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The pharmacokinetics of xylazine hydrochloride: an interspecific study

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The pharmacokinetic disposition of xylazine hydrochloride is described after both intravenous and intramuscular injection of a single dose, in four domestic species: horse, cattle, sheep and dog, by an original high performance liquid chromatographic technique. Remarkably small interspecific differences are reported. After intravenous administration, systemic half-life ($t_{1/2\beta}$) ranged between 22 min (sheep) and 50 min (horse) while the distribution phase is transient with half-life ($t_{1/2\alpha}$) ranging from 1.2 min (cattle) to 5.9 min (horse). The peak level of drug concentration in the plasma is reached after 12-14 min in all the species studied following intramuscular administration. Xylazine bio-availability, as measured by the ratios of the areas under the intravenous and intramuscular plasma concentration *versus* time curves, ranged from 52% to 90% in dog, 17% to 73% in sheep and 40% to 48% in horse. The low dosage in cattle did not permit calculation. Kinetic data are correlated with clinical data and the origins of interspecific differences are discussed.

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INTRODUCTION

Xylazine hydrochloride (Rompun, Bayer, Puteaux, France) is the generic name for 2-(2.6 dimethylphenylamino)-4H-5.6 dihydro-1.3 thiazine hydrochloride, a drug extensively used in veterinary practice for its potent sedative, analgesic and myorelaxant properties (Clarke & Hall, 1969). In spite of numerous clinical studies, no extensive work in the pharmacokinetics of xylazine has been reported in domestic animals.

In rats, Duhm, Maul, Medenwald, Patzschke & Wegner (1969) using radio-labelled xylazine,

found that after intravenous (i.v.) injection (0.2-1.0 mg/kg) the drug was rapidly distributed to different tissues and that 70% of the radio-activity was eliminated in urine with a half-life of about 2-3 h, only 8% of the activity corresponding to the unchanged form of the drug.

In sheep, following intramuscular (i.m.) administration (1.0 mg/kg) Putter & Sagner (1973) found that two-thirds of the dose was absorbed within 10 min. In the urine of cattle, they reported that less than 1% unchanged xylazine was eliminated during the first 2 h, with an apparent half-life of 40 min. The peak excretion of metabolites occurred between 2 and 4 h after the administration of the drug,

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thus suggesting that xylazine is extensively metabolized, as has been reported to occur in rats. In the horse, Sams (1979) reported a half-life of 49 min for xylazine after an intravenous (i.v.) bolus injection, but only one horse was used and no details of the assay method were given.

The paucity of pharmacokinetic data in domestic animals is probably related to the lack of an appropriate analytical method. Recently, a rapid, sensitive and specific high performance liquid chromatography (HPLC) technique has been proposed by Alvinerie & Toutain (1981) for an accurate evaluation of xylazine in biological fluids.

The aim of the present work was to determine the pharmacokinetics of xylazine hydrochloride, after both i.v. and i.m. administration, in four domestic species: horse, cattle, sheep and dog.

MATERIALS AND METHODS

Animals

Healthy and sexually-mature horses, cattle, sheep and dogs were used. The number of animals, weights and diets are listed in Table I.

Drug applications and blood sampling

Xylazine hydrochloride was administered intravenously into the right jugular vein in horse, cattle and sheep and into the cephalic vein in dog. Intramuscular injections were made into the deep muscles of the neck in horses and cattle, and into the gluteus muscle in sheep and dogs. The dosage regimen was that generally recommended and is shown in Table I.

A catheter was inserted into the left jugular

vein 2 h before the administration of the drug in all the species except the dog. In dogs, a polyvinyl catheter filled with heparinized saline was surgically implanted under general thiopentone anaesthesia (20 mg/kg) 1 week before starting the experiment.

Blood samples (5 ml) were collected into dry heparinized tubes. The same schedule was used for the four species and the two routes of administration *viz*: control and 1, 2, 4, 8, 16, 30, 60 and 120 min after drug injection. After each sampling the catheter was rinsed with heparinized 0.9% saline solution. Blood was centrifuged and the plasma fraction was frozen at -20°C until assay. In sheep, urine was collected every 10 min after i.v. administration.

