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Effect of food, fluid and dosage form on the absorption of 52-522, a potential antianxiety agent, in the dog

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The absorption of 52-522 in the dog was studied by measuring blood concentrations of radioactivity after single oral doses of [^{14}C] 52-522 in a capsule with and without water, also as a food-drug mixture, and a solution in polyethylene glycol 400. Absorption was rapid, and its rate moderate with no significant differences in peak times among treatments. The extent of absorption was lowest after the capsulated [^{14}C] 52-522. The solution dose gave elevated blood concentrations, that were statistically significantly different when compared with the capsules. Hence, it appears that the absorption of [^{14}C] 52-522 is governed by the degree of dispersion of drug in the dosage form.

3-(α-Iminobenzyl)-4-hydroxy-6-phenyl-1-methyl-2(1H)-pyridinone [Sandoz compound number 52-522] has been investigated as a potential antianxiety agent. Preliminary animal pharmacokinetic studies showed consistent and efficient absorption from oral doses in the rat but erratic absorption in the dog, with approximately 10-fold differences in circulating levels of unchanged drug following equal doses in the same animal (unpublished data). In those dog studies, drug capsules were administered without water, although fluid intake was not controlled and the animals were allowed free access to food and water before and during the experiments. The present study was conducted to examine the effect of concomitant administration of food, vehicle, or water volume on the absorption of radiolabelled drug after a single oral dose in the dog.

Materials and methods

Capsule doses. Four male beagle dogs of ca 10 kg were used. Radioactive 52-522 (labelled with ^{14}C at the 6-position of the pyridinone ring, specific activity 0·15 μCi mg^{-1}) was supplied by the Synthetic Tracer Laboratory, Sandoz, Inc. The dose, 40 mg kg^{-1} based on individual weights, was well mixed with an equal mass of lactose and placed in a gelatin capsule.

The dogs were fasted overnight before each experiment. At 1 h before dosing, each dog received thiethylperazine maleate (Boehringer Ingelheim, 3 mg) intravenously to minimize the possibility of emesis. Dogs 1 and 2 then received the [^{14}C] 52-522 capsules, followed immediately by 100 ml of water, while dogs 3 and 4 each received a capsule without water. Thereafter, both groups of dogs were not allowed access to water for 2 h postdosing. Venous blood samples were collected in heparinized syringes immediately before and at 0·25, 0·5, 1, 2, 3, 4, 6, 8, 12, 24 and 32 h after drug administration, and aliquots pipetted for assay. After a washout period of 2 weeks, the experiment was repeated in a crossover fashion so that each animal received a dose with and without water during the study.

Dose with food. Dogs 1, 2 and 4 were used after allowing 2–3 weeks for drug washout, Dog 3 which died of non-drug-related causes, was replaced by Dog 5. Each individual dose of [^{14}C] 52-522 (40 mg kg^{-1}) was wetted with ca 0·5 ml of polyethylene glycol 400 (PEG 400) and blended into 50 g of moist dog food (Cadillac Pet Foods, Pennsauken, New Jersey, U.S.A.). The dogs were fasted overnight for approximately 20 h so that the drug-food mixture, given 1 h after thiethylperazine maleate (3 mg i.v.) was consumed within 15 min. An additional 100 g of moist dog food was then made available, and serial venous blood sampling began and continued for 32 h. No water or additional food was allowed for 2 h post-dosing.

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Table 1. Mean (± s.d.) blood concentrations of radioactivity obtained from all treatments.

	Blood 52-522 equivalents (μg equiv ml^{-1})				
Time (h)	1. Capsule with water	2. Capsule without water	3. With food	4. Solution	*t*-test[a]
0·25	1·76 ± 2·28	1·60 ± 2·44	2·32 ± 3·92	7·80 ± 1·00	4 > 1, 2
0·5	3·12 ± 2·52	2·00 ± 1·56	3·96 ± 3·72	17·16 ± 0·76	4 > 1–3
1	7·08 ± 5·24	4·40 ± 2·28	9·84 ± 4·00	26·84 ± 6·60	4 > 1–3
2	9·08 ± 4·92	7·88 ± 4·08	15·56 ± 3·84	28·92 ± 7·60	4 > 1, 2; 3 > 2
3	9·84 ± 4·08	8·88 ± 5·76	13·96 ± 6·84	25·48 ± 9·44	4 > 1, 2
4	8·08 ± 3·96	6·80 ± 4·12	11·24 ± 5·44	19·68 ± 7·84	4 > 1, 2
6	4·16 ± 1·60	4·72 ± 2·64	4·24 ± 1·80	10·96 ± 7·08	NSD
8	2·56 ± 1·00	3·00 ± 1·84	3·12 ± 1·20	6·68 ± 2·76	4 > 1
12	2·28 ± 1·64	3·08 ± 3·44	2·56 ± 1·52	5·28 ± 1·80	4 > 1
24	2·52 ± 1·08	1·76 ± 1·52	2·48 ± 2·56	3·48 ± 2·00	NSD
32	1·56 ± 0·56	1·36 ± 1·56	1·16 ± 1·36	3·04 ± 1·68	NSD

[a] Significant at $P < 0·05$.
NSD No significant differences between treatments.

Solution dose. The dose of [^{14}C] 52-522, 40 mg kg^{-1}, was prepared as a solution in PEG 400, 8 mg ml^{-1}. Following an overnight fast and 1 h after thiethylperazine maleate (3 mg i.v.), Dogs 1, 2, 4 and 5 each received 5 ml of the solution per kg by gavage, followed by a 5 ml rinse with water. Thereafter, the dogs were not allowed access to water for 2 h. Serial venous blood samples were collected for 32 h postdosing.

