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First pass conjugation of phenol following rectal administration in rats

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The systemic availability of phenol following rectal administration to rats has been compared to intraduodenal and intravenous administration via the hepatic portal and jugular veins. Phenol blood concentration-time curves after the rectal route of dosing indicate that first pass conjugation by the intestinal mucosa and liver is drastically reduced when compared to the other routes of administration.

The use of rectally administered drugs has been recently reviewed from the viewpoint of clinical pharmacokinetics (de Boer et al 1982) and biopharmaceutics (de Blaey & Polderman 1980). A feature of this route of administration is the possibility of reducing the first pass metabolism evident with some drugs following oral administration. Drugs with a high metabolic clearance show a low systemic availability and hence are often not efficacious after oral administration (Rowland & Tozer 1980). Drugs absorbed from the small intestine pass through the intestinal mucosa to reach the capillaries of the hepatic portal vein and then cross the liver before reaching the systemic circulation. Both tissues are well endowed with drug metabolizing enzymes and extensive first pass metabolism of drugs may occur. In contrast, the blood supply from the rectum drains primarily into the vena cava thus it may be postulated that any first pass hepatic metabolism is avoided. Although no information is available on the ability of the rectal mucosa to metabolize drugs, it is known that the activity of the intestinal mucosal enzymes decreases progressively from duodenum to large intestine (Caldwell & Marsh 1982). Hence both metabolic barriers may be by-passed if the rectal route of drug administration is adopted.

Phenol has been used as a model compound to compare extrahepatic and hepatic conjugation reactions in-vivo (Cassidy & Houston 1980; Houston & Cassidy 1982). Extensive conjugation in both the intestinal mucosa and liver has been detected via a judicious choice of route of administration. Comparison of area under the blood concentration-time curves following intraduodenal and hepatic portal venous administration of phenol allows the role of the intestinal mucosa to be assessed. Comparison of area under the blood concentration-time curves following intravenous phenol administration via the hepatic portal and jugular veins provides an estimation of the extent of hepatic metabolism. Therefore phenol is an ideal compound to assess to what degree rectal administration may reduce first pass metabolism of intestinal and hepatic origin.

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Method

Male Sprague-Dawley rats (mean weight 280 g, s.d. 59) were anaesthetized with urethane (1·3 g kg^{-1}). Administration of [U-^{14}C]phenol (0·4 mg kg^{-1}; 10–30 μCi kg^{-1}) in aqueous solution was achieved intravenously, via either the hepatic portal vein (h.p.v.) or the jugular vein (i.v.), and intraduodenally (i.d.) as previously described (Cassidy & Houston 1980). Rectal administration (p.r.) was achieved via a septum (a 2 ml syringe plunger rubber)–needle–syringe assembly secured in the rectal orifice by tissue adhesive. The exposed needle on the distal side of the septum was sheathed with tubing (PE 50, Intramedic) to avoid tissue damage. Blood samples (100 μl) were removed via a cannula in the right carotid artery over 120 min. Each sample was assayed for phenol by specific radiometric analysis and for phenyl conjugates (the sum of phenyl glucuronide and phenyl sulphate) as described by Cassidy & Houston (1980). Area under the blood phenol concentration-time curve (AUC) was determined by the trapezoidal rule from time zero to the last data point with extrapolation to infinity. The trapezoidal rule was also applied to the phenyl conjugate concentration time data to obtain a metabolite area under the curve (AUC(m)) from time zero to 120 min.

Fig. 1 shows typical blood concentration-time curves after p.r., i.d., h.p.v. and i.v. administration of phenol. It is evident from the p.r. blood profile that rectal absorption of phenol is comparatively rapid with peak concentrations achieved after 10 min and the terminal half-life averages 10 (s.d. 5) min. Phenol administration by the other routes produced maximum blood concentrations in the first sample (2 min) and terminal half-lives (from i.v. and h.p.v.) between 3–5 min. These kinetic profiles would suggest that following rectal administration the disposition of phenol is absorption rate limited (Rowland & Tozer 1980).

The mean AUCs for each route of administration are shown in Table 1. The p.r., i.d. and h.p.v. routes result in substantially lower AUCs than the i.v. route indicating incomplete systemic availability in each case. This may be due to first pass metabolism or incomplete absorption from site of administration or both.

