

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

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Abogado JUAN CARLOS URIBE RESTREPO

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 Trámite 011
 Evento 379
 Actuación 519
 Oficio
 Folios 004

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Patente de Invención ☐

Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (Fase Nacional) ☐

Cap. I ☐

Cap. II ☐

No. Solicitud Internacional PCT/IB2007/000907

Fecha de Presentación Internacional 10 Abril 2007

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

1. Documentos estudiados

Descripción:	Folios 5 a 41	10/Octubre/2008
	Folios 77 a 109	10/Octubre/2008
	Reivindicaciones: Folios 42 a 50	10/Octubre/2008
	Folios 70 a 75	10/Octubre/2008
	Folios 110 a 118	10/Octubre/2008
Dibujos	Folios 138 a 141	10/Octubre/2008
	Folios 119 a 124	10/Octubre/2008
Prioridad:	MX PA/a/2006/004020	10/Abril/2006

2. Análisis de la Prioridad

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

3. Objeto de la invención

Título de la solicitud: "Composición farmacéutica que comprende la combinación de una sal de ketorolaco y vitaminas del complejo para el tratamiento de la neuralgia".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una composición farmacéutica con alta eficacia terapéutica y un amplio margen de

Expediente 08 108 827 1er Art 45

seguridad útil en el tratamiento de pacientes que poseen dolor moderado a severo y neuralgias de diversa localización. (Ver folio 80; línea 7 - 17).
Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica de ketorolaco y complejo B.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/405; 31/51; 31/4415; 31/714, A 61 P 29/00.

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

El objeto de la reivindicación 1 y las reivindicaciones dependientes 2 a 15 no son patentables de acuerdo con el Art citado.

Se aclara al solicitante que a pesar de que la materia reivindicada en las clausulas 1 a 15 no es patentable, ya que si bien la reivindicación no reclama implícitamente un método de tratamiento, el objeto de la invención y la forma de caracterizarlo, define implícitamente un método de tratamiento.

De igual manera se aclara que la materia reivindicada en la presente solicitud ha sido divulgada previamente en el estado de la técnica en el documento D1, el efecto sinérgico entre compuestos de tipo AINE, en este caso ketorolaco, y vitaminas del complejo B(ver pág. 95, resumen; (folio 179). De igual manera, ya es conocido en el estado de la técnica, de acuerdo con el documento D2, las composiciones farmacéuticas disponibles en el mercado de las vitaminas del complejo B.

Item	Documento	Título	Fecha de Publicación*
D1	Roberto Medina-Santillan, Gerardo Reyes-Garcia, Hector I. Rocha-Gonzalez and Vinicio Granados-Soto; Western Pharmacology Society	B Vitamins Increase the Analgesic Effect of Ketorolac in the Formalin Test in the Rat	2004
D2	Trissel LA. Handbook on injectable drugs. American Society of Health-System Pharmacist. 13th edition	Trissel (Handbook on Injectable Drugs) 13 th edition	Octubre/2004

D1<http://www.medicine.nevada.edu/wps/Proceedings/47/95-99-V47P95T99.pdf>
Divulga (Pág. 1, párrafo 1) un estudio realizado con el fin de evaluar la posible actividad sigérgica entre ketorolaco y vitaminas del complejo B, (Pág.95, resumen; (folio 179)). El estudio revela el aumento en el efecto analgésico cuando se administra ketorolaco en conjunto con vitaminas del complejo B, tiamina, piridoxina y cianocobalamina en las siguientes proporciones 100:100:5 o 100:100:1, es decir, 100mg/kg de tiamina y piridoxina, 5 o 1 mg/kg de cianocobalamina respectivamente (Pág.96; párrafo 1;(folio 179).

D2 Trissel (Handbook on Injectable Drugs) 13th edition, da a conocer diferentes composiciones farmacéuticas inyectables, individuales de ketorolaco y las diferentes composiciones disponibles de vitaminas del complejo B. Las composiciones inyectables de la sal de trometamina de ketorolaco, se encuentran en concentraciones de 15mg/ml y 30 mg/ml (Folio 182), contienen diferentes sustancias como cloruro de sodio, API, etanol y acido cítrico como agente preservarte, además puede contener hidróxido de sodio o acido clorhídrico para ajustar el pH, el cual se encuentra entre 6.9 a 7.9, para ser administrado por vía intramuscular o intravenosa. Sugiere además la administración en Y con otros medicamentos. (Folio 182).

Por otro lado, el documento D2 da a conocer las composiciones farmacéuticas de vitaminas del complejo B. Cianocobalamina, esta disponible en concentraciones de 100mcg/ml, 0.1 y 1 mg/ml, con excipientes como cloruro de sodio, alcohol bencílico como preservante e hidróxido de sodio o acido clorhídrico para ajuste de pH, es de administración intramuscular o subcutánea y enseña la administración en Y, con otros medicamentos (Folio 185). Clorhidrato de piridoxina, otra vitamina del complejo B, es divulgada en D2, el cual enseña la solución acuosa de 100mg/ml que incluye preservantes como alcohol bencílico o clorobutanol, y para ajuste de pH hidróxido de sodio o acido clorhídrico, es de administración intramuscular e intravenosa, (Folio 187). El cloruro de tiamina es divulgado en D2 como solución acuosa para administración intramuscular e intravenosa de 100mg/ml, y contiene clorobutanol como agente preservante antimicrobiano, acido clorhídrico o hidróxido de sodio para ajustar el pH.

