tration of 35.5 ± 5.3 ng/ml was obtained, compared to 36.0 ± 4.3 ng/ml ($P > 0.05$) when administered with metoclopramide. The mean time to reach peak concentration was similar ($P > 0.05$) for LA propranolol (6.1 ± 0.4 h) and for LA propranolol plus metoclopramide (5.6 ± 0.5 h). The area under the curve for LA propranolol plus metoclopramide (501.2 ± 67.8 ng ml⁻¹ h) was slightly higher than for LA propranolol alone (434.5 ± 54.4 ng ml⁻¹ h). This difference was not statistically significant ($P > 0.05$). The similar bioavailability of propranolol calculated from the results of the two treatments is also indicated by the serum propranolol concentration-time curves in Figure 1.

The rate and extent of drug absorption is frequently affected by changes in gastric emptying and intestinal motility (Nimmo, 1973; Mayersohn, 1979). In particular, the rate of absorption of propranolol from a conventional formulation of the drug is signifi-

cantly increased by metoclopramide-induced changes in gastro-intestinal motility (George & Castleden, 1977). The results of the present study suggest that the bioavailability of propranolol from long acting propranolol is not significantly affected by increased gastro-intestinal motility and, in this regard, offers a distinct advantage over conventional formulations of the drug.

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COMPARISON OF THE DURATION OF EFFECT OF METOPROLOL AND A SUSTAINED RELEASE FORMULATION OF METOPROLOL (BETALOC-SA)

Several β -adrenoceptor blocking drugs have plasma elimination half-lives in the region of 2–5 h which necessitates their oral administration 2–4 times per day. These drugs include metoprolol, oxprenolol, acebutolol and propranolol. Although the once daily administration of the total dose of these drugs may be effective in the control of hypertension (Reybrouck, Amery, Fagard, Jousten, Lijnen & Meulepas, 1978; Douglas-Jones, Baber & Lee, 1978; Frick & Kala, 1980), there is minimal blockade of cardiac β -adrenoceptors 24 h after the dose. Once a day dosing regimes may not be effective in angina and cardiac arrhythmias (Frick & Kala, 1980). Recently a number of these drugs have become available in slow or delayed release formulations which are designed to prolong the plasma concentration after a dose and to maintain β -adrenergic receptor blockade for a longer period than occurs with the conventional formulation. Kendall and his colleagues (Quarterman, Kendall & Welling, 1979; Kendall, John, Quarterman &

Welling, 1980), have compared the plasma concentration and effect on an exercise tachycardia of 200 mg conventional metoprolol (Lopresor, Ciba-Geigy) and 200 mg slow release metoprolol (Slow Lopresor, Ciba-Geigy) in healthy volunteers. The peak plasma concentration after slow release metoprolol was less and occurred 1 h after the peak with conventional metoprolol but at 24 h there were only minimal plasma concentrations after both formulations. At 14 and 24 h after dosing, 200 mg conventional metoprolol did not produce a significant reduction in the exercise tachycardia in comparison to placebo; although the effect of 200 mg slow release metoprolol (Slow Lopresor) was significant at these times, there was no significant difference between the effects of the two formulations (Quarterman *et al.*, 1979).

Metoprolol is available in another slow-release formulation, Betaloc-SA, Astra, and apparently this formulation is different from that of Slow Lopresor. Each capsule of Betaloc-SA contains 200 mg meto-

prolol in the form of a Durule, Astra, which consists of active drug enclosed in a porous plastic shell. It is important that the efficacy and pharmacokinetics of Betaloc-SA are studied as this formulation is in current use in the United Kingdom.

Observations were made in five healthy male volunteers aged 18 to 33 years. The subjects were administered in random order after an over-night fast, placebo, 200 mg metoprolol (Betaloc, Astra) and 200 mg slow release metoprolol Durules (Betaloc-SA, Astra) with 1 week between treatments. The subjects exercised before and 2, 3, 6, 8, 24, 33 and 48 h after drug administration, by stepping on and off a box 46 cm high at the rate of 32 steps/min for 3 min. Heart rate was determined from Lead I of the electrocardiogram recorded within 5 s of completing the exercise. The effect of each treatment on the exercise heart rate was determined by expressing the reduction in exercise heart rate at each time interval as a percentage of the control (pre-drug) exercise heart rate (Carruthers, Shanks & McDevitt, 1976). Blood samples were withdrawn from a forearm vein before and at intervals after drug administration. The samples were centrifuged and the plasma stored at -20°C until analysed for metoprolol using the method described by Kinney (1981). This method uses a smaller amount of plasma and is more rapid than those described by Ervik (1975) and by Degen & Reiss (1976).

