Improvement in angina pectoris with alpha adrenoceptor blockade

PETER COLLINS, DESMOND SHERIDAN
From the Department of Cardiology, Welsh National School of Medicine, Cardiff

SUMMARY The effects of indoramin, a selective alpha, adrenoceptor antagonist, on exercise tolerance were studied in 15 patients using a random double blind crossover protocol. All patients had chronic stable angina, for which 13 had been receiving beta adrenoceptor blocking drugs and nitrates, and these were continued unchanged throughout the study. An initial open challenge with indoramin in eight patients with chronic stable angina showed no serious adverse effects. In a dose of 25 mg three times daily indoramin prolonged exercise duration and increased oxygen consumption during exercise, while the maximal double product was unchanged. The increased exercise capacity was associated with a reduction in ST segment depression during exercise. Side effects included failure of ejaculation in one patient and tiredness in five.

These results indicate that alpha, adrenoceptor blockade may provide useful additional benefit to patients with stable angina pectoris who are already receiving beta blockers and nitrates.

Medical treatment of angina pectoris remains inadequate for many patients, despite the introduction of beta adrenoceptor blocking agents, long acting nitrates, and calcium antagonists. In addition, the side effects of these drugs—for example, bronchospasm, headache, and myocardial depression respectively—may limit their use in individual patients. The afterload and preload reducing effects of alpha adrenoceptor blockade should, theoretically, be beneficial to patients with angina pectoris, but as yet there are no controlled studies available to support or refute this.

Indoramin, a selective postsynaptic alpha, adrenoceptor antagonist, reduces systemic vascular resistance and preload in man, but without the usual reflex sympathetic activation, and is an effective antihypertensive agent. We report the results of a double blind crossover study, in which its effects on exercise tolerance were studied in 15 patients with chronic stable angina.

Patients and methods

STUDY POPULATION Fifteen men (aged 42 to 67 (mean 54.6) years) were studied; Table 1 shows their clinical details. Thirteen had been receiving beta blockade and 14 long acting nitrates. All patients were limited on treadmill exercise testing by angina pectoris accompanied by horizontal or downsloping ST segment depression of >2 mm persisting to 80 ms beyond the J point, following the Bruce protocol. These changes were observed in the anterior or anterolateral chest leads in 10 patients and in the inferior chest leads in five. Fourteen had undergone coronary arteriography which showed significant (>70% stenosis) single vessel disease in seven patients, two vessel disease in six, and three vessel disease in one. With one exception, all of these had normal left ventricular end diastolic pressures (Table 1). For ethical reasons previous antiangina treatment was continued unchanged throughout the study. All patients had had frequent attacks of exercise induced chest pain occurring in a constant and predictable pattern for at least six months before the study. There was no previous history of myocardial infarction, heart failure, or atrioventricular conduction abnormalities.
Improvement in angina pectoris with alpha adrenoceptor blockade  

Table 1 Clinical features of patients studied

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (yr)</th>
<th>LVEDP (mm Hg)</th>
<th>No of coronary vessels affected</th>
<th>Drug treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>10</td>
<td>1</td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>15</td>
<td>3</td>
<td>Acebutol 400 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>8</td>
<td>1</td>
<td>Isosorbide dinitrate 30 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>6</td>
<td>1</td>
<td>Isosorbide dinitrate 30 mg/day</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>5</td>
<td>1</td>
<td>Isosorbide dinitrate 40 mg/day</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>5</td>
<td>2</td>
<td>Isosorbide dinitrate 30 mg/day</td>
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<td>7</td>
<td>47</td>
<td>7</td>
<td>2</td>
<td>Atenolol 50 mg/day</td>
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<td>8</td>
<td>67</td>
<td>8</td>
<td>2</td>
<td>Metoprolol 200 mg/day</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>4</td>
<td>2</td>
<td>Dyazide two tabs/day</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>7</td>
<td>1</td>
<td>Propranolol 160 mg/day</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>8</td>
<td>1</td>
<td>Acebutol 400 mg/day</td>
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<tr>
<td>12</td>
<td>55</td>
<td>7</td>
<td>2</td>
<td>Isosorbide dinitrate 80 mg/day</td>
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<tr>
<td>13</td>
<td>58</td>
<td>—</td>
<td>Not known</td>
<td>Propranolol 160 mg/day</td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>7</td>
<td>2</td>
<td>Propranolol 160 mg/day</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>12</td>
<td>1</td>
<td>Isosorbide dinitrate slow release 40 mg/day</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end diastolic pressure.

PILOT STUDY
A pilot study was undertaken before the trial to determine the effect of indoramin, in doses of 25 mg twice daily to 50 mg twice daily, on blood pressure in patients with stable angina. This study included a further eight male patients with chronic stable angina who received indoramin 25 mg twice daily for the first week, 25 mg three times daily for the second week, and 50 mg twice daily for the third week. Blood pressure and heart rate were measured at the end of each week and a history relating to possible side effects was taken.

MAIN STUDY
The angina trial design was double blind; each patient received indoramin 25 mg three times daily and matching placebo capsules for three weeks each, separated by a washout period of one week. Twelve lead maximal exercise treadmill tests were carried out according to the Bruce protocol. Electrocardiograms were recorded before exercise, at the end of each three minute stage, at peak exercise, immediately after exercise, and at two minutes and 10 minutes after stopping exercise. Significant ST segment depression was taken as a shift of ≥2 mm 80 ms from the J point. The electrocardiograms were produced by a Picker International semiautomated electrocardiograph model CM 3400. Routine blood pressure measurements were made before, during, and after exercise.

