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DISPOSITION OF FLUVASTATIN, AN INHIBITOR OF HMG-COA REDUCTASE, IN MOUSE, RAT, DOG, AND MONKEY

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ABSTRACT

The physiological disposition of fluvastatin, a potent inhibitor of hydroxymethylglutaryl-CoA reductase and thus cholesterol synthesis, has been studied in the mouse, rat, dog, and monkey using ^{14}C- or ^{3}H-labeled drug. Oral doses of fluvastatin were absorbed at a moderate to rapid rate. The extent of absorption was dose-independent and was essentially complete in all four species studied. However, the drug was subject to extensive presystemic hepatic extraction followed by direct excretion via the bile, thus minimizing the systemic burden and yielding high liver/peripheral tissue concentration gradients for fluvastatin and its metabolites. Only at high doses far exceeding the intended human daily dose of ca 0·6 mg kg^{-1} did fluvastatin bioavailability approach unity, apparently due to saturation of the first-pass effect. Dose-normalized blood levels of fluvastatin and total radioactivity were higher in the dog than in the other species, suggesting a smaller distribution volume in the former. Fluvastatin was partially metabolized before excretion, the extent of metabolism being smallest in the dog and greatest in the mouse. The half-life of intact fluvastatin ranged from 1–2 h in the monkey to 4–7 h in the dog. Regardless of the dose or dose route, the administered radioactivity was recovered predominantly in feces, with the renal route accounting for less than 8 per cent of the dose. No tissue retention of radioactivity was observed, and material balance was essentially achieved within 96 h after dosing.

KEY WORDS Fluvastatin HMG-CoA reductase Absorption Disposition

INTRODUCTION

Fluvastatin (Sandoz compound XU 62–320), [R*,S*-(E)]-(±)-sodium-3, 5-dihydroxy-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indole-2-yl]-hept-6-enoate, is currently under investigation as a hypolipidemic and antiatherosclerotic agent. It is a potent inhibitor of hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis. Previous studies have shown significant reduction in serum total cholesterol, LDL cholesterol, and serum triglyceride levels in rats, dogs, and monkeys treated with fluvastatin.[1] It was also demonstrated that fluvastatin is more

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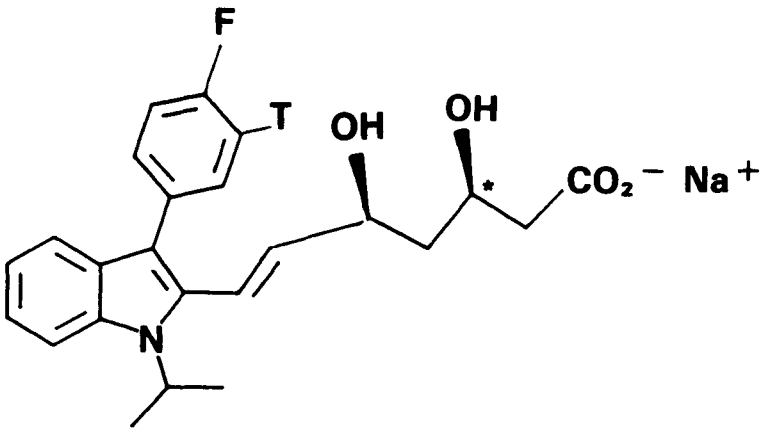

Figure 1. Fluvastatin labeled with ^3H (T) or ^{14}C (*)

potent than compactin and lovastatin in inhibiting HMG-CoA reductase *in vitro* and cholesterol biosynthesis *in vivo*.[2]

The present report is an overview of the absorption, distribution, and excretion of fluvastatin in the mouse, rat, dog, and monkey. Additional results concerning the biotransformation of the drug in these species will be reported elsewhere.

METHODS

Radiolabeled compound

Fluvastatin was labeled with ^{14}C in the 3-position of the heptenoic acid chain or with ^3H in the 3-position of the *p*-fluorophenyl moiety (Figure 1). [^{14}C]Fluvastatin (15·1 $\mu Ci\,mg^{-1}$) was used in the rat and dog studies while [^3H]fluvastatin (45·2 $\mu Ci\,mg^{-1}$) was used in the mouse and monkey studies. Further dilutions with unlabeled carrier were prepared when necessary so that the maximum doses of ^{14}C were approximately 10 $\mu Ci\,kg^{-1}$ in the rat and 5 $\mu Ci\,kg^{-1}$ in the dog, and the maximum ^3H doses were ca 50 $\mu Ci\,kg^{-1}$ in the mouse and 30 $\mu Ci\,kg^{-1}$ in the monkey. The radiochemical purity of all dilution batches was > 95 per cent. In this report, all doses are expressed as the equivalent weights of the free acid.

