Slow Release Beta-Adrenoceptor Blocking Drugs

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Beta adrenoceptor blocking drugs have been one of the most important group of drugs introduced for the treatment of hypertension during the last 20 years. They are effective and have a low incidence of adverse effects but, as the treatment of hypertension is usually life-long and must be taken regularly, patients may not remain compliant. However, the development of new drugs with a longer duration of action, and the availability of delayed release formulations, have led to the simplification of dosage regimens and greater attention has been focused recently on patient compliance.

**Patient Compliance**

The successful clinical use of beta adrenoceptor blocking drugs depends on patient compliance, which is influenced by the patient’s perception of the illness, the efficacy of the therapy[1, 2], the adverse effects of the drugs, the number of daily doses[3, 4] and the complexity of the dosing regimen[5, 6]. Good patient compliance is difficult to achieve: in 10 patients with refractory hypertension[7], nine were found to have a poor understanding of the meaning and relevance of hypertension, its prognosis and the reasons for treatment; three patients noted that they felt better when not taking anti-hypertensive therapy and eight were experiencing adverse effects. In a study[3] of 50 patients on anti-hypertensive treatment the authors showed that the more tablets the patients had to take in a day, the less likely they were to take them and that the most compliant patients reported the least adverse effects. Caldwell and his colleagues[8], while examining the reason for non-compliance in 42 hypertensive patients readmitted as emergencies, showed that 7 per cent discontinued treatment because of adverse effects. They also showed that patient compliance in the treatment of hypertension decreased with the number of years that the patients had been on treatment.

Several authors have suggested ways of improving compliance in patients with hypertension. Bullen[2] suggested that it could be improved by discussing with the patients some of the more common adverse effects they might experience, such as exacerbation of asthma and tiredness, both before therapy was started and during treatment. This might lead to an improvement in the patient’s understanding of the treatment and its action. Alternatively, Vidt[9] suggested that a more individualistic approach to each patient’s therapeutic programme would be beneficial. When using a combination of drugs, the constituents could be titrated to suit each patient’s requirements, thus minimising the incidence of distressing adverse effects. Compliance could also be regularly monitored by routine urine drug analysis[10]. However, other work[11] has indicated that improvement in follow-up may not in itself lead to better blood pressure control in hypertensive patients.

Although compliance is a multifactorial problem, it would appear that it can be improved by administering a preparation that is required once daily only. The main parameters determining whether a beta adrenoceptor blocking drug can be given once daily are the plasma elimination half-life of the drug, the dose of drug administered, the formulation (conventional or a slow release preparation), and the condition to be treated.

**Plasma Elimination Half-life**

The relationship between the plasma elimination half-life of a beta adrenoceptor blocking drug and the duration of cardiac beta adrenergic blockade can be demonstrated by studying the effect on exercise tachycardia. The increase in heart rate produced by severe exercise results largely from an increase in sympathetic drive to the heart, and reduction in the exercise heart rate is regarded as a sensitive and reproducible way of assessing cardiac beta adrenergic blockade in man[12, 13].

The results of a comparison of 40 mg betaxolol with propranolol 160 mg, oxprenolol 160 mg, sotalol 400 mg...
and atenolol 200 mg on exercise tachycardia showed similar maximum effects at 3 hours[14] (Table 1). However, there were striking differences in the duration of action. At 24 hours oxprenolol had no effect on the exercise tachycardia and had the shortest half-life of 3.6 ± 0.8 hours, propranolol produced a 12.1 ± 3.2 per cent reduction with a half-life of 6.3 ± 0.6, and atenolol and sotalol caused similar reductions in the exercise tachycardia at 24 hours and had similar plasma elimination half-lives (12.7 ± 1.9 and 10.4 ± 1.8 hours). Betaxolol had the longest half-life of 24.5 ± 6.8 hours and produced a 36.2 ± 2.6 per cent reduction in exercise tachycardia at 24 hours. In this study (Fig. 1) marked changes in plasma levels occurred with sotalol, oxprenolol, propranolol and atenolol, whereas the plasma concentrations of betaxolol did not change significantly between 2 and 24 hours.