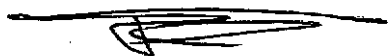
Invención	D1	D2	D2
Composición farmacéutica que comprende dos unidades de soluciones parenterales	Uso Ketorolaco disuelto en solución salina.	Composición inyectables para administración por vía intramuscular	Composición de cianocobalamina
			Composición piridoxina hidrocloreuro viales multidosis
			Composición de Tiaminia
a.Solución con cantidad efectiva de una sal de ketorolaco y vehículo farmacéuticamente aceptable y el pH de la solución es de 7.5 a 9.5	Complejo de vitamina B (tiamina, piridoxina y cianocobalamida). Pera demostrar la interacción sinérgica entre los compuestos mencionados	15mg/ml o 30 mg/ml de Ketorolaco trometamina; pH 6.9 a 7.9	No se menciona
b.Solución con cantidad efectiva de vitaminas del complejo B y vehículos farmacéuticamente aceptables y pH de la solución es de 2.5 a 4.5		Cianocobalamina de 100mcg/ml y 1 mg/ml, estable en pH 3 a 7 y mas estable de 4.5 a 5 Piridoxina hidrocloreuro de 100mg/ml; pH 2 a 3.8 Tiamina hidrocloreuro de 100mg/ml; estable a ph máximo 2	

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 16 y 17 no son patentables, de acuerdo con el Art 14.

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

08 JUN. 2012

Elaborado por: Paola Duarte *Paola D.*
Revisado por: Consuelo Leguizamón Leguizamón
Aprobado Por: José Luis Salazar López *JL*

B Vitamins Increase the Analgesic Effect of Ketorolac in the Formalin Test in the Rat

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ABSTRACT

The purpose of this study was to assess the possible synergistic interaction between ketorolac and B-vitamins in the rat formalin test. Female Wistar rats were injected into the dorsal surface of the right hind paw with 50 µl of diluted formalin (1%). Reduction of the number of flinches was considered as antinociception. Ketorolac (0.32-10 mg/kg, po), B-vitamins (56-316 mg/kg), or a combination of B-vitamins (either 100:100:1 or 100:100:5 proportion of vitamin B₁, B₆ and B₁₂, respectively) and ketorolac was administered orally and the antinociceptive effect was determined. Isobolographic analyses were used to define the nature of the functional interactions between B-vitamins and ketorolac in a proportion (0.5:0.5, ketorolac:B-vitamins). Ketorolac (ED₅₀ 3.5 ± 0.7 mg/kg), B-vitamins in a 100:100:1 (ED₅₀ 277.1 ± 30.2 mg/kg) or 100:100:5 (ED₅₀ 157.3 ± 13.7 mg/kg) proportion and fixed-ratio B-vitamins-ketorolac combinations dose-dependently reduced flinching behavior during second phase of the test. Theoretical ED₅₀ values for the combination ketorolac-B vitamins estimated from the isobolograms were 140.3 ± 15.1 and 80.4 ± 6.8 mg/kg for 100:100:1 and 100:100:5 proportions, respectively. These values were significantly higher than experimental ED₅₀ values which were 73.3 ± 6.3 and 47.7 ± 6.4 mg/kg for 100:100:1 and 100:100:5 proportions, respectively. Results indicate that oral ketorolac and B-vitamins can interact synergistically to reduce inflammatory pain in the formalin test and suggest the use of those combinations to relief this kind of pain in humans

INTRODUCTION

B vitamins have been used as analgesic drugs to treat pain disorders associated with their deficiency [1]. In addition, B vitamins have been reported to be clinically useful alone or combined with non-steroidal anti-inflammatory drugs (NSAIDs) in some painful disorders such as polyneuropathy [2], neuritis [3], painful vertebral syndrome [4] or rheumatic diseases [5]. There is evidence that B vitamins are able to increase the antinociceptive activity of diclofenac in animals [6-7]. In humans, B vitamin preparations

have been extensively used as analgesic adjuvant combined with diclofenac for the treatment of acute lumbar vertebral pain [4,8]. However, since some negative results have also been reported [9-11] the adjuvant properties of the B vitamins complex are not completely established. In the present study, we evaluated the analgesic activity of ketorolac alone and combined with the B vitamins complex (B₁, B₆ and B₁₂) using the formalin test in the rat.

METHODS: Female Wistar rats of 7-8 weeks (weight range, 180-200 g) from our own breeding facilities were used in this study. Rats had free access to drinking water, but food was restricted 12 hr before the experiment. All experiments followed the Guidelines on Ethical Standards for Investigation of Experimental Pain in Animals [12]. Additionally, the study was approved by the Institutional Animal Care and Use Committee (Centro de Investigación y Estudios Avanzados del Instituto Politécnico Nacional, México, DF, MEXICO).

Evaluation of antinociceptive activity: Antinociception was assessed by the formalin test. Rats were placed in an open Plexiglas® observation chamber for 30 min to allow them to accommodate to their surroundings, then they were removed for formalin administration. The rats were injected into the dorsal surface of the right hind paw with 50 µl of dilute formalin (1%), using a 30-gauge needle. The animal was then returned to the chamber for observation. A mirror was placed behind the chamber to enable unhindered observation of the formalin-injected paw. The rats were observed for nociceptive behavior immediately after formalin injection.

Nociceptive behavior was quantified as the number of flinches of the injected paw during 1 min periods every 5 min up to 60 min after injection. Flinching was readily discriminated and was characterized as rapid and brief withdrawal or flexing of the injected paw. As reported, formalin-induced flinching behavior was biphasic [13]. The initial acute phase (0-10 min) is followed by a relatively short, quiescent period, which is then followed by a prolonged tonic response (15-60 min). At the end of the experiment, rats were sacrificed in a CO₂ chamber.

