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.

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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-

Table 1 Effect (mean $\pm$ s.e. mean) of labetalol infusion (100 mg in 10 min) on basal and submaximal pentagastrin ($0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$)-stimulated gastric acid output and juice volume in 7 mildly hypertensive patients respectively. Labetalol was infused from 60 to 70 min. Asterisks indicate significant differences v the basal period estimated as the mean of two 30 min periods (* $P < 0.05$; ** $P < 0.01$).

		0-60 2	Time (min) 60-90	90-120
Acid output (mmol/30 min)	Basal	1.4 ± 0.2	$0.7 \pm 0.1^{**}$	$0.8 \pm 0.1^{**}$
	Stimulated	6.1 ± 0.9	$3.8 \pm 0.6^*$	$4.7 \pm 0.8^*$
Volume (ml/30 min)	Basal	29 ± 6.2	$18 \pm 2.4^*$	$20 \pm 3.0^*$
	Stimulated	58 ± 8.3	$39 \pm 7.2^*$	$43 \pm 7.5^*$
Acid concentration (mmol/l)	Basal	50.3 ± 8.1	39.4 ± 6.2	41 ± 6.5
	Stimulated	110 ± 10.4	91 ± 10	96 ± 8.3

tion between the values of acid secretion and heart rate or blood pressure was found. Serum gastrin level did not change (Table 2).

These findings confirm the above mentioned study performed in rats showing inhibition of basal gastric acid secretion by subcutaneous labetalol injection at dose levels between 1-30 mg/kg body weight (Sharma *et al.*, 1978). The dose used in the present investigation (about 1.5 mg/kg body weight) is slightly higher than the lowest effective dose in the rat, although infused intravenously, and is commonly used in clinical practice because of its efficacy in reducing blood pressure.

The role of α - and β -adrenoceptors in the regulation of gastric acid secretion has been widely investigated in the experimental animals and in man with sometimes conflicting results. However the general agreement is that both stimulation and blockade of either α - and β -receptors inhibit gastric acid secretion, with predominant influence of the stimulatory effect (Pradhan & Wingate, 1966; Bass & Patterson, 1967; Christensen & Stadil, 1976a; Christensen & Stadil, 1976b; Daly *et al.*, 1978). The combined action on α - and β -adrenoceptors had not previously been evaluated. The present findings as well as those obtained in the rats (Sharma *et al.*, 1978) show that concomitant α - and β -adrenoceptor blockade by labetalol administration is again associated with in-

hibition of gastric acid secretion, and indicate that adrenoceptor blockade is effective in lowering gastric acidity. However, it cannot be excluded that this effect may be primarily of pharmacological rather than physiological significance. To explain the paradoxically similar effect of both stimulation and blockade of adrenoceptors on gastric acidity, it has been suggested that receptor blockade may act through increase of plasma concentration or biological half-life of catecholamines (Bass & Patterson, 1967). It has in fact been reported that labetalol administration significantly augments plasma nor-adrenaline concentration (Christensen *et al.*, 1978). The finding of unchanged fasting serum gastrin levels following labetalol infusion is in agreement with some data obtained after administration of α - (Barbieri *et al.*, 1980) and β -adrenoceptor blocking drugs in man, although reduced gastrin levels have also been reported by others (Hayes *et al.*, 1972; Kronborg *et al.*, 1974; Seino *et al.*, 1980).

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Table 2 Effect (mean $\pm$ s.e. mean) of labetalol infusion (100 mg in 10 min) on serum gastrin levels in 7 mildly hypertensive patients. Labetalol was infused from 60 to 70 min.

	Time (min)					
	0	60	75	90	105	120
Serum gastrin (pg/ml)	65 ± 10	68 ± 8	62 ± 8	67 ± 7	65 ± 8	63 ± 7

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ABSORPTION OF MEXILETINE AFTER TREATMENT WITH GASTRIC ANTACIDS

Mexiletine is a lignocaine-like antiarrhythmic drug. Due to its high bioavailability (between 80 and 88%: Prescott *et al.*, Clements, 1977; Campbell *et al.*, 1978b; Häselbarth *et al.*, 1981) it can also be administered orally. Side effects of oral mexiletine therapy include gastrointestinal disturbances such as indigestion, vomiting, and nausea (Campbell *et al.*, 1978a; Opie, 1980). Such symptoms are often treated with gastric antacids. However, no information is available as to whether antacids might influence the gastrointestinal absorption of mexiletine.

Therefore, we investigated in normal subjects the effect of a commonly prescribed antacid on the absorption of this antiarrhythmic drug.

The study was designed as a randomized single-blind crossover trial with respect to the administration of the antacid. Ten volunteers (5 male and 5 female) aged between 19 and 43 years (29 ± 7 years, mean $\pm$ s.d.) and with bodyweights between 60.6 and 105.3 kg (75.9 ± 12.1 kg) took part. They underwent a general clinical examination and were considered healthy.

After an overnight fast the subjects ingested

either 12 ml of a commercially available antacid suspension (Gelusil liquid®), containing 1.87 g magnesium-aluminium-silicatehydrate, neutralizing capacity 7.1 mEq/5 ml, pH 3.5, 37° C; Holtermüller *et al.*, 1981) or 12 ml of a non-buffering suspension (7.2 mg $\text{Ca}_3(\text{PO}_4)_2$, 120 mg aerosil, 30 mg TiO_2 , 108 mg methylcellulose; pH 8.0) of similar taste and colour. One hour later they swallowed two capsules of mexiletine (Mexitil®, each containing 200 mg mexiletine-hydrochloride) with 100 ml of water. Two hours later the subjects ate a standard breakfast. Blood samples were drawn from a forearm vein through an indwelling catheter before and 0.5, 1, 2, 3, 4, 6, 8, 16, 24, and 34 h after administration of mexiletine. Crossover studies were performed about 4 weeks later.

Plasma concentrations of mexiletine were determined in the laboratories of Bioscientia (Ingelheim, FRG), according to the gas chromatographic method described by Häselbarth *et al.* (1981). Plasma concentration-time data was fitted according to a two-compartment oral pharmacokinetic model, assuming first order absorption with correction for lag-time