### Dose of Drug

The effect of dose on the duration of action of beta-blocking drugs was demonstrated in a comparison of the effects of 25 mg, 50 mg, 100 mg, 200 mg atenolol and placebo on exercise tachycardia[15]. The maximum reduction in exercise heart rate occurred at 2-3 hours after each dose and ranged from 18.7 ± 2.8 per cent for 25 mg to 36.1 ± 1.7 per cent for 200 mg. The effect on exercise heart rate fell in a dose-dependent manner with time, and at 24 hours, 25 mg atenolol was not significantly different from placebo. However, 50 mg, 100 mg and 200 mg of atenolol still caused significant reductions in the exercise heart rate of 12.3 ± 3.5 per cent, 15.2 ± 2.6 per cent and 24.4 ± 1.1 per cent respectively at 24 hours. Similar dose effects were with sotalol[15] and betaxolol[14].

### Formulation

One method of prolonging the duration of action of beta adrenoceptor blocking drugs is to incorporate the active constituent into a slow-release mechanism. The beta adrenoceptor blocking drugs currently available in the UK in slow release formulations are: metoprolol 200 mg (Betaloc SA, Astra; Lopressor SR, Geigy), propranolol 160 mg (Inderal LA, ICI), oxprenolol 160 mg (Slow Trasicor, Ciba) and oxprenolol 160 mg combined with 0.25 mg cyclopenthiazide (Trasidrex, Ciba).

The formulations of these slow-release preparations are different. Metoprolol is formulated as a Durule, consisting of a porous plastic matrix with the drug contained in a three-dimensional network of pores. The active substance is released by diffusion from the Durule during its passage along the gastrointestinal tract and is normally released in 6 to 8 hours. The long-acting propranolol preparation consists of a hard gelatine capsule filled with a multitude of 1 mm spheroids containing 160 mg of propranolol hydrochloride individually coated with a semi-permeable membrane to allow diffusion release of the drug in a controlled manner[16]. In vitro dissolution studies indicated that the time taken for 90 per cent of the propranolol in the long-acting dose to dissolve is more than 12 hours. The slow-release oxprenolol preparation consists of 160 mg oxprenolol, the individual crystals of oxprenolol being coated with an inert polymer of high molecular weight to form small granules. After the addition of excipients these granules are compressed into tablets. The compression reduces the surface area of the crystals and granules, thus delaying absorption. The tablets are finally coated with a semi-permeable film that further reduces the release rate, especially in the first hour. In comparison, the slow-release formulation of Trasidrex consists of 160 mg of oxprenolol in a sustained release core and 0.25 mg of cyclopenthiazide in the tablet coating.

The effect of formulation on duration of the beta-blocking action of these drugs has been determined by comparing the plasma concentration and effect on exercise tachycardia of propranolol 160 mg given as conventional tablets (Inderal) and in the sustained-release form (Inderal LA)[17]. The results are summarised in Fig. 2(a,b). Peak plasma levels occurred at 2 hours after conventional propranolol and 8 hours after slow-release.

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**Table 1.** The plasma elimination half-lives (T½ (h)) and percentage reductions in exercise heart rate (EHR) at 3 and 24 hours after the oral administration of placebo, 40 mg betaxolol, 200 mg atenolol, 400 mg sotalol, 160 mg propranolol and 160 mg oxprenolol.

|          | % reduction in EHR 3 hr | % reduction in EHR 24 hr | T½ (h) |
|----------|------------------------|--------------------------|--------|
| Placebo  | 1.4 ± 1.2              | 3.0 ± 1.1                | —      |
| Betaxolol 40 mg | 41.0 ± 3.0          | 36.2 ± 2.6               | 24.5 ± 6.8 |
| Atenolol 200 mg | 34.3 ± 3.8         | 18.5 ± 1.6               | 12.7 ± 1.9 |
| Sotalol 400 mg | 37.8 ± 2.7           | 19.0 ± 2.3               | 10.4 ± 1.8 |
| Oxprenolol 160 mg | 32.4 ± 1.9          | 12.1 ± 3.2               | 6.3 ± 0.6  |
| Oxprenolol 160 mg | 31.7 ± 4.3          | 3.6 ± 1.9                | 3.6 ± 0.8  |

