DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(6), 1075-1083 (1994)

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

PHARMACOKINETICS OF KETOPROFEN AFTER INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATIONS TO RABBITS

Chi-Yin Wong[1] and Da-Peng Wang[2]

[1]Department of Orthopaedics, National defense Medical Center, Taipei, Taiwan and Kao-Shung Veterans General Hospital, Kao-Shung, Taiwan, R.O.C.

[2]Department of Clinical Pharmacy, Tri-Service General Hospital and School of Pharmacy, National Defense Medical center, Taipei, Taiwan, R.O.C.

ABSTRACT

The pharmacokinetics of ketoprofen was studied in rabbits following intravenous and intramuscular administrations of ketoprofen, both at a dose of 4.0 $mg.Kg^{-1}$. Plasma levels of ketoprofen, as a function of time, were determined by a reversed-phase high performance liquid chromatography. The disposition of ketoprofen was described by a two-compartment open model with elimination from the central compartment. A model-independent method using the statistical moment theory was also applied. Pharmacokinetics of ketoprofen was characterized as a drug with terminal half-life of 3.15 hr, low apparent volumes of distribution (V_{c-1} = 0.031 $L.Kg^{-1}$, Vd_{ss} = 0.070 $L.Kg^{-1}$ and Vd_{β} = 0.130 $L.Kg^{-1}$). The mean residence time (MRT) was found to be 1.44 hr for i.v. injection and 2.86 hr for i.m. injection. The clearance (CL) and apparent volume of distribution at steady state (Vd_{ss}) after i.v. injection was determined to be 0.027 $L.Kg^{-1}.hr^{-1}$ and 0.039 $L.Kg^{-1}$, respectively. The absorption rate constant from the limb muscle site into systemic circulation was calculated to be 2.19 hr^{-1} and peak plasma concentration after i.m. injection was observed to be at 0.31 ± 0.11 hr. The systemic availability of ketoprofen after intramuscular administration was determined to be 0.38, relative to the equal i.v dose.

Copyright © 1994 by Marcel Dekker, Inc.

RIGHTSLINK

INTRODUCTION

Ketoprofen is a phenylpropionic derivative and is primarily used as an anti-inflammatory analgesic for the treatment of osteoarthritis[1-2] and rheumatic arthritis[3]. The mode of action for ketoprofen is believed to be the inhibition of prostaglandin synthesis[4-5].

Clinical Pharmacokinetic studies of ketoprofen enantiomers in healthy[6] and in arthritic[7] patients following single and multiple doses were reported. The disposition of ketoprofen enantiomers in man was also studied[8]. Recently, the influence of physical and chemical properties of the dosage form on the extent of ketoprofen absorption was reported in dogs[9].

The purpose of this study was to investigate and compare the influence of administration routes on the absorption and distribution of a hydrophilic nonsteroidal anti-inflammatory drug (NSAID), ketoprofen, following intravenous and intramuscular administration modes to rabbits.

EXPERIMENTAL

Materials

Ketoprofen was obtained from Sinbiotik, S.A. Tlaln Epantla Edo-De Mesico; N,N-Dimethylformamide was purchased from Aldrich Chemical Compnay Inc., Milwaukee, WI; Propylene glycol was received from J.T. Baker Chemical Company, Phillipsburg, NJ; Acetonitrile was purchased from ALPS Chemical Co., Ltd., Taipei, Taiwan. Acetic acid glacial was obtained from Fisher Scientific, Fair Lawn, NJ. Isopropyl phenazone was obtained from Scandinavian Chemicals, Denmark. All materials were used as received.