Drugs: Ketorolac was purchased from Sigma (St. Louis, MO, USA). B vitamins were kindly provided by Merck S.A. de C.V. (Mexico City). All drugs were dissolved in saline.

Study design: Association of thiamin, pyridoxine and cyanocobalamin was used in a proportion of 100:100:1 and

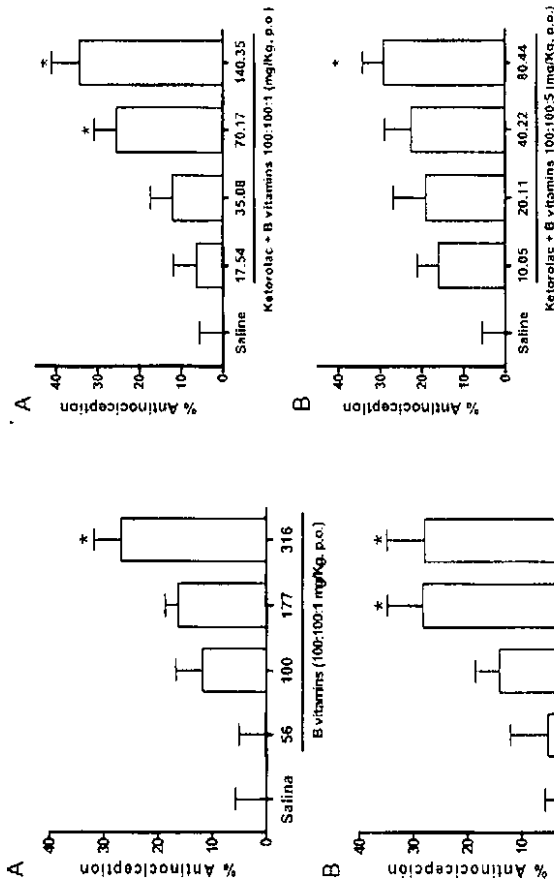


Figure 1. Antinociceptive effect observed after oral administration of ketorolac (A) and the mixture of B vitamins either 100:100:1 proportion (B) or 100:100:5 proportion (C) on the 1% formalin test. Rats were orally pretreated with vehicle (VEH) or drugs before formalin injection. Data are expressed as % of antinociception. Bars are the means ± SEM for 6 animals. * Significantly different from the vehicle group (P < 0.05), as determined by analysis of variance followed by Tukey's test.

Figure 2. Antinociceptive effect observed after oral administration of the combination of ketorolac and B vitamins either at a 100:100:1 (A) or 100:100:5 (B) proportion on the 1% formalin test. Rats were orally pretreated with vehicle (VEH) or the combinations before formalin injection. Data are expressed as % of antinociception. Bars are the means ± SEM for 6 animals. * Significantly different from the vehicle group (P < 0.05), as determined by analysis of variance followed by Tukey's test.

100:100:5. This means that a dose of 100 mg/kg of thiamin-pyridoxine-cyanocobalamin indicates 100 mg/kg of thiamin, 100 mg/kg of pyridoxine, and 1 mg/kg of cyanocobalamin or 5 mg of cyanocobalamin, respectively. Rats received the oral administration of saline (4 ml/kg) or increasing doses of B vitamins (56-316 mg/kg, either a 100:100:1 or 100:100:5 proportion of vitamin B₁, B₆, and B₁₂, respectively), ketorolac (0.32-10 mg/kg) or dose-fixed ratio combinations of B vitamins and ketorolac 10 min before formalin injection. After formalin injection, flinching behavior was assessed for the next 60 min.

Data analysis and statistics: All results are presented as means ± SEM for at least 6 animals per group. The area under the number of flinches against time curves (AUC) was calculated by the trapezoidal rule [14]. Dose-response curves for each compound tested were established based on the percent maximum possible effect (expressed as % Antinociception) calculated from AUC of the phase 2 of each individual rat: % Antinociception = (vehicle-post-compound/vehicle) × 100. For evaluation of the interaction between ketorolac and B vitamins, isobolograms were

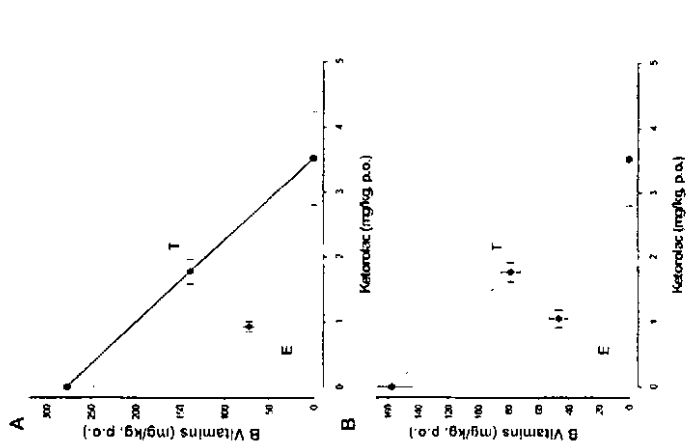


Figure 3. Isobolograms showing the synergistic interaction between ketorolac and B vitamins either at a 100:100.1 (A) or 100:100.5 (B) proportion on the 1% formalin test. Horizontal and vertical bars indicate SEM. The oblique line between the x axis and y axis is the theoretical additive line. The point in the middle of this line is the theoretical additive point calculated from the separate ED₅₀ values. In both cases, the experimental point lies far below the additive line, indicating a significant synergism ($P < 0.05$).

