Pharmacokinetics of an indomethacin pro-drug: Apyramide after intravenous administration in dog

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SUMMARY

The pharmacokinetics of apyramide, an ester of indomethacin and acetaminophen (paracetamol), were determined after intravenous administration to nine beagle dogs. Indomethacin and its pro-drug, apyramide, were extracted from acetonitrile-precipitated plasma by a solvent-demixing procedure and the concentration of these two drugs was measured by a reversed-phase liquid chromatographic assay.

The kinetic evolution with time of plasma levels of apyramide and of indomethacin resulting from enzymatic hydrolysis was compared with values obtained for indomethacin injected in equimolar dose. Plasma levels of apyramide quickly decreased and the mean (± SD) half life was 0.15 ± 0.08 h. For metabolic indomethacin, the mean (± SD) area under curve was 12.36 ± 4.80 mg.h/l and the mean (± SD) half life of terminal phase was 16.71 ± 9.46 h. After administration of indomethacin, these values were 17.60 ± 4.12 mg.h/l and 7.89 ± 2.20 h, respectively.

INTRODUCTION

Apyramide, an original combination of paracetamol and indomethacin, belongs to the group of non steroidal anti-inflammatory drugs (NSAIDs) as a pro-drug of indomethacin. It was synthesized by Laboratoire M. Richard for the purpose of both reducing the toxicity and prolonging the plasma kinetics of indomethacin (Serrano J.J., toxicological expert's reports, 1978, 1979, 1981).

The aim of the present study was to assess the kinetic profile of apyramide, 50 mg by intravenous route in beagle dogs, then to compare the kinetics of the metabolite indomethacin to that of an equimolar amount of indomethacin, that is 36.5 mg, injected by the same route.

MATERIALS AND METHODS

Chemicals

Apyramide (batch 484) and indomethacin (batch 576) were provided by Laboratoire M. Richard (Sauzet, France).

Animals

The study involved nine female beagle dogs, weighing 11 ± 2 kg. Dogs number 1 to 5 were given apyramide, dogs number 6 to 9, indomethacin.
Experimental protocol

The doses, dissolved in 0.5 ml dimethylsulfoxide, were injected within 30 s into the saphenous vein of the right forelimb of fasted dogs. Animals were first placed on a contention table, and blood samples were taken from the left forelimb with an indwelling catheter. Twelve hours after injection, the catheter was removed and the animals were transferred to metabolic cages. The last sample was taken from the right forelimb by venipuncture and animals were then monitored for a 48 h period.

Blood sampling

Blood (1.5 ml aliquots) was sampled into heparinized tubes at times: 5, 10, 15, 20, 30, 45 min, then 1, 1.5, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, and 24 h. Plasma samples were kept at -20°C. until analyzed.

Analytical method

Apyramide and indomethacin were assayed in plasma by high performance liquid chromatography and UV absorption measurement at 250 nm, after solvent demixing extraction (1, 2).

Pharmacokinetic analysis

The time-plasma concentration curves of indomethacin were analyzed by the method of residuals, with the interactive program IG PHARM (3), on a Tektronix model 4051 calculator (Bres J., Pharmacokinetic expert’s report, 1986). The concentration-time equations were:

\[ C = C_1 \exp(-\lambda_1 t) + C_2 \exp(-\lambda_2 t) \]

for apyramide and intravenous indomethacin; and

\[ C = C_m \exp(-k_{me} t) + C_1 \exp(-\lambda_1 t) + C_2 \exp(-\lambda_2 t) \]

for indomethacin resulting from the enzymatic hydrolysis of apyramide — \( k_{me} \) is the rate constant corresponding to the generation of metabolite indomethacin.

The pharmacokinetic model is thus an open, two-compartment model with first-order transfer and elimination processes.

The calculated constants are:

- \( t_{1/2} (\lambda_1) \) and \( t_{1/2} (\lambda_2) \) : half-lives of the rapid phase and of the slow phase respectively;
- \( \text{AUC}_{\text{obs}} \) and \( \text{AUC}_{\text{tot}} \) : observed and total areas under the curve, where

\[ \text{AUC}_{\text{tot}} = \text{AUC}_{\text{obs}} + C_{\text{sh}} / \lambda_2, \ C_{\text{sh}} \text{ being the last measurable plasma concentration.} \]

\[ \text{AUC}_{\text{obs}} \text{ was calculated as } CL_t = \text{Dose} / \text{AUC}_{\text{tot}}. \]

The rate constants \( k_{1,0} \) (elimination from the central compartment), \( k_{1,2} \) and \( k_{2,1} \) (transfer from and to the central compartment respectively) were calculated by solving the equivalence relationships:

\[ k_{1,0} + k_{1,2} + k_{2,1} = \lambda_1 + \lambda_2 \]
\[ k_{1,0} \times k_{2,1} = \lambda_1 \times \lambda_2 \]

\[ k_{1,0} = \frac{C_1 + C_2}{C_1 + C_2} \]

The distribution volumes were:

- initial distribution volume \( V_1 \)
- steady-state distribution volume \( V_{ss} \), calculated from the transfer microscopic rate constants \( k_{1,2} \) and \( k_{2,1} \) as: \( V_{ss} = V_1 (k_{1,2} + k_{2,1}) / k_{2,1} \)
- total distribution volume \( V_{tot} = CL_t / \lambda_2 \)

Statistical analysis

Comparisons of pharmacokinetic parameters of indomethacin either injected as such or metabolically generated from apyramide were performed by:

- a one-factor analysis of variance (Anova) if homoscedasticity was not disproven by Bartlett’s test (4), the deviation being then assigned to the factor – injected substance;
- or the Mann and Whitney’s non-parametric U test if Bartlett’s test (4) reached significance.

RESULTS

The average pharmacokinetic profile of indomethacin after intravenous administration of either apyramide or indomethacin is shown in Figure 1. The points represent mean plasma concentrations ± standard deviations.

Pharmacokinetic parameters of apyramide

Results from dogs 1, 2 and 3 were compatible with a two-compartment open model; in dogs 4 and 5, only the first rapid phase was detected (Fig. 2). Apyramide distribution and elimination parameters as estimated by fitting the concentration-time curve are presented in