Metoprolol in the aged hypertensive: a comparison of two dosage schedules

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Summary: Thirty-one patients aged 65 y or over suffering from moderate hypertension were studied for 16 weeks using a cross-over design in which metoprolol 100 mg daily and metoprolol 200 mg daily were compared. Both treatment regimes were effective in controlling hypertension and no difference was found between the two with regard to efficacy. The 100 mg regime was, however, better tolerated and we propose this as the preferred metoprolol dose for the aged hypertensive.

Introduction

The indications for treating hypertension in the elderly are under constant discussion, but there is evidence from both the Hypertension Detection and Follow-up Program Cooperative Study Group (1979) and the Veterans Administration Cooperative Study Group (1972) that some benefit is shown from lowering elevated diastolic blood pressure. The Framingham Study (Kannel, 1974; Kannel & Gordon, 1978) also shows that there is a close correlation between the height of the systolic blood pressure and cardiovascular morbidity and mortality in individuals up to the age of 74 y and, in both men and women aged between 65 and 74 y, the risk of cardiovascular death in those with a systolic blood pressure of 160 mm Hg or above is more than twice as great as for those with pressures of 130 mm Hg or less. The same study also shows that the probable incidence of cardiovascular disease increases progressively with the rise in systolic blood pressure.

When the physician decides to prescribe antihypertensive medication for elderly hypertensive patients, the choice of drug will depend on a number of factors (Gavras & Gavras, 1983). Important among these are the changes in physiology and the development of pathology that can occur with ageing and which may influence the pharmacodynamics and pharmacokinetics of drug therapy in the elderly (O'Malley et al., 1980; Vestal, 1978). It has been proposed, for example, that the response to beta-blockers may be diminished in older patients (Vestal et al., 1979), whilst the metabolism and elimination of many drugs are altered with age.

The cardioselective beta-blocker metoprolol is well established as an agent for the control of hypertension and many physicians consider beta-blockers to be the drug of first choice for the treatment of hypertension in the elderly (O'Malley & O'Brien, 1980). However, the metabolism of metoprolol is dependent upon age-related hepatic function, and Kendall et al. (1977) and O'Malley et al. (1980) have shown that among elderly patients peak plasma levels were higher, and occurred later after dosing than in younger individuals.

A prospective, double-blind, within-patient comparison of metoprolol (Lopresor®) at two dosage levels – 100 mg and 200 mg, taken as a single daily dose – was made in elderly hypertensives to determine which dose is the more efficacious and better tolerated.

Patients and methods

Patients aged 65 y or more of either sex, with untreated hypertension as defined by diastolic blood pressure (Korotkoff Phase V) of 100 mm Hg or above, or those already receiving anti-hypertensive treatment with a pressure of 110 mm Hg or above, were eligible for inclusion if they sustained these levels on two out of three occasions, each 2 weeks apart, in the sitting position after 5 min rest and again after 3 min standing.

Patients were excluded if already taking metoprolol or clonidine, if they had suffered a myocardial infarction within the previous 3 months, showed signs of atrio-ventricular block, cardiac failure, brady...
(less than 50 beats/min), or had evidence of severe pulmonary, renal, hepatic or haematological disease.

After a 4-week run-in period during which baseline measurements were made, all medication was stopped except diuretics, which were permitted throughout provided the dose was kept constant. According to a previously determined randomization schedule, patients were then allocated to receive metoprolol either 100 mg or 200 mg as a single morning dose for 6 weeks. At the end of this time they were switched to the alternative dosage regimen for a further 6 weeks.

Patients were assessed after 2 and 6 weeks of each treatment period. At each attendance blood pressure, taken approximately 4–8 h post dosing, was measured using a random zero sphygmomanometer with the patient sitting and standing, and radial pulse rate counted. In addition, after the run-in period and each treatment period the patient was weighed and various haematological and chemical measurements made. Any unwanted effects were recorded at each visit and the patient’s compliance with the treatment prescribed was checked by counting residual tablets.

Student’s t test (Armitage, 1971) was used to determine the changes in the clinical and biochemical parameters during the first treatment period for each dosage regimen. The effects of the two dosages of metoprolol and possible order effect were analysed by Grizzle’s method (Grizzle, 1965) using the data obtained at the end of each treatment period.