Total body oxygen consumption was continuously measured during each exercise test using a PK Morgan oxygen analyser Model 500. This was used as a direct measure of total body work and hence an indirect measure of myocardial work during exercise.

Results were expressed as mean (standard error of mean) and comparisons were made using analysis of variance.

Results
Results of the pilot study showed that indoramin in doses of 25 mg twice daily to 50 mg twice daily had no appreciable adverse effects on these patients. Table 2

Table 2 Effect of indoramin on blood pressure (n=8)

<table>
<thead>
<tr>
<th>Position</th>
<th>Mean (SEM) pressure (mm Hg)</th>
<th>Before indoramin</th>
<th>End of week 3 (50 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Systolic</strong></td>
<td><strong>Diastolic</strong></td>
</tr>
<tr>
<td>Lying</td>
<td>120 (10)</td>
<td>130 (4)</td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>126 (8)</td>
<td>124 (6)</td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>82 (9)</td>
<td>81 (6)</td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>83 (8)</td>
<td>79 (4)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1  Effects of indoramin 25 mg three times daily on (a) exercise duration, (b) rate pressure product (DPmax), and (c) total oxygen consumption (VO2) in each patient studied. The horizontal bar indicates the mean for each group.

shows the results of blood pressure measurements. No significant changes were observed in the group as a whole, and blood pressure did not fall below 105/50 mm Hg in any patient.

EXERCISE TOLERANCE
Figure 1 shows the effects of indoramin on exercise duration and oxygen consumption during exercise. Indoramin significantly increased mean exercise duration (17%) from 402 (39) s to 470 (35) s (p<0.01), and mean total oxygen consumption during exercise (21%) from 9.9 (1.2)1 to 12.0 (1.3)1 (p<0.01). Regression analysis showed a significant correlation between oxygen consumption and exercise duration (r=0.75-0.83, p<0.01 in each case).

Completed diary cards for all stages of the study were returned by only six patients and were considered unreliable for evaluation.

HEART RATE AND BLOOD PRESSURE DURING EXERCISE
Mean heart rate increased from 66 (3) beats/minute at
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rest to 112 (3) beats/min at peak exercise during placebo treatment. Heart rate at peak exercise was slightly increased by indoramin (to 118 (5) beats/min from 68 (4) beats/min at rest). The rise in mean systolic pressure at peak exercise was also affected little by indoramin (161 (8) mm Hg compared with 164 (6-6) mm Hg with placebo). Thus the rate pressure product at peak exercise was not significantly affected by indoramin (18934 (1263) compared with 18311 (795) with placebo).

ST SEGMENT CHANGES
Figure 2 shows the changes in ST segment during exercise. Prolongation in exercise capacity was associated with a significant reduction in ST depression at three minutes (p<0.02) and six minutes (p<0.005) of exercise. The extent of ST depression was similar at peak exercise in each group.

SIDE EFFECTS
Failure of ejaculation occurred in one patient during active treatment, but he elected to continue the study. One patient withdrew from the study because of pronounced tiredness with active treatment. Five other patients complained of tiredness with active treatment compared with two with the placebo.

Discussion
These results indicate that alpha adrenoceptor blockade may be a useful adjunct to the treatment of stable angina pectoris in patients already receiving conventional antianginal treatment. Alpha adrenoceptor blockade has been extensively investigated in the treatment of hypertension and cardiac failure. Little is known, however, about its effect on angina pectoris. Prazosin has been shown to be unhelpful in treating variant angina. Labelotol possessing both alpha and beta adrenoceptor blocking properties improves exercise tolerance in angina pectoris. The beta blocking potency of this compound is, however, four to eight times greater than that of alpha, and the contribution of alpha adrenoceptor blockade to the antianginal effect is unclear. Because of the relative paucity of information available about the effects of alpha blocking agents in patients with angina pectoris it was considered unethical to stop current treatment during this study. For this reason, the present results can be interpreted only as indicating benefit in patients already receiving beta blockers or nitrates or both.

In this study, exercise capacity before the onset of angina was improved, as indicated by increases in exercise duration and oxygen consumption during exercise. In contrast, the maximal double product changed little. These findings indicate that indoramin significantly increased total work but that cardiac work was similar at maximal exercise with placebo and active treatment. This implies that cardiac work at lower workloads was reduced by the drug, and the reduction in ST segment depression at three and six minutes of exercise supports this. This in turn suggests that the antianginal effect observed here reflects actions of the drug on peripheral arterioles and veins; however, further work is needed to clarify this. Indoramin frequently produced tiredness in the present study, and one patient withdrew for this reason. Serious cardiovascular side effects such as hypotension or worsening of angina did not occur. The incidence of side effects observed here was lower than in previous studies, in which higher doses were used to treat hypertension, but is comparable with previous studies using calcium antagonists and beta adrenoceptor antagonists.

In conclusion alpha adrenoceptor blockade with indoramin produced significant improvement in exercise capacity in patients already receiving beta blockers and nitrates. Further work is needed to establish whether or not this is a general property of alpha adrenoceptor blockade and to determine its haemodynamic mode of action.

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Improvement in angina pectoris with alpha adrenoceptor blockade.

P Collins and D Sheridan

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