

## The effect of propranolol on paracetamol metabolism in man

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Ten healthy volunteers were treated for 4 days with 160 mg propranolol HCl and placebo in random order. At the end of each treatment salivary antipyrine kinetics and the plasma kinetics and urinary excretion of paracetamol and its major metabolites were measured following a 1500 mg oral dose. Propranolol prolonged the half-life of antipyrine by  $11 \pm 5\%$  (mean  $\pm$  s.e. mean) and lowered its clearance by  $14 \pm 3\%$  ( $P < 0.05$ ). Propranolol increased the half-life of paracetamol by  $25 \pm 12\%$  ( $P < 0.05$ ) and lowered its clearance by  $14 \pm 3\%$  ( $P < 0.05$ ). Propranolol decreased the partial clearance of paracetamol to its cysteine and mercapturate derivatives by  $16 \pm 3\%$  ( $P < 0.05$ ) and  $32 \pm 7\%$  ( $P < 0.05$ ), respectively. The partial clearance to the glucuronide conjugate was decreased by  $27 \pm 6\%$  ( $P < 0.05$ ), whereas that to sulphate was not changed significantly. Propranolol inhibits paracetamol metabolism predominantly through inhibition of the oxidation and glucuronidation pathways.

**Keywords** drug metabolism drug interaction propranolol paracetamol antipyrine

### Introduction

Since paracetamol is oxidised to a hepatotoxic intermediate metabolite *N*-acetyl *p*-benzoquinoneimine (Corcoran *et al.*, 1980; Meredith & Goulding, 1980), interactions with drugs that induce hepatic mono-oxygenases (Mitchell *et al.*, 1983; Perucca & Richens, 1979; Prescott *et al.*, 1981) and those that inhibit them (Mitchell *et al.*, 1984; Sanchez-Martinez *et al.*, 1985) are of interest.

Propranolol inhibits the metabolism of chlorpromazine (Peet *et al.*, 1980), lignocaine (Ochs *et al.*, 1980) and theophylline (Conrad & Nyman, 1980; Miners *et al.*, 1985) and, in common with some other  $\beta$ -adrenoceptor antagonists, antipyrine (Bax *et al.*, 1983; Greenblatt *et al.*, 1978; Parker *et al.*, 1984). The inhibition of oxidative metabolism by propranolol is related to its lipid solubility (Bax *et al.*, 1981; Deacon *et al.*, 1983), it may be selective for different forms of cytochrome P450 and is possibly concentration dependent (Miners *et al.*, 1984).

In animal studies propranolol in large doses has a protective effect against paracetamol-induced hepatic necrosis (Bax *et al.*, 1983; Legors, 1976). However, in a study of six individuals a relatively small dose of propranolol (80 mg daily for 6 days) did not affect the kinetics of paracetamol (Sanchez-Martinez *et al.*, 1985).

The aim of this study was to re-investigate the effect of propranolol on paracetamol disposition in man. In order to confirm the effect of propranolol on drug metabolising capacity a measurement of antipyrine kinetics was incorporated in the study design.

### Method

#### Subjects

Six males and four females, all clinically healthy, aged between 21 and 32 years and weighing from 51 to 85 kg (median 68 kg) participated in the

study which was approved by the Bristol and Weston Health Authority Ethics Committee. All were non-smokers, used alcohol in moderation and did not take other drugs, including the oral contraceptive.

### Study design

The study was a double-blind, crossover investigation comprising two periods of 5 days each separated by 12 days. Subjects received in a random order either racemic propranolol HCl 80 mg or matched placebo tablets twice daily for 4 days. Subjects refrained from taking alcohol during the study and reported to the clinical laboratory at 09.00 h after an overnight fast on days 4 and 5 of each treatment period.

On day 4 a single oral dose of paracetamol (1500 mg) was administered and the subjects continued to fast for 2 h. Venous blood samples (5 ml) were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 h. A complete urine collection was made for the first 24 h following drug administration.

On day 5 the subjects received a single oral dose of 600 mg antipyrine. Saliva (2 ml) was obtained at 0, 3, 6, 9, 12 and 24 h. All plasma samples were separated immediately and together with aliquots of the urine and saliva samples they were frozen and stored at  $-20^{\circ}\text{C}$  until assayed.