Dosing and sample collection

Male Charles River CD-1 mice (ca 25 g), Sprague-Dawley rats (ca 500 g), beagle dogs (ca 10 kg), and rhesus monkeys (ca 3 kg) were housed in appropriate metabolism cages and were provided with food and water *ad libitum*. A low and a high oral dose as well as an intravenous dose of radiolabeled fluvastatin

Table 1. Doses of fluvastatin tested

Species	Compound	Dose (mg kg^{-1})	Route and mode of administration
Mouse	[^{3}H]fluvastatin	34	p.o. by gavage as suspension in 1% aqueous CMC
		410	p.o. by gavage as suspension in 1% aqueous CMC
		34	i.v. tail vein injection as aqueous solution
Rat	[^{14}C]fluvastatin	0·24	p.o. by gavage as suspension in 1% aqueous CMC
		19	p.o. by gavage as suspension in 1% aqueous CMC
		0·24	i.v. jugular vein injection as aqueous solution
Dog	[^{14}C]fluvastatin	0·95	p.o. in gelatin capsule
		34	p.o. in gelatin capsule
		0·95	i.v. cephalic vein injection as aqueous solution
Monkey	[^{3}H]fluvastatin	0·57	p.o. in gelatin capsule
		46	p.o. in gelatin capsule
		0·95	i.v. saphenous vein injection as aqueous solution

CMC: carboxymethylcellulose, p.o.: oral, i.v.: intravenous.

were tested in each species as outlined in Table 1. These doses encompassed the dose ranges used in the subchronic toxicity studies for fluvastatin and were prepared in the same form as in the toxicity trials. Tissues were obtained from groups of 3 mice and rats sacrificed at designated times after dosing. Blood was obtained from the sacrificed mice also, but was collected serially from 3 or 4 rats, dogs, and monkeys for each dose studied. Complete urine and feces were collected for 4 days from separate groups of 5 mice per dose level, and also from the serially bled rats, dogs, and monkeys. Additionally, bile, urine, and feces were collected from 4 rats with cannulated bile ducts for 48 h following an oral (0·24 mg kg^{-1}) dose.

Analysis of radioactivity

Radioactivity was measured in a liquid scintillation spectrometer (Model 460, Packard Instrument Co.). Urine and bile were assayed by directly counting aliquots in ACS® scintillant (Amersham). Blood and tissue and fecal homogenates were air-dried and combusted in a sample oxidizer (Model 306, Packard) before counting. Radioactivity concentrations are given as ng or μg equivalents of fluvastatin per ml.

Determination of tritiated water

The amount of tritiated water formed by biotransformation of [^{3}H]fluvastatin in the mouse and monkey was determined by measuring the specific activity (dpm ml^{-1}) of the distillates of urine samples from selected time intervals.[3] These values were extrapolated to time zero and the body contents of tritiated water calculated based on known values of tritiated water half-life and volume of exchangeable body water in the respective species.[4]

Analysis of unchanged fluvastatin

Blood concentrations of fluvastatin were determined by high pressure liquid chromatography (HPLC) with fluorescence detection (Kalafsky *et al.*, submitted for publication). Fluvastatin was extracted from buffered (pH 7) blood samples (0·5 ml) into methyl tertiary butyl ether (MTBE) followed by evaporation of an aliquot of the ether phase. The sample residue was dissolved in an acetonitrile-5 mM hexyltriethylammonium phosphate, pH 6·5 (1:19, v/v) mixture. The solution was chromatographed on an octyl (C_8) bonded phase column held at 50° and equilibrated with a mobile phase of acetonitrile-5 mM hexyltriethylammonium phosphate, pH 6·5 (2:3, v/v). Fluvastatin was detected by monitoring the intrinsic fluorescence at 380 nm following excitation at 305 nm. A standard curve was prepared by analyzing blood samples containing known quantities of fluvastatin on each day of analysis. The minimum detection limit was 2 ng ml^{-1}. Due to insufficient sample volume, blood concentrations of fluvastatin were not measured in the rat. Using HPLC with radioactivity monitoring, fluvastatin was also determined in all bile and feces samples.