constructed using ED₅₀ values obtained when the drugs were administered alone or combined. We used ED₅₀ instead of ED₅₀ values because neither drug was able to reach more than 33% of antinociception in our model [14]. The construction of the dose-response curves and the determination of doses producing 25% maximum possible effect (ED₂₅) were computed. To perform the isobolographic analysis, ketorolac and B vitamins were administered in combination as fixed ratios of equieffective ED₂₅ dose for each drug (ketorolac/B vitamins=0.5:0.5). The ED₅₀ values ($\pm$ SEM) for ketorolac and B vitamins alone were plotted on the x and y axes, respectively, and the theoretical additive point was calculated according to Tallanda et al [14]. From the dose-

response curve of the combined drugs, the ED₅₀ value of the total dose of the combination was calculated. Statistical significance between the theoretical additive point and the experimentally derived ED₅₀ value was evaluated using Student's *t* test. An experimental ED₅₀ significantly less than the theoretical additive ED₅₀ ($P < 0.05$) was considered to indicate a synergistic interaction between ketorolac and B vitamins.

RESULTS: Formalin administration produced a typical pattern of flinching behavior. The first phase started immediately after administration of formalin and then diminished gradually in about 10 min. The second phase started at 15 min and lasted until 1 hr. Oral administration of B vitamins (56-316 mg/kg) dose-dependently reduced flinching behavior induced by formalin during the phase 2 (Figure 1) reaching a maximum effect of 26 (ED₅₀ 277.1 $\pm$ 30.2 mg/kg) and 28% (ED₅₀ 157.3 $\pm$ 13.7 mg/kg) for the 100:100.1 and 100:100.5 proportion, respectively. In addition, oral administration of ketorolac (0.32-10 mg/kg) significantly reduced formalin-induced nociceptive behavior in the rat, reaching a maximum effect of 33% (ED₅₀ 3.5 $\pm$ 0.7 mg/kg).

Oral coadministration of ketorolac and B vitamins induced a dose-dependent increase in the % antinociception (Fig. 2). The antinociceptive effect of the combination was observed mainly on the second phase of the test. Theoretical ED₅₀ values for the combination ketorolac-B vitamins estimated from the isobolograms were 140.3 $\pm$ 15.1 and 80.4 $\pm$ 6.8 mg/kg for 100:100.1 and 100:100.5 proportions, respectively. These values were significantly higher than experimental ED₅₀ values which were 73.3 $\pm$ 6.3 and 47.7 $\pm$ 6.4 mg/kg for 100:100.1 and 100:100.5 proportions, respectively. As shown in figure 3, the experimentally derived ED₅₀ ($\pm$ SEM) in the isobologram are below the theoretically additive dose line, indicating a significant synergistic interaction between ketorolac and B vitamins in the formalin test ($P < 0.05$).

DISCUSSION: The present study demonstrated that oral administration of ketorolac and the mixture of B vitamins (100:100.1 or 100:100.5 proportion of B₆ and B₁₂, respectively) is able to significantly reduce formalin-induced nociception in the rat. We also demonstrated in this work that orally co-administered ketorolac and B vitamins have a synergistic antinociceptive interaction against noxious stimuli produced by 1% formalin. Ketorolac produced a significant antinociceptive effect as previously demonstrated in inflammatory pain models [15-19] and human beings [20-21]. In addition, oral

administration of the mixture of B vitamins also produced antinociception in the formalin test. However, the antinociceptive effect observed with B vitamins was less than 40% of the maxim possible effect in the test. These results agree with our previous observation that B vitamins are able to significantly reduce the pain induced by formalin in the rat [22-25] and confirm that B vitamins are effective to diminish inflammatory pain. In our work, we observed that the 100:100.5 proportion was slightly better than the 100:100.1 proportion to reduce inflammatory pain in the rat as greater doses of the 100:100.1 proportion were needed to reach the same reduction in pain. When co-administered, lower doses of ketorolac and B vitamins were necessary to reach an antinociceptive effect of 25%. In addition, isobolographic analyses showed a synergistic interaction between ketorolac and the mixture of B vitamins either in 100:100.1 or 100:100.5 proportions. Previously we have found a synergistic interaction between the mixture of B vitamins and gabapentin [26], diclofenac [24-25], acetaminophen and metanzolol, but not nimesulide.

The mechanism of the antinociceptive interaction between these drugs remains to be elucidated. The mechanism of the synergy observed could be due to the different sites of action of ketorolac and B vitamins. In the case of ketorolac, there is evidence that this drug produces its antinociceptive effect through the inhibition of cyclooxygenase 1 [27]. However, other observations suggest that ketorolac could also activate the nitric oxide-cyclic GMP-K⁺ channel pathway in order to reduce pain in the rat [17,28]. On the other hand, B vitamins are able to diminish pain through the activation of afferent inhibitory control of nociceptive neurons at the spinal cord [29]. In addition, our group has found that the antinociception induced by B vitamins can be partially reduced by naloxone and L-NAME, but not by D-NAME or methiothepin thus suggesting that opioid and nitergic, but not serotonergic, mechanisms could participate in their antinociceptive effect [24-25].

In summary, we have found that ketorolac and the mixture of different proportions of B vitamins are able to reduce inflammatory pain in the formalin test. In addition, a synergistic interaction was observed between ketorolac and B vitamins thus suggesting that this combination could be useful to treat inflammatory pain in humans.