Pharmacokinetics Studies

Twelve male rabbits (New Zealand strain) in the weight range of 2.5 Kg to 3.5 Kg were used in this study. A catheter for blood withdrawal was inserted into the left arterenol of each rabbit while it was anesthetized by injecting appropriate dose of ketamine. Ten milliliter of whole blood was withdrawn from each rabbit before dosing and used as the blank. Six rabbits were administered by intramuscular injection through the right limb at a dose of 4.0 $mg.Kg^{-1}$. The other six rabbits received the intravenous injections through their right ear veins at the same dose of 4.0 $mg.Kg^{-1}$. Animals were kept conscious and individually

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK

housed throughout the entire study. Food and water were supplied ad libitum. About 3 mL of whole blood samples were collected each time from the catheter into evacuated blood collection tubes (Borosilicated glass disposable culture tube, 15 x 150 mm, Corning Glass Works, Corning, NY) containing 0.5 mg disodium edentate, at 0.08, 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.75, 4.50, 5.50, 6.50, 8.00, and 10.00 (i.m. only) hr after injections. Whole blood samples were centrifuged at 3000 rpm (Model L8-M, Beckman Instruments, Inc., Palo Alto, CA) for 15 minutes immediately after withdrawal and supernatants were frozen at -20 °C until analyzed.

Sample Preparation

To each plasma sample (1 mL), one milliliter isopropyl phenazone solution (0.002 $mg.mL^{-1}$ in water) was added. The mixture was then gently shakened (Model 1105, Adams Nutator, Clay Adams, Parsippany, NJ) for one minute before subjection to a centrifugation process at 3000 rpm for 15 minutes. The supernatant was filtered through a 0.22 μm membrane filter (Type GV, Millipore Corp., Milford, MA) and 20 μL of the filtrate was injected into HPLC for analysis.

Standard Solutions

A series of spiked ketoprofen plasma solutions in the concentration ranges of 0.4 $\mu g.mL^{-1}$ to 2.0 $\mu g.mL^{-1}$ was prepared. The linearity of the standard curve was found to be 0.9995. The intra- and inter-day assay precisions were determined to be 0.75% and 0.42% (n=5), respectively.

Recovery studies for ketoprofen in plasma was done by adding a specific amount of ketoprofen to plasma and analyzing the actual quantities of ketoprofen recovered after the extraction processes using the external standard method by HPLC. When compared to the actual amount of ketoprofen added to the plasma, the measured absolute recovery rate (n=5) was determined to be 82.7 ± 4.1 %.

Chromatographic Conditions

A reverse-phase high performance liquid chromatographic system equipped with a single piston pump (Waters model 501, Millipore Corp., Milford, MA), an autosampler with 20 μL injection loop (Waters model 712 WISP), a UV absorbance detector (Waters model 441) set at 254 nm, and a μBondapak C_{18} column (Waters 3.9 mm x 30 cm with 10 μm packaging) was used. The mobile

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK

TABLE 1

Ketoprofen Concentration in Plasma of Rabbits at Indicated Sampling Times After Intravenous Administration of Ketoprofen at A Dose of 4.0 mg.Kg^{-1}.

Time, hr	Ketoprofen Concentration in Plasma[a], μg.mL^{-1} i.v.	i.m.
0	152.0 ± 38.2	0
0.08	112.7 ± 18.8	10.5 ± 2.2
0.17	78.0 ± 19.6	15.5 ± 4.6
0.25	67.8 ± 11.7	19.3 ± 2.2
0.33	59.2 ± 11.3	20.5 ± 1.7
0.50	50.0 ± 8.5	18.5 ± 3.3
0.75	42.1 ± 11.4	16.1 ± 3.1
1.00	32.0 ± 11.5	13.7 ± 1.9
1.50	28.0 ± 11.4	12.0 ± 1.7
2.00	19.4 ± 6.5	9.9 ± 1.3
2.50	15.8 ± 5.6	8.4 ± 0.9
3.00	13.4 ± 4.7	7.1 ± 0.9
3.75	10.5 ± 4.1	5.1 ± 0.7
4.50	8.5 ± 4.0	3.6 ± 0.3
5.50	5.8 ± 2.5	2.4 ± 0.6
6.50	4.1 ± 2.0	1.7 ± 0.5
8.00	2.7 ± 1.4	1.2 ± 0.4
10.0	-[b]	0.6 ± 0.1

