PHARMACOKINETICS OF ELTOPRAZINE IN THE DOG

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CONTENTS

SUMMARY

Pharmacokinetics of eltoprazine in male and female beagle dogs was studied in two separate cross-over experiments after administration of different intravenous and oral doses. After

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intravenous administration of 0.5 $mg.kg^{-1}$, the mean volume of distribution was 5.7 ± 1.1 $l.kg^{-1}$. Clearance was 25.5 ± 1.4 $ml.min^{-1}.kg^{-1}$. About 25% of the doses was excreted in urine, resulting in a renal clearance of 6.1 ± 1.4 $ml.min^{-1}.kg^{-1}$. The mean elimination half-life ($t_{1/2}$) after intravenous dosing was about 2.6 h.

After oral dosing the plasma peak levels (C_{max}) were proportional with the dose. The mean time to reach C_{max} (t_{max}) varied between 1.5 and 1.9 h, and $t_{1/2}$ was about 2.4 h, which was not significantly different ($p > 0.05$) from the half-life obtained after intravenous dosing. Plasma pharmacokinetics after single and multiple dosing of 4 $mg.kg^{-1}$ showed no difference. Absolute bioavailability was 67% ± 20%.

I. INTRODUCTION

As part of its pre-clinical development programme, the pharmacokinetics of eltoprazine hydrochloride (hereafter called eltoprazine) was studied in a number of animal species to confirm and support toxicological observations and to predict from animal experiments the safety of the compound in humans.

Radioactive studies in rat and mouse showed complete absorption from the gastro-intestinal tract; peak levels in plasma and tissues were found one to three hours after oral dosing of 5 $mg.kg^{-1}$.

In dogs, peak plasma levels were found 1 h after oral dosing of 5 $mg.kg^{-1}$, radioactive absorption and excretion were complete and about 80% of the excreted radioactivity was found in urine.

The aim of the present studies in the dog was to establish the pharmacokinetics of eltoprazine in the dog. Dose-proportionality in kinetics over a 64-fold dose-range, bioavailability, changes of pharmacokinetics caused by repeated dosing as well as substantial sex differences in kinetics were also investigated.

II. MATERIALS AND METHODS

2.1 Compound

Eltoprazine with a purity of >98% (determined by HPLC-analysis) was used.

2.2 Dosages

Oral doses were weighed into hard gelatine capsules. Intravenous infusion liquids were prepared in normal saline by dissolving 0.2 mg or 0.5 mg eltoprazine per ml.

2.3 Analytical assay

Plasma and urine levels were determined using HPLC-analysis as described previously /1/.

2.4 Studies

Two studies were performed in a cross-over design in male and female beagle dogs, which were supplied by CPB-TNO, Zeist, The Netherlands. The body weight of the dogs ranged between 10.2 and 13.8 kg. All dogs were housed in a conditioned room (17-19°C, 50-70% relative humidity). During the experiments, the dogs were placed individually in cages providing for separate collection of urine. Tap water was available *ad libitum*. Approximately 250 grams of food (LD-B Hope Farms, Woerden, The Netherlands) was supplied daily at 09.00 h, except during the dosing period, when food was supplied 3-4 hours after dosing. No food was available during the night (18.00 h - 09.00 h). Dosing was always between 08.00 h and 09.00 h. Time intervals between dosing sessions were between two and three weeks.

In experiment I, eltoprazine was given orally and intravenously to three beagles of each sex. The intravenous dose levels were 0.2 $mg.kg^{-1}$ and 0.5 $mg.kg^{-1}$. Rate of infusion was 2 $ml.min^{-1}$, so a mean infusion time of 6.2 ± 0.5 min. was used. For infusion in the brachial vein, a Braun infusion pump was used. The oral dose was 0.5 $mg.kg^{-1}$.

In experiment II eltoprazine was given at single oral doses of 0.5 $mg.kg^{-1}$, 4 $mg.kg^{-1}$ and 32 $mg.kg^{-1}$ and at repeated oral doses of 4 $mg.kg^{-1}$ for 8 consecutive days.

In both experiments, blood samples (6 ml) were taken from a brachial vein prior to dosing and at 10, 20, 30, 45, 60 minutes and 1.5, 2, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 24 and 32 hours after dosing. Intravenous infusion and blood sampling were always in opposite legs. Urine, for the determination of excreted eltoprazine, was collected in portions up to 48 hours after dosing.

2.5 Pharmacokinetic analysis

AUC was calculated using the trapezoidal rule. For single doses, values up to the last data point and extrapolation to infinity was used. For repeated dosing, values up to 24 h after the last dose were used. The elimination half-life was calculated from the regression analysis of the terminal part of the concentration-time curve. Volume of distribution was calculated as $V_d = D/C_{(0)}$, in which $C_{(0)}$ is the concentration at zero-time obtained after back-extrapolation of the regression curve. Clearance (CL_S) after intravenous dosing

was calculated from CL_S = D/AUC. Renal clearance (CL_R) after both intravenous and oral dosing from CL_R = Ae/AUC. Bioavailability (F) is expressed as the ratio between the AUC of the oral and intravenous route at the dose level of 0.5 $mg.kg^{-1}$.

