the frog spinal cord is in agreement with the earlier observations of Davidoff & Sears (1974) who suggested that this compound has a selective blocking action at central excitatory synapses. Later results (Potashner 1978; Ault & Evans 1978) suggest that the depressant action is confined to terminals which release excitatory amino acids.

The present finding that transmission in the vas deferens is resistant to baclofen further emphasizes the selective action of this drug. It does not support the involvement of a β-phenethylamine receptor in this action (Curtis et al 1974) since β-phenethylamine, a sympathomimetic amine which acts indirectly by stimulating α-adrenoceptors in the mouse vas, would be expected to depress transmission in the vas deferens (Ambache et al 1972).

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Elimination of drugs by active intestinal transport

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When drugs are recovered in the faeces after intravenous administration, it is often assumed that they have undergone excretion in the bile. However, with some drugs, metronidazole and ouabain for example, there is evidence that their removal in the faeces may be due, in part, to elimination across the intestinal wall (Ings et al 1975; Selden et al 1974). Acebutolol (DL-1-(2-acetyl-4-butyramidophenoxy)-2-hydroxy-3-isopropylamino propane hydrochloride), a β-adrenoceptor antagonist, is another drug which is handled in this manner. After intravenous administration to the dog, 35% can be recovered in the faeces and accumulation has been shown to occur in isolated sacs of canine intestine in vivo (Collins & George 1976). However, the mechanism of intestinal elimination of this (and other drugs) is not understood. We have, therefore, undertaken experiments both in vivo and in vitro in an attempt to elucidate this process.

The role of active and passive processes was initially determined by a study of the transport of [^{14}C]acebutolol (labelled on the ring carbonyl) against a concentration gradient in the dog. Three mongrel bitches (12–15·5 kg) were anaesthetized and intestinal loops measuring 15–17 cm were prepared in the manner described by George et al (1974). Each dog received an i.v. injection of [^{14}C]acebutolol 2–2·5 mg kg^{-1} (20–25 μ Ci) in 10 ml 0·9% w/v NaCl (saline) followed by a continuous infusion of half this amount per hour (since the half-life of the drug in this species is 1 h). Forty minutes after the bolus dose the loops were perfused for periods each lasting 10 min alternately with saline at 37 °C at a rate of 2·2 ml min^{-1} or 10^{-3} M acebutolol solution in saline for a total of 40 min. Blood samples were obtained from the aorta at 10 min intervals and radioactivity was measured by liquid scintillation counting. The nature of radioactive material in plasma was investigated by h.p.l.c. Perfusate from the loops was collected and the rates of elimination of [^{14}C]acebutolol were compared for the saline and acebutolol periods.

A further series of experiments was undertaken in vitro on segments of intestine from albino rats, ~250 g. Pairs of isolated everted intestinal sacs measuring 8 cm long were prepared from the upper 16 cm of the duodenum/jejunum. After adding [^{14}C]acebutolol solution (1 ml in Krebs) to the lumen these were incubated in Krebs bicarbonate solution and bubbled with 5% CO_2 in oxygen. One of each pair of sacs was treated with a possible inhibitor of active transport. In one series of experiments the temperature of the fluid surrounding the experimental loop was varied between 20 and 52 °C. In another, anoxia was produced by gassing with nitrogen: potential inhibitors which have been studied include cyanide 10^{-3} M, 2,4-dinitrophenol 10^{-4} M, ouabain 10^{-4} M, probenecid 10^{-3} M and ethacrynic acid 10^{-3} M. 3-*O*-Methylglucose and 2-deoxyglucose were tried as substitutes for glucose in the Krebs medium. Finally, the transport of acebutolol against a concentration gradient was studied at an initial concentration of 10^{-3} M acebutolol on both serosal and mucosal sides. Samples of incubate were removed at 15, 30, 45 and

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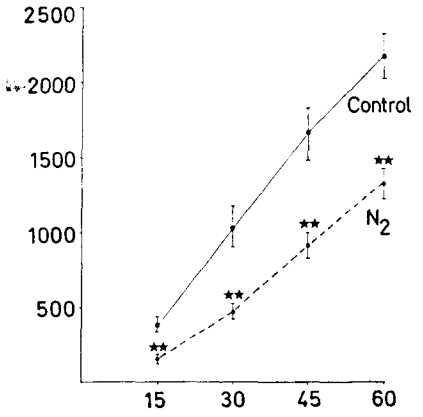