Analysis of radioactivity. Radioactivity was measured in a liquid scintillation spectrometer (Model 2450, Packard). Aliquots (0·2 ml) of blood samples were combusted in a sample oxidizer (Model 306, Packard), while dose preparations were assayed by both combustion and direct counting in a scintillation cocktail consisting of 2,5-bis-2-(5-t-butylbenzoxazolyl)-thiophene (BBOT, Scintillation Grade, Packard) in toluene (8·3 g litre^{-1}). The quench correction and efficiencies of the oxidizer and counter were determined using ^{14}C-labelled hexadecane of known specific activity as an internal standard. Blood concentrations of radioactivity are expressed as μg equivalents of 52-522 per ml.

Statistical analysis. Blood concentrations at each sampling time and pharmacokinetic parameters from individual treatments were compared by Student's *t*-test.

Results

Analysis of the food pan rinse confirmed complete dose uptake of [^{14}C] 52-522. In the PEG solution study, emesis occurred in Dogs 4 and 5, resulting in 29 and 13% losses of the administered doses, respectively, as determined by analyses of the vomitus so the observed radioactivity levels were normalized. Mean blood concentrations of radioactivity, together with statistical analysis, are given in Table 1. The pertinent pharmacokinetic parameters are in Table 2.

The onset of absorption was generally rapid, with measurable radioactivity in the first (15 min) blood sample after all treatments. However, drug concentrations in the 0–4 h samples were significantly higher after the solution doses than after solid doses. In addition, the concomitant administration of food also resulted in elevated, although not statistically significant blood values, as did dosing with water. While no significant differences in the time to reach peak concentrations (t_{max}) were observed between treatments, the peak blood concentrations (C_{max}) from the capsule doses were approximately three times lower than those from the solution. The food-drug mixture yielded intermediate results. The elimination of radioactivity from blood occurred rapidly until approximately 8 h and more slowly thereafter. Although the blood concentra-

Table 2. Mean (± s.d.) pharmacokinetic parameters after oral doses of [^{14}C] 52-522 in the dog.

	Treatment				
Parameter	1. Capsule with water	2. Capsule without water	3. With food	4. Solution	*t*-test
AUC[a] (μg equiv h ml^{-1})	103·2 ± 42·4	97·6 ± 68·0	123·6 ± 64·4	243·2 ± 85·2	4 > 1, 2
C_{max}[b] (μg equiv ml^{-1})	10·64 ± 4·56	9·68 ± 5·04	16·24 ± 5·08	29·20 ± 7·80	4 > 1, 2
t_{max}[c] (h)	2·5 ± 0·6	2·5 ± 0·6	2·3 ± 0·5	1·8 ± 0·5	NSD

[a] Area under blood concentration vs time curve from zero to 32 h obtained by trapezoidal rule.
[b] Maximum observed concentration of radioactivity in blood.
[c] Time of maximum radioactivity concentration in blood.

tions from the solution dose still appeared higher than those from the solid doses during 8–32 h, the differences were generally not significant. The area under blood concentration vs time curve (AUC) values ranged from 97·6 μg equiv h ml^{-1} for the capsule without water to 243·3 μg equiv h ml^{-1} for the solution, and the differences between the solution and both capsule doses were statistically significant.

Discussion

It has been suggested that increased fluid volumes can enhance the absorption of some drugs, particularly those in a dosage form with long disintegration or dissolution times (Toothaker & Welling 1980). On the other hand, large fluid volumes could reduce the absorption of drugs that are readily soluble, probably due to a decreased concentration gradient across the gastrointestinal wall (Welling et al 1976). Since 52-522 is only slightly soluble in water (0·01 g/100 ml at room temperature), the former suggestion would apply. Table 1 shows that concurrent administration of water does increase the blood concentrations from the capsules, at least during the absorption phase, although the differences were not statistically significant.

Compared with the capsule doses, [^{14}C] 52-522 mixed in food yielded slightly elevated AUC and C_{max} values, although the differences were not statistically significant (Table 2). The concept of food promoting drug bioavailability has been discussed (Toothaker & Welling 1980; Welling & Tse 1982). By delaying gastric emptying (Bates & Gibaldi 1970), the presence of food generally increases drug residence time in the stomach. Similar phenomena have been reported for the antimicrobial agents nitrofurantoin (Bates et al 1974; Rosenberg & Bates 1976), sulphamethoxydiazine (Kaumeier et al 1979), and hetacillin (Jusko & Lewis 1973). Furthermore, by evenly mixing [^{14}C] 52-522 powder with moist food, the drug was better dispersed than in the capsules, which also could have contributed to the higher blood concentrations.

A higher degree of dispersion may be obtained by dissolving the drug in an appropriate solvent, which could enhance both the rate and efficiency of absorption of a poorly water-soluble compound such as 52-522. Previous investigators (O'Grady et al 1978) have suggested that a solvent factor is responsible for the enhanced absorption of digoxin from a solution of 90% PEG 400. Our present results (Tables 1, 2) showed that the solution dose in PEG 400 resulted in significantly increased AUC and C_{max} values as well as elevated blood radioactivity concentrations at most sampling times, especially when compared with the capsule doses. The solution also appeared to be absorbed more rapidly than the solid doses, although no significant differences in t_{max} were shown between treatments.

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