RESULTS

Blood concentrations

The mean blood concentrations of total radioactivity and fluvastatin are shown in Figures 2 and 3, respectively. In the figures, the concentrations have been dose-normalized in order to facilitate comparisons between species and dose levels. Relevant pharmacokinetic parameters are summarized in Table 2. In Table 2 clearance and Vd_{ss} represent, respectively, the total body clearance and the steady-state volume of distribution calculated by the method of Benet and Galeazzi.[5]

Following oral administration, peak concentrations of radioactivity and fluvastatin were generally achieved in less than 2 h. The only notable exceptions were in the mouse after the high dose and in the rat after the low dose, where peak times averaged ca 6 h. The dose-normalized radioactivity concentrations were considerably higher in the dog than in the other species following oral as well as intravenous administration. In each species, the high oral dose yielded greater dose-normalized area under curve (AUC) values of radioactivity than

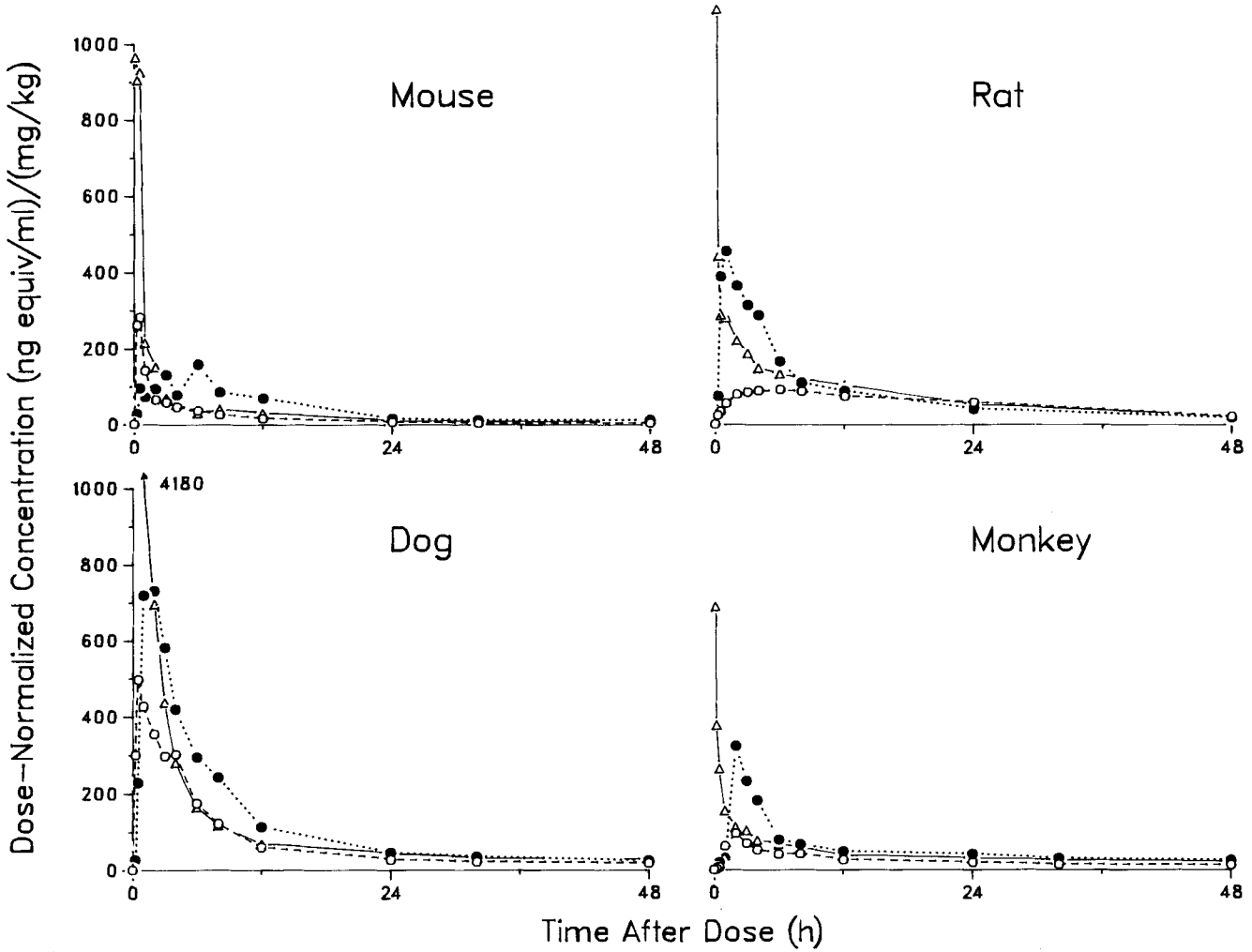

Figure 2. Dose-normalized blood concentrations of total radioactivity following a single dose of ^{3}H- or ^{14}C-labeled fluvastatin to mice, rats, dogs, and monkeys. All data are mean values with $n = 3$ or 4 and are normalized to 1 mg kg^{-1} dose; ○ low oral dose; ● high oral dose; △ i.v. dose. The exact doses are shown in Table 1

