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Absorption of propranolol and practolol in coeliac disease[1]

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SUMMARY Plasma concentrations of propranolol and practolol were measured in patients with coeliac disease and normal subjects. The mean plasma propranolol concentration in the coeliac patients was higher throughout the period of study, the differences being significant at one, six, and eight hours. The plasma concentration profile of practolol in the coeliacs followed a similar pattern but lagged behind that of the normal subjects. A possible reason for these differences is an alteration in the rate of drug diffusion across the atrophic mucosa of the upper jejunum in coeliac disease. Analysis of the results of the propranolol study suggests that an increase in the rate of absorption combined with saturation of first pass extraction may account for the increased plasma concentrations of unchanged propranolol found in coeliac disease. These abnormalities of drug absorption do not appear to be related to the duration of treatment with a gluten free diet.

Earlier studies (Parsons *et al.*, 1974a; Parsons *et al.*, 1974b; Parsons and Kaye, 1974) have demonstrated significant differences from normal in the plasma concentrations and urinary excretion of a number of drugs given to patients with coeliac disease. There are probably several factors responsible for the altered patterns of antibiotic absorption that we have previously demonstrated in this condition (Parsons *et al.*, 1975). One way of delineating the abnormality of drug absorption is to compare the plasma concentrations produced by chemically related compounds in coeliac disease with those produced by the same drugs in normal individuals. Underlying factors controlling the degree of drug absorption (Hogben *et al.*, 1959; Brodie, 1964) may each be individually assessed by comparing related drugs that differ from one another by a single characteristic—for example, molecular weight, pKa, degree of lipid solubility. For these reasons, we decided to measure the plasma concentrations of propranolol and practolol, two drugs fulfilling these criteria.

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Methods

SUBJECTS AND PATIENTS

Fourteen patients (six males and eight females; mean (± SEM) height 172·01 ± 2·38cm, weight 64·56 ± 3·40 kg; age 45 ± 4·8 years) with coeliac disease confirmed by small intestinal biopsy at the time of diagnosis and clinical response to withdrawal of gluten, were compared with 10 normal subjects (five males, five females; mean (± SEM) height 173·17 ± 2·82 cm, weight 67·86 ± 3·65 kg, age 27 ± 1·9 years). At the time of study, the patients with coeliac disease, who had all been receiving a gluten free diet for periods ranging from two months to 18 years, were judged clinically to be in remission. Clinical, haematological, and biochemical details are given in Table 1.

Approval of the Ethical Committee of Guy's Hospital Medical School and the written informed consent of each participant were obtained before the study. Both groups had normal laboratory values for haemoglobin, total and differential white blood count, red cell morphology, ESR (Westergren), blood urea, total and differential proteins and electrphoretic strip, serum electrolytes, calcium, phosphate, alkaline phosphatase, total and indirect bilirubin, serum iron and creatinine clearances. These haematological and biochemical results were obtain-

		Patient (sex and age)											
		PE (F)31	TB (M)48	KRO (F)	AG (M)40	SH (F)22	KW (M)21	KRI (F)54	HA (M)62	GR (F)61	YP (F)41	EM (F)69	MH (M)44	AC (M)42
Time on gluten free diet (yr)		0·9	0·9	0·25	0·7	1·1	10	3	1·4	2·1	4	12	0·5	2
Parameter	Normal range													
Haemoglobin	g/dl	19·0	14·0	13·9	14·4	15·0	16·0	14·0	15·4	11·2	14·5	13·6	14·5	15·7
Film		N	N	N	N	N	N	N	N	N	N	N	N	N
ESR (mm) Westergren	<20 mm/h	10	14	3	2	15	5	3	5	8	13	6	6	1
Serum B_{12}	200-850 pg/ml	190	335	190	345	154	235	630	230	1680	1140	275	660	305
Serum folate	5-20 ng/ml	4·9	12·4	4·9	8·4	1·9	6·9	5·2	>25	2 2	2·5	6·6	8·4	3·6
Total proteins	5·9-7·5 g/100 ml	7·5	6·5	6·1	6·6	6·3	7·8	7·4	6·4	6·2	6·9	6·9	6·4	7·3
Albumin	3·0-4·6 g/100 ml	4·1	3·4	3·2	4·4	3·4	5·6	4·3	3·8	3·8	3·6	3·4	4·1	4·7
Globulin	2·0-3·8 g/100 ml	3·4	3·1	1·9	2·2	2·9	2·2	3·1	2·6	2·4	3·3	3·5	2·3	2·6
Electrophoresis		NAD	NAD		NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
Serum calcium	8·3-10·4 mg/100 ml	9·7	9·4	9·6		9·3	9·7	12·0	10·6	8·8	9·6		9·3	10·0
Serum phosphate	2·5-4·7 mg/100 ml	2·1	2·7	3·6		3·6	3·0	3·5	2 4	2·9	2·2		3·5	3·8
Alkaline phosphatase	1-15 KAU%	6	14	9	11	8	8	11	6	15	9	8	6	7

Table 1 *Clinical haematological, and biochemical details of adult patients with coeliac disease at time of study*
N: normal

ed by standard laboratory methods. No participant received any other drug before or during the course of the study period. Each experiment was separated from the subsequent one by a period of not less than seven days.

