LACK OF EFFECT OF ATENOLOL ON ANTIPYRINE CLEARANCE

Greenblatt *et al.* (1978) showed a 48% lowering of mean antipyrine clearance in six healthy subjects following oral administration of propranolol HC1 400 mg in divided doses over 36 h. Bax *et al.* (1981) found that propranolol HC1 80 mg twice daily for 5 days and metoprolol tartrate 100 mg twice daily for 5 days significantly lowered mean antipyrine clearance in five healthy subjects by 37% and 18%, respectively. Subsequently, Daneshmend & Roberts (1982) failed to show such a large decrease in antipyrine clearance in 13 healthy subjects following propranolol treatment. A regimen of 40 mg propranolol HC1 three times daily for 3 days significantly lowered mean antipyrine clearance by 15%. A similar change was found after atenolol 100 mg twice daily and labetalol HC1 100 mg three times daily for 3 days.

The similar effects on antipyrine clearance produced by propranolol and atenolol in the latter study were surprising in view of evidence suggesting a strong correlation between the extent of enzyme inhibition produced by β -adrenoceptor blockers and their lipid-solubility (Deacon *et al.*, 1981). Atenolol has an octanol/buffer pH 7.4 partition coefficient at 37°C of 0.013 whereas that of propranolol is 22.4. In addition, the metabolism of propranolol is extensive whereas atenolol is excreted almost entirely unchanged in the urine. However, the doses of the β -adrenoceptor blockers used in the study of Daneshmend & Roberts (1982) were not based upon therapeutic equivalence and may have weighed against the inhibitory effects of propranolol and in favour of atenolol. Furthermore, dosage of the β -adrenoceptor blockers was not continued following the administration of antipyrine and this may account, in part, for the relatively small degree of inhibition that was observed. In view of these findings, we have re-examined the possibility that atenolol, in a standard daily dose of 100 mg, might inhibit the metabolic clearance of antipyrine.

Five healthy male subjects (aged 26–39 years; weight 62–86 kg) received an oral dose of 750 mg antipyrine on two occasions separated by a 2–3 week interval. One dose served as a control and the other followed the oral administration of atenolol, 100 mg daily for 3 days. Atenolol was continued for a further two days, until sampling was complete. The order of the control and atenolol-treatment studies was randomised. None of the subjects were smokers and they were taking no other drugs. Antipyrine concentrations in saliva samples collected at 3, 6, 9, 12, 15, 24, 27 and 30 h after dosage and in plasma samples taken at 6 and 30 h after dosage were measured by h.p.l.c. (Bax *et al.*, 1981). The elimination half-life ($t_{1/2}$) of antipyrine was calculated from least squares

regression of the log salivary drug concentration-time profile; an apparent volume of distribution (V) was calculated from the ratio of dose to the extrapolated salivary drug concentration at zero time and clearance was calculated as the product of $V \times 0.693/t_{1/2}$. The percentage decrease in exercise heart rate following a 1 min step test performed before and on the third day of treatment with atenolol was used to assess the extent of β -adrenoceptor blockade. In the control period the exercise heart rates in four subjects were all over 155 beats min^{-1} . The fifth subject was an athlete whose exercise heart rate was 129 beats min^{-1} .

Treatment with atenolol had no effect on the clearance, volume of distribution or elimination half-life of antipyrine (Table 1). Values of r^2 for the fit of a monoexponential equation to the salivary antipyrine

Table 1 Parameters describing the kinetics of antipyrine determined from measurements of salivary drug concentrations.

Parameter	Subject	Control study	Atenolol-treatment study
Clearance (l h^{-1})	1	3.45	3.91
	2	2.84	2.89
	3	2.99	3.24
	4	2.79	2.56
	5	2.74	2.65
	Mean	2.96	3.05
	s.d.	0.29	0.54
Volume of distribution (l)	1	43	44
	2	51	50
	3	52	59
	4	46	39
	5	52	54
	Mean	49	49
	s.d.	4	8
Elimination half-life (h)	1	8.6	7.8
	2	12.5	12.1
	3	12.0	12.7
	4	11.3	10.6
	5	13.2	14.2
	Mean	11.5	11.4
	s.d.	1.7	2.2

No statistically significant differences were detected between control and atenolol-treatment values using the paired *t*-test.

data sets ranged from 0.901 to 0.993 (median, 0.975). Salivary/plasma antipyrine concentration ratios were similar for the control and atenolol-treatment studies and averaged 1.04 ± 0.18 s.d. and 0.93 ± 0.17 s.d.,

respectively. The mean percentage decrease in exercise heart rate produced by atenolol was 30 ± 3 s.d. %.

