A kinetic study of the fate of SL 73033 (antrafenine) in the rat

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The kinetics of SL 73033 (antrafenine, 2-[4-(*m*-trifluoromethyl-phenyl)-1-piperazinyl] ethyl 2-(7-trifluoromethyl-4-quinolinylamino) benzoate), a new analgesic agent (Branceni, Proteau, Manoury, Najer & Giudicelli, 1975; Caille & Bassano, 1977), have been studied in the rat.

Male rats were dosed either orally with a suspension of SL 73033 (50 mg/kg, labelled either at C-4 in the quinoline ring (Q form) or at C-1 and 2 in the piperazine ring (P form)) or intravenously (5 mg/kg, either Q or P form dissolved in a 0.25% tartaric acid solution).

Plasma concentrations of both total radioactivity and unchanged drug were determined and pharmacokinetic analyses carried out using an interactive graphic programme (IGPHARM) on a Tektronix 4051 computer.

After i.v. administration, the plasma levels of the unchanged drug during the first 2 h represented a significant proportion of the radioactivity (30–50%) but was much less at 8 h (10%). During the later time intervals most of the radioactivity in the plasma was shown to be due to the acid and alcohol hydrolysis products plus conjugates of the latter. The decay curve for the unchanged drug could be best fitted by a triexponential curve from which the following parameters were derived: K_{el} (h^{-1}) 0.031, $T_{1/2}$ (h) 2.19, $AUC_{0\rightarrow\infty}$ ($\mu g\ l^{-1}$ h) 3867, CL (l/kg) 1.29, Vd (l/kg) 4.07. The percentage of the dose of [^{14}C] recovered in the urine and faeces after 72 h was 95% for the P form and 99% for the Q form. On the other hand there was a marked difference in the route of excretion of radioactivity between the two forms; only 7% of the dose was excreted in the urine after the Q form but 36% after the P form.

The AUC of total plasma radioactivity after i.v. administration expressed as μg equivalents of the parent drug was 8773 $\mu g\ l^{-1}$ h for the Q form and 13,170 $\mu g\ l^{-1}$ h for the P form. After oral administration the AUC of total plasma radioactivity expressed as above was ten times as great for the Q form (86,534 $\mu g\ l^{-1}$ h) but only four times as great for the P form (54,196 $\mu g\ l^{-1}$ h).

If a comparison is made of the two routes of dosing and the two labelled forms it can be seen that the AUC of the Q form of the oral versus the i.v. route is ten times greater, as would be expected, but only four times as great for the P form. This would indicate: (a) good absorption of the compound and (b) a substantial 'first pass' loss for the P form on oral dosing, or probably of the alcohol metabolite and/or its metabolites.

The [^{14}C] excretion in bile of bile-duct-cannulated rats was examined after i.v. administration of SL 73033 as either the Q or P form. After 6 h, 84% and 67% of the dose was recovered after dosage with the Q and P forms respectively.

Metabolism would also seem to have an influence on the amount of [^{14}C] excreted in the bile since there is a marked difference between the Q and P forms. The Q form would give rise to the labelled acidic hydrolysis product (M.W. 332) and the P form to the labelled alcohol hydrolysis product (M.W. 274). These compounds are respectively just above and below the molecular weight necessary for extensive biliary excretion in the rat (Millburn, Smith & Williams, 1967). That hydrolysis of the compound is extensive would also be indicated from the bile results, since more of the [^{14}C] is excreted after dosing with the Q form than the P.

From the biliary data it was possible to calculate the apparent half lives of total radioactivity for both the P and Q forms (1.74 h and 1.69 h respectively). Comparison with the plasma data (7.22 h and 2.66 h for P and Q respectively) showed that the half lives in the bile were consistently shorter than in the plasma which suggested an enterohepatic circulation. Support for this idea was gained when it was shown that when bile from a rat dosed with the P + Q form of SL 73033 was introduced into the duodenum of a second rat substantial amounts of radioactivity (64% of dose) were excreted in the bile of the second rat.

It would appear that antrafenine is well absorbed after oral administration but undergoes a substantial 'first pass' loss together with an enterohepatic recirculation.

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