[a]mean ± s.d. (n=6); [b]not determined

phase consisted of 38% (v/v) acetonitrile and 62% acetic acid (1%). Its flow rate was maintained at 1.5 mL.min^{-1}. The absorbance of the drugs was recorded using a data station (Waters model 745 data module) at a chart speed of 0.5 cm.min^{-1}. A peak area ratio method was used to determine the concentration of ketoprofen in reference to the internal standard from the calibrated standard curve. The relative retention time for ketoprofen and isopropyl phenazone was determined to be 6.8 and 10.7 minutes, respectively. There was no apparent interference of other peaks with the peaks of interest. The sensitivity of the ketoprofen assay was 0.4 μg.mL^{-1} in plasma at an aufs of 0.01 on the detector and an attenuation of 8 on the recorder. The precision of the HPLC method at the concentration ranges of 0.4 μg.mL^{-1} to 2.0 μg.mL^{-1} in plasma was determined to be ±0.03%.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK

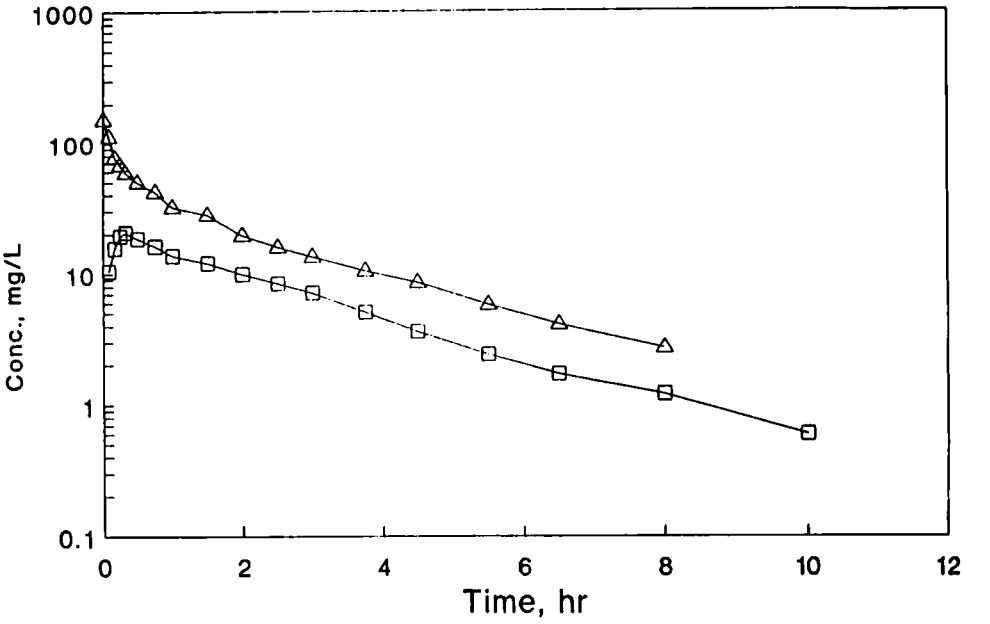

FIGURE 1

Mean concentration of ketoprofen in plasma of rabbits (n=6) after i.v. (◇) and i.m. (□) administrations of ketoprofen at a dose of 4.0 $mg.Kg^{-1}$.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RESULTS AND DISCUSSION

Results of mean plasma concentration of ketoprofen in rabbits versus time after i.v. and i.m. injections of 4.0 $mg.Kg^{-1}$ are listed in Table 1.

Intravenous Administration

The pharmacokinetic profile (Figure 1) after i.v. administration showing a biexponential declination on ketoprofen plasma levels versus time indicates a suitable application of using a two compartment open model with elimination from the central compartment. This can be described as the following equation:

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C_p^t is the plasma concentration of ketoprofen at time t, and A and B are two pre-exponential constants.