We conclude that, in a standard therapeutic dose, atenolol does not inhibit the metabolism of antipyrine in man. Taken together with our earlier observations concerning the inhibitory effects of propranolol and metoprolol this finding supports the proposed relationship between the lipid-solubility of β -adrenoceptor blockers and their ability to inhibit oxidative drug metabolism.

References

- BAX, N.D.S., LENNARD, M.S. & TUCKER, G.T. (1981). Inhibition of antipyrine metabolism by β -adrenoceptor antagonists. *Br. J. clin. Pharmac.*, **12**, 779–984.
- DANESHMEND, T.K. & ROBERTS, C.J.C. (1982). The short term effects of propranolol, atenolol and labetalol on antipyrine kinetics in normal subjects. *Br. J. clin. Pharmac.*, **13**, 817–820.
- DEACON, C.S., LENNARD, M.S., BAX, N.D.S., WOODS, H.F. & TUCKER, G.T. (1981). Inhibition of oxidative drug metabolism by β -adrenoceptor antagonists is related to their lipid-solubility. *Br. J. clin. Pharmac.*, **12**, 429–430.
- GREENBLATT, D.J., FRANKE, K. & HUFFMAN, D.H. (1978). Impairment of antipyrine clearance in humans by propranolol. *Circulation*, **57**, 1161–1164.

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

Received June 21, 1982,
accepted July 20, 1982

EFFECT OF LABETALOL, AN α -AND β -ADRENOCEPTOR ANTAGONIST, ON GASTRIC ACID AND GASTRIN SECRETION IN MAN

Labetalol is a recently introduced antihypertensive agent with both α - and β -adrenoceptor blocking properties (Frishman & Halprin, 1979). The available data obtained from *in vitro* as well as *in vivo* studies indicate that labetalol is markedly weaker than phentolamine at α -adrenoceptors and is relatively less potent than propranolol at β -adrenoceptors (Brittain & Levy, 1976). It has been reported that subcutaneous injection of labetalol significantly reduced basal gastric acid secretion in pylorus-ligated rats (Sharma *et al.*, 1978). Therefore, we have evaluated the effect of intravenous labetalol administration on basal and pentagastrin-stimulated gastric acid secretion and on basal serum gastrin concentration in man.

Fourteen mildly hypertensive, non-obese men, aged 28–60 years, who had no history of gastrointestinal disease, volunteered for the study. Informed consent was obtained from all subjects and the research was carried out according to the Declaration of Helsinki. After an overnight fast, a nasogastric tube was passed into the stomach and its position was checked by fluoroscopy. Gastric juice was collected by continuous aspiration and pooled in 15 min fractions. After the first 45 min portion had been discarded, basal ($n = 7$) and submaximal pentagastrin ($0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ infused intravenously) – stimulated

($n = 7$) gastric acid secretion were evaluated for 120 min; labetalol 100 mg was infused intravenously for 10 min from 60 to 70 min. Gastric acid concentration was measured by titration with 0.1 M NaOH to pH 7.0 using a semiautomatic titrator.

Serum gastrin concentration was determined by radioimmunoassay (Caldara *et al.*, 1978) before and after labetalol infusion in the seven subjects in whom basal gastric acid secretion was evaluated.

Statistical analysis was performed by using the two-tailed paired Student's *t*-test after a log transformation of the data. The gastric secretion of the first hour, estimated as the mean of two 30 min periods, was compared with the acidity measured in two 30 min periods after labetalol injection.

No side effects were reported other than a transient scalp tingling in two subjects. Labetalol infusion was associated with reduction in heart rate ($P < 0.05$ at 90–120 min) and systolic as well as diastolic ($P < 0.01$ at 75–120 min) blood pressure in comparison with the preinfusion values (data not shown). Basal and pentagastrin-stimulated gastric acid output decreased promptly and significantly after labetalol infusion as compared to basal period; since only a slight but not significant decrease in acid concentration was observed, this reduction was mainly due to a fall in the volume of juice (Table 1). No significant correla-