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CONTRIBUTION OF INDIVIDUAL DIFFERENCES IN GASTRIC EMPTYING TO VARIABILITY IN PLASMA PROPRANOLOL CONCENTRATIONS

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1 No correlation was found between the rate of gastric emptying and peak plasma propranolol concentrations in six hypertensive patients after single oral doses of 80 mg.

2 In four normal subjects given oral propranolol the peak plasma concentration was highest when a simultaneous injection of metoclopramide and lowest when propantheline was given. The mean time to peak was 1.5 h after metoclopramide, 2.8 h after normal saline and 4.5 h after propantheline.

3 Gastric emptying has some influence on the time of peak plasma propranolol concentrations but individual variation in its bioavailability is determined mainly by first-pass metabolism in the liver.

Introduction

Marked individual differences in peak plasma propranolol concentrations have been described after both single and multiple oral dosing (McLean & Deane, 1970; Shand, Nuckolls & Oates, 1970; Evans & Shand, 1973). These have been attributed to differences in extraction and metabolism of propranolol during the 'first-pass' through the liver (Shand & Rangno, 1972; George, Orme, Buranapong, Macerlean, Breckenridge & Dollery, 1976). There is, however, evidence that metabolism at the first-pass can be saturated; thus, the rate of drug absorption which governs the rate of presentation of propranolol to the liver could determine the amount reaching the systemic circulation unchanged (bioavailability). If so, individual differences in the rate of gastric emptying might be expected to influence peak plasma propranolol concentrations. We have, therefore, attempted to elucidate the relative contribution of variations in gastric emptying and first-pass metabolism to individual differences in plasma propranolol concentrations.

Methods

Six hypertensive patients (four female, two male) aged 48–60 years who were receiving regular propranolol gave informed consent to take part in the first study. Each was asked to discontinue their propranolol 24 h prior to the study. After an overnight fast, propranolol (80 mg) was administered orally with a standard breakfast labelled with 100 μCi ^{129}Cs on zirconium phosphate. A venous cannula was inserted in a forearm vein and blood samples were drawn prior to administration of propranolol and at 15 min intervals thereafter for 2 h. The patient was then positioned under a gamma camera and gastric emptying studied using the technique of Jones, Clark, Kocak, Cox & Glass (1970). The half-time of gastric emptying was derived from a regression of the logarithm of radioactivity measuring in the gastric area with time using the method of least squares. This measurement was later related to the peak plasma concentration and the time at which it occurred; the latter being derived from the concentration-time curve.

In the second study, four healthy male volunteers aged 31–34 years received propranolol (80 mg) orally on three occasions, each separated by at least 7 days. At the time of taking propranolol an i.v. injection of normal saline, metoclopramide (10 mg) or propantheline (30 mg) was given. Venous blood samples were collected at 0.5, 1, 1.5, 2, 4, 6 and 8 h after dosing. Plasma propranolol concentrations were estimated in all blood samples using the fluorometric technique of Shand *et al.* (1970).

Results

There were wide inter-individual differences in the maximum plasma concentrations seen after oral dosing; these ranged from 24–185 mg/ml. However,

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in the hypertensive patients there was no correlation between the rate of gastric emptying and either the time to peak or the concentration attained (Table 1). In contrast, peak plasma concentration of propranolol was highest in all four normal subjects after metoclopramide and lowest in all but one after propantheline. The mean time taken to reach these values was 1.5 h after metoclopramide compared 2.8 h with normal saline and 4.5 h after propantheline (Table 2). Pharmacological alteration in the rate of gastric empyting produced 1.6–3.5-fold differences in the peak plasma concentration, but there was no relationship between peak values obtained after normal saline and those seen following metoclopramide or propantheline.

Discussion

The present studies confirm that wide individual differences in peak plasma propranolol concentrations occur after oral dosing. In addition, they show that in individual subjects the rate of gastric emptying, as influenced by anticholinergic drugs or metoclopramide, has some effect on the height of peak concentration and the time at which this occurs. Nonetheless, in a group of patients no correlation was seen between gastric emptying and the bioavailability of propranolol. From this we conclude that individual variation in the bioavailability of propranolol is determined mainly by first-pass metabolism in the liver, rather than by differences in gastric emptying.

Table 1 Gastric emptying and plasma propranolol concentrations after oral dosing (80 mg)

		Plasma propranolol	
Patient	*Gastric emptying* $T_{\frac{1}{2}}$ *(min)*	*Peak concentration (mg/ml)*	*Time to peak (min)*
1	108	24.0	93
2	65	87.4	90
3	95	185.0	60
4	58	40.0	120
5	70	43.0	105
6	95	56.3	120

Table 2 Peak plasma propranolol concentrations and time attained in four subjects after oral dosing (80 mg) plus normal saline, metoclopramide (10 mg) or propantheline (30 mg) i.v.

	Normal saline		*Metoclopramide*		*Propantheline*	
	Peak (ng/ml)	*Time (h)*	*Peak (ng/ml)*	*Time (h)*	*Peak (ng/ml)*	*Time (h)*
A	87.8	(1)	113.1	(1.5)	59.8	(6)
B	54.6	(4)	112.5	(2)	71.5	(2)
C	21.5	(2)	33.0	(2)	20.0	(6)
D	69.0	(4)	105.8	(0.5)	30.0	(4)
Mean	53.8	(2.8)	69.9	(1.5)	41.8	(4.5)

References

EVANS, G.H. & SHAND, D.G. (1973). Disposition of propranolol. V. Drug accumulation and steady-state concentrations during chronic oral administration in man. *Clin. Pharmac. Ther.*, **14**, 487–493.

McLEAN, C.E. & DEANE, B.C. (1970). Propranolol dose determinants including blood levels studies. *Angiology*, **21**, 536–545.

JONES, T., CLARK, J.C., KOCAK, N., COX, A.G. & GLASS, H.I. (1970). Measurement of gastric emptying using the scintillation camera and ^{129}Cs. *Radiology*, **43**, 537–541.

GEORGE, C.F., ORME, M.L'E., BURANAPONG, P., MACERLEAN, D., BRECKENRIDGE, A.M. & DOLLERY, C.T. (1976). Contribution of the liver to overall elimination of propranolol. *J. Pharmacok. Biopharm.*, **4**, 17–27.

SHAND, D.G., NUCKOLLS, E.M. & OATES, J.A. (1970). Plasma propranolol levels in adults with observations in four children. *Clin. Pharmac. Ther.*, **11**, 112–120.

SHAND, D.G. & RANGNO, R.E. (1972). The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology*, **7**, 159–168.

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