RIGHTSLINK

TABLE 2

Estimation of Pharmacokinetic Parameters following The Intravenous Administration of Ketoprofen at A Dose of 4.0 mg.Kg^{-1} to Rabbits, Using A Two Compartment Open Model with Elimination from The Central Compartment.

Parameter (Units)		Estimate
A	($\mu g.mL^{-1}$)	43.71
B	($\mu g.mL^{-1}$)	85.61
α	(hr^{-1})	0.37
β	(hr^{-1})	0.22
k_{12}	(hr^{-1})	2.14
k_{21}	(hr^{-1})	1.70
k_{10}	(hr^{-1})	0.92
AUC	($\mu g.hr.mL^{-1}$)	148.65
V_c	($L.Kg^{-1}$)	0.031
Vd_{ss}	($L.Kg^{-1}$)	0.070
Vd_β	($L.Kg^{-1}$)	0.130
$t_{1/2,\beta}$	(hr)	3.15

The compartmental analysis was attempted using the CSTRIP[10] and PCNONLIN[11] programs. The results of the calculated pharmacokinetic parameters are depicted in Table 2. The mean terminal half-life of ketoprofen was determined to be 3.15 hr (n=6) based on the equation:

$$t_{1/2,\beta} = 0.693/\beta \qquad (2)$$

The apparent volume of distribution in the central compartment immediately after i.v. injection but before the drug was distributed, V_c, was calculated to be 0.031 $L.Kg^{-1}$ according to $V_c = D/(A+B)$, where D is the i.v. bolus dose in $\mu g.Kg^{-1}$. The apparent volume of distribution based on the terminal elimination rate constant and area under the plasma concentration-time curve in the post-distributive phase, Vd_β, was determined to be 0.130 $L.Kg^{-1}$ following $Vd_\beta = k_{10}V_c/\beta$, and where k_{10} is the elimination rate constant from the central compartment. The apparent volume of distribution at steady state, Vd_{ss}, was obtained to be 0.070 by the equation of $Vd_{ss} = V_c(k_{21}+k_{12})/k_{21}$, where k_{12} and k_{21} are the distribution constants between central and peripheral compartments. The values of Vd_β and Vd_{ss} are larger than that of V_c indicating a significant distribution of ketoprofen into peripheral compartment at steady and post-distributive stages. At

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK

TABLE 3

Estimate of Model-Independent Pharmacokinetic Parametersafter Intravenous Administration of Ketoprofen at A Dose of 4.0 mg.Kg^{-1} to Rabbits, Using A Statistical Moment Theory Method.

Parameter (Units)		Estimate
AUC	($\mu g.hr.mL^{-1}$)	148.65
AUMC	($\mu g.hr^{-2}.mL^{-1}$)	214.45
MRT	(hr)	1.44
CL	($L.Kg^{-1}.hr^{-1}$)	0.027
Vd_{ss}	($L.Kg^{-1}$)	0.039

distribution equilibrium when the net transfer of ketoprofen between central and peripheral compartments is equal to zero, the fraction of total ketoprofen in the central compartment, F_c^*, remained constant and can be calculated to 0.24 according to the following equation:

$$F_c^* = \beta/k_{10} \quad (3)$$

A significant amount of ketoprofen (76%) was found to be in the peripheral compartment at the stage of distribution equilibrium.

Model-independent pharmacokinetic parameters were also obtained by the conventional methods[12] following the equations:

$$CL = D/AUC \quad (4)$$

$$MRT = AUMC/AUC \quad (5)$$

$$Vd_{ss} = D(AUMC/AUC^2) \quad (6)$$

where CL is the clearance, AUMC is the area under the first moment (Product of plasma concentration and time versus time) curve, and MRT is the mean residence time. Results of these estimates are listed in Table 3. The values of CL and MRT are determined to be 0.027 $L.Kg^{-1}.hr^{-1}$ and 1.44 hr respectively. A lower value of 0.039 $L.Kg^{-1}$ for Vd_{ss} was found from this statistical moment theory in comparison with 0.070 $L.Kg^{-1}$ predicted by the compartmental model.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

