

## Differential effect of continuous administration of $\beta$ -adrenoceptor antagonists on antipyrine and phenytoin clearance

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1 Antipyrine (1000 mg orally) clearance was studied 3 days before treatment with either atenolol (50 mg twice daily), metoprolol (100 mg twice daily), propranolol (80 mg twice daily) or placebo, and at day 5 and 18 during treatment. Phenytoin (100 mg intravenously) clearance was measured on days 0, 7 and 21 during treatment.

2 Antipyrine clearance was decreased by about 20% after 5 days of treatment with either propranolol or atenolol and this decrease persisted after 18 days of treatment. Antipyrine clearance did not change during treatment with either metoprolol or placebo. Phenytoin clearance did not change during any of the treatments.

**Keywords** antipyrine atenolol metoprolol phenytoin propranolol

### Introduction

$\beta$ -adrenoceptor antagonists impair the elimination of several drugs (Editorial, 1984). It has been assumed that these interactions result mainly from changes in hepatic drug metabolism. Propranolol and metoprolol have been reported to decrease hepatic drug metabolism (Greenblatt *et al.*, 1978; Bax *et al.*, 1981; Tucker *et al.*, 1982) but the influence of atenolol is controversial. Daneshmend & Roberts (1982) found a decreased antipyrine clearance using a high dose of atenolol (100 mg twice daily) whereas Tucker *et al.* (1982) were not able to show any effect of 100 mg atenolol once daily for 3 days. It was also shown that penbutolol did not inhibit antipyrine clearance in man possibly due to the low dose of penbutolol given and a low availability of penbutolol at the enzyme site (Bax *et al.*, 1985). Where inhibitory effects of  $\beta$ -adrenoceptor antagonists have been demonstrated, it is not known whether they are transient or persistent.

Phenytoin clearance has not previously been

studied during treatment with  $\beta$ -adrenoceptor antagonists.

The purpose of the present study was to investigate the effect of both 1 and 3 weeks treatment with  $\beta$ -adrenoceptor antagonists (atenolol, metoprolol and propranolol) on antipyrine and phenytoin clearance in a placebo controlled study.

### Methods

Thirty-two non-smoking male volunteers, age 24 years (21-25) (median (interquartile range)) were randomized into four groups of eight and given 3 weeks treatment with either atenolol 50 mg twice daily (cardioselective, hydrophilic), metoprolol 100 mg twice daily (cardioselective, lipophilic), propranolol 80 mg twice daily (non-cardioselective, lipophilic) or placebo (1 tablet twice daily). The doses are equipotent in anti-hypertensive effect and comparable with those

used in previous studies (Bax *et al.*, 1981; Tucker *et al.*, 1982).

During the treatment period the drug was given at 08.00 h. Compliance was tested after 1 and 3 weeks, measuring the fasting serum concentrations of the  $\beta$ -adrenoceptor antagonists and the pulse rate after a 20 min period of rest (09.00 h). The protocol was approved by the local ethics committee and the subjects were included in the study after written informed consent.

All blood samples and saliva samples in this study were coded before being analyzed.

#### Antipyrine clearance

The clearance of antipyrine was measured 3 days before the clearance of phenytoin. Antipyrine clearance was determined before the start of treatment with  $\beta$ -adrenoceptor antagonists or placebo, again after 5 days treatment and then after 18 days treatment. Antipyrine (1000 mg) was given orally and after 24 h a salivary sample was collected for measurement of the drug by h.p.l.c. (Pilsgaard & Poulsen, 1984). Thus, the clearance was determined by the one-sample technique (Poulsen & Loft, 1988). This technique has been extensively evaluated by Døssing *et al.* (1983) and it has been shown that calculating the volume of distribution this way does not bias the clearance estimate (Poulsen & Loft, 1988).

#### Phenytoin clearance

The clearance of phenytoin was measured before and after 7 and 21 days of treatment with  $\beta$ -adrenoceptor antagonists or placebo. Phenytoin (100 mg) to which 20  $\mu$ Ci [ $4$ - $^{14}$ C]-labelled phenytoin was added, was injected intravenously and blood samples were taken after 3, 6, 9 and 12 h to measure the radioactivity (Hansen *et al.*, 1968). Pharmacokinetic parameters were calculated according to an open one-compartment model as described by Lumholtz *et al.* (1975).

#### Statistical methods

Differences within groups were tested using Wilcoxon's signed rank sum test and the differences between the groups were tested by the Kruskal-Wallis test.

## Results

#### Antipyrine clearance

The median antipyrine clearance before treatment was similar in the four groups (Table 1) as was the estimated volume of distribution ( $V$ , (e.g. 50 l (48–54) (median range)) in the metoprolol treated group). Antipyrine clearance was decreased by 20% (–7 to 38) (median (range)) after 5 days and 29% (–27 to 62) (median (range)) after 18 days treatment with propranolol ( $P < 0.05$ ); it decreased by 17% (–3 to 48) (median (range)) after 5 days and 24% (0 to 32) (median (range)) after 18 days treatment with atenolol ( $P < 0.05$ ) (Table 1). Significant differences were not apparent after either 5 or 18 days treatment with metoprolol or placebo.

The estimated values of  $V$  did not change in any of the groups during treatment.