Assays

The plasma concentration of xylazine hydrochloride was measured by an original HPLC method already published. The main steps of the procedure were as follows: after addition of 1 g of internal standard (doxapram) and 1 ml of 0.05 M borax buffer solution to aliquots of plasma (0.5 ml), the sample was vortexed for 5 sec and then shaken with 10 ml of chloroform for 10 min; after centrifugation at 11.400 g for 10 min, the organic phase was isolated and evaporated at 70°C under a nitrogen gas stream. The evaporated extract was redissolved in 100 μl of mobile phase (2% glacial acetic acid in water, methanol, heptane sulphonic acid; 55 : 45 : 0.2; v/v/v). The entire sample was injected in the HPLC system (Model 6000 A, Waters Assoc., Milfordt, Mass, U.S.A.). The ultraviolet (u.v.) detector (GM 770, Schoeffel Instruments) was operated at a wavelength of 225 nm; this assay procedure is sensitive enough to estimate blood concentrations of xylazine down to 10 ng per ml.

TABLE I. Doses and experimental conditions

	Animals (n)	Weight (kg)	Diet	Dosage (mg/kg)*
Horse	4	415-550	Pelleted food 7 kg/day Straw and water <i>ad libitum</i>	0.6
Cattle	4	240-440	Hay and water <i>ad libitum</i>	0.2
Sheep	6	42-65	Hay and water <i>ad libitum</i>	1.0
Dog	4	14-24	Canned food <i>ad libitum</i>	1.4

*Dosage expressed as xylazine-base.

Mathematical and statistical methods

Pharmacokinetic analysis was performed by least square regression analysis using a programmed Hewlett Packard 41 C calculator, according to the generally accepted methods (Baggot, 1977).

RESULTS

Intravenous administration studies

Figure 1 shows the semi-logarithmic plot of plasma xylazine concentration *versus* time, after i.v. dosage in the four species. Decay of xylazine concentration is biphasic and the pharmacokinetic analysis of data is performed by applying the appropriate biexponential equation for a two-compartment open model

$$C_p^t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where C_p^t is the plasma xylazine concentration ($\mu\text{g}/\text{ml}$) at time t (min); A, B are the zero-time intercepts of plasma drug concentration obtained by extrapolation of the distribution and elimination curves; α , β are the hybrid rate constants of a two-compartment open model. The other calculated parameters included transfer rate constants for distribution and elimination (k_{12} , k_{21} , k_{e1}), apparent volume of distribution ($V_d(\text{area})$) and body clearance

(Cl_B). The values of these different parameters are shown in Table II. In all species, half-time of distribution was very short (1.2–5.9 min), half time of elimination varied from 23 to 50 min and the volumes of distribution were large (2–2.7 l/kg); in the urine of sheep, xylazine was not detectable.

Intramuscular administration studies

Figure 2 shows the semi-logarithmic plot of plasma xylazine concentration *versus* time after i.m. dosage in the four species. Levels of drug peaked rapidly and then declined exponentially over the next 150 min, except for cattle, in which xylazine was not detected in the plasma. These data were well fitted by a one-compartment open model with a transient absorption (invasion) phase followed by an elimination phase. The Bateman function can be applied.

$$C_p^t = \frac{k_a B_0}{k_a - k_{e1}} (e^{-k_{e1}t} - e^{-k_a t})$$

where C_p^t is the plasma xylazine concentration ($\mu\text{g}/\text{ml}$) at time t (min); k_a is the rate constant for absorption; k_{e1} is the rate constant for elimination and B_0 is the zero-time concentration intercept of plasma drug concentration *versus* time curve.

Table III gives the values of k_a and k_{e1} , C_{max} (maximal plasma concentration), T_{max}

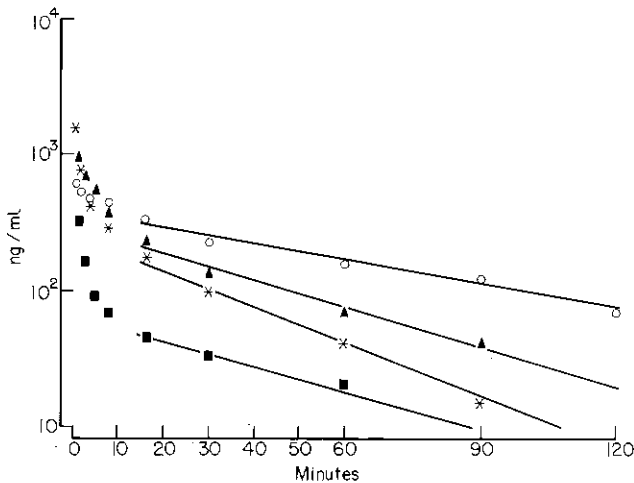


FIG. 1. Semi-logarithmic plot of average xylazine plasma concentration *versus* time in the four species studied after intravenous injection of a single dose: only the elimination phase (regression line) of the disposition curve is drawn. (○) Horse 0.6 mg. kg^{-1} ; (▲) dog 1.4 mg. kg^{-1} ; (*) sheep 1.0 mg. kg^{-1} ; (■) cattle 0.2 mg. kg^{-1} .