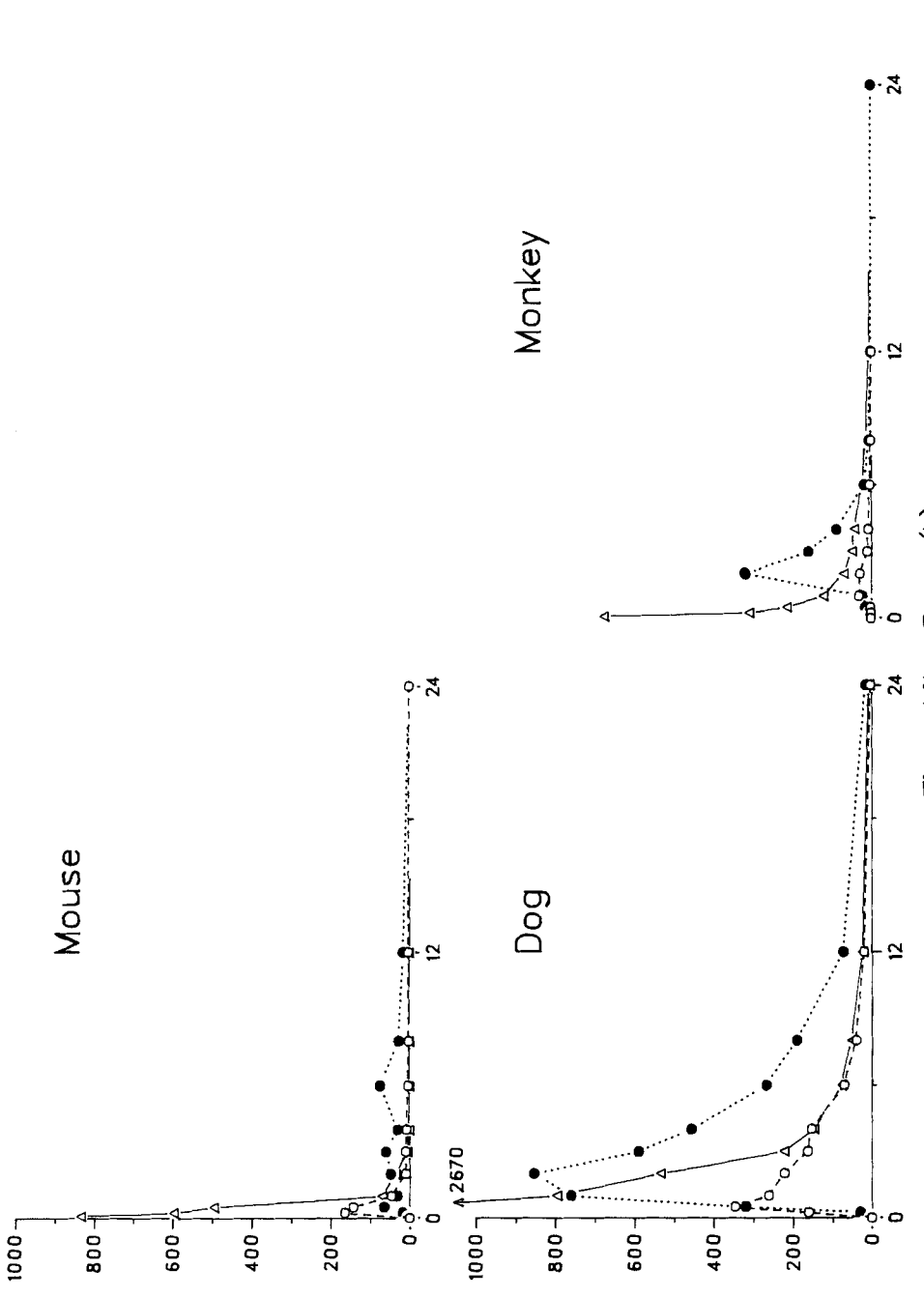

Figure 3. Dose-normalized blood concentrations of fluvastatin following a single dose of ^{3}H- or ^{14}C-labeled fluvastatin to mice, dogs, and monkeys. All data are mean values with $n = 3$ or 4 and are normalized to 1 mg kg^{-1} dose; ○ low oral dose; ● high oral dose; △ i.v. dose. The exact doses are shown in Table 1