SAMPLING AND ANALYSIS

After a 12 hour fast, blood samples were collected before and at 30 minutes, one, one and a half, two, four, six, eight hours and, during the practolol study, at 10 hours, after the administration of tablets of either propranolol (40 mg) or practolol (200 mg) which were given with 50 ml water. Eight of the coeliac patients (four male and four female) and nine of the normal subjects (five male and four female) received both propranolol and practolol. Plasma from the centrifuged blood samples was stored at −20°C until analysed. Fluids were permitted after one hour and food after the two hour sample had been collected.

Total plasma propranolol was measured by the method of Shand *et al.* (1970). This fluorimetric method is specific for propranolol and does not measure metabolites such as the pharmacologically active 4-OH propranolol (Paterson *et al.*, 1970). Total plasma practolol was measured by the spectrophotometric method of Turner *et al.* (1971). Practolol is a beta-adrenergic blocking agent that is virtually unmetabolised in man (Bodem and Chidsey, 1973).

Results

The mean (± SEM) plasma concentrations of propranolol and practolol in the normal subjects and coeliac patients are given in Table 2.

This raw data has been further analysed by 'curve fitting' techniques based on the method of Wagner and Nelson (1964) from which the values for the computer predicted peak plasma concentration (C_{max}), the time at which it occurred (T_{max}), the time after entry of the drug into the systemic circulation for its plasma concentration to rise from zero to C_{max} (T_{asc}), and the time for C_{max} to fall to zero (T_{desc}), together with the overall area under the

Timing (h)	Group		Student's t test P
	Normal (n = 10)	Adult coeliac disease (n = 11)	
	Mean (± SEM) Plasma propranolol concentration (ng/ml)		
½	5·17 ± 2·63	11·55 ± 2·84	NS
1	20·28 ± 7·46	38·90 ± 6·93	<0·05
1½	24·20 ± 6·14	42·11 ± 9·49	NS
2	24·55 ± 6·33	40·68 ± 8·72	NS
4	14·60 ± 4·03	22·96 ± 5·27	NS
6	6·45 ± 1·90	14·55 ± 4·09	<0·05
8	5·25 ± 1·82	10·00 ± 2·95	<0·05
	Mean (± SEM) Plasma practolol concentration (μg/ml)		
½	0·64 ± 0·14	0·17 ± 0·03	<0·0005
1	0·99 ± 0·17	0·57 ± 0·10	<0·025
½	1·22 ± 0·26	0·79 ± 0·13	NS
	1·35 ± 0·22	1·04 ± 0·15	NS
	·25 ± 0·12	1·40 ± 0·12	NS
	1·01 ± 0·11	1·10 ± 0·10	NS
8	0·84 ± 0·08	0·87 ± 0·08	NS
10	0·66 ± 0·06	0·66 ± 0·05	NS

Table 2 *Plasma concentrations of propranolol and practolol in normal subjects and coeliac disease. (Mean ± SEM)*

plasma concentration/time curve for propranolol and practolol have been calculated (Table 3).

The values for the lag time, absorption (Ka), and elimination (Ke) rate constants, the apparent volume of distribution (practolol only), and the area under the plasma concentration/time curve for these drugs calculated by another programme (Saunders and Natunen, 1973) are given in Table 4.

The mean plasma concentration of propranolol in the coeliac patients was higher at all sampling times than the comparable value for the normal subjects. This increase was significant ($P < 0.05$) at one, six, and eight hours. Although C_{max} of propranolol in the coeliacs (48·70 ± 8·01 ng/ml) was considerably higher than that of the normal subjects (33·12 ± 6·64 ng/ml), this difference was just outside the limits of statistical significance. The computer calculated area under the curve for propranolol in the coeliac group (228·2 ng.ml^{-1}h and 265·34 ± 55·10 ng.ml^{-1}h) were double ($P < 0.01$) those of the normal subjects (122·4 ng.ml^{-1}h and 147·08 ± 35·91 ng.ml^{-1}h).

The small differences in the area under the curve calculated by these two programmes is due to differences in mathematical methodology.