#### Phenytoin clearance

The median values of phenytoin clearance before treatment were similar in the four groups (Table 2) as were the estimates of  $V$  (e.g. 48 l (40–60) (median (range)) in the metoprolol treated group before treatment). Phenytoin clearance was unchanged after 1 and 3 weeks treatment in all four groups (Table 2). No correlation was found between the clearance of antipyrine and phenytoin, either before treatment or when comparing the changes in antipyrine and phenytoin clearance of the individual subjects after either 1 or 3 weeks of treatment.

All subjects on  $\beta$ -adrenoceptor antagonists had measurable concentrations of the drugs in

**Table 1** Clearance ( $\text{ml min}^{-1}$ ) of antipyrine in four groups of eight young healthy men before and after 1 and 3 weeks treatment with either one of three different  $\beta$ -adrenoceptor antagonists or placebo (median (range)):

	Day 0	1 week	3 weeks
Atenolol	68.5 (40.8–105.7)	53.8 (31.6–87.8)*	50.4 (32.1–80.2)*
Metoprolol	65.0 (46.7–98.7)	64.1 (49.7–76.8)	58.4 (50.2–80.0)
Propranolol	59.1 (43.4–91.7)	49.5 (41.4–64.6)*	49.6 (33.0–61.8)*
Placebo	47.7 (38.6–89.8)	51.2 (40.9–82.6)	50.0 (38.4–63.6)

\* $P < 0.05$

**Table 2** Clearance ( $\text{ml min}^{-1}$ ) of phenytoin in four groups of eight young healthy men before and after 1 and 3 weeks treatment with either one of three different  $\beta$ -adrenoceptor antagonists or placebo (median (range)):

	Day 0	1 week	3 weeks
Atenolol	37.6 (27.5–71.5)	43.3 (24.7–79.6)	50.3 (28.7–76.9)
Metoprolol	55.2 (28.8–73.7)	52.4 (22.1–71.2)	52.8 (26.5–76.6)
Propranolol	56.4 (35.8–71.9)	49.7 (41.5–77.5)	52.7 (40.4–69.8)
Placebo	41.6 (25.7–65.8)	45.1 (32.1–63.4)	40.6 (28.4–69.9)

the blood (atenolol 1538 (628–2668), metoprolol 274 (178–490) and propranolol 392 (116–474)  $\text{nmol l}^{-1}$  (median (interquartile range))). No correlation was found between the concentration of any of the drugs and the antipyrine or phenytoin clearance or changes in clearance. A significant decrease in the resting pulse rate was found after both 1 and 3 weeks treatment (data not shown) in all subjects except during the placebo treatment.

## Discussion

In this study we have investigated whether changes in antipyrine clearance during 3 weeks of treatment with  $\beta$ -adrenoceptor antagonists are persistent or transient.

In agreement with others (Bax *et al.*, 1981, 1985), we found a decrease in antipyrine clearance after 5 days treatment with propranolol. This decrease persisted for a further 2 weeks of treatment. However, contrary to the results of a previous study (Bax *et al.*, 1981), we did not find any change in antipyrine clearance during treatment with metoprolol. The same doses of metoprolol and propranolol were used in both studies. However, while Bax *et al.* (1981) found a decrease in antipyrine clearance after 5 days treatment of about 18% for metoprolol and 37% for propranolol decreases in our study were only 8% and 19% respectively after 5 days treatment. After 18 days of treatment antipyrine clearance was still unchanged (median 1%) in our metoprolol treated group.

Although previous studies have failed to show an interaction between atenolol 100 mg daily and antipyrine clearance (Tucker *et al.*, 1982), we found a consistent decrease in antipyrine clearance both after 5 days, as also demonstrated by Danshmend & Roberts (1982) using atenolol 100 mg twice daily and 18 days of treatment. Furthermore, this was of the same magnitude as that found in the propranolol

treated subjects. We have no explanation for these discrepancies, except that atenolol might be partly metabolized in the liver (Perrild *et al.*, 1983).

Antipyrine clearance was estimated from a single saliva sample taken 24 h after the dose. Saliva and plasma are in equilibrium due to simple passive diffusion, and since antipyrine is not bound to plasma proteins, there is no reason to believe that  $\beta$ -adrenoceptor antagonists affect its transfer from plasma to saliva. The antipyrine clearance varied between individuals from 30  $\text{ml min}^{-1}$  to 100  $\text{ml min}^{-1}$ , probably due to inherited differences in clearance, nevertheless, individuals had persistently high or low antipyrine clearance throughout the study, in accordance with previous studies showing a low variation in the intraindividual clearance of antipyrine (Døssing *et al.*, 1983).

Phenytoin clearance was unchanged during the 3 weeks treatment with  $\beta$ -adrenoceptor antagonists. Whereas phenytoin undergoes aromatic hydroxylation (Hansen *et al.*, 1978), possibly a 4-hydroxylation (Sloan *et al.*, 1981), antipyrine is both *N*-dealkylated, 3-methylhydroxylated and 4-hydroxylated. Propranolol and metoprolol are also 4-hydroxylated and *N*-dealkylated (Clark, 1985; Poulsen & Loft, 1988). Propranolol has previously been shown to decrease antipyrine clearance by decreasing its 4-hydroxylation (Greenblatt *et al.*, 1978). Thus it seems difficult to predict drug-interaction *in vivo* from knowledge on biochemical pathways of metabolism.

In conclusion, we have demonstrated that changes in antipyrine or phenytoin clearance are persistent for 3 weeks during treatment with atenolol, metoprolol or propranolol, indicating that over this time period, no contra-regulatory changes occur in their metabolism.

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