J. Pharm. Pharmacol. 1981, 33: 50–51
Communicated April 18, 1980

0022–3573/81/010050–02 $02.50/0

Avoidance of first pass elimination of propranolol after rectal administration to rats

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Although there is a common belief that absorption of drugs from the rectum bypasses the liver, evidence to support this is scanty. Recently we have shown that when the high-clearance drug lignocaine is administered rectally (aqueous solution) to healthy subjects, the systemic availability of unchanged drug is twice as high as the oral availability (De Boer et al 1979) while the mean rectal systemic availability in rats is approximately 15 times the oral systemic availability (De Boer et al 1980a). These findings indicate that the rectal route of administration does offer the possibility of bypassing the liver. In this communication similar results are described after rectal administration to rats of another high-clearance drug, propranolol.

Six male wistar rats (200–250 g), which had been fasted for one night, were orally and rectally administered 2·0 mg propranolol as an aqueous propranolol HCl solution (volume 0·5 ml) in a balanced cross-over design. There was one week's interval between oral and rectal administration. Six other rats were given 2·0 mg propranolol as an aqueous solution of propranolol HCl in 0·9% NaCl (saline) (volume 0·5 ml) by means of an i.a. infusion during 10 min. In all cases blood samples were collected from a cannula in the vena jugularis up to 5 h after administration. After extraction and derivatization plasma propranolol concentrations were determined by a method based on capillary gas chromatography with a solid injection system and nitrogen selective detection (De Boer et al 1980b).

The areas under the plasma concentration-time curves (AUC) were calculated by means of the trapezoidal rule, while extrapolation to infinity was carried out by dividing the last measured plasma concentration by the rate constant of the terminal phase (β). The bioavailability (F) after oral and rectal administration was calculated for each rat by dividing the AUC_{or} and AUC_{rect} by the mean $AUC_{i.a.}$. Statistical evaluation of the differences between oral and rectal results were made using a paired t-test.

Fig. 1 shows the mean semi-log plasma concentration time curves after administration of 2·0 mg propranolol orally and rectally to the same rats and intra-arterially to another group of rats. Whereas the AUC_{rect} is in the same order of magnitude as that found for i.a. administration the difference between the mean AUC following oral and rectal administration is considerable. Table 1 shows that the mean oral (F_{or}) and mean rectal (F_{rect}) systemic availabilities are 3·1 and 101·1% respectively, indicating that the mean F_{rect} is 35·7 times larger than the mean F_{or}.

These results demonstrate that for propranolol after rectal absorption there is a considerable or almost complete bypass of the liver (Table 1) and are in agree-

Table 1. The systemic availabilities (F) following oral and rectal administration of 2·0 mg propranolol to six rats. In addition the ratios F_{rect}/F_{or} are given.

Rat	F_{or}[a] (%)	F_{rect}[a] (%)	F_{rect}/F_{or}
1	4·6	106·3	23·1
2	0·9[b]	201·0[b]	223·3[b]
3	2·5	91·3	36·5
4	2·9	108·5	37·4
5	3·5	107·9	30·8
6	1·8	91·4	50·7
mean	3·1[c]	101·1[c]	35·7
s.d.	1·1	8·9	10·1

[a] in all cases the AUC_{FJ} and AUC_{rect} were divided by the mean AUC_{or} (100 μg min ml^{-1}) obtained following i.a. infusion of 2·0 mg propranolol to six other rats.

[b] not taken into account for the calculation of the mean value.

[c] $P < 0.002$.

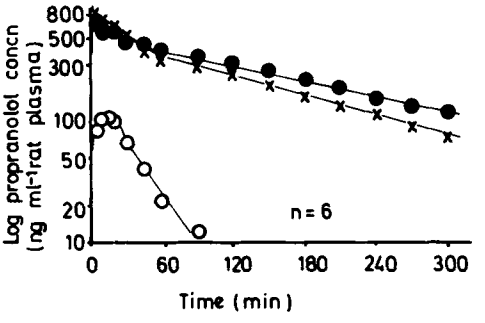

FIG. 1. The mean semi-log plasma concentration-time curves after administration of 2·0 mg propranolol orally and rectally to the same rats, and intra-arterially to another group of rats. ● rectal. ○ oral × i.a.

