32P

FIRST-PASS METABOLISM OF OXAMNIQUINE: A QUANTITATIVE STUDY IN THE RABBIT

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A previous study of the metabolism of the schistosomicidal agent, oxamniquine, (6-hydroxymethyl-2- isopropylaminomethyl-7- nitro-1,2,3,4- tetrahydroquinoline), has reported a significant presystemic metabolism in the dog, which was attributed mainly to enzymatic activity in the gut wall (Kaye and Roberts, 1980). In the present study, eight New Zealand white rabbits (4 females and 4 males), weighing 3.04 ± 0.54kg (mean ± s.d.), previously fasted for 16 hours were anaesthetised with Hypnorm (fluanisone 10 mg ml^{-1}, fentanyl 0.2 mg ml^{-1}), 0.3 ml kg^{-1} and administered oxamniquine (15 mg kg^{-1}) orally (po) as a suspension in 10% (v/v in water) Tween 80, rectally (rec) as a suppository (PEG 6000/PEG 1540/water - 47/33/20% w/w) and intravenously (iv) and via the portal vein (pv) as a solution in citrate-phosphate buffer, pH 5.0. A random cross-over design, with a one week "wash-out" period in between administration, was followed. Intraportal administration was always last. Area under the plasma drug concentration-time curve (AUC) was determined from serial plasma concentration data, and availability (F) was computed with reference to iv data (Rowland, 1972). The results (mean ± s.d.) are given in the table below:

Route	Dosage form	No. of animals	AUC (μg hr ml^{-1})	F
iv	Solution	8	5.49 ± 3.75	
pv	Solution	5	6.25 ± 4.68	1.01 ± 0.62
po	Suspension	6	2.27 ± 0.69	0.45 ± 0.19
rec	Suppository	6	2.18 ± 0.94	0.46 ± 0.33

Mean oral availability was less than 50% indicating considerable first-pass metabolism, since a previous report (Kaye and Woolhouse, 1976) indicated that the drug is well absorbed in the rabbit. Gut wall metabolism appeared to account for the major fraction of first-pass effect, although considerable variation between animals was also observed. Similar variations have been observed in the dog (Kaye and Roberts, 1980). Overall hepatic first-pass appeared to be minimal; in two cases AUC after pv administration was greater than after iv administration. Rectal administration did not result in any significant difference in availability compared to oral administration, despite suggestions that the presence of enzymes in the gut wall might decrease progressively from the jejunum to the rectum (de Boer et al., 1982). Formulation factors, rectal physiology and/or metabolism in the rectal mucosa could have contributed to poor availability.

It is concluded that gut wall is a major site for metabolism of orally administered oxamniquine and rectal administration would probably not result in significant increase in the systemic availability. Hepatic first-pass appears to be minimal in the rabbit.

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