ACKNOWLEDGEMENTS: The authors greatly appreciate the bibliographic assistance of Héctor Vázquez Héctor I. Rocha-González is a CONACYT fellow

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KETOROLAC TROMETHAMINE

ATC Class: 28.08.04.92 (Other Nonsteroidal Anti-inflammatory Agents)

Tradenames:

- Toradol

Products

Ketorolac tromethamine is available as a 15-mg/ml solution in 1-ml vials and also as a 30-mg/ml solution in 1-ml vials. Ketorolac tromethamine 30 mg/ml is also available in 2-ml vials for intramuscular use. Each milliliter of the two concentrations contains 10.02%.

Ketorolac tromethamine	15 mg	30 mg
Ethanol	10% (w/v)	10% (w/v)
Sodium chloride	6.68 mg	4.35 mg
Citric acid	0.1%	0.1%
Water for injection	qs	qs

The product also contains sodium hydroxide or hydrochloric acid to adjust the pH. 10022

pH

From 6.9 to 7.9. 4

Tonicity

Both ketorolac tromethamine concentrations are isotonic. 4

Administration

Ketorolac tromethamine is administered slowly by deep intramuscular injection or by intravenous injection over no less than 15 seconds. 10022, 4 The 60 mg/2 ml injection is for intramuscular use only. 10022

Stability

Ketorolac tromethamine injection should be stored at controlled room temperature and protected from light. The injection is clear and has a slight yellow color. 10022, 4 Prolonged exposure to light may result in discoloration of the solution and precipitation. 4 Ketorolac tromethamine is chemically stable over a wide pH range from about pH 3 to 11 10022, but precipitation may occur in solutions having a relatively low pH. 4

Freezing Solutions

Ketorolac tromethamine (Roche) 20 mg/100 ml of dextrose 5% in water in polyolefin bags was stored frozen at -20 °C for three months, microwave thawed, and stored refrigerated at 4 °C for 60 days. No visual changes were observed and less than 10% loss of ketorolac tromethamine was found by stability-indicating HPLC analysis. 10022

Sorption

Ketorolac tromethamine (Syntex) 30 mg/50 ml in dextrose 5% in sodium chloride 0.9%, dextrose 5% in water, Plasma-Lyte A (pH 7.4), Ringer's injection, Ringer's injection, lactated, and sodium chloride 0.9% and 30 mg/500 ml in Plasma-Lyte A (pH 7.4) and Ringer's injection did not exhibit sorption to PVC containers over 48 hours or to administration set tubing in static contact or in simulated infusion. 10022

Compatibility

Solution Compatibility

Ketorolac tromethamine

Test Soln Name	Test Soln Mfr	Base Drug Mfr	Base Drug Conc	Remarks	Refs	Compat
Dextrose 5% in sodium chloride 0.9%	TR ^a	SY	600 mg	Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	1, 4	C
Dextrose 5% in water	TR ^b	SY	600 mg	Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	1, 4	C
Dextrose 5% in water	BA ^a	RC	600 mg	Visually compatible with little or no loss by HPLC in 7 days and 14% loss in 14 days at 25 °C. Less than 2% loss in 50 days at 5 °C.	1, 4	C
Dextrose 5% in water	1	RC	300 and 600 mg	Visually compatible with little or no loss in 21 days at 4 and 23 °C	2, 12	C
Dextrose 5% in water	1	RC	200 mg	Visually compatible with less than 10% loss by HPLC after -20 °C storage for 90 days, microwave thawing, and storage at 4 °C for 60 days	1, 10, 1	C
Plasma-Lyte A, pH 7.4	TR ^a	SY	600 mg	Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	1, 4	C
Plasma-Lyte A, pH 7.4	TR ^b	SY	60 mg	Physically compatible by visual examination and particle assessment. Little or no ketorolac loss by HPLC in 48 hr at	1, 4	C

181
182
182

Ringer's injection	TR ^a	SY	600 mg	room temperature	Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	C
Ringer's injection	TR ^b	SY	600 mg		Physically compatible by visual examination and particle assessment. Little or no ketorolac loss by HPLC in 48 hr at room temperature	C
Ringer's injection, lactated	TR	SY	600 mg		Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	C
Sodium chloride 0.9%	TR	SY	600 mg		Physically compatible by visual examination and particle assessment. No ketorolac loss by HPLC in 48 hr at room temperature	C
Sodium chloride 0.9%	BA	RC	600 mg		Visually compatible with no loss by HPLC in 35 days at 25 °C and in 50 days at 5 °C	C

^a Tested in PVC containers.

^b Tested in both glass and PVC containers.

^c Tested in polyolefin containers.

• Drugs in Syringe Compatibility

Ketorolac tromethamine						
Test Drug	Test Drug Mfr	Test Drug Conc	Base Drug Mfr	Base Drug Conc	Remarks	Refs/Compat
Diazepam	PS	15 mg/3 ml	SY	180 mg/6 ml	Visually compatible for 4 hr at 24 °C under ambient light. Spectrophotometric absorbance increases immediately and persists for 30 min but dissipates by 1 hr	1, 2
Flupentidol lactate	SC	5 mg/1 ml	SY	30 mg/1 ml	White crystalline precipitate forms immediately	3
Hydromorphone HCl	KN	10 mg/1 ml	SY	30 mg/1 ml	Cloudiness forms immediately but clears with swirling	4
Hydromorphone HCl	KN	1 mg/1 ml ^a	SY	30 mg/1 ml	Visually compatible for 24 hr at 25 °C	5, 6
Hydromorphone HCl	KN	1 ^a and 10 mg/1	SY	15 mg/1	Visually compatible for 24 hr at 25 °C	6