(time corresponding to C_{\max}); the latter two parameters were calculated from appropriate equations. Half-time of absorption was short in the three species (2.7–5.5 min); the maximal concentration was obtained in 13 min.

Bioavailability

The calculation of systemic bioavailability is based on the ratio of total area under curves obtained after i.v. and i.m. administration of equal doses. The areas were determined by the trapezoidal method. The extrapolation of the curve to infinity was obtained from $C_p^{tl} \cdot \beta$, where C_p^{tl} was the last measured concentrations of drug and β the overall elimination rate constant. The bioavailability varied less in the horse (extreme range of 40% to 48%) than in the sheep (extreme range 17% to 73%) and the dog (52% to 90%), (Table III). It was impossible to measure bioavailability in cattle as xylazine was not detected in the plasma.

DISCUSSION

After an intravenous administration, the differences noticed between the four species under study are remarkably small. After a rapid distribution, with a half-life comprised between 1.2 and 6 min, the apparent volume

of distribution is large (1.9–2.7 litres/kg) suggesting that xylazine, as expected for a weak organic base, diffuses extensively. The rapid elimination of xylazine is probably related to an intense metabolism rather than to a rapid renal excretion of unchanged xylazine. This hypothesis is supported by the lack of significant amounts of intact drug found in urine collected every 10 min in sheep. Moreover, preliminary results from three anaesthetized rabbits indicate that no modifications of pharmacokinetics of xylazine occur after occlusion of the two renal arteries. No attempts were made in order to identify the different catabolites of xylazine, but according to Duhm *et al.* (1969) using radio-labelled xylazine in rats, this drug undergoes a rapid metabolism yielding about twenty end products. After intramuscular administration, absorption of xylazine is rapid with a half-time of absorption of 2.8–5.4 min. However, plasma concentrations are not detectable in cattle, a point which could be explained by the low dosage used for this very xylazine-sensitive species.

The pharmacokinetic results obtained in the present experiment are in good agreement with clinical data in horses and dogs; by contrast the pharmacokinetic data are difficult to relate to the known clinical effects of xylazine in cattle.

TABLE II. Pharmacokinetic parameters of xylazine hydrochloride in the four studied species after intravenous injection of a single dose

Kinetic parameter	Horse (n = 4)	Cattle (n = 4)	Sheep (n = 6)	Dog (n = 4)
C_p^0 ($\mu\text{g} \cdot \text{ml}^{-1}$)	0.598	1.050	1.551	1.382
A ($\mu\text{g} \cdot \text{ml}^{-1}$)	0.217	0.990	1.298	1.072
α (min^{-1})	0.116	0.575	0.367	0.270
$t_{1/2\alpha}$ (min)	5.970	1.205	1.889	2.567
B ($\mu\text{g} \cdot \text{ml}^{-1}$)	0.381	0.065	0.259	0.306
β (min^{-1})	0.014	0.022	0.030	0.023
$t_{1/2\beta}$ (min)	49.51	36.48	23.105	30.130
$V_d(\text{area})$ ($\text{l} \cdot \text{kg}^{-1}$)	2.456	1.944	2.740	2.517
Cl_B ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	21	42	83	81
k_{12} (min^{-1})	0.030	0.318	0.183	0.135
k_{21} (min^{-1})	0.079	0.057	0.086	0.078
k_{el} (min^{-1})	0.021	0.022	0.128	0.080

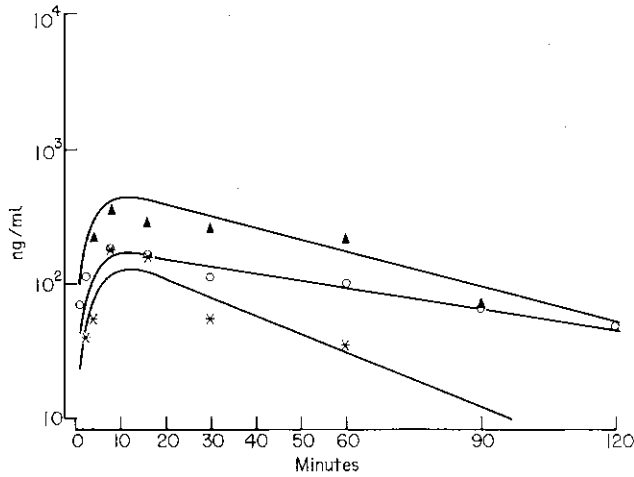


FIG. 2. Semi-logarithmic plot of average xylazine plasma concentration *versus* time in the four species studied after intramuscular injection of a single dose; invasion and elimination phases are drawn. (▲) Dog 1.4 mg. kg⁻¹; (○) horse 0.6 mg. kg⁻¹; (*) sheep 1.0 mg. kg⁻¹.