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ment with those found for lignocaine in rats (De Boer et al 1980a).

From the literature it is known that oral absorption of propranolol is almost complete (Paterson et al 1970), but systemic availability is only 3%. No data are available about the extent of its rectal absorption. From our experiments it can be concluded that the rectal route of propranolol in rats is practically entirely a non-hepatic route, resulting in almost complete systemic availability.

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J. Pharm. Pharmacol. 1981, 33: 51–53
Communicated April 22, 1980

0022–3573/81/010051–03 $02.50/0

In vivo effect of toxic alkaloids on drug metabolism

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Although the involvement of hepatic drug-metabolizing enzymes in the biotransformation of nicotine (Booth & Boyland 1971; Tsujimoto et al 1972; Dohi et al 1973), colchicine (Schonharting et al 1973; 1974), and reserpine (Stitzel et al 1972; Stitzel 1974) has been reported, much less is known about the microsomal metabolism of boldine, brucine, emetine, sanguinarine, solanine and strychnine, and their effect on the biotransformation of other drugs. The present study reports on the comparative effect of these alkaloids on the alteration of the activity of hepatic drug-metabolizing enzyme system in rats.

The alkaloids, boldine, brucine suphate, colchicine, emetine hydrochloride, nicotine, reserpine, scopolamine hydrochloride and strychnine sulphate were purchased from Sigma Chemical Co., St. Louis, Mo., U.S.A. Sanguinarine nitrate was obtained from Aldrich Chemical Co., Milwaukee, Wis., U.S.A. Solanine was a generous gift from Dr T. J. Fitzpatrick, ARS-USDA, Philadelphia, Pa., U.S.A. All other chemicals used were analytical or reagent grade.

Male Sprague-Dawley rats (200–250 g) (Southern Animal Farms, Prattville, Alabama) were maintained in a temperature- and light-controlled room with access to Purina chow feed and tap water at all times except otherwise stated.

Groups of at least three animals were injected intraperitoneally with freshly made 0·9% NaCl (saline) solutions of brucine (2 mg kg^{-1}), colchicine (1 mg kg^{-1}), emetine (4 mg kg^{-1}), sanguinarine (10 mg kg^{-1}) and scopolamine (2 mg kg^{-1}). Boldine (5 mg kg^{-1}), nicotine (4 mg kg^{-1}), reserpine (2·5 mg kg^{-1}). solanine (10 mg kg^{-1}) or strychnine (2 mg kg^{-1}) was suspended in corn oil (Mazola brand) and administered intraperitoneally to the respective groups. The two control groups were injected with saline or corn oil. Injections were given daily for three successive days and the animals were used to determine pentobarbitone sleeping time or killed to isolate liver microsomes 24 h after the last injection. In an experiment designed to assess the effect of the alkaloids on the ability of phenobarbitone to induce hepatic microsomal enzymes, animals were given an alkaloid and phenobarbitone sodium (75 mg kg^{-1}, i.p.) simultaneously for three successive days, and killed on the fourth day to isolate liver microsomes (Dalvi & Robbins 1978).

To determine whether the alkaloids possess microsomal enzyme-inducing or -inhibiting properties, pentobarbitone sleeping times were measured in the rats according to Dalvi & Howell (1977).

The cytochrome P-450 content of the microsomal preparations was determined by the procedure of Omura & Sato (1964). The ability of microsomal enzymes isolated from treated and untreated rats to metabolize drugs was examined using benzphetamine and aniline as substrates (Dalvi & Howell 1977). The amount of protein in each sample was estimated using biuret method modified to include deoxycholate in samples (Dalvi et al 1974).

Table 1. Effect of pretreatment of the alkaloid compounds on pentobarbitone sleeping time in rats.

Compound	Dose (mg kg^{-1})	Sleeping time (% of control)
Boldine	5	113
Brucine	2	72
Colchicine	1	208
Emetine	4	122
Nicotine	4	53
Reserpine	2·5	202
Sanguinarine	10	272
Scopolamine	2	85
Solanine	10	275
Strychnine	2	73

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