2.6 **Statistical analysis**

Data evaluation was performed using appropriate ANOVA for cross-over study designs. ANOVA analysis for C_{max} and AUC was done after logarithmic transformation of the data /2/.

III. RESULTS

A representative example of plasma-concentration versus time-curves after intravenous dosing of 0.2 $mg.kg^{-1}$, 0.5 $mg.kg^{-1}$ and oral dosing of 0.5 $mg.kg^{-1}$ is given in Figure 1. This figure shows that the decline of plasma concentration proceeds parallel and according to a one-compartment open model. The experimental results (Table 1) show that after intravenous infusion at different dose levels, no differences in CL_S, CL_R, V_d and $t_{1/2}$ were found. The average bioavailability was 67%.

Dose-corrected pharmacokinetic parameters after single-dose oral administration of eltoprazine in experiment II are given in Table 2. Peak concentrations were almost always attained within 2 hours and increased linearly with the dose in the 0.5 to 32 $mg.kg^{-1}$ dose range. Similarly, the AUC increased linearly in this range. The plasma eltoprazine profile after a single dose of 4 $mg.kg^{-1}$ was comparable with the profile from plasma values after chronic dosing for 8 consecutive days. The mean dose-normalized AUC was 684 and 668 $ng.h.ml^{-1}$ per mg/kg body weight; mean dose-normalized C_{max} was 153 and 118 $ng.ml^{-1}$; mean $t_{1/2}$ was 2.9 h and 2.6 h after single and repeated dosing, respectively.

Renal clearances as measured in experiment II are given in Table 3. Mean values, about 4-7 $ml.min^{-1}.kg^{-1}$ are comparable with those measured in experiment I (see Table 1). No statistically significant differences were observed in CL_R between single and multiple dosing.

Apparently, no considerable sex differences in pharmacokinetic parameters exist (Table 2).

IV. DISCUSSION

The aim of this study was to establish the pharmacokinetics of eltoprazine in dogs after single and multiple dose oral and single dose intravenous administration.

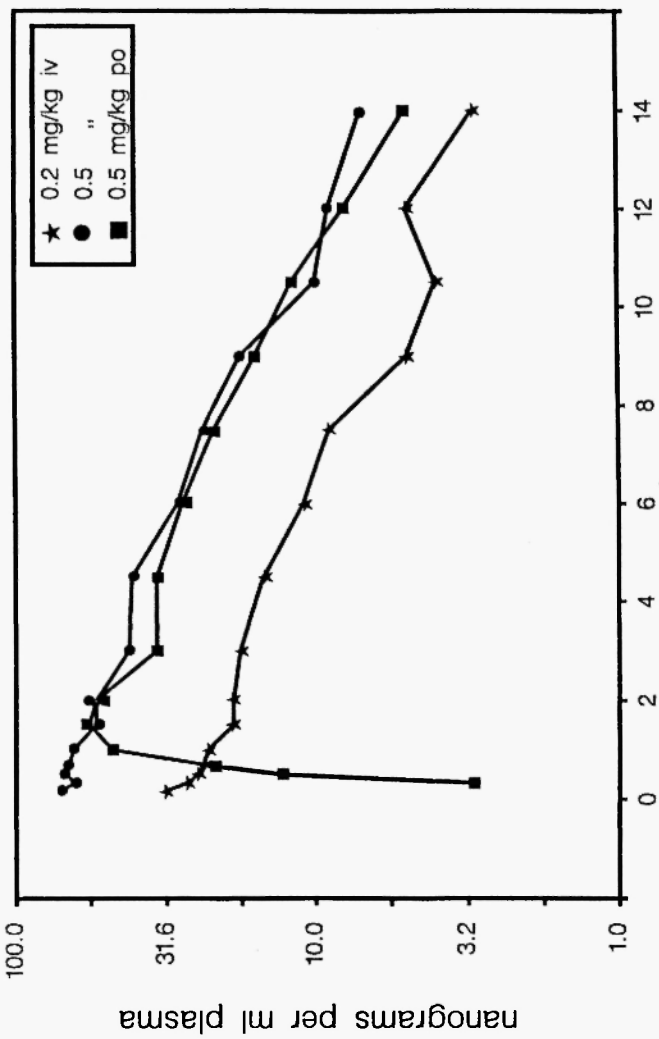

Fig. 1: Representative individual plasma concentration-time curves of eltoprazine after single-dose oral administration of 0.5 mg.kg^{-1} of eltoprazine and after single-dose intravenous administration of 0.2 mg.kg^{-1} and 0.5 mg.kg^{-1} of eltoprazine to one dog.