**Fig. 1.** The mean (± SE mean) plasma concentrations at 1, 2, 3, 6, 8, 10, 12, 24, 33 and 48 hours betaxolol (SL 75212), oxprenolol, propranolol, atenolol and sotalol after oral administration of 40 mg betaxolol (○), 160 mg oxprenolol (●), 160 mg propranolol (△), 200 mg atenolol (■) and 400 mg sotalol (△)[14]. (Courtesy British Journal of Clinical Pharmacology.)
propranolol, the peak plasma concentration with the former being four times that of the latter. At 24 hours the plasma level was significantly higher after long-acting propranolol. The maximum reductions in exercise heart rate were 27.8 ± 2.4 per cent at 3 hours and 32.0 ± 1.7 per cent at 6 hours after conventional and long-acting propranolol respectively; at 24 hours the effects were 9.24 ± 1.5 per cent and 16.8 ± 2.2 per cent respectively. After eight days of repeated administration of propranolol 160 mg daily, the maximum reduction in exercise heart rate after conventional propranolol ranged from 33-37 per cent and 24 hours after the dose from 12-21 per cent; the corresponding values after long-acting propranolol were 27-31 per cent and 20-25 per cent respectively. These results suggest that the effect at 24 hours increased on chronic dosing: Barnett and his colleagues[18] also showed in a similar study that the effect 24 hours after dosing increased during a seven day period.

Single-dose comparisons have been made with conventional and slow-release formulations of metoprolol — Betaloc SA[19, 20] and Lopressor SR[21]. The results of these studies showed a significant reduction in exercise heart rate at 24 hours with the sustained-release preparation, but not with the conventional preparation. Chronic studies, using conventional metoprolol and the two slow-release formulations, Betaloc[22] and Lopressor[23], showed differing results between the preparations. The degree of beta-blockade with the conventional and sustained release preparations of Lopressor and Slow Lopressor was similar and the plasma levels achieved with the two regimens were not significantly different. However, when Betaloc and Betaloc SA were administered for three days, the maximum plasma concentration of metoprolol following the slow release preparation was 429 ± 84.0 mmol/litre and 914 ± 132 mmol/litre following the conventional preparation. The corresponding minimum plasma levels were 43.9 ± 15.9 and 23.3 ± 9.3 mmol/litre, i.e., plasma levels fluctuated less with the sustained release formulation.

This difference between the sustained action and the conventional preparations cannot be demonstrated with all formulations. It was shown in a comparison of oxprenolol, slow-release oxprenolol, and the combined oxprenolol and diuretic preparation[24] that no significant differences occurred in the plasma concentration produced by the three formulations during a 24-hour period; furthermore, at 24 hours the effects of the three preparations on exercise heart rate were not significantly different from placebo. West and his co-workers[25] compared conventional and slow-release oxprenolol, and showed that at 24 hours the effects on post-exercise pulse rates for both preparations were not significantly different from placebo. Bobik et al.[26] compared the effects of 160 mg oxprenolol conventional tablets and 160 mg slow-release oxprenolol on the exercise heart rate in healthy subjects. The results indicated that while the maximum plasma levels following the sustained release preparation were half those of the conventional preparation, at 24 hours the oxprenolol plasma concentration for both preparations was only 5 μg/ml. Despite the different time courses of the oxprenolol plasma concentrations, there was little differ-

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**Fig. 2(a).** The mean (± SE mean) plasma propranolol concentrations during the 24-hour period after the oral administration of 160 mg propranolol (○) and 160 mg LA propranolol (△) to each of 10 subjects[17]. (Courtesy British Journal of Clinical Pharmacology.)

**Fig. 2(b).** The mean (± SE mean) percentage reductions of an exercise tachycardia during the 24-hour period after the oral administration of 160 mg propranolol (○) and 160 mg LA propranolol (△) to each of nine subjects[17]. (Courtesy British Journal of Clinical Pharmacology.)
ence between the time course of inhibition of exercise rate for the two formulations over 24 hours.

Studies in healthy volunteers have indicated that the duration of action of drugs that block beta adrenergic receptors can be extended by using drugs with longer plasma elimination half-lives, or by giving higher doses of the drugs with shorter half-lives, or by using drugs with sustained-release characteristics. Two advantages of using drugs with sustained-release characteristics are first, that patient compliance is improved by once daily administration, and second, that the slow-release formulation leads to substantially less variation in drug plasma levels, and consequently produces a more even control of heart rate and blood pressure. The slow-release formulation also avoids peaks in plasma concentration, which may be associated with adverse effects, and plasma troughs, when the drug levels are below the therapeutic threshold.

Clinical Implications of long Duration of Action

Although studies of healthy volunteers give a good indication of the cardiovascular effects of beta adrenoceptor blocking drugs, it is important to study their efficacy in patients with the relevant clinical conditions. The beneficial effect of beta-blocking drugs in angina results from blockade of cardiac beta adrenergic receptors and the effect of beta-blockade parallels inhibition of exercise tachycardia. Thus, in angina, a beta-blocking drug, if it is to be administered as a single daily dose, must be effective over 24 hours. Equally, since the effect of beta-blocking drugs on cardiac arrhythmias probably results from blockade of beta receptors rather than from the membrane stabilising activity, the anti-arrhythmic efficacy of beta-blocking drugs would be expected to parallel their ability to inhibit exercise tachycardia.