The time profile for the phenyl conjugates after phenol p.r. administration differs from the other routes investigated. There is a gradual build up of metabolites to a peak concentration after approximately 40 min. In the i.v. case (as well as h.p.v. and i.d. administration of phenol) maximum metabolite concentrations are

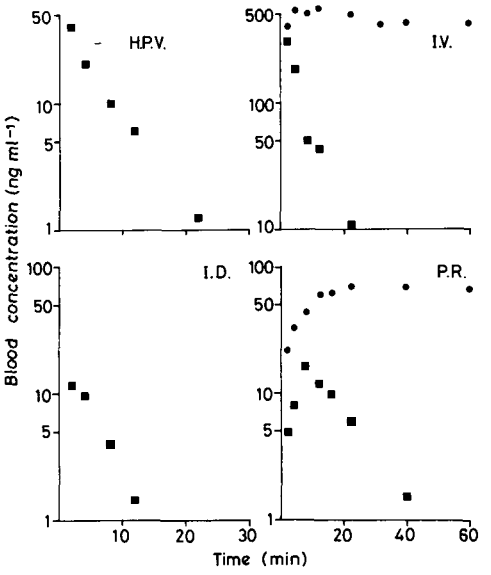

FIG. 1. Typical blood phenol (■) and phenyl conjugates (●) concentration-time curves after administration of phenol intravenously via either the jugular vein (i.v.) or hepatic portal vein (h.p.v.), intraduodenally (i.d.) or rectally (p.r.) to rats. Phenyl conjugate concentrations after h.p.v. and i.d. were in the region of 500 ng ml^{-1}.

achieved within 5 min. This is in accord with previous investigations using a higher phenol dose (Cassidy & Houston 1980). As illustrated in Fig. 1, the maximum metabolite concentration after p.r. administration is much lower than after i.v. administration. Consequently a much reduced AUC(m) is obtained when phenol is given p.r. than by the other routes investigated (Table 1). This reduction in AUC(m) is statistically significant ($P < 0.01$ by the Student-Newman-Keul's multiple range test) and suggests incomplete absorption by the p.r. route. In contrast, there is no statistical difference between AUC(m) after i.d., h.p.v. and i.v. phenol administration indicating that the complete dose enters the body via these routes.

Table 1. Area under the blood phenol concentration-time curve and area under the blood phenyl conjugates concentration-time curve following administration of phenol intravenously via either the jugular vein (i.v.) or hepatic portal vein (h.p.v.), intraduodenally (i.d.) or rectally (p.r.) to rats.

	Route of administration			
	i.v.	h.p.v.	i.d.	p.r.
n[a]	3	3	5	5
Area under blood phenol concentration-time curve (ng ml^{-1} min)	2413[b] (516)[c]	289 (127)	107 (138)	315 (62)
Area under blood phenyl conjugates concentration-time curve (μg phenol equivalents ml^{-1} min)	47·5 (29·6)	54·2 (11·9)	59·0 (32·3)	12·5 (2·6)

[a] Number of rats per group.
[b] Mean.
[c] Standard deviation.

Table 2. Ratio of areas under the blood phenol concentration-time curve after administration of phenol intravenously via either the jugular vein (i.v.) or hepatic portal vein (h.p.v.), intraduodenally (i.d.) or rectally (p.r.) to rats.

	Area Ratio × 100	
Routes of administration	Complete absorption for all routes	Corrected for 23% rectal absorption[a]
i.d./i.v.	4·4	—
h.p.v./i.v.	12·0	—
p.r./i.v.	13·1	57
i.d./h.p.v.	37·0	—
p.r./h.p.v.	109	474
p.r./i.d.	295	1280

[a] Based on area under the blood phenyl conjugates concentration-time curve, see text.

Table 2 presents the ratio of AUCs for the different routes of administration studied. The AUC ratios for h.p.v./i.v. administration and i.d./h.p.v. administration estimate the fraction of the phenol dose escaping metabolism by the liver and intestinal mucosa respectively. In both cases extensive metabolism is evident (63–88% of dose) during the first pass. In contrast the AUC ratios for p.r./h.p.v. administration and p.r./i.d. administration would indicate that only hepatic first pass metabolism occurs when phenol is given p.r.