Table 2. Pharmacokinetic parameters of fluvastatin

Species	Dose (mg kg^{-1})	Dose route	n	Peak blood conc. (μg or μg equiv. ml^{-1}) Radio-activity	Peak blood conc. (μg or μg equiv. ml^{-1}) Fluva-statin	Time of peak conc. (h) Radio-activity	Time of peak conc. (h) Fluva-statin	Area under curve (μg or μg equiv. h ml^{-1}) Radio-activity	Area under curve (μg or μg equiv. h ml^{-1}) Fluva-statin	Half-life (h) Radio-activity	Half-life (h) Fluva statin	Clearance (l h^{-1} kg^{-1}) Fluva-statin	Vd_{ss} (l kg^{-1}) Fluva-statin
Mouse	34	p.o.	3	9·6	5·6	0·5	0·25	33	6·6	13	4·5	–	–
	410	p.o.	3	65	31	6	6	911	231	13	5·4	–	–
	34	i.v.	3	33	29	0·08	0·08	65	19	12	3·4	1·9	1·0
Rat	0·24	p.o.	4	0·024 ± 0·005	–	6·5 ± 1·9	–	0·78 ± 0·17	–	24 ± 1·5	–	–	–
	19	p.o.	3	11 ± 1·6	–	0·8 ± 0·3	–	83 ± 5·8	–	31 ± 1·5	–	–	–
	0·24	i.v.	3	0·26 ± 0·19	–	0·08 ± 0	–	1·1 ± 0·19	–	26 ± 2·3	–	–	–
Dog	0·95	p.o.	3	0·65 ± 0·25	0·40 ± 0·21	1·8 ± 1·9	1·7 ± 2·0	3·9 ± 0·49	1·3 ± 0·21	40 ± 16	4·1 ± 0·9	–	–
	34	p.o.	3	29 ± 24	31 ± 31	3·7 ± 3·8	3·7 ± 3·8	234 ± 162	160 ± 138	35 ± 12	7·3 ± 1·8	–	–
	0·95	i.v.	3	4·0 ± 1·5	2·6 ± 0·62	0·08 ± 0	0·1 ± 0·1	7·1 ± 2·2	3·2 ± 1·5	35 ± 0·7	4·4 ± 0·5	0·3 ± 0·1	0·7 ± 0·3
Monkey	0·57	p.o.	4	0·062 ± 0·022	0·024 ± 0·014	1·8 ± 0·5	1·8 ± 1·0	0·85 ± 0·37	0·051 ± 0·030	32 ± 21	1·3 ± 0·7	–	–
	46	p.o.	3	15 ± 13	16 ± 12	2·7 ± 1·2	2·3 ± 0·6	160 ± 44	32 ± 16	62 ± 11	1·2 ± 0·4	–	–
	0·95	i.v.	3	0·71 ± 0·61	0·69 ± 0·59	0·1 ± 0·1	0·1 ± 0·1	2·6 ± 0·30	0·54 ± 0·23	61 ± 12	1·9 ± 1·0	2·1 ± 1·1	3·7 ± 1·8

Values for mouse are based on mean blood levels and those for rat, dog, and monkey are mean ± S.D.

the low oral dose. The dose-normalized peak radioactivity concentration (C_{max}) also increased with dose except in the mouse which showed prolonged and erratic absorption from the high dose. The decline of blood radioactivity was multiexponential in all four species. The terminal half-life, which was calculated by regression analysis of the terminal log-linear phase and represented the most slowly eliminated metabolite or group of metabolites, ranged from approximately 12 h in the mouse to 62 h in the monkey.

Comparison of the concentration profiles in Figure 3 with those shown in Figure 2 indicated that in the mouse, dog, and monkey, blood radioactivity during the absorption phase consisted largely of the parent drug. With respect to dose-normalized blood levels of unchanged fluvastatin, the dog again clearly exceeded the other species. As observed for total radioactivity, the AUC and C_{max} of fluvastatin also showed a disproportionate increase with increasing oral dose in all species examined. Calculated using intravenous data, the steady-state volume of distribution (Vd_{ss}) ranged from $0{\cdot}7\,l\,kg^{-1}$ in the dog to $3{\cdot}7\,l\,kg^{-1}$ in the monkey, while total body clearance was 0·3, 1·9, and $2{\cdot}1\,l\,h^{-1}\,kg^{-1}$ in the dog, mouse, and monkey, respectively. Fluvastatin concentrations in blood declined biexponentially, with terminal half-lives averaging 1–2 h in the monkey, 3–5 h in the mouse, and 4–7 h in the dog.

Tissue distribution of radioactivity

In Figure 4, tissue and organ radioactivity levels at 2 h postdose are used to illustrate the distribution of fluvastatin related material in the mouse and rat. In general dose-normalized concentrations were considerably higher in the rat than in the mouse. In both species, the highest concentrations of radioactivity were observed in the liver, followed at a distance by the kidney, heart, and adrenals. The concentrations in all other tissues were below circulating blood levels. At 2 h postdose, the relative tissue concentrations in mice receiving the low and high oral doses were similar, and were approximately half the corresponding values in the intravenously dosed mice. In the rat, the high oral dose yielded higher dose-normalized tissue concentrations than the low dose. This was apparently due to slower drug absorption from the low dose which was also reflected in the dose-related differences in relative blood concentrations (Figure 2). With the exception of the liver, tissue radioactivity levels in the rat following intravenous administration were in the same concentration range as observed after the oral doses. The decline of tissue radioactivity in the mouse and rat was approximately parallel to the blood level decay and concentrations were fairly low after 24 h. At 96 h after dosing, little residual radioactivity was found in the tissues and organs of all animals.