In the horse, following intravenous administration of xylazine, maximum sedation occurs within 4–8 min after injection (Hoffman, 1974; McCashin & Gabel, 1971) a delay which is comparable with the half-time of distribution (6 min). In the same way, duration of deep sedation after intravenous administration (15–20 min) and recovery (30–60 min) from time of injection (Clarke & Hall, 1969) are comparable with the half-time of plasma concentration (50 min). After intramuscular administration, sedation is usually evident by 10 min and reaches its maximum effect by 15 min (McCashin & Gabel, 1971) a delay

which corresponds to the time necessary to obtain the maximal plasma concentration (13 min). Doses recommended by the manufacturer for the i.m. route are double the doses recommended for the i.v. route. This recommendation based on clinical data is well explained by the incomplete absorption of xylazine since the bioavailability is about 45%. Thus, in horses, clinical and pharmacokinetic data are well correlated, suggesting that xylazine itself, and not a metabolite, is the active drug.

In the dog, recommended dosage is higher than in other species (1–3 mg/kg i.v.). Ac-

TABLE III. Pharmacokinetic parameters and bioavailability of xylazine hydrochloride in the four species after intramuscular injection of a single dose

	Horse (n = 4)	Cattle (n = 4)	Sheep (n = 6)	Dog (n = 4)
k_a (min ⁻¹)	0.251	ND*	0.127	0.201
$t_{1/2ka}$ (min)	2.720	ND	5.450	3.441
$k_{el} = \beta$ (min ⁻¹)	0.012	ND	0.031	0.020
$t_{1/2\beta}$ (min)	57.70	ND	22.36	34.65
T_{max} (min)	12.92	ND	14.68	12.70
C_{max} ($\mu\text{g} \cdot \text{ml}^{-1}$)	0.167	ND	0.129	0.432
Bioavailability mean \pm SD	44.6 \pm 4.16	ND	40.75 \pm 23.81	73.9 \pm 17.89
Range	40–48		17–73	52–90

*ND, not determined (the assay method is not sensitive enough to evaluate xylazine plasma concentrations lower than 0.01 $\mu\text{g} \cdot \text{ml}^{-1}$)

ording to Newkirk & Miles (1974), the time of onset of action is 3–5 min after i.v. administration and 10–15 min after i.m. injection and the period of analgesia is relatively short (about 15–30 min); these data are compatible with our kinetic parameters.

In sheep, the dosage regimen is higher than in cattle and bioavailability determination is possible. After i.m. dosage, absorption is rapid and rather similar to results reported by Putter & Sagner (1973) who estimated that two-thirds of the dose was absorbed within 10 min from the injection site. The extent of absorption is about 40%, a fact which explains the higher dosage recommended for i.m. injection in this species.

Cattle are very sensitive to xylazine and dose rates that produce deep sedation and analgesia are one-tenth those required to produce the same effects in horses (Hopkins, 1972). This difference cannot be explained in terms of plasma concentration of xylazine since plasma concentration is six to seven times lower in cattle than in the horse for a similar behavioural effect. Moreover, some sustained effects of xylazine in cattle are not explained in terms of plasma kinetics. The short half-time of xylazine in cattle (36 min) contrasts with duration of hyperthermia: 18 h (Young, 1979), hyperglycemia: 24 h (Eichner, Prior & Kuasnicka, 1979), and prostration following high dosage: 36 h (Clarke & Hall, 1969). Finally, after i.m. administration, we were not able to detect xylazine in bovine plasma in spite of evident sedative and analgesic effects. The lack of correlation between xylazine concentration and the different pharmacological responses may suggest that cattle rapidly produce one or several long-acting metabolites. The special sensitivity of this species to xylazine is thus more probably related to the drug metabolism than to a special reactivity to xylazine.

Finally, the HPLC assay of xylazine allows an accurate assessment of drug plasma concentration and the estimation of the different kinetic parameters. The results explain some clinical data and suggest hypotheses concerning interspecific variability in sensitivity to xylazine.

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