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Pharmacokinetics of Antipyrine, Warfarin and Paracetamol in the Brushtail Possum

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The plasma pharmacokinetics of antipyrine, warfarin and paracetamol have been studied in the Australian brushtail possum (*Trichosurus vulpecula*). The plasma elimination half-lives ($t_{1/2}$) were 1.2 h for antipyrine, 11.9 h for warfarin and 5.2–12.9 h for paracetamol. Our data indicate that the clearance of these three xenobiotics in the possum is similar to that reported in eutherian mammals. There was no dose-dependent increase in paracetamol plasma $t_{1/2}$ over the dose range 100–1000 mg kg^{-1}, indicating a lack of capacity saturation. This observation may in part explain the unusual resistance of the possum to the hepatotoxic effect of high doses of paracetamol.

INTRODUCTION

Much has been learnt over the last 50 years about the pharmacokinetics of foreign compounds such as pesticides and pharmaceutical agents in humans and laboratory animals. In contrast, relatively little is known about the absorption, biotransformation and excretion of these same xenobiotics in other species, including domestic animals and wildlife.[1–3]

The brushtail possum (*Trichosurus vulpecula*) is a marsupial native to Australia. This animal was introduced into New Zealand to establish a fur trade over 150 years ago, and has since become established in virtually every subalpine habitat in the country. Possums are regarded as the most important vertebrate pest in New Zealand. They are the principal wildlife reservoir for bovine tuberculosis, and transmit the disease to livestock and farmed deer.[4] In addition, they predate on native birds, and the browsing damage they inflict on important native tree species has had major adverse effects on indigenous forests.[5]

Brushtail possums have highly diverse feeding habits, and may have evolved biotransformation enzymes capable of metabolizing a broad range of xenobiotic substrates found in plant tissue, including a tolerance in some parts of Australia to fluoroacetate.[6] In this paper we report the plasma pharmacokinetics of three compounds—a metabolic indicator (antipyrine), a common vertebrate pesticide (warfarin) and a common human pharmaceutical agent (paracetamol)—in the brushtail possum.

Before these investigations, metabolic studies in possums focused on their ability to survive on the foliage of *Eucalyptus* trees, which is low in nutritional value and contains significant levels of toxic secondary plant compounds such as alkaloids, cyanogenic glycosides, essential oils and a wide range of polyphenols.[7] For example, Hinks and Bolliger[8] observed a several-fold increase in the excretion of glucuronide-conjugated metabolites in the urine of the brushtail possum following exposure to *Eucalyptus* leaves. The authors concluded that the formation of glucuronides was directly related to detoxification of essential oils found in the foliage. McManus and Ilett[9] noted the lack of information about marsupial xenobiotic metabolism as a basis for investigating microsomal metabolism in a range of species, including the brushtail possum.[10] Their *in vitro* results indicated that the rate of oxidative metabolism of xenobiotics in marsupials was generally lower than that in rats, in spite of similar cytochrome P-450 concentrations. These authors suggested that marsupials may be further disadvantaged in terms of overall hepatic xenobiotic metabolising capacity by a lower liver/body weight ratio in comparison with the rat.

Awaluddin and McLean[11] studied the excretion of benzoic acid in seven marsupial species. The overall pattern of benzoic acid metabolism in marsupials appeared to be similar to that observed in other mammals, with most being excreted as hippuric acid, β-hydroxyphenylpropionic acid or benzolyl glucuronide.[11,12] These conflicting conclusions on the apparent differences in xenobiotic metabolism between eutherian and marsupial animals led to this study of the pharmacokinetics of antipyrine, warfarin and paracetamol in brushtail possums. In addition, we hoped to identify (through increased understanding of biotransformation capabilities) a physiological idiosyncrasy that might be exploited in the development of target-specific toxicants. Currently, the control of this species in New Zealand is reliant on the use of sodium monofluoroacetate (1080), cholecalciferol, brodifacoum and cyanide, and none of these toxicants could be regarded as species-specific.[13]

Antipyrine clearance was evaluated because this compound is almost completely metabolized by hepatic cytochrome P-450 enzymes[14,15] and therefore provides

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a test of hepatic microsomal enzyme function. Antipyrine clearance is frequently used as a quantitative index of liver function in the presence of liver disease,[16,17] and has also been used to indicate likely sex, species and strain differences in hepatic metabolism.[18–20] The clearance of this compound has now been investigated in a wide variety of placental mammals but not in a marsupial species.