Excretion

The urinary and fecal excretion data following a single dose of ^{3}H- or ^{14}C-labeled fluvastatin are summarized in Table 3. In all four species, the renal

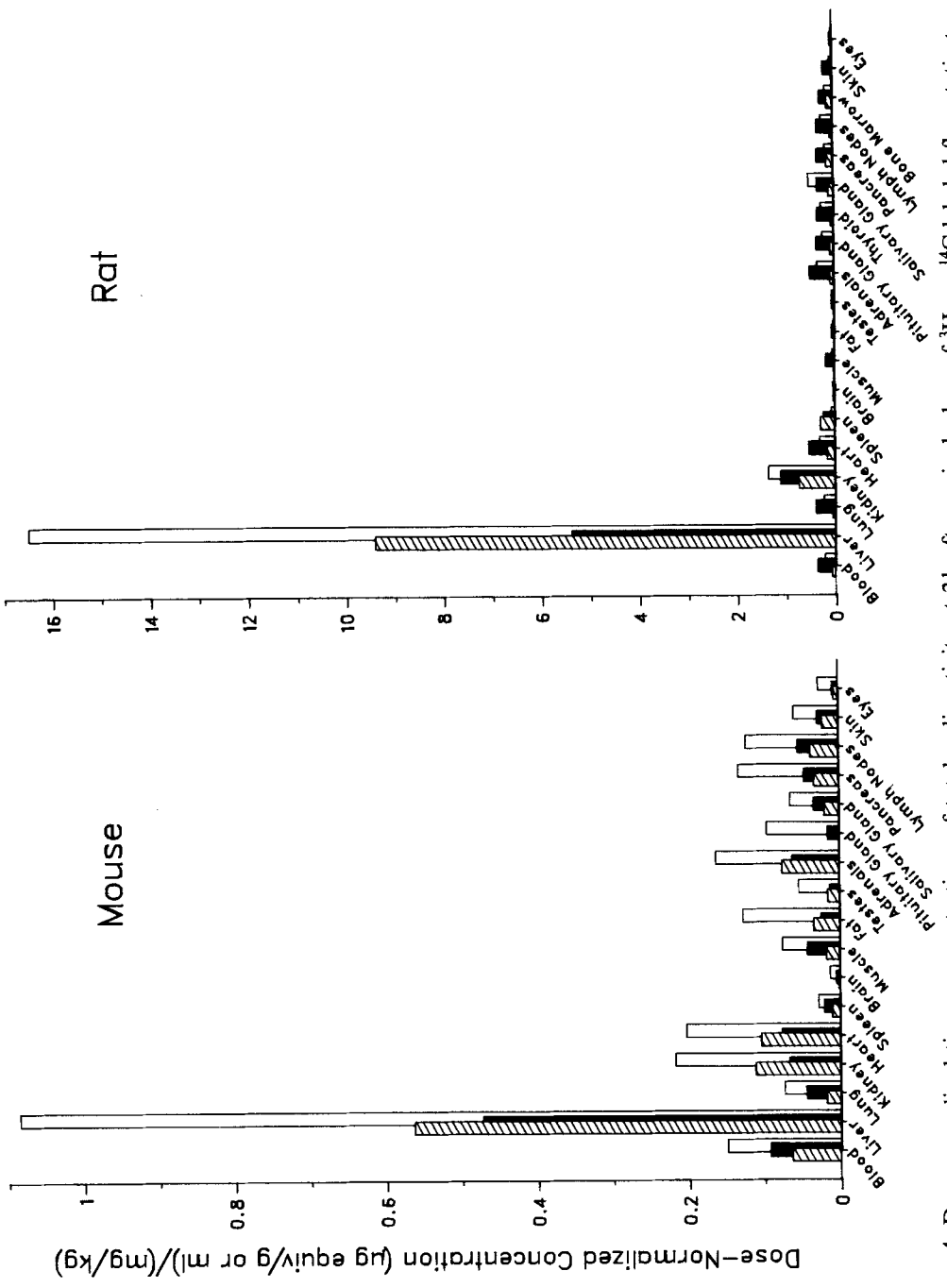

Figure 4. Dose-normalized tissue concentrations of total radioactivity at 2 h after a single dose of ^{3}H- or ^{14}C-labeled fluvastatin to mice and rats. All data are mean values with $n = 3$ and are normalized to 1 mg kg^{-1} dose; ▨low oral dose; ■high oral dose; □i.v. dose. The exact doses are shown in Table 1