		ml	ml ^a			
Hydroxyzine HCl	SO	150 mg/3 ml	SY	180 mg/6 ml	Heavy white precipitate forms immediately, separating into two layers over time	1, 2 ^a
Nalbuphine HCl	DU	30 mg/3 ml	SY	180 mg/6 ml	Solid white precipitate forms immediately and settles to bottom	3, 4
Prochlorperazine edisylate	STS	15 mg/3 ml	SY	180 mg/6 ml	Heavy white precipitate forms immediately, separating into two layers over time	5
Promethazine HCl	IS	75 mg/3 ml	SY	180 mg/6 ml	Heavy white precipitate forms immediately, separating into two layers over time	6, 7
Sufentanil citrate	JN	50 mcg/ml	SY	30 mg/ml	Physically compatible with no subvisual haze or particle formation in 24 hr at 23 °C	8, 11
Thiethylperazine maleate	ROX	5 mg/1 ml	SY	30 mg/1 ml	White crystalline precipitate forms immediately	12 ^a

^a Dilutions prepared with sterile water for injection.

• Y-Site Injection Compatibility (1:1 Mixture)

Ketorolac tromethamine						
Test Drug	Test Drug Mfr	Test Drug Conc	Base Drug Mfr	Base Drug Conc	Remarks	Refs/Compat
Alatorloxacin mesylate	PF	1.43 mg/ml ^a	AB	15 mg/ml	Usually and microscopically compatible with the ketorolac pushed through a Y-site over 20 sec	22 ^a
Azithromycin	PF	2 mg/ml ^b	AB	15 mg/ml ^b	Amber microcrystals found upon filter inspection	23 ^a
Azithromycin	PF	2 mg/ml ^b	AB	15 mg/ml ^b	Amber microcrystals found upon filter inspection	23 ^a
Cisatracurium besylate	GW	0.1, 2, 5 mg/ml ^a	RC	15 mg/ml ^a	Physically compatible with no change in measured turbidity or increase in particle content in 4 hr at 23 °C	24, 1
Dexmedetomidine HCl	AB	4 mcg/ml ^b	AB	15 mg/ml	Physically compatible with no increase in measured haze or particle content in 4 hr at 23 °C under fluorescent light	25 ^a

182

CYANOCOBALAMIN

VHFS Class: 88-08 (Vitamin B Complex)

ACTH

Products

Cyanocobalamin is available in concentrations of 100 mcg/ml and 1 mg/ml with sodium chloride 0.9%, benzyl alcohol 1.5%, and sodium hydroxide and/or hydrochloric acid to adjust pH during manufacturing.

pH

From 4.5 to 7.0

Administration

Cyanocobalamin is administered by intramuscular or deep subcutaneous injection. The intravenous route is not recommended because the drug is excreted more rapidly and almost all of the cyanocobalamin is lost in the urine.

Stability

The clear pink to red solutions are stable at room temperature and may be autoclaved at 121 °C for short periods such as 15 to 20 minutes. Cyanocobalamin is light sensitive, so protection from light is recommended. Exposure to light results in the organometallic bond being cleaved, with the extent of degradation generally increasing with increasing light intensity.

pH Effects

Cyanocobalamin is stable at pH 3 to 7 but is most stable at pH 4.5 to 5.0. It is stated to be incompatible with alkaline and strongly acidic solutions.

Sorption

Cyanocobalamin (Organon) 30 mg/L did not display significant sorption to a PVC plastic test strip in 24 hours.

Filtration

Cyanocobalamin (Weyeth) 1 mg/L in dextrose 5% in water and in sodium chloride 0.9% was filtered at a rate of 120 mL/hr for six hours through a 0.22-µm cellulose ester membrane filter (Ivex-2). No significant reduction in potency due to binding to the filter was noted.

Compatibility

Solution Compatibility

Cyanocobalamin

Test Soln Name	Test Soln Mfr	Base Drug Mfr	Base Drug Conc	Remarks	Refs	Compat
Dextran 6% in dextrose 5%	AB	AB	1000 mcg	Physically compatible		C
Dextran 6% in sodium chloride 0.9%	AB	AB	1000 mcg	Physically compatible		C
Dextrose-Ringer's injection combinations	AB	AB	1000 mcg	Physically compatible		C
Dextrose Ringer's injection, lactated, combinations	AB	AB	1000 mcg	Physically compatible		C
Dextrose-saline combinations	AB	AB	1000 mcg	Physically compatible		C
Dextrose 2½% in water	AB	AB	1000 mcg	Physically compatible		C
Dextrose 5% in water	AB	AB	1000 mcg	Physically compatible		C
Dextrose 10% in water	AB	AB	1000 mcg	Physically compatible		C
Fructose 10% in sodium chloride 0.9%	AB	AB	1000 mcg	Physically compatible		C
Fructose 10% in water	AB	AB	1000 mcg	Physically compatible		C
Invert sugar 5 and 10% in sodium chloride 0.9%	AB	AB	1000 mcg	Physically compatible		C
Invert sugar 5 and 10% in water	AB	AB	1000 mcg	Physically compatible		C
Isonosal products	AB	AB	1000 mcg	Physically compatible		C
Ringer's injection	AB	AB	1000 mcg	Physically compatible		C
Ringer's injection, lactated	AB	AB	1000 mcg	Physically compatible		C
Sodium chloride 0.45%	AB	AB	1000 mcg	Physically compatible		C
Sodium chloride	AB	AB	1000 mcg	Physically compatible		C

188
1830

0.9%	AB	mg	mg		
Sodium lactate 1/6 M	AB	1000 mg	Physically compatible		C
TPN #11 to #15*	SQ	1 mg	Physically compatible for 24 hr at 22 °C. TLC changes of amino acids in similar solutions attributed to M V.I or vitamin B complex with C were observed		C
TPN #16 to #20*	SQ	0.5 and 1 mg	Physically compatible for 24 hr at 22 °C. UV spectra of amino acids solution unaltered		C
* Refer to Appendix I for the composition of parenteral nutrition solutions. TPN indicates a 2-in-1 admixture.					