Warfarin metabolism and clearance is also well documented in a wide range of species, including humans and rats. Warfarin undergoes oxidative metabolism mediated via the hepatic microsomal mixed-function oxidase system, followed by glucuronidation.[21] Warfarin kinetics were of particular interest because the possum appears to be relatively resistant to the toxic effects of first-generation anticoagulants.[22]

The pharmacokinetics and the hepatotoxicity of paracetamol have been documented in a wide range of eutherian species. Paracetamol undergoes both Phase 1 and Phase 2 metabolism, and hepatotoxicity is mediated through a reactive metabolite. The biochemical basis for species variation in response to the hepatotoxic potential has been elucidated, with hamsters, mice and cats being more susceptible than rats.[23] The marked species variation in the response to paracetamol is believed to be related to species differences in the ability to glucuronidate and excrete this drug.

MATERIALS AND METHODS

Adult possums were collected in cage traps in Ashley Forest near Christchurch, New Zealand, and were acclimatized to captivity for 2 months or more before the experiment. All animals were housed individually and allowed free access to feed and water. The possums in all groups were observed regularly for 2 weeks after dosing with the chemicals. All results are expressed as mean ± SEM.

Antipyrine pharmacokinetics

Six male and six female possums were injected intravenously with 50 mg kg^{-1} antipyrine (Sigma, St Louis, MO) made up as a 50 mg ml^{-1} solution in sterile water. Blood samples were collected by jugular venapuncture at 0.5, 1, 2, 4 and 8 h after dosing. Serum antipyrine levels were estimated in triplicate using the method of Brodie *et al.*[24]

Warfarin pharmacokinetics

Warfarin (Animal Control Products, Wanganui) was prepared as a 0.75% suspension in carboxymethyl cellulose. Four male and four female possums were dosed orally under light ether anaesthesia at a dose-volume of 2 ml kg^{-1}. A dose of 50 mg kg^{-1} was selected. Blood samples were collected as above, before dosing and at regular intervals following dosing for up to 48 h. Warfarin was analysed using an HPLC method suitable for all the coumarin anticoagulants.[25]

Paracetamol pharmacokinetics

Three male possums were dosed orally under light ether anaesthesia with paracetamol (Sterling Pharmaceuticals N.Z. Ltd) in 0.75% carboxymethyl cellulose at 100, 500 and 1000 mg kg^{-1} (dose-volume 2 ml kg^{-1}). The dose levels were based on a previous study in rats and mice.[23] Blood samples were collected as above at 0.5, 1, 2, 3, 4 and 6 h after dosing.

Paracetamol concentrations were measured using a commercial diagnostic kit (Sigma, USA).

In a separate study to measure hepatocellular damage, 12 additional possums were dosed with paracetamol at 100, 500, 1000 or 2000 mg kg^{-1} and blood samples were collected 24 h after dosing to determine plasma urea concentration and plasma activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP).

RESULTS

Antipyrine

The initial plasma concentration for antipyrine was 41.9 ± 3.2 μg ml^{-1} and it appeared to be higher in females (47.7 μg ml^{-1}) than males (36.2 μg ml^{-1}), although the difference was not significant ($P = 0.068$). The $t_{1/2}$ was 1.26 ± 0.12 h and tended to be higher in males (1.42 h) than females (1.01 h). This difference, too, was not significant ($P = 0.213$) (Fig. 1). No peak plasma concentration was determined because this compound was administered by intravenous injection.

Warfarin

Peak plasma warfarin concentrations occurred 6 h after oral dosing. The plasma elimination $t_{1/2}$ was 12.9 h in female and 10.9 h in male possums. Slightly higher plasma warfarin concentrations were achieved in the female possums (Table 1 and Fig. 2).