However, the relationship between the duration of action of a beta-blocking drug and the control of raised arterial pressure is more complex. The administration of a single daily dose of most conventional beta adrenoceptor blocking drugs satisfactorily controls arterial pressure over 24 hours, despite a low level of cardiac beta-blockade at the end of the dose interval[17, 27].

Angina

Slow-release preparations of metoprolol, propranolol and oxprenolol have been studied in angina. Uusitalo and Keyrilainen[28] compared conventional and long-acting metoprolol (Durules) in a placebo-controlled double-blind cross-over study in 16 patients with typical, exercise-induced angina. The patients underwent a baseline run-in period when they received placebo for two weeks and subsequently entered a cross-over period with one month of 100 mg conventional metoprolol twice daily or one metoprolol Durule daily. Standardised bicycle ergometer exercise tests, with heart rate and blood pressure measurements, were performed two hours after all the treatments, 12 hours after conventional metoprolol and 24 hours after Durules. The patients kept diaries of their anginal attacks throughout the study. The results indicated that there were no significant differences in total work (30-watt increase in work-load every six minutes starting at 30 watts) between conventional metoprolol and Durules when the 12 and 24 hours post-dose values were compared. Heart rate and systolic blood pressure during exercise were significantly decreased 24 hours after Durules, as compared with placebo.

Metoprolol 200 mg (Durules) given once daily was compared with conventional metoprolol 100 mg given twice daily, in a group of 10 patients with stable angina pectoris[29]. Similar changes in heart rate and blood pressure at rest and at the end of exercise were noted in the different treatment groups at two, 12 and 24 hours, together with similar exercise tolerance levels. The ST segment depression was of the same order in the two treatments at two hours after the dose, but there was significantly less change at 24 hours after the Durule formulation in comparison with the results 12 hours after conventional metoprolol. Houtzagers[30] evaluated the efficacy and duration of action of metoprolol Durules administered once daily in angina and concluded that the Durules were clinically effective in 11 out of 15 patients, the drug having significant anti-anginal effects at 24 hours. In a multicentre study of four weeks' duration involving 618 patients with inadequately controlled, stable angina pectoris, 92 per cent of whom had failed to respond adequately to other anti-anginal treatment, 200 mg of metoprolol given in a slow-release formulation produced a 39 per cent reduction in angina attack rate and a 43 per cent fall in glyceryl trinitrate consumption. Half the patients were aged 60 years or over and these patients had a similar response[31].

Halkin and colleagues[32] demonstrated that, in angina patients, long-acting propranolol was as effective as multiple doses of conventional propranolol when assessed by exercise tolerance, glyceryl trinitrate consumption, anginal attack rate and ST segment depression. In a double-blind cross-over study[33] the investigators used 24-hour Holter monitoring to compare the control of heart rate in 14 angina patients taking a slow-release formulation of propranolol (160 mg or 320 mg daily as a single dose) and conventional propranolol (40 mg or 80 mg four times daily). The results indicated that the number of anginal attacks and glyceryl trinitrate tablets taken were similar in all four treatment periods. However, the number of adverse effects reported was significantly lower and patient compliance (as assessed by pill counts) was significantly better with the once-daily slow-release preparation of propranolol.

Scott and Balnave[34], in a double-blind cross-over study of 12 patients with moderately severe angina pectoris, reported no significant differences in exercise tolerance or blood levels between propranolol long-acting 160 mg and conventional propranolol 40 mg four times a day, and McIlmoyle et al.[35] also reported that in patients with angina the long-acting preparation was as effective as multiple doses of conventional propranolol.

Forrest's group[36], reporting the results of a multi-centre hospital out-patient study in which 102 patients with stable angina (previously successfully controlled on multi-dose beta-blocker therapy) were treated with once-daily oxprenolol, stated that 70 per cent of patients
achieved significant benefit from the single morning dose of 160 mg sustained-release oxprenolol, with a reduction in the number of anginal attacks and glyceryl trinitrate tablets consumed. The once-daily treatment pattern was preferred by 68 per cent of patients. Another study[37] also reported that oxprenolol 160 mg slow-release, given once daily, is a potent and well tolerated anti-anginal agent. Goldstraw et al.[38] treated six previously untreated male patients with angiographically-proven, uncomplicated, stable exercise-induced angina pectoris in a randomised double-blind study with placebo, conventional oxprenolol 160 mg twice daily and oxprenolol sustained-release 320 mg, and it was concluded that the sustained-release formulation offered advantages over the conventional formulation of oxprenolol in the treatment of patients with exercise-induced angina pectoris.