• Additive Compatibility

Cyanocobalamin

Test Drug	Test Drug Mfr	Test Drug Conc	Base Drug Mfr	Base Drug Conc	Solution	Remarks	Refs	Compat
Ascorbic acid injection	AB	1 g	AB	1000 mcg		Physically compatible		C
Chloramphenicol	PD	1 g	AB	1000 mcg		Physically compatible		C
Sodium succinate	MSD	100 mg	AB	1000 mcg		Physically compatible		C
Metaraminol bitartrate	AB	2 ml	AB	1000 mcg		Physically compatible		C

• V-Site Injection Compatibility (1:1 Mixture)

Cyanocobalamin

Test Drug	Test Drug Mfr	Test Drug Conc	Base Drug Mfr	Base Drug Conc	Remarks	Refs	Compat
Heparin sodium	UP	1000 units/mL	PD	0.1 mg/ml	Physically compatible for at least 4 hr at room temperature by visual and microscopic examination	11	C
Hydrocortisone sodium succinate	UP	10 mg/mL	PD	0.1 mg/ml	Physically compatible for at least 4 hr at room temperature by visual and microscopic examination	11	C
Potassium chloride	AB	40	PD	0.1	Physically compatible for at	11	C

	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL
Vitamin B complex with C	RC	2 mL/L	PD	0.1 mg/mL	Physically compatible for at least 4 hr at room temperature by visual and microscopic examination
Tested in dextrose 5% in Ringer's injection, dextrose 5% in Ringer's injection, lactated, dextrose 5% in water, Ringer's injection, lactated, and sodium chloride 0.9%.					

Additional Compatibility Information

• Other Drugs

It has been stated that cyanocobalamin with ascorbic acid can be stored for 24 hours at room temperature protected from light without loss of activity. It also has been stated that the drug is compatible with other vitamins of the B complex and with iron-dextran complex. 2

Some incompatibilities of cyanocobalamin reported in the literature were actually due to hydroxocobalamin, which was formerly present as a contaminant. 2

Cyanocobalamin (Abbott) 1000 mcg/L has been reported to be conditionally compatible with hydrocortisone sodium succinate (Upjohn) 250 mg/L. The mixture is physically compatible in most Abbott infusion solutions. 3

Cyanocobalamin injection has been reported to be incompatible with ascorbic acid, chlorpromazine hydrochloride, dextrose, phytanadione, prochlorperazine edisylate, and warfarin sodium. It is also stated to be incompatible with heavy metals, oxidizing agents, and reducing agents. 3

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References

For a list of references cited in the text of this monograph, consult the monograph titled *Hand references*

183
184

PYRIDOXINE HYDROCHLORIDE

ATC Class: B8-08 (Vitamin B Complex)

Products

Pyridoxine hydrochloride injection is available from several manufacturers in 1-, 10-, and 30-ml multiple-dose vials as an aqueous solution providing 100 mg/ml. Also present are antimicrobial preservatives, such as benzyl alcohol 1.5% or chlorobutanol 0.5%. Sodium hydroxide and/or hydrochloric acid may have been used to adjust pH.

pH

From 2 to 3.8

Osmolality

The osmolality of pyridoxine hydrochloride (Lilly) 100 mg/ml was determined to be 870 mOsm/kg by freezing-point depression and 852 mOsm/kg by vapor pressure.

Administration

Pyridoxine hydrochloride may be administered by intramuscular, subcutaneous, or intravenous injection.

Stability

The product should be stored at controlled room temperature and protected from freezing and from light.

Because pyridoxine hydrochloride is photosensitive and degrades slowly when exposed to light, protection from light has been recommended.

Sorption

Pyridoxine hydrochloride (Sigma) 40 mg/l did not display significant sorption to a PVC plastic test strip in 24 hours.

Compatibility

Solution Compatibility

Pyridoxine HCl				
Test Soln Name	Test Drug Mfr	Base Drug Mfr	Base Drug Conc	Refs/Compat
Remarks				

Test Drug	Test Drug Mfr	Base Drug Mfr	Base Drug Conc	Remarks	Refs/Compat
Fat emulsion 10%, intravenous	KA	KA	98 mg	Physically compatible for 24 hr at 26 °C with little loss of pyridoxine HCl and of most other vitamins by HPLC, up to 52% ascorbate loss	C
From multivitamins.					

Drugs in Syringe Compatibility

Pyridoxine HCl				
Test Drug	Test Drug Mfr	Test Drug Conc	Base Drug Mfr	Base Drug Conc
Doxapram HCl	KB	400 mg/20 ml		10 mg/1 ml
Remarks				Refs/Compat
Physically compatible with 6% doxapram loss in 24 hr				C

Additional Compatibility Information

Infusion Solutions

Pyridoxine hydrochloride in infusion solutions under hospital conditions is reported to be stable. However, addition of riboflavin phosphate sodium promoted decomposition of the pyridoxine so that approximately 8% remained after three hours in the light. Addition of an antioxidant such as ascorbic acid or protection from light reduced the rate of degradation of pyridoxine.