The mean control exercise heart rates in the five subjects before drug administration were 158.8 ± 8.0 , 154.8 ± 9.8 and 159.4 ± 7.4 beats/min in the placebo, metoprolol and metoprolol Durule groups respectively. These are not significantly different. The effects of the three treatments on exercise heart rate are given in Figure 1. There was no significant change

in the exercise heart rate during the 48 h after placebo administration. Two hours after metoprolol there was a $31 \pm 2.5\%$ reduction in the tachycardia. The effect of metoprolol declined rapidly so that at 24 h there was no effect on the exercise tachycardia. Two hours after metoprolol Durules, the exercise tachycardia was reduced by $27.2 \pm 1.4\%$; this effect is significantly less than that of metoprolol ($P < 0.05$). The effect of slow release formulation declined gradually throughout the period of observation. At 24 h there was a reduction in the tachycardia of $11.0 \pm 2.3\%$; this was significantly greater than the placebo group and the metoprolol group ($P < 0.05$).

Figure 2 The mean ($\pm$ s.e. mean, $n = 5$) plasma metoprolol concentrations after the oral administration of 200 mg metoprolol (●) and 200 mg metoprolol Durules (○).

The mean plasma concentrations after metoprolol and metoprolol Durules are given in Figure 2. The peak plasma concentration occurred 1.5 h after administration of metoprolol, after which it declined rapidly with an elimination half-life of 3.6 ± 0.6 h. After metoprolol Durules, the peak plasma concentration occurred at 1.5 h but at 103.6 ± 31.3 ng/ml was only one third that of conventional metoprolol. The plasma concentration changed little from 1 to 8 h and at this time it was 92.4 ± 36.8 ng/ml which was greater than the value at 8 h after conventional metoprolol (65.2 ± 28.1 ng/ml). There was a small decrease between 8 and 10 h and a more marked fall to 24 h when it was still greater than the value after metoprolol.

Metoprolol is rapidly metabolised in man, with a plasma elimination half-life of about 3 h (Quarterman *et al.*, 1979; Kendall *et al.*, 1980). As a result the duration of blockade of cardiac β -adrenoceptors assessed by reduction of an exercise tachycardia is short. Twenty-four hours after oral administration,

Figure 1 The mean ($\pm$ s.e. mean, $n = 5$) percentage reductions of an exercise tachycardia after the oral administration of placebo (▲), metoprolol 200 mg (●) and metoprolol Durules 200 mg (○).

200 mg metoprolol produced no effect on an exercise tachycardia (Quarterman *et al.*, 1979; Kendall *et al.*, 1980). A slow release preparation of metoprolol (Slow Lopresor) was developed to prolong the duration of action but in comparison with conventional metoprolol, no significant difference in the effects of the two formulations on an exercise tachycardia was observed (Quarterman *et al.*, 1979). The present studies confirm these earlier results with conventional metoprolol and also show that the slow release formulation (Durules) of metoprolol, Betaloc-SA, has a longer duration of effect than metoprolol and at 24 h produced a significantly greater reduction in an exercise tachycardia than metoprolol. Similar results have recently been described (Johnsson, Jordo, Lundborg, Regardh & Ronn, 1980). Thus this formulation shows a significant improvement in duration of action over conventional metoprolol which does not occur with Slow Lopresor. Slow Lopresor is not at present on the market in the United Kingdom, but as its formulation and duration of effect are different to those of Betaloc-SA confusion may arise if it does become available.

Although short acting β -adrenergic receptor blocking drugs may be effective in controlling arterial pressure in hypertension throughout a 24 h period

when the total daily dose is given as a single dose, there may be minimal blockade of cardiac β -receptors at the end of the dose interval (Reybrouck *et al.*, 1978). If it is believed that in such patients once daily dosing should maintain blockade of cardiac receptors throughout the 24 h, β -adrenoceptor blocking drugs with a long duration of action should be used. These include atenolol (Brown, Carruthers, Johnston, Kelly, McAinsh, McDevitt & Shanks, 1976), sotalol (Brown, Carruthers, Kelly, McDevitt & Shanks, 1976), nadolol (Dreyfuss, Brannick, Vukovich, Shaw & Willard, 1977) and long acting propranolol (Leahey, Neill, Varma & Shanks, 1980a,b). The present observations show that metoprolol used as Betaloc-SA belongs to this group.

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