FLUORESCEIN PHARMACOKINETICS IN THE BEAGLE

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The pharmacokinetics of fluorescein (I) were investigated in the Beagle prior to its use as a pharmacologically inert marker in formulation assessment. Its bioavailability was determined after administration as oral (p.o.), intratracheal (i.t.) and intramuscular (i.m.) aqueous solutions of its disodium salt. The compound is currently employed in intravenous doses of the order of 14 mg kg^{-1} for various diagnostic purposes. It is excreted unchanged and as a glucuronide in urine and bile (Webb et al 1962).

Accurate determination of I (>2 ng ml^{-1}) in aqueous solution, 10% $^{v}/_{v}$ heparinised plasma and urine was possible at pH > 9 by fluorimetry (λ_{ex} = 486 nm, λ_{em} = 516 nm). The presence of the glucuronide conjugate does not interfere with the assay (Chen et al 1980).

An intravenous dose ranging study revealed that the pharmacokinetics of I in the Beagle were linear and described by a two-compartment open body model [$(t_{0.5})_{\alpha}$ = 3.3 min, $(t_{0.5})_{\beta}$ = 17.9 min] when plasma concentration, C_p < 7.0 μg ml^{-1}. The pharmacokinetics were reproducible in a second animal. Under these conditions, where i.v. dose <0.9 mg kg^{-1}, total body clearance was 13.0 ± 0.4 (S.D.) ml min^{-1} kg^{-1} with renal clearance = 8.97 ± 0.23 ml min^{-1} kg^{-1} indicating active tubular elimination. The fraction of I excreted unchanged in the urine as time, $t \rightarrow \infty$ (FEU^{∞}) = 0.68 ± 0.13 after extravascular administration.

Higher intravenous doses produced values for C_p > 7.0 μg ml^{-1}. Under these circumstances, total body clearance fell as a function of increasing dose, from 13.0 to 4.01 ml min^{-1} kg^{-1} at doses up to 9.8 mg kg^{-1}. Fluorescein therefore displays non-linear pharmacokinetics in accord with a tendency to saturate elimination processes at the large (14 mg kg^{-1}) i.v. doses conventionally employed for this compound.

Extravascular doses of aqueous solutions of I ranging from 0.67 to 2.24 mg kg^{-1} were administered to determine the compounds bioavailability by three routes. Plasma concentrations were always <7.0 μg ml^{-1} and thus the pharmacokinetics of I were linear. Table 1 summarises data for the bioavailable fraction, F, determined by conventional comparison of areas under C_p versus t profiles.

Table 1. Bioavailable fractions of fluorescein after extravascular administration

Route	Dose (mg kg^{-1})	F
p.o.	0.83	0.33
p.o.	0.90	0.53
i.m.	1.13	1.03
i.t.	0.67	1.01
i.t.	1.51	1.02
i.t.	2.24	0.90

Values for F determined from FEU^{∞}/0.68 (0.68 is the mean fraction eliminated unchanged in urine) were in excellent agreement with those in Table 1. Fluorescein was variably and incompletely available from the gastrointestinal tract but was totally available i.m. and i.t. Its inclusion in small quantities in delivery systems not intended for oral administration permits the effect of formulation upon its bioavailability to be assessed. The assessment is simple and rapid owing to the compound's short biological half-life and ease of assay. When its pharmacokinetics are linear the fraction absorbed may be estimated after its determination in either plasma or urine.

Chen, S. C. et al (1980) Chem. Pharm. Bull. 28: 2812-2816
Webb, J. M. et al (1962) J. Pharmacol. Exptl. Therap. 137: 141-147

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