Attention was paid to dose linearity, effects of repeated dosing, and also to possible sex differences in the pharmacokinetics of eltoprazine. From radioactive studies in dogs it was found that absorption of radioactivity from the gastro-intestinal tract was complete. In this study an oral bioavailability of 67% was measured, which indicates that the compound is partly subject to presystemic

TABLE 1

Pharmacokinetic parameters (geometric means; in parentheses 95% confidence limits) after administration to dogs of 0.2 $mg.kg^{-1}$ (i.v.) and 0.5 $mg.kg^{-1}$ (i.v. and p.o.) eltoprazine per kg body weight.

Pharmacokinetic Parameter	Eltoprazine dose 0.2 $mg.kg^{-1}$ i.v.		0.5 $mg.kg^{-1}$ i.v.		0.5 $mg.kg^{-1}$ p.o	
CL_S ($ml.min^{-1}.kg^{-1}$)	26.6	(21.1-33.5)	25.5	(19.2-33.8)		
CL_R ($ml.min^{-1}.kg^{-1}$)	5.7	(2.6-12.9)	6.1	(2.4-15.4)	7.0	(3.7-13.2)
V_d ($l.kg^{-1}$)	6.4	(5.2-7.9)	5.7	(4.4-7.5)		
$t_{1/2}$ (h)	2.9	(2.0-4.0)	2.7	(2.0-3.4)	2.4	(1.7-3.5)
F					0.67	(0.4-1.0)

TABLE 2

Dose corrected C_{max} ($ng.ml^{-1}$) and AUC ($ng.h.ml^{-1}$ per mg/kg body weight) and $t_{1/2}$ (h) after single oral dosing of 0.5 $mg.kg^{-1}$ (I), 4 $mg.kg^{-1}$ (II) and 32 $mg.kg^{-1}$ (III) to three male and three female dogs.

dog	sex		C_{max}	AUC	$t_{1/2}$		C_{max}	AUC	$t_{1/2}$		C_{max}	AUC	$t_{1/2}$
A	m	I	98	596	9.4	III	123	585	2.6	II	164	1134	3.6
C	m	II	134	709	4.0	I	223	1175	3.5	III	223	1175	3.8
E	m	III	84	376	3.0	II	143	530	2.0	I	133	756	3.1
B	f	I	186	870	4.2	II	147	828	2.8	III	64	323	3.1
D	f	III	128	662	4.0	I	126	930	3.5	II	206	916	2.9
F	f	II	112	612	3.6	III	129	773	3.1	I	223	1219	2.4

elimination. To date, it is not clear whether this is due to metabolism in the intestinal lumen, in the gut-wall or due to hepatic first-pass extraction.

The volume of distribution of eltoprazine was 5.7 $l.kg^{-1}$, indicating extensive tissue distribution.

Plasma kinetics were linear over the 64-fold dose range studied in these experiments. After daily dosing for eight consecutive days, the dose-corrected AUC was the same as dose-corrected AUC after single dosing. Plasma peak levels did not increase after repeated daily oral dosing, due to the relatively fast elimination from the plasma compartment.

Although it should be realized that most of the eltoprazine was metabolised, not less than 20% of eltoprazine was excreted unchanged in urine. Given the fact that the mean bioavailability was 67%, it could be anticipated that excretion of the unchanged compound after intravenous dosing, expressed as percentage of the dose, will be higher than excretion after oral dosing. Indeed, on average 18% and 29% of the dose was excreted after oral and intravenous dosing of 0.5 $mg.kg^{-1}$, respectively (results not shown). This difference, however, was not statistically significant.

Renal clearance was about 72 $ml.min^{-1}$, close to the renal plasma flow in dogs (about 90 $ml.min^{-1}$), and more than the glomular filtration rate of about 30 $ml.min^{-1}$ /3/, indicating active secretion of eltoprazine in urine.

TABLE 3

Renal clearance in $ml.min^{-1}.kg^{-1}$ after single oral dosing of 0.5 $mg.kg^{-1}$ (I), 4 $mg.kg^{-1}$ (II), 32 $mg.kg^{-1}$ (III) and repeated daily oral dosing of 4 $mg.kg^{-1}$ (IV) for eight consecutive days

Dog No.	I	II	III	IV
A	2.7	4.1	n.s.*	4.0
B	7.9	5.4	4.6	9.6
C	6.7	3.4	4.7	7.6
D	4.0	6.4	3.0	10.4
E	4.7	3.8	n.s	7.1
F	5.3	3.0	21.5	6.1
mean	4.9	4.2	5.9	7.3
(95% conf. lim.)	3.3-7.3	3.1-5.6	2.9-12.0	5.1-10.4

* No sample available

Since the metabolic profile of eltoprazine is similar in dog and man /4/, it is foreseen that in humans eltoprazine will be well absorbed from the gastro-intestinal tract, and that the drug will partly be excreted unchanged in urine. No considerable sex differences in pharmacokinetic parameters were observed.

V. ACKNOWLEDGEMENTS

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VI. REFERENCES

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