FIG. 1. The effect of nitrogen on the in vitro transfer of [^{14}C]acebutolol across isolated everted sacs of rat intestine. The 4 control sacs were incubated in Krebs solution (50 ml) at 37 °C and bubbled with 5% CO_2 in oxygen: the experimental sacs (4) were gassed with nitrogen. The results show the mean concentration ± standard error at each time, $^{**}P < 0.01$. Ordinate: d min^{-1} ml^{-1} in mucosal fluid. Abscissa: time (min).

60 min after the start of the experiment. The acebutolol content was analysed by liquid scintillation counting. The rate of transfer of drug from serosal to mucosal surface was compared for at least four sacs and analysed statistically by means of Student's *t*-test for paired data. In addition, for each sac the rate of transfer across the intestine was calculated from the regression of [^{14}C]-acebutolol content in the bathing medium on time (15–60 min). The slope of the regression line was then compared for the treated and control sacs.

The results of the dog experiments showed that a steady arterial blood concentration was achieved during the studies and that almost all of the material present was in the form of parent acebutolol (since no acetyl metabolite was detected in either plasma or loop contents). In these experiments, there was no evidence of a reduction in the rate of intestinal elimination of acebutolol when the loop was perfused with a high concentration of drug. The excretion rate was 1298 (s.d. 383) d min^{-1} during acebutolol perfusion compared with 1079 (s.d. 352) during saline perfusion.

The transfer of [^{14}C]acebutolol in vitro was temperature-dependent between 20 and 52 °C: at 25 °C the rate of transfer was 75% of that at 37 °C and rose to 173% at 52 °C. Treatment with nitrogen (Fig. 1), cyanide and 2,4-dinitrophenol significantly reduced the rate of transfer (see Table 1) but the combination of these treatments did not enhance the effects of cyanide. Ethacrynic acid caused a 33% reduction in the rate of acebutolol transfer, but ouabain (on either the serosal or mucosal surface), 3-*O*-methylglucose, 2-deoxyglucose and acebutolol in 10^{-3} M solution in the bath fluid were without effect.

Table 1. The effect of inhibitors and other additives on the transfer rate of acebutolol across the rat intestine.

Inhibitor or other additive	N	Rate of excretion* (%) compared with control (with s.d.)	*P* at 60 min
Nitrogen	4	60·2 (10·5)	<0·01
Cyanide 10^{-3} M	4	44·7 (19·2)	<0·01
2,4-Dinitrophenol 10^{-4}M	4	63·6 (12·8)	<0·05
N_2/Cyanide/DNP mixture	2	48·3 (12·1)	—
Ouabain 10^{-4}M	4	98·0 (10·5)	n.s.
Probenecid 10^{-3}M	5	113·9 (15·6)	n.s.
Ethacrynic acid 10^{-3}M	5	66·8 (11·5)	<0·05
3-*O*-Methylglucose	4	106·0 (17·4)	n.s.
2-Deoxyglucose	4	95·5 (5·2)	n.s.
Acebutolol 10^{-3}M	6	96·1 (22·2)	n.s.

* For each sac the rate of transfer across the intestine was calculated from the regression of [^{14}C]acebutolol content in the bathing medium on time (15–60 min). The slope of the regression line was then compared for the treated and control sacs.

The present results indicate that acebutolol elimination across the intestine is dependent on active transport since the transfer is effective against a concentration gradient both in vivo and in vitro, and is temperature-dependent. This process is dependent on tissue respiration as it is inhibited by cyanide, 2,4-dinitrophenol and the exclusion of oxygen. The inhibition of transfer caused by ethacrynic acid and the lack of effect of ouabain suggests the possibility that an electrogenic pump is involved (Wittembury 1968). The role of active transport across the intestinal wall on the elimination of other drugs is as yet unknown. However, this route may be potentially important in situations where elimination either via the kidneys or by metabolism is impaired.

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