In the above considerations it is assumed that rectal absorption is complete. Comparison of AUC(m)s may be used to assess the extent of absorption of a compound given by an extravascular route (Houston 1981). AUC(m) p.r. is only 23% of that observed following dosing by the other 3 routes (mean AUC(m) for i.v., h.p.v. and i.d. being 53·6 μg phenol equivalents ml^{-1} min). The AUC ratios corrected for this degree of rectal absorption are also shown in Table 2. The enhanced systemic availability of p.r. relative to h.p.v. and i.d. routes is very marked—p.r. is approximately 5 fold greater than h.p.v., and approximately 13 fold greater than i.d. However, the extent of first pass metabolism via the rectal route is not avoided completely. On average 43% of the rectally absorbed phenol is metabolized during the first pass. This may be rationalized by the occurrence of no rectal mucosal metabolism with an approximate reduction in hepatic first pass by half. Alternatively if metabolism occurs in the rectal mucosa, albeit to a minimal extent relative to the small intestinal mucosa, the reduction in hepatic first pass is greater than 50%.

De Boer et al (1980, 1981) have demonstrated that rectal administration reduces the hepatic first pass oxidative metabolism of propranolol and lignocaine in the rat. We have confirmed this phenomenon using phenol which undergoes extensive hepatic conjugation. Also our data indicates that intestinal first pass metabolism of phenol is partially if not completely avoided when the rectal route is employed. As discussed by De Boer et al (1982) it is unlikely that hepatic first pass metabolism can be completely by-passed using rectally administered drugs since only the inferior and middle haemorrhoidal veins drain into the vena cava. The superior haemorrhoidal vein feeds into the hepatic protal vein and there exists extensive anastomoses between all the rectal veins.

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Effect of diamorphine, Δ^9-tetrahydrocannabinol and ethanol on intravenous cocaine disposition

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The disposition of cocaine (1 mg kg^{-1}) was altered by diamorphine (0.1 mg kg^{-1}) and that of morphine (1 mg kg^{-1}) was altered after their concurrent administration as a bolus i.v. injection to rats by cocaine, without any changes in the metabolism of the drugs. Δ^9-Tetrahydrocannabinol (10 mg kg^{-1} i.p.) did not affect the cocaine disposition. Chronic ethanol treatment (2.5 g kg^{-1} orally twice daily for 16 days) produced a significantly higher brain-to-plasma cocaine concentration ratio than did saline as control, without any changes in cocaine metabolism.

Concomitant intravenous use of cocaine with diamorphine ("Speedballing") or with Δ^9-tetrahydrocannabinol (Δ^9-THC) or ethanol is currently popular with drug abusers. Aside from some work on the behavioural interaction of cocaine with morphine (Nott 1968), diamorphine (Pickett 1970). Δ^9-THC (Pryor et al 1976) or ethanol (Kissin 1974), no information is available on the drug dispositional aspects of these interactions. This investigation was undertaken to obtain this information.

Materials and methods

[^{3}H] Ring-labelled cocaine as prepared by Nayak et al, (1974) was diluted with non-radioactive cocaine hydrochloride to provide a specific activity of approximately 10 μCi mg^{-1}. All doses were expressed as free base. [6-^{3}H (N)] Morphine (specific activity 9.84 Ci m mol^{-1}) (New England Nuclear Corp, Boston, Mass.) was diluted with non-radioactive morphine hydrochloride to provide a specific activity of 10 μCi mg^{-1}. Diamorphine (heroin) was prepared in the laboratory by the acetylation of morphine base.

Δ^9-THC (0.5 ml) (from sealed ampoules of 1g/5 ml ethanol USP as supplied by the Research Triangle Institute through the courtesy of Dr. R. Hawks, NIDA, Rockville, Md.) was transferred to a volumetric flask (5 ml) and evaporated to dryness under nitrogen. The residue was resuspended in 10% v/v Tween 80 (0.5 ml) by thorough mixing in a vibro mixer and the solution diluted to 5 ml with 0.9% NaCl (saline). The final suspension (20 mg ml^{-1}) was transferred to a 5 ml amber multidose injection vial, and was freshly prepared.

Cocaine-diamorphine combination. Male Wistar rats (250–300 g) were injected i.v. either with a 1 mg kg^{-1} dose of [^{3}H]cocaine or a solution containing 1 mg kg^{-1} dose of [^{3}H]cocaine and 0.1 mg kg^{-1} dose of diamorphine. The animals were killed 10 min later and the

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