by measuring pulse and respiratory rates and determining Brazelton states at each step of the circumcision. Videotapes were made of each procedure to allow later scoring by a single blinded observer for Brazelton states. Brazelton state scores increase with increased infant pain and distress, as do heart and respiratory rates. Means were compared by *t* test and proportions by χ^2 . A *P* value of .05 was considered statistically significant.

Results: A total of 60 infants were randomized, 29 to DPNB and 31 to EMLA. Preoperative Brazelton state scores, heart rates, and respiratory rates were similar in both groups. Brazelton state scores were lower in the DPNB group at each step of the procedure— injection, dissection of the foreskin, clamp placement, and clamp removal—and postoperatively and overall, but the differences only reached statistical significance during dissection and clamp removal. Heart and respiratory rates also were lower at all surgical steps in the DPNB group but only reached statistical significance during postoperative observation.

Conclusions: Although both EMLA and DPNB have been shown in other studies to decrease pain during neonatal circumcisions, DPNB has greater effectiveness in relieving the pain of circumcision.