Paracetamol

Paracetamol was rapidly absorbed, reaching peak plasma concentrations at ca. 1–2 h. The overall plasma

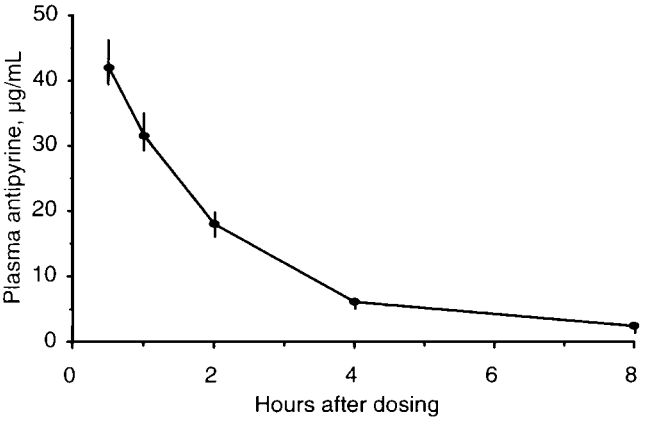

Figure 1. Mean plasma antipyrine in six male and six female possums following an intravenous injection of 50 mg kg^{-1} antipyrine.

Table 1. Warfarin pharmacokinetics in the possum

	n	C_{max}	t_{max}	$t_{1/2}$
Females	4	53.3 (16.8)	6.0 (1.41)	12.9 (3.2)
Males	4	34.5 (7.6)	6.0 (0.82)	10.9 (3.1)
Combined	8	43.9 (9.23)	6.0 (0.82)	11.9 (2.1)

Values are means with SEM in parentheses. C_{max}, maximum plasma concentration (μg ml^{-1}); t_{max}, time after dosing when peak plasma concentrations occurred in an hour; $t_{1/2}$, plasma elimination half-life.

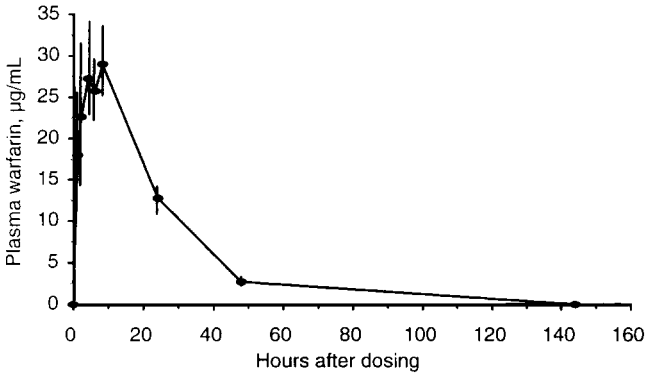

Figure 2. Mean plasma warfarin in four male and four female possums following an oral dose of 50 mg kg^{-1} warfarin.

Table 2. Plasma pharmacokinetics of paracetamol in the possum between 0 and 6 h after dosing

Dose (mg kg^{-1})	*n*	C_{max}	t_{max}	$t_{1/2}$
100	3	35.7 (4.6)	2.00 (0.70)	5.2 (1.7)
500	3	88.7 (1.7)	1.05 (0.20)	12.9 (3.5)
1000	3	217.7 (16.2)	2.07 (0.70)	10.74 (3.1)

See footnote to Table 1.

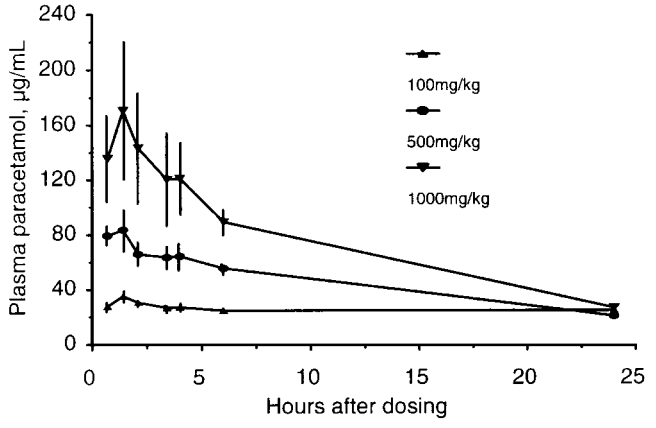

Figure 3. Mean plasma paracetamol in each of three male possums following oral doses of 100, 500 and 1000 mg kg^{-1} paracetamol.