route was a minor elimination pathway regardless of the dose or dose route, accounting for less than 8 per cent of the administered radioactivity. Nonetheless, urinary excretion was rapid and was nearly complete within 24 h of dosing. The remainder of the dose was eliminated in the feces and material balance was essentially achieved within the 96 h collection interval. In the rats with biliary fistulae, 5·4 ± 5·1 per cent (S.D., $n = 4$) of an oral dose was recovered in urine, compared with 40·8 ± 6·0 per cent in bile and 33·1 ± 5·0 per cent in feces. Intact fluvastatin was not detected in mouse feces but accounted for as much as 30 per cent of the fecal radioactivity in the other species, representing 4–12 per cent of the dose in the monkey, 12–16 per cent in the rat, and 22–30 per cent in the dog. Fluvastatin also accounted for 11·0 ± 2·6 per cent of the radioactivity excreted in rat bile.

Analysis of urine distillates indicated that 0·04% of the intravenous dose and 0·1–0·7% of the oral doses of [^{3}H]fluvastatin in the monkey were converted to tritiated water. In the mouse, tritiated water amounted to 0·2% of the intravenous dose and 1–2% of the oral doses of [^{3}H]fluvastatin.

DISCUSSION

The absorption of orally administered fluvastatin was characterized by a rapid onset and a moderate to rapid rate in the four species studied. To estimate the extent of absorption, the ratio of the cumulative urinary excretion of the oral dose to that of an intravenous dose, normalized by the total recoveries, was calculated (Table 4). It appears that absorption was complete in all species except for the low dose in dog and high dose in monkey where it was ca 70 per cent. However, judging by the relative amounts of intact drug recovered in feces after oral and intravenous dosing (Table 3), unabsorbed drug accounted for no more than 7 per cent of the dose in all cases. Thus, it can be concluded that the extent of fluvastatin absorption was complete in the mouse and almost complete (95–100 per cent) in the rat, dog, and monkey. The error associated with the urine quotient method, i.e. underestimation in the two dog and monkey studies and overestimation (> 100 per cent absorption) in the other studies, can be explained by the renal route being a minor elimination pathway for fluvastatin: thus any experimental error in urine collection or analysis could result in relatively large deviations in absorption estimates.[6] In bile duct cannulated rats, 33·1 per cent of the administered radioactivity was recovered in feces, suggesting incomplete absorption. Reduced absorption in these animals compared with the intact rats would indicate that bile played an important role in the solubilization and subsequent absorption of fluvastatin.

Despite efficient oral absorption, the absolute bioavailability of fluvastatin as indicated by the oral:i.v. AUC ratios (Table 4) was incomplete from the low doses and ranged from 16 per cent in the monkey to 41 per cent in the dog, suggesting a greater first-pass effect in the former. However, the pre-

Table 3. Excretion of fluvastatin and total radioactivity after a single dose of ^{3}H- or ^{14}C-labeled fluvastatin

Species	Dose (mg kg^{-1})	Dose route	n	Amount excreted (% dose)				
				Urine Radioactivity		Feces Radioactivity		Fluvastatin
				0–24 h	0–96 h	0–24 h	0–96 h	0–96 h
Mouse	34	p.o.	5	5·1 ± 3·4	7·3 ± 1·7	93·1 ± 10·3	95·2 ± 9·8	n.d.
	410	p.o.	5	4·4 ± 3·0	6·7 ± 1·9	74·9 ± 15·7	79·5 ± 17·9	n.d.
	34	i.v.	5	4·4 ± 2·9	5·7 ± 1·7	81·3 ± 2·5	83·1 ± 4·5	n.d.
Rat	0·24	p.o.	4	3·5 ± 1·1	5·8 ± 1·8	32·9 ± 17·2	79·7 ± 13·2	16·4 ± 2·7
	19	p.o.	3	5·9 ± 2·2	6·8 ± 2·3	64·4 ± 7·7	87·0 ± 8·2	12·3 ± 5·3
	0·24	i.v.	3	3·5 ± 0·8	5·2 ± 0·7	42·0 ± 11·1	83·8 ± 9·6	13·0 ± 3·6
Dog	0·95	p.o.	3	0·9 ± 0·3	1·4 ± 0·3	64·3 ± 48·1	100 ± 4·7	29·6 ± 5·8
	34	p.o.	3	1·5 ± 0·6	2·2 ± 0·8	72·6 ± 8·6	104 ± 7·4	23·4 ± 3·5
	0·95	i.v.	3	1·6 ± 0·3	2·0 ± 0·4	74·4 ± 19·3	97·7 ± 3·1	22·4 ± 4·3
Monkey	0·57	p.o.	4	2·1 ± 0·9	2·9 ± 0·8	39·7 ± 24·9	75·1 ± 3·8	3·9 ± 2·5
	46	p.o.	3	1·2 ± 0·7	2·0 ± 0·8	39·5 ± 14·5	82·0 ± 1·7	12·3 ± 4·6
	0·95	i.v.	3	2·5 ± 0·6	3·0 ± 0·7	53·9 ± 21·4	86·7 ± 2·4	6·8 ± 1·1

Values are mean ± S.D.
n.d.: Not detected.