Parenteral Nutrition Solutions

The stability of pyridoxine hydrochloride 15 mg/l was studied in representative parenteral nutrition solutions exposed to fluorescent light, indirect sunlight, and direct sunlight for eight hours. One 5-ml vial of multivitamin concentrate (L-lyphened) containing 15 mg of pyridoxine hydrochloride and also 1 mg of folic acid (Lederle) was added to a liter of parenteral nutrition solution composed of amino acids 4.25%-dextrose 25% (Travenol) with standard electrolytes and trace elements. Pyridoxine hydrochloride was stable over the eight-hour study at room temperature under fluorescent light and indirect sunlight. However, eight hours of exposure to direct sunlight caused an 86% loss of pyridoxine hydrochloride.

Dahl et al. reported the stability of numerous vitamins in parenteral nutrition solutions composed of amino acids (Kabi-Vitrum), dextrose 30%, and fat emulsion 20% (Kabi-Vitrum) in a 2:1:1 ratio with electrolytes, trace elements, and both fat- and water-soluble vitamins. The admixtures were stored in darkness at 2 to 8 °C for 96 hours with no significant loss of retinyl palmitate, alpha-tocopherol, thiamine mononitrate, sodium riboflavin-5'-phosphate, pyridoxine hydrochloride, nicotinamide, folic acid, biotin, sodium pantothenate, and cyanocobalamin. Sodium ascorbate and its biologically active degradation product, dehydroascorbic acid, totaled 59 and 42% of the nominal starting concentration at 24 and 96 hours, respectively. However, the actual initial concentration was only 66% of the nominal concentration.

Antibiotics

185

THIAMINE HYDROCHLORIDE

ATPS Class: 88-08 (Vitamin B Complex)

Products

Thiamine hydrochloride is available in a concentration of 100 mg/ml in 1-ml syringe cartridges, units and 1- and 2-ml vials. Each milliliter of solution may also contain chlorbutanol 0.5% as an antibacterial preservative and monothymeglenol 0.5%. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH. (USDA 4, 5)

pH

From 2.5 to 4.5 (USDA 4, 5)

Administration

Thiamine hydrochloride injection may be administered by intramuscular or slow intravenous injection. An intradermal test dose has been recommended for patients with suspected thiamine sensitivity. (USDA 4)

Stability

Thiamine hydrochloride in intact containers should be stored at controlled room temperature and protected from light and freezing (USDA 4)

pH Effects

Thiamine hydrochloride is stable in acid solutions (USDA 4), losing activity very slowly at pH 4 or less. It is maximally stable at pH 2-3. Thiamine hydrochloride is unstable in neutral or alkaline solutions. (USDA 4, 5)

Syringes

Thiamine hydrochloride (Lilly) 100 mg/ml was repackaged in glass syringes (Glaspak), back-fill glass syringes (Hy-Pod), and plastic syringes (Stylex). Half of the syringes were filled with thiamine hydrochloride injection filtered through 5-µm stainless steel depth filters (F-sterp filter pin), and the rest were filled with unfiltered drug. The syringes containing 1 ml of thiamine hydrochloride injection were stored protected from light (amber UV-light-inhibiting plastic bags) at 22 to 24 °C for 84 days. No color changes were observed, and changes in pH were minimal. Furthermore, no differences between filtered or unfiltered samples occurred, with all solutions retaining approximately 100% of the initial potency over the 84 days. (4)

Sorption

Thiamine hydrochloride (Merck) 30 mg/l did not display significant sorption to a PVC plastic test strip in 24 hours. (2)

Compatibility

Solution Compatibility

Thiamine HCl

Test Soln Name	Test Soln Mfr	Base Drug Mfr	Base Drug Conc	Remarks	Refs	Compat
Dextran 6% in dextrose 5%	AB		100 mg	Physically compatible	1	C
Dextran 6% in sodium chloride 0.9%	AB		100 mg	Physically compatible	1	C
Dextrose-Ringer's injection combinations	AB		100 mg	Physically compatible	1	C
Dextrose-Ringer's injection, lactated combinations	AB		100 mg	Physically compatible	1	C
Dextrose-saline combinations	AB		100 mg	Physically compatible	1	C
Dextrose 2½% in water	AB		100 mg	Physically compatible	1	C
Dextrose 5% in water	AB		100 mg	Physically compatible	1	C
Dextrose 10% in water	AB		100 mg	Physically compatible	1	C
Fat emulsion 10% intravenous	N.A.	N.A.	118 mg	Physically compatible for 24 hr at 26 °C with little loss of thiamine HCl and of most other vitamins by 100°C; up to 52% ascorbate loss	2,3,4	C
Fructose 10% in sodium chloride 0.9%	AB		100 mg	Physically compatible	1	C
Fructose 10% in water	AB		100 mg	Physically compatible	1	C
Invert sugar 5 and 10% in sodium chloride 0.9%	AB		100 mg	Physically compatible	1	C
Invert sugar 5 and 10% in water	AB		100 mg	Physically compatible	1	C
Isonol products	AB		100 mg	Physically compatible	1	C
Ringer's injection	AB		100 mg	Physically compatible	1	C
Ringer's injection, lactated	AB		100 mg	Physically compatible	1	C
Sodium chloride 0.45%	AB		100 mg	Physically compatible	1	C

189
186