$t_{1/2}$ was 9.6 h (Table 2 and Fig. 3). Paracetamol was apparently not toxic to possums, even at 2000 mg kg^{-1}, which is the highest dose tested. Plasma activities of AP, ALT or AST were unaffected at 24 h after dosing (Table 3).

Table 3. Plasma enzyme activities (with ranges in parentheses) in possums 24 h after dosing with paracetamol

Dose (mg kg^{-1})	*n*	AST (IU l^{-1})	ALT (IU l^{-1})	AP (IU l^{-1})	Urea (mmol l^{-1})
0	3(m)	35.0 (28–40)	25.0 (21–27)	615.0 (503–808)	7.0 (6.1–8.5)
100	2(m)	50.5 (40–61)	48.0 (43–53)	1040.5 (891–1190)	8.9 (8.0–9.8)
500	3(m)	36.6 (31.40)	43.0 (37–47)	620.6 (595–634)	9.6 (9.3–9.9)
1000	3(m)	37.3 (26–45)	29.0 (21–44)	558.7 (313–939)	14.1 (12.8–15.8)
2000	4(m)	–	33.5 (23–46)	429.5 (109–861)	14.5 (8.0–20.8)
	4(f)	–	41.0 (28–52)	485.5 (267–786)	12.9 (10.7–15.1)

m, Male; f, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase.

DISCUSSION

The clearance rate of antipyrine in the possum was relatively rapid, but within the range reported for placental mammals (Table 4). Sex differences in antipyrine clearance rates have been reported in some species (see Table 4) but there appear to be no sex-related differences in the clearance of this compound in the possum. The plasma clearance of warfarin in the possum ($t_{1/2}$ = 10.9–12.9 h) is similar to that reported for other species. For example, in rabbits the plasma elimination $t_{1/2}$ is 6 h,[26] and in rats it is 18 h in males and 28 h in females.[27] Hence, a faster rate of metabolism cannot be implicated as the reason for the possums' relative resistance to first-generation anticoagulants.[22]

Table 4. Half-lives ($t_{1/2}$) of antipyrine in plasma/serum in different species

Species	Sex	$t_{1/2}$ (h)	Source
Mouse	F	0.18	Quinn *et al.* (1958)[14]
Dwarf goat	F	0.83	Whitkamp *et al.* (1991)[20]
Dwarf goat	M	0.91	Whitkamp *et al.* (1991)[20]
Rabbit	F	1.05	Quinn *et al.* (1958)[14]
Rabbit	M	1.16	Whitkamp *et al.* (1991)[20]
Rabbit	F	1.43	Whitkamp *et al.* (1991)[20]
Cattle	F	1.69	Whitkamp *et al.* (1991)[20]
Rat	M	1.75	Whitkamp *et al.* (1991)[20]
Dog	F	1.78	Quinn *et al.* (1958)[14]
Guinea pig	F	1.83	Quinn *et al.* (1958)[14]
Rat	F	2.35	Quinn *et al.* (1958)[14]
Rat	F	2.36	Whitkamp *et al.* (1991)[20]
Nubian goats	M	2.58	Elsheikh *et al.* (1991)[19]
Cattle	M	2.69	Whitkamp *et al.* (1991)[20]
Desert sheep	M	4.04	Elsheikh *et al.* (1991)[19]
Man	M	12.00	Branch *et al.* (1973)[16]
Camel	M	18.70	Elsheikh *et al.* (1991)[19]
Possum	M	1.42	
	F	1.09	

The toxicokinetics of brodifacoum, a 'second-generation' anticoagulant related to warfarin, has also been assessed in the possum and it would appear that the persistence of brodifacoum in the liver is similar in possums to that found in other species.[28]