Table 4. Estimated absorption and bioavailability of oral doses of fluvastatin

Species	Dose ($mg\ kg^{-1}$)	Absorption ($urine_{p.o.}/urine_{i.v.}$)	Bioavailability ($AUC_{p.o.}/AUC_{i.v.}$)
Mouse	34	1·10	0·35
	410	1·21	1·01
Rat	0·24	1·15	–
	19	1·25	–
Dog	0·95	0·67	0·41
	34	1·02	1·40
Monkey	0·57	1·11	0·16
	46	0·73	1·22

The urinary excretion quotients ($Urine_{p.o.}/Urine_{i.v.}$) were normalized by the total recovery of radioactivity while the AUC ratios of fluvastatin were normalized by the dose.

systemic elimination of fluvastatin was saturable and bioavailability appeared to be complete from the high oral doses in all three species examined.

The steady-state volume of distribution was 1·0 and $3·7\,l\,kg^{-1}$ in the mouse and monkey, respectively, but was only $0·7\,l\,kg^{-1}$ in the dog, suggesting less extensive tissue uptake of the drug in the latter. Tissue concentration data in the mouse and rat showed little or no difference in drug distribution between high and low doses or between oral and intravenous administration. Dose-normalized tissue concentrations of radioactivity were considerably higher in the rat than in the mouse. Both species showed marked hepatic sequestration of the drug, with total radioactivity levels in the liver at least 5–10 times those in blood or other tissues. Furthermore, it is believed that part of the absorbed drug extracted by the liver was excreted via the bile without ever reaching the systemic circulation. The saturation of this biliary pathway as a consequence of increased amounts of drug being presented to the liver would explain the disproportionate increase in blood levels of fluvastatin and total radioactivity with increasing dose, a phenomenon observed in all four species. Based on the data in the mouse and rat, there was no evidence of tissue retention following cessation of dosing.

Fluvastatin was partially metabolized before excretion. Compared with the other species, the dog had the greatest recovery of parent drug in excreta and, therefore, the smallest extent of metabolism. This finding concurred with the six- to seven-fold lower clearance of fluvastatin in the dog compared to the mouse and monkey. Within each species the bioavailability based on AUC values tended to exceed unity following the high dose (Table 4), which could suggest a decreased clearance due to saturation of elimination pathways at high drug concentrations after the higher dose. Nonetheless, the fraction of fluvastatin dose metabolized prior to excretion was similar between low and high dose levels (Table 3). The minimal quantity of tritiated water formation showed that the 3-position of the *p*-fluorophenyl moiety was metabolically

stable in the mouse and monkey, as it also was in the dog and rat (F. L. S. Tse and F. Ballard, unpublished work).

In all four species studied, the renal route was a minor elimination pathway accounting for less than 8 per cent of the administered radioactivity. The remainder of the dose was excreted, partially intact, via the bile into the feces. The half-life of fluvastatin ranged from 1–2 h in the monkey to 4–7 h in the dog, suggesting no accumulation of parent drug upon multiple daily administration in these species. The comparatively longer terminal half-life of total radioactivity probably reflected the slower elimination of certain metabolites which would show moderate accumulation following multiple doses in the rat, dog, and monkey but not in the mouse, in which the recovery of radioactivity was essentially complete within 24 h of dosing.

In summary, fluvastatin possesses the pharmacokinetic properties most desirable for inhibitors of HMG-CoA reductase and thus of cholesterol synthesis. Unlike lovastatin, which is the hydrophobic lactone or prodrug form of an enzymatically active product,[7] oral doses of fluvastatin are almost completely absorbed. The absorbed dose is largely extracted by the liver which, as the primary site of cholesterol synthesis and regulation, is the single target organ for drugs of this class. Furthermore, a major portion of fluvastatin and its metabolites is preferentially excreted in the bile without ever reaching the general circulation, thus minimizing the systemic burden at dose levels comparable to the intended human daily dose of no more than 40 mg, i.e., ca $0{\cdot}6\,mg\,kg^{-1}$. The drug and its metabolites are readily excreted and show no retention in body tissues. These favorable pharmacokinetic characteristics as well as the established efficacy of fluvastatin[2] fully warrant further investigation of its use as a hypolipidemic and antiatherosclerotic agent in humans.

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