Antipyrine was assayed in saliva by h.p.l.c. (Danhof *et al.*, 1979). Paracetamol and its metabolites in plasma and urine were assayed by the h.p.l.c. method of Adriaenssens & Prescott (1978) modified by the use of metacetamol as internal standard. The mobile phase was 0.1 M potassium dihydrogen phosphate, 98% v/v formic acid and propan-2-ol (100:0.16:1.5 v/v/v). This method was able to measure paracetamol and its metabolites at  $0.1\text{ }\mu\text{g ml}^{-1}$  at a signal to noise ratio of 2:1 or better. The inter-assay coefficients of variation for paracetamol and all the metabolites were no greater than 7% at  $2\text{ }\mu\text{g ml}^{-1}$ , 4% at  $10\text{ }\mu\text{g ml}^{-1}$  and 3% at  $50\text{ }\mu\text{g ml}^{-1}$ . The paracetamol metabolites used as standards were donated by Sterling Winthrop Laboratories (Alnwick). The standard metabolite solutions were prepared and stored at  $-20^{\circ}\text{C}$  for 8 weeks during which time repeated assay against freshly prepared solutions showed no evidence of instability. All urine samples were assayed within 6 weeks of collection.

### Pharmacokinetic analysis

The plasma elimination half-life ( $t_{1/2}$ ) of paracetamol was computed by least squares linear

regression of the terminal part of the log drug concentration-time curve. The area under the plasma drug concentration-time profile (AUC) was calculated as follows: the area up to the end of sampling was calculated using the linear trapezoidal rule and the remaining area was extrapolated to infinity using the terminal log drug concentration-time slope. The systemic clearance of paracetamol could not be assessed in the absence of a measurement of bioavailability. However, the oral clearance ( $\text{CL}_{\text{po}}$ ) was estimated from:

$$\text{CL}_{\text{po}} = \text{Dose}/\text{AUC}$$

The partial clearance of paracetamol to each of its metabolites ( $\text{CL}_m$ ) was calculated from

$$\text{CL}_m = \frac{\text{Ae}(m)}{\text{AUC}}$$

where  $\text{Ae}(m)$  = Amount of metabolite recovered in urine.

### Statistical analysis

Student's *t*-test for paired data was used to compare measurements on propranolol with those on placebo.

## Results

All subjects completed the study without adverse effects. One or more urine collections had been collected incorrectly by three subjects and their urinary results were excluded from the analysis.

### Antipyrine kinetics

Propranolol increased the elimination half-life of antipyrine from  $11.2 \pm 2.5\text{ h}$  (mean  $\pm$  s.d.) to  $12.4 \pm 3.5\text{ h}$  ( $P < 0.05$ ) and decreased its clearance from  $58.1 \pm 19.3\text{ ml min}^{-1}$  to  $51.5 \pm 18.3\text{ ml min}^{-1}$  ( $P < 0.05$ ) compared with placebo.

### Paracetamol and metabolites in plasma and urine

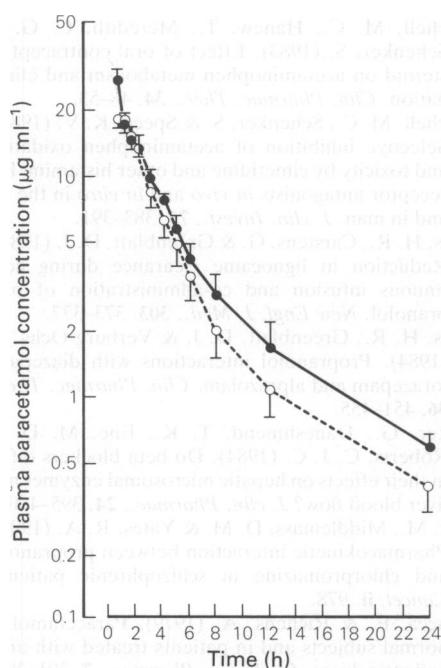
The plasma concentration of paracetamol reached a peak of  $27.0 \pm 10.8\text{ }\mu\text{g ml}^{-1}$  after propranolol compared with  $18.0 \pm 6.1\text{ }\mu\text{g ml}^{-1}$  following placebo ( $P < 0.01$ ) (Figure 1). Propranolol increased the half-life of paracetamol from  $2.7 \pm 0.6$  to  $3.4 \pm 0.3\text{ h}$  ( $P < 0.05$ ) and lowered its oral clearance from  $364 \pm 92\text{ ml min}^{-1}$  to  $313 \pm 28\text{ ml min}^{-1}$  ( $P < 0.05$ ).