The plasma concentration/time profile for practolol in the coeliac patients followed a similar outline but was delayed behind that of the normal subjects. This delay was due to prolongation of the lag time in the coeliac patients.

Statistical parameter	*Normal subjects*	*Coeliac disease*	*Student's t test P*
Propranolol			
C_{max} (ng/ml)	33·12 ± 6·64	48·70 ± 8·01	NS
T_{max} (h)	2·14 ± 0·31	1·58 ± 0·12	<0·05
T_{asc} (h)	1·16 ± 0·19	0·77 ± 0·07	<0·05
T_{desc} (h)	4·73 ± 0·45	4·79 ± 0·50	NS
Area under curve (ng.ml^{-1}h)	147·08 ± 35·91	265·34 ± 55·10	NS
Practolol			
C_{max} (μg/ml)	1·47 ± 0·17	1·41 ± 0·12	NS
T_{max} (h)	3·11 ± 0·41	3·89 ± 0·32	NS
T_{asc} (h)	0·86 ± 0·14	1·35 ± 0·14	<0·0125
T_{desc} (h)	9·23 ± 0·67	9·58 ± 0·47	NS
Area under curve (μg.ml^{-1}h)	15·47 ± 1·86	13·36 ± 1·11	NS

Table 3 *Computer predicted parameters calculated by programme of Wagner and Nelson (1964) for normal subjects and coeliac patients*

Statistical parameter	*Propranolol*		*Practolol*	
	Normal subjects	*Coeliac disease*	*Normal subjects*	*Coeliac disease*
Absorption rate constant (Ka)	0·97	1·34*	0·60	0·38†
Lag time (h)	0·38	0·38	0·00	0·34†
Apparent volume of distribution (D) in litres	—	—	103·6	106·2
Area under curve (ng.ml^{-1}h)	122·4	228·2*		
(μg.ml^{-1}h)			16·18	15·46
Elimination rate constant (Ke)	0·256	0·208*	0·106	0·106

Table 4 *Computer predicted values as calculated by programme of Saunders and Natunen (1973) for absorption rate constant (Ka), lag time, apparent volume of distribution, area under curve (AUC), and elimination rate constant (Ke) for propranolol and practolol in normal subjects and coeliac disease*

*$P < 0.05$ (Student's t test).
†$P < 0.01$ (Student's t test).

Discussion

Although propranolol and practolol are pharmacologically and structurally related beta-adrenoreceptor blocking drugs with similar molecular weights and pKa values (Figure), they differ considerably in their lipid solubility (Kaye *et al.*, 1973). They are therefore suitable drugs to indirectly determine the effect of the lipid solubility of a drug on its pattern of oral absorption.

At first sight, it might appear that at least two separate abnormalities operate in coeliac disease. The most likely explanation of the findings is a difference in the rate of drug diffusion across the abnormal upper jejunum in coeliac disease. The rates of absorption, distribution, metabolism, and excretion all simultaneously contribute to the final overall plasma concentration/time profile during blood level studies; these other factors *must* be considered before attributing the findings to differences in absorption.

TOTAL AMOUNT OF DRUG ABSORBED

Since, in man, orally administered propranolol is

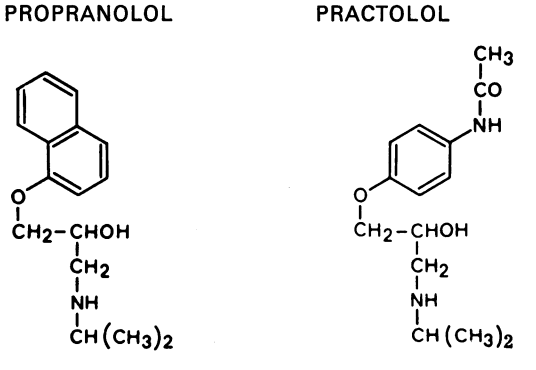

Figure *Structural formulae and pharmacology of propranolol and practolol. Molecular weight 295·8 (pr) 266·3 (pract). Partition coefficient 28·5 (pr) 0·19 (pract). pKa 9·45 (pr) 9·5 (pract).*

almost entirely (84-92%) absorbed (Paterson *et al.*, 1970), the higher *initial* plasma concentrations in the coeliacs and higher C_{max} are likely to be related to differences in the *rate* rather than in the *amount* of drug absorbed. This is confirmed by the significantly ($P < 0.05$) increased absorption rate constant (Ka) for propranolol (Table 4) in the coeliac patients (1·341) compared with that of the normal subjects (0·969).

The increased intraluminal pH which occurs in coeliac disease (Benn and Cooke, 1971) might marginally improve the bioavailability of basic drugs with alkaline pKas such as propranolol and practolol (Kaye *et al.*, 1973).

