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Department of Pharmacology and Therapeutics,
McGill University,
Montreal, Quebec, Canada.

D. R. VARMA
D. GOLDBAUM

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Depot fluphenazine enanthate and decanoate: comparative rates of release in dogs

While many studies in man demonstrate the clinical efficacy of long-acting esters of fluphenazine, (Blachly, 1965; Keskiner, Simeon & others, 1968), there is scarcely any metabolic data in the literature that enables the quantitation of their slow-release from a depot (Ebert & Hess, 1965; Dreyfuss, Ross & Schreiber, 1971). Metabolic studies with these compounds in man have had only limited success owing to the small concentrations of drug or metabolites that are present at any time in the circulation (Schreiber & Grozier, 1973).

Two groups of five male purebred beagles, $\sim$ 10 kg, were given average doses of either [^{14}C] fluphenazine enanthate (4·92 μCi mg^{-1}) or [^{14}C] fluphenazine decanoate (4·84 μCi mg^{-1}), containing about 100 μCi of radioactivity. Both esters were formulated in sesame oil (*ca* 41 mg ml^{-1}) containing 1·6% benzyl alcohol and injected intramuscularly into the *biceps femoris* of the thigh muscle (0·5 ml of formulation for each 10 kg). The single dose of drug administered to dogs on the basis of body weight [1·89 $\pm$ 0·11 mg kg^{-1} for the enanthate (mean $\pm$ s.e.); 2·03 $\pm$ 0·04 mg kg^{-1} for the decanoate] was about 4 times that which would be administered to man clinically (DeWolfe, Barrell & others, 1971; Chacon & Harper, 1973). Samples of blood were taken periodically for 35 days; total urine and faeces were collected separately each day.

Plasma (0·8 ml) was dissolved in 4 ml of NCS solubilizer (Amersham, Searle) and counted in 15 ml of scintillation fluid containing, per litre of toluene, 5 g of 2,5-diphenyloxazole and 300 mg of 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene, using a Packard Tri-Carb liquid scintillation spectrometer, Model 3380. Quench correction was by automatic external standardization. Faeces were homogenized with 2–3 volumes of methanol, and 800 mg samples of the homogenate were combusted for counting in an oxidizer (Harvey Instrument Corp.). Samples of urine (1 ml) were counted directly in scintillation fluid (Bray, 1960).

The times required to attain maximum concentrations of total radioactivity in plasma were 3·8 ± 0·5 days (± s.e.) for enanthate and 10·6 ± 1·1 days for decanoate ($P < 0.05$); maximum concentrations of radioactivity in the plasma at these times were 16·7 ± 1·1 and 11·1 ± 1·2 ng ml^{-1}, respectively ($P < 0.05$). However, 35 days after dosing, concentrations of radioactivity in plasma were greater for decanoate (6·1 ± 0·4 ng ml^{-1}) than for enanthate (2·2 ± 0·5 ng ml^{-1}) ($P < 0.01$). The times required for 50% of the dose to be excreted in the urine and faeces were 7·8 ± 0·5 days for enanthate and 22·6 ± 4·4 days for decanoate ($P < 0.05$). Lines of best fit for the total excretion of radioactivity after dosing with each ester, as determined by analysis of linear regression, indicate that the half-time for the release of radioactivity from the depot and body was 5·55 days for enanthate and 15·4 days for decanoate. The total amounts excreted in 35 days were 85·4 ± 1·8 and 68·8 ± 6·6% of the dose for enanthate and decanoate respectively; during the 35 days, only 1 to 4% of the dose was present in the urine of any of the dogs. When total excretion is considered on a weekly basis, the rate of release of radioactivity was greatest for enanthate during the first week after dosing, whereas it was greatest for decanoate during the second week after dosing ($P<0.01$). Thirty-five days after dosing, the amounts of the dose present in the injection sites, as determined by homogenization of the entire thigh muscle in chloroform–methanol (1 : 1), followed by combustion as described for faeces, were 4·6 ± 1·6% of the dose for enanthate and 18·6 ± 5·7% of the dose for decanoate ($P<0.1$).

Pharmacological studies were also conducted in dogs employing the apomorphine test for studying the duration of action of long-acting neuroleptics (Laffan, High & Burke, 1965). The esters were administered subcutaneously in sesame oil at approximately 8 mg kg^{-1}. Two groups of six dogs (3 male, 3 female) were dosed with either ester, and the first day was determined on which emesis occurred in response to an increasing intravenous dose of apomorphine (20–640 μg kg^{-1}). Protection against the emetic effects of all the doses of apomorphine was more than twice as long with decanoate than with enanthate after single doses of either ester in sesame oil ($P<0.05$).

While it should be emphasized that our metabolic studies measured undifferentiated radioactivity, we conclude that in these dogs decanoate was released from its site of injection as a depot at less than one-half the rate of enanthate. Whether or not these data in dogs have any clinical significance remains to be determined.

Departments of Drug Metabolism and Pharmacology,
Squibb Institute for Medical Research,
New Brunswick, New Jersey 08903, U.S.A.

J. DREYFUSS
J. J. ROSS, JR.
J. M. SHAW
I. MILLER
E. C. SCHREIBER

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