Intramuscular Administration

The mean plasma concentration-time curve of ketoprofen after intramuscular administration at a dose of 4.0 $mg.Kg^{-1}$ is also shown in Figure 1. After the i.m. injection of ketoprofen, it was rapidly absorbed into blood stream. This is reflected in that plasma concentration reached maximum at only 0.31 ± 0.11 hr (n=6) (range 0.17 hr - 0.50 hr). The observed maximum plasma concentration was found to be at 21.3 ± 1.9 $\mu g.mL^{-1}$ (n=6) (range 20.08 $\mu g.mL^{-1}$ - 25.14 $\mu g.mL^{-1}$). The MRT of ketoprofen after intramuscular administration was calculated to be 2.86 hr using the statistical moment theory (Eq. 5). The MRT was found to be longer (almost double) for i.m. administration than that of i.v. administration. The extent of absorption after i.m. administration of ketoprofen to rabbits at a dose of 4.0 $mg.Kg^{-1}$ was estimated to be 0.38 by the following equation:

$$F = AUC_{i.m.}/AUC_{i.v.} \quad (7)$$

where the $AUC_{i.m.}$ was 55.88 $\mu g.hr.mL^{-1}$.

The absorption rate constant of ketoprofen from limb muscle to systemic circulation, k_a, was calculated to be 2.19 hr^{-1} from the slope ($-k_a/2.303$) of the plot of log fraction of ketoprofen unabsorbed against time, according to the Loo-Riegelman method[13].

In conclusion, ketoprofen was characterized as a drug with a terminal half-life of 3.15 hr, low volume of distribution and low systemic clearance, from this study of ketoprofen pharmacokinetics. The disposition of ketoprofen following the form of biphasic declination in plasma concentration indicates the existence of two distinguishable compartments in peripheral tissues. From the intramuscular study, incomplete absorption of ketoprofen was observed because only 38% of total drug administered was absorbed into systemic circulation.

REFERENCES

1. J.P. Famaly and E. Colinet, Scan. J. Rheumatol., 5, 129 (1976).
2. M.J. Williams, J.W. Digby, J.R. Topp, E. Arendt-Racine, A. Pepin et al., Current Therap. Res., 25, 35 (1979).
3. D.L.G. Howard, Current Therap. Res., 23, 678 (1978).
4. T. Kubota, H. Komatsu, H. Kawamoto and T. Yamada, Arch. Int. Pharmacodyn. Therap., 237, 169 (1979).
5. S.O.A. Lundstam, K.H. Leissner, L.A. Wahlander and J.G. Kral, Lancet, 1, 1096 (1982).

RIGHTSLINK

6. R.T. Foster, F. Jamali, A.S. Russell and S.R. Alballa, J. Pharm. Sci., 77, 70 (1988)
7. R.T. Foster, F. Jamali, A.S. Russell and S.R. Alballa, J. Pharm. Sci., 77, 191 (1988).
8. B.C. Sallustio, Y.J. Purdie, A.G. Whitehead, M.J. Aherm and P.J. Meffin, Br. J. Clin. Pharmac., 26, 765 (1988).
9. M. Schmitt and T.W. Guentert, J. Pharm. Sci. 79, 614 (1990).
10. A.J. Sedman and J.G. Wagner, J. Pharm. Sci. 65, 1006 (1976).
11. C.M. Metzler and D.L. Weiner, "PCNONLIN user's guide", Statistical Consultants, Kentucky, 1986.
12. M. Gibaldi and D. Perrier, "Pharmacokinetics", 2nd Edn, Dekker, New York, 1982, p. 52, 205, 321, 414.
13. J.C.K. Loo and S. Riegelman, J. Pharm. Sci. 57, 918 (1968).

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Xavier University on 01/28/12
For personal use only.

RIGHTSLINK