Hypertension

The relationship between duration of action of beta adrenoceptor blockade and control of raised arterial pressure is very complex. Of equal complexity is the mechanism of the hypotensive effect of these drugs. This was well illustrated by Reybrouck et al.[39] when they administered in random order to each of 16 hypertensive patients placebo or 300 mg of metoprolol daily, given either as a single dose or as 100 mg three times a day. With the multiple daily dosing regimen there was only a small difference between the trough and the two-hour plasma concentrations. However, the once-daily administration caused much greater fluctuations in plasma concentration, with higher peak plasma levels and lower trough values than were obtained with the multiple dosage regimen. These fluctuations in plasma concentrations were reflected in the level of beta-blockade achieved, as was demonstrated by the effect of the two-dosage regimens on the reduction of exercise tachycardia; the tachycardia at 0 hours was significantly less with the three times daily dosage than with once-daily dosing, while two hours after dosage administration the effect of the two regimens was very similar. However, there was no difference in the control of arterial pressure produced by the two dosage regimens at either of the observation times.

Having demonstrated that the hypotensive effect of beta-blockers lasts longer than the ability to antagonise cardiac beta receptors, it is important to consider whether it is necessary or beneficial to ensure 24-hour beta-blockade when treating hypertension. If the reduction in morbidity of coronary disease in hypertensives is related to beta-blockade rather than reduced blood pressure, it would be advisable to ensure that the cardiac beta-blockade lasts throughout 24 hours. This can be achieved by using frequent doses of beta-blocking drugs with a short half-life, or once-daily doses with a longer duration of action or a slow-release formulation.

Tuomilehto and Nissinen[40], in a comparative trial of metoprolol given as conventional tablets twice daily and as slow-release metoprolol (200 mg once daily), demonstrated that while the anti-hypertensive effect 24 hours after administration of both formulations was equal, the resting heart rate 24 hours after the slow-release metoprolol was significantly less than in patients treated with conventional tablets. Oro[41] showed similar effects on arterial pressure in a trial which also compared 100 mg conventional metoprolol twice daily and the sustained-release metoprolol preparation and he suggested that the degree of beta-blockade achieved by the two formulations was similar over the 24-hour period. In a multicentre double-blind cross-over study involving 113 hypertensive hospital outpatients[42], it was shown that resting and exercise blood pressure and heart rate were significantly reduced in comparison with placebo 12 hours after metoprolol given as 100 mg twice daily and 24 hours after the previous dose of slow-release metoprolol Durules respectively. The reduction in blood pressure and heart rate achieved after one month on either treatment did not differ significantly, but the incidence of spontaneously reported adverse events during the two therapy periods was 40 per cent lower during treatment with metoprolol Durules. However, another study[43] compared 200 mg of slow-release metoprolol and 100 mg twice daily of the conventional preparation in 30 patients with essential hypertension and demonstrated that the two treatments were equally effective and equally well tolerated. Nievle and Havard[44] compared 200 mg of metoprolol (Lopresor) as a single dose and the 200 mg of slow-release metoprolol (Slow Lopressor) in 50 patients. At 22 hours after the previous dose both were equipotent, significantly reducing the supine, sitting and standing systolic and diastolic blood pressure and heart rate.

In a study comparing conventional propranolol given twice daily and the long-acting preparation in 29 patients with hypertension, Douglas-Jones[45] showed no significant difference in clinical response to the two treatments. He suggested that the once-daily administration of the LA preparation should greatly aid patient compliance. Similar results were obtained in other studies[46, 47]. Mann et al.[48], using continuous recording of intrarterial blood pressure, showed that in seven ambulant patients with untreated hypertension treatment with propranolol LA once daily in the morning gave smooth control of blood pressure and heart rate throughout 24 hours. These conclusions have, however, been disputed[49].