Propranolol decreased the partial clearance of paracetamol to the oxidised metabolites—the cysteine and mercapturate—by  $16 \pm 3\%$  and

**Table 1** Partial metabolic clearances of paracetamol metabolites and percentage recovery of administered dose in seven healthy volunteers ( $\text{ml min}^{-1}$ ; mean  $\pm$  s.d.)

	Glucuronide	Sulphate	Cysteine	Mercapturate	% Recovery
Placebo	241.0 $\pm$ 91.0	91.2 $\pm$ 19.6	9.2 $\pm$ 2.4	12.7 $\pm$ 3.7	77.9 $\pm$ 16.3
Propranolol	177.0 $\pm$ 66.9*	75.2 $\pm$ 19.5	7.7 $\pm$ 2.1*	8.0 $\pm$ 3.7*	88.3 $\pm$ 10.4

\* $P < 0.05$  compared with placebo; Student's  $t$ -test



**Figure 1** Plasma paracetamol concentrations following oral administration of 1500 mg paracetamol to 10 healthy subjects after treatment with placebo (○) or propranolol (●) for 4 days (mean  $\pm$  s.e. mean).

32  $\pm$  7% ( $P < 0.05$ ), respectively and to the glucuronide by 27  $\pm$  7% ( $P < 0.05$ ). However, the partial clearance of paracetamol to sulphate was not changed significantly by propranolol treatment (Table 1).

## Discussion

The results of this study suggest that the increase in the plasma half-life and the lowered clearance of paracetamol caused by propranolol are mainly due to inhibition of glucuronidation and oxidative pathways.

The dose of propranolol used in this study was shown to be sufficient to inhibit hepatic drug metabolising enzymes by the significant lowering of antipyrine clearance, although this was

less than that reported by others (Bax *et al.*, 1981; Greenblatt *et al.*, 1978).

The decreased oral clearance of paracetamol was in contrast to the findings of Sanchez-Martinez *et al.* (1985) who reported a lack of effect of propranolol at a dose of 80 mg once a day for 6 days on the kinetics of 1 g oral paracetamol. However, in that study no independent measurement of enzyme inhibition was made. In the present study we have used twice the dose of propranolol and have provided a positive control for enzyme inhibition by the changes in antipyrine clearance. The dose used may be critical as the extent of enzyme inhibition by propranolol is dose dependent (Miners *et al.*, 1985).

The decreased partial clearance to the cysteine and mercapturate metabolites suggests that propranolol significantly inhibits the oxidative pathway of paracetamol. Although the mean decrease in partial clearance to the mercapturate was greater than that to the cysteine derivative this was not significant. This mechanism may explain the observation that propranolol had a protective effect on paracetamol-induced hepatic necrosis in mice (Bax *et al.*, 1983; Legors, 1976). Propranolol significantly impaired the glucuronidation of paracetamol but sulphonation was not affected. This contrasts with the finding of Brunk *et al.* (1974) that propranolol did not inhibit the metabolism of morphine which mainly undergoes conjugation and with those of Ochs *et al.* (1984) and Hawksworth *et al.* (1984) who found a decrease in the clearance of diazepam (which undergoes oxidation to the *N*-desmethyl product) but no effect of propranolol on the kinetics of two benzodiazepines which are glucuronidated, namely lorazepam and alprazolam. These differences may reflect the fact that glucuronidation is carried out by several isoenzymes with varying substrate specificity (Dutton, 1966).

There are two possible implications of our findings. Thus, propranolol may afford some protection against paracetamol-induced hepatic damage and it may prolong the effect of paracetamol.

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