The plasma clearance of paracetamol was rapid in the possum and similar to the clearance rates already described for other species. However, a unique feature of the possum was the rapid clearance of paracetamol even at high doses. In a study of rats and mice there was a dose-dependent increase in the plasma elimination $t_{1/2}$ from 1 to 10 h over a dose range of 100–1000 mg paracetamol kg^{-1}.[23] This did not occur in the possum over the same dose range, indicating that the metabolic processes responsible for safely eliminating paracetamol are not readily saturable in the possum. In contrast to eutherian species, the possum was not susceptible to paracetamol-induced hepatotoxicity even at the highest doses tested (2000 mg kg^{-1}). In rats, hepatotoxicity, detected by increases in plasma AP, AST and ALT, is evident 24 h after dosing with 1000 mg kg^{-1},[23] and occurs at doses as low as 200 mg kg^{-1} in mice.[29]

At therapeutic doses, most species (including humans) metabolize paracetamol to non-toxic glucuronide and sulphate conjugates. At high doses, the amount of paracetamol greatly exceeds the capacity of the liver to form glucuronide and sulphate conjugates. Consequently, a highly toxic metabolite is formed that depletes hepatic glutathione stores and subsequently binds to liver macromolecules causing hepatic damage.[29,30] A detailed study of the metabolic profile in the possum was beyond the scope of this investigation. Nevertheless, it appears that the response of possums to paracetamol is unique because plasma clearance was not saturated, even at high doses. It seems likely that the possum retains the ability to convert unusually large amounts of paracetamol to non-toxic metabolites, and this defence mechanism may be assisted by a large reserve of hepatic glutathione.

Species differences in the hepatotoxicity of paracetamol are thought to be due to differences in the rate of conversion to the reactive cytotoxic intermediate *N*-acetyl *p*-benzoquinone imine (NAPQI),[29] and not to any intrinsic differences in sensitivity or any difference in the fate of NAPQI once formed. Hence, it is more probable that the resistance of the possum is due to a greater ability to detoxify paracetamol without forming significant quantities of NAPQI. In most mammals, the LD_{50} for paracetamol varies between 150 and 1000 mg kg^{-1} (e.g. in mice the LD_{50} is 338 mg kg^{-1}). In possums, there were no major changes in plasma AST, AP and ALT activities 24 h after dosing, even at 2000 mg kg^{-1} (Table 3), indicating no significant liver damage. Mean plasma urea concentrations increased in male possums given paracetamol in a dose-dependent fashion (Table 3). Mean urea concentrations exceeded normal reference values for possums[31] in animals given 1000 or 2000 mg kg^{-1}, indicative of minor renal damage or dehydration. The lack of susceptibility of the possum was not apparently due to altered bioavailability over the dose range tested, because plasma concentrations recorded in the possums were comparable to those associated with hepatotoxicity in other species. The current study failed to identify metabolic weakness in the possum, but has instead identified potential physiological strengths. Elucidation of the mechanism by which the possum is protected from the hepatotoxic effects of paracetamol may be useful to those interested in mechanistic toxicology and in the development of improved antidotes for paracetamol poisoning.

In conclusion, our *in vivo* studies confirm that the metabolism and excretion of representative xenobiotics in the possum are similar to, or more efficient than, eutherian mammals. The same conclusion was reached by Gooneratne[32] in a study to compare cytochrome P-450 enzyme activities in the possum, rat, sheep, rabbit and chicken *in vitro*, and by Awaluddin and McLean[11] in their investigation of the metabolism of benzoic acid in the possum. In this regard, our findings appear to contradict the suggestions of earlier researchers[10] and a recent review by Bolton and Ahokas,[33] who suggest that marsupials are potentially more vulnerable to xenobiotics than eutherian species. However, we agree with Bolton and Ahokas[33] in their conclusions that there is an extraordinary lack of information about the effects of environmental contaminants on Australia's native marsupials, and although some tolerance has been shown to paracetamol in this study, and to malathion in the possum,[13] there may be other classes of compounds to which the possum is uniquely sensitive.

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