### Results

Four of the 31 patients eligible for study had to be withdrawn. One patient sustained a cerebrovascular accident, one developed a sub-arachnoid haemorrhage, while 2 withdrew because of unwanted effects. Of the 27 patients completing the study, 11 were male and 16 female, the mean age being 72.7 years. The 2 treatment groups were well matched for age, sex, weight and smoking habits. During the first treatment period, 12 patients received the 100 mg dose, the remaining 15 patients being given the higher dosage regimen. Four patients randomized to the low dose group and 8 to the high dose group continued their cyclopenthiazide unchanged throughout the study. Both dosage regimens produced a statistically significant lowering of systolic and diastolic blood pressure in the sitting and standing position.

At the end of the first treatment period after 6 weeks’ therapy with metoprolol 100 mg/day, mean sitting blood pressure fell from an initial level of 200/113 mm Hg to 179/101 mm Hg (P < 0.001), the mean standing blood pressure showing a similar decline. With the 200 mg/day dosage, mean sitting blood pressure fell from 208/115 mm Hg to 185/96 mm Hg (P < 0.001), the mean standing blood pressure reflecting a like fall.

When the overall effects of the 2 dosages of metoprolol from both treatment periods were combined and compared, no significant differences were found (Table 1). However, if a diastolic blood pressure of 100 mm Hg or below is taken as indicating satisfactory control, then after 6 weeks’ treatment this had been achieved in 20/27 cases, and after 12 weeks 24/27, regardless of dose.

The 100 mg dose of metoprolol brought about a fall in mean sitting pulse rate of 7 beats/min from pretreatment values (P < 0.11), whereas the 200 mg dosage produced significant falls both from pre-treatment values [10 beats/min] (P = 0.006) and from those with the 100 mg dose (P = 0.02). Neither dosage had any clinically or statistically significant effect on mean body weight, oculi fundi, or any of the haematological and biochemical variables measured. Compliance with the protocol, as gauged by counting residual tablets, was good in all but 2 cases.

Although tolerability was generally good, adverse effects of gastrointestinal and central nervous system origin occurred more often with the 200 mg than with the 100 mg dosage. Unwanted effects were reported by 9 patients on both dosage regimens, by 2 on 100 mg only and by 6 on 200 mg only. No complaints were recorded by 10 patients on either dosage.

### Discussion

This study has demonstrated that metoprolol, alone or with a diuretic, is an effective agent when used to control moderate hypertension in patients of an older age group. The majority of individuals can be controlled with a dose of up to 200 mg daily.

There would seem to be no demonstrable difference in the degree of control gained by using 200 mg daily rather than 100 mg daily since both doses reduced systolic and diastolic pressure to a similar degree.

#### Table 1  Overall effect of 100 mg and 200 mg metoprolol on mean blood pressure and pulse rate in elderly hypertensives (means ± s.d.)

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol 100 mg</th>
<th>Metoprolol 200 mg</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting: systolic</td>
<td>183 ± 31</td>
<td>181 ± 34</td>
<td>0.52</td>
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<tr>
<td></td>
<td>97 ± 10</td>
<td>95 ± 11</td>
<td>0.12</td>
</tr>
<tr>
<td>Standing: systolic</td>
<td>183 ± 33</td>
<td>178 ± 36</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>98 ± 12</td>
<td>96 ± 11</td>
<td>0.13</td>
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<tr>
<td><strong>Pulse rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>65 ± 10</td>
<td>62 ± 12</td>
<td>0.02</td>
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Neither dose produced symptoms of hypotension on getting up to the standing position. The two doses of metoprolol were well tolerated by the majority of individuals but amongst those few who suffered unwanted effects there seemed to be a higher incidence on the larger dose – a not altogether unexpected finding.

Compliance is extremely important in the management of an asymptomatic condition but perhaps more so in this older age group where complex regimens are more likely to give rise to confusion. Overall, the simplicity of once daily treatment caused no problems in this respect to the patients studied.

In summary, the results of our study suggests that for the management of moderate hypertension metoprolol is effective when used as either 100 mg or 200 mg given as a single daily dose. The lower dose, however, would seem to give the same degree of control with a lower incidence of unwanted effects and would appear to be the optimal dose for the elderly hypertensive.

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