CHANGES IN VOLUME OF DISTRIBUTION

A reduction in the total blood volume in coeliac disease, which could explain our findings with propranolol, would be expected to produce similar changes after practolol. Since this did *not* occur, this explanation is unlikely. The identical value in both groups for the apparent volume of distribution of practolol, demonstrates that the differences are not due to differences in distribution volume between the groups. The value calculated in the normal subjects is marginally less than that determined experimentally in hypertensive subjects (Bodem and Chidsey, 1973).

CHANGES IN RENAL ELIMINATION OF THESE DRUGS

Since less than 1% of unchanged propranolol is normally excreted in the urine (Kaye *et al.*, 1973), the reduced ($P < 0.025$) Ke of propranolol in the coeliac patients (0·208) compared with the normal subjects (0·256) is unlikely to be related to impaired renal excretion.

This is the major route of elimination for practolol (Bodem and Chidsey, 1973), but Ke for this drug was identical in both groups. It is therefore highly improbable that the findings are due to altered renal elimination of either drug.

CHANGES IN HEPATIC ELIMINATION

Since practolol is normally entirely excreted unchanged in the urine (Bodem and Chidsey, 1973), its hepatic elimination is unimportant. The higher initial blood levels, C_{max}, and reduced Ke of propranolol in the coeliac patients are all related to the less rapid decline in plasma levels in this condition. These findings suggest that the hepatic clearance of propranolol is reduced in coeliac disease.

EFFECT OF AGE

There was no significant difference in the mean plasma propranolol concentration between the older and younger coeliac patients. Therefore, the findings in this condition cannot be explained by the age differences between the groups (Castleden *et al.*, 1975).

PROPOSED MECHANISM OF ABNORMAL ABSORPTION IN COELIAC DISEASE

Since the lag time for propranolol in both groups was identical and the lag time for practolol in the coeliac patients was increased, it is unlikely that differences in drug absorption would be explained by the more rapid gastric emptying that occurs in coeliac disease (Moberg and Carlberger, 1974). It is more likely that the rate of drug diffusion across the atrophic mucosa of the upper jejunum is altered. The earlier peak (1½ hours) and significantly ($P < 0.05$) earlier T_{max} for propranolol in the coeliac patients (1·58 hours) compared with that of the normal subjects (peak at two hours, T_{max} at 2·14 hours) was related to a significant ($P < 0.05$) shortening of the T_{asc} of propranolol from normal (1·16 ± 0·19 hours) to 0·77 ± 0·07 hours in the coeliac patients. After practolol, the opposite changes occurred—namely, a lengthening of the T_{asc} from the normal (0·86 ± 0·14 hours) to 1·35 ± 0·14 hours in the coeliac patients. These findings suggest that the transport of lipid soluble drugs such as propranolol is improved in coeliac disease, while the diffusion of water soluble drugs such as practolol across the abnormal jejunum is impaired in this condition. Impaired diffusion of practolol across the upper small bowel followed by improved absorption of previously unabsorbed drug further down across more normal mucosa is more likely to account for our findings with practolol in the coeliac patients.

An additional mechanism explaining our findings with propranolol is a reduction in its metabolic breakdown. The analytical method used was specific for propranolol and does not measure metabolites such as 4-OH propranolol. Several studies have shown that orally administered propranolol normally undergoes extensive first pass metabolism before the entry of propranolol and its pharmacologically active metabolite from the liver into the systemic circulation. First pass metabolism within the liver has been demonstrated in animals (Hayes and Cooper, 1971) and man (Paterson *et al.*, 1970; Shand and Rangno, 1972). Since propranolol is almost completely absorbed after oral administration, and first pass metabolism is largely confined to the liver, our findings with this drug in coeliac disease cannot be due to either an increase in the total amount absorbed, or reduced first pass metabolism within the abnormal gut mucosa of the coeliac patient, since propranolol is not extensively metabolised at this site (Paterson *et al.*, 1970).

Variable degrees of saturation of hepatic first pass metabolism during the early phase of intestinal

absorption is more likely to explain the wide range (Shand, 1974) associated with higher initial plasma concentrations and doubling of the area under the curve in the coeliac patients who have received this drug. More rapid absorption high up the jejunum across the abnormal mucosa of the whole dose of propranolol would increase its concentration within the portal circulation. The increased concentrations of propranolol presented to the liver from the portal circulation would then rapidly saturate first pass metabolism within the liver. In these circumstances, higher concentrations of unchanged propranolol would bypass normal hepatic first pass metabolism and enter the systemic circulation. This is the most likely explanation of the higher mean plasma concentrations, doubling of the area under the curve, and reduced T_{asc} after the administration of propranolol to patients with coeliac disease.

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