The effectiveness of a once-daily dosage regimen of slow-release oxprenolol in controlling blood pressure throughout the 24 hours is not as unequivocal as with metoprolol and propranolol. In studies comparing slow-release oxprenolol and conventional oxprenolol in the treatment of hypertension it was shown that both formulations significantly reduce blood pressure and pulse rate[50-52]. Although there was little difference in their effects and both formulations were well tolerated, the once-daily formulation was preferred[50]. In a multicentre study[53] involving 4,400 patients with essential hypertension who were transferred to once-daily slow-release oxprenolol from either a multiple dose beta adrenoceptor blocking antagonist given alone or in combination with a diuretic, an improvement in the control of blood pressure was recorded in the majority of patients. In another study by the same author, 1,295 hypertensive patients in general practice, previously treated with methyldopa, were transferred to sustained
release oxprenolol. The average pre-treatment blood pressure of the 1,118 patients who completed the study fell from 180/100 mmHg to 159/95 mmHg. In addition, there was a reduction in the incidence of adverse effects when the patients were transferred to SR oxprenolol[54]. However, in contrast to these results, Petrie’s group[55] in a comparative cross-over study of once-daily atenolol (100 mg), sustained release oxprenolol and long-acting propranolol in 23 selected hypertensive patients, showed that after four weeks of treatment, blood pressure in the 2-4 hours before the next dose was not significantly lower after sustained release oxprenolol than after the placebo, while the hypotensive effectiveness of once-daily atenolol and long-acting propranolol was confirmed. The authors suggested that the present formulation of sustained release oxprenolol should be reconsidered.

In another comparative single-blind cross-over study in 25 patients with moderate essential hypertension, Wilcox and Hampton[36] compared placebo, atenolol 100 mg, metoprolol Durules, slow-release oxprenolol 160 mg and slow-release oxprenolol 320 mg. While all the drugs were significantly better than placebo in reducing resting blood pressure at 24 hours, atenolol and metoprolol Durules were significantly more effective than either dose of slow-release oxprenolol. A similar ranking was seen in relation to the reduction in blood pressure and the response of heart rate to exercise. These authors state that their results confirm the disappointing hypotensive effect of slow release oxprenolol in comparison with other drugs given once daily. Other authors have also expressed a similar view[17, 55]. A cross-over study[57] comparing the therapeutic control of blood pressure throughout the 24-hour period with slow-release formulations of metoprolol and oxprenolol in 10 hypertensive patients indicated that metoprolol Durules satisfactorily controlled both resting and exercise levels of blood pressure throughout the 24-hour period, in contrast to the significantly poorer control by slow-release oxprenolol at 24 hours.

Slow-release oxprenolol 160 mg has also been studied when administered alone (Slow Trasidrex) and in a fixed combination with cyclopenthiazide 0.25 mg (Trasidrex) in the treatment of 89 hypertensive patients in general practice. The results obtained from the 49 patients who completed the study indicated that the combination of slow-release oxprenolol and cyclopenthiazide produced a significantly lower systolic and diastolic pressure and there were no obvious differences in the incidence of adverse effects between the treatment groups. Finally, in an open general practice study[58] involving 578 patients whose pre-study blood pressure was inadequately controlled (diastolic blood pressure 100 mmHg) by their current beta-blocker, it was shown that after four weeks of treatment with a fixed combination of slow oxprenolol and cyclopenthiazide the blood pressure fell significantly from a mean value of 179/108 mmHg to 155/93 mmHg with no increased reporting of unpleasant adverse effects.

Myocardial Infarction

Previous studies have shown that beta adrenergic blockade with conventional preparations will control about 50 per cent of supraventricular and ventricular arrhythmias after acute myocardial infarction[59].

Recently, several studies[60-62] involving timolol, propranolol and metoprolol respectively have shown reduced mortality with long-term treatment following myocardial infarction. However, no studies have yet investigated the cardioprotective effect of beta-blockers with a sustained-release formulation.

Adverse Effects

The results of studies comparing conventional and slow-release beta adrenoceptor blocking drugs usually indicate that the incidence of adverse effects associated with beta-blockade are reduced with slow-release preparations, regardless of their additional properties. This may be due to the lower peak plasma concentration developed with the slow-release formulation.

Conclusion

The increasing use of sustained release preparations of metoprolol, propranolol, oxprenolol, and oxprenolol combined with cyclopenthiazide, which now account for 25 per cent of the total market, indicates a clinical awareness of the benefits, in terms of patient compliance, of once-daily drug administration. Sustained action preparations have an added advantage over once-daily administration of high doses of beta adrenoceptor blocking drugs and those with long plasma elimination half-lives; fewer fluctuations in plasma levels (possibly associated with adverse effects) occur between daily dosages. However, only the sustained release preparation of metoprolol and propranolol can be used successfully as a once-daily regimen in the treatment of angina and hypertension.

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