Sotalol in Angina Pectoris

A Double-Blind Study

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SUMMARY

The effect of sotalol, a β-adrenergic blocking drug, on the frequency of angina pectoris attacks and on exercise tolerance was evaluated by a double-blind cross-over study in 30 selected patients suffering from stable angina pectoris.

Sotalol significantly reduced the mean number of attacks of angina, the consumption of glyceryl trinitrate tablets and the pulse rate at rest and in response to exercise.

Effort tolerance as judged by a suboptimal 2-step test was improved significantly, as was electrocardiographic response. A relatively moderate dose of sotalol, 320 mg per day (160 mg twice daily), was sufficient in 80% of the patients. Side-effects were negligible.


This report presents the results of a study of sotalol, a cardioselective β-receptor antagonist, in the treatment of patients with established angina pectoris. The pharmacological properties of sotalol were first described in 1965 by Lish and his colleagues, and have since been extensively studied in experimental animals and man. The drug is cardioselective in its blocking action, has little or no local anaesthetic ('membrane stabilising') effect, and is devoid of intrinsic sympathomimetic effect.

The fluctuations which occur in angina pectoris under natural circumstances complicate the accurate assessment of the response to any particular treatment. Therefore the present study examined the effects of sotalol on the frequency of angina attacks, and its influence on exercise tolerance as judged by a modified Master's 2-step test carried out under conditions which were standardised as far as practical.

PATIENTS AND METHODS

Selection of Patients

Patients whose angina was stable and exercise-induced were selected for the trial. The diagnosis was confirmed in all patients by electrocardiographic abnormalities at rest or on exertion. During the course of the study no long-acting nitrates could be taken; nitroglycerine could be used during attacks but not prophylactically. Drugs which were not to be taken included other β-adrenergic blockers, phenothiazine, methyldopa, mono-amine oxidase inhibitors, Rauwolfia alkaloids and other drugs which might influence angina. Patients were excluded if their resting pulse rate was below 60 per minute or if there was any evidence of hyperthyroidism, bronchial asthma, myocardial infarction in the previous 3 months, uncompensated heart failure, previous cardiac surgery, second- and third-degree heart block or severe hepatic or renal impairment. All patients gave informed consent to the trial. A total of 30 patients met the criteria of the protocol and were included in the study and in this analysis. Patients ranged in age from 37 to 65 years with a mean of 54 years; there were 20 males and 10 females. The duration of the angina before the trial varied from 2 months to 10 years with a mean of 30 months.

Phases of the Study

At the first visit patients who met the criteria of the study were assessed and instructed in the recording of attacks and the number of glyceryl trinitrate (TNT) tablets to be used. A 6-week baseline period was then commenced, during which time all patients received placebo tablets and recorded the number of anginal attacks per day, the number of TNT tablets used per week and any other relevant information. Then followed a 2-week titration period during which all patients received 160 mg of sotalol per day (80 mg two times a day), the dose being increased to an upper limit of 400 mg per day depending on response. Patients were then assigned to either sotalol or placebo in random order on a double-blind basis for 6 weeks and finally crossed over to the opposite medication for 6 weeks during the cross-over phase; again this was on a double-blind basis.

In the statistical evaluation, Student's t test has been applied.

Assessment of Effects

The patients were studied for a total of 20 weeks. They were examined every third week, at which time the pulse rate and blood pressure in supine and erect positions were recorded, as well as ECGs and laboratory tests to monitor safety. These tests included measurements of haemoglobin, haematocrit, red and white cell counts, blood urea, SGOT and cholesterol levels. Exercise tests used in this study were based on the standard Master's 2-step test, but submaximal effort was performed rather than a set.
number of trips over Master's staircase based on weight and age. At the first visit each patient's tolerance was carefully assessed with stopwatch timing, and subsequent exercise tests were tailored to the individual's ability, the same rate of exercise being critical. Each test was stopped at the first sign of chest pain or discomfort. The heart rate at the conclusion of the test was measured immediately the endpoint was reached. To control factors which might influence effort tolerance, the patients were not tested for 1 hour after a meal and were rested for 20 minutes before each exercise. One test was performed every third week. Between the examinations the patients continued their normal lives and activities.

RESULTS

Results were similar whether patients received sotalol or placebo during the first 6-week treatment period; the data for these 2 groups have therefore been combined in this report.

Dose of Sotalol

Twenty patients took 320 mg per day throughout the study and 4 patients took 160 mg or 240 mg for the first few weeks and were eventually stabilised on 320 mg; thus, in 24 patients (80%) 320 mg of sotalol per day turned out to be the best dose. One patient received 320 mg during the titration period and for the first 4 weeks of the sotalol treatment period, and the dose was then reduced to 160 mg. In 5 patients the dose of sotalol was increased to and maintained at 480 mg, in most of them at the beginning of the sotalol treatment period.

Anginal Attack Rate and TNT Consumption

The weekly attack rate and TNT consumption for each phase of the trial are shown in Table I. All 30 patients (100%) had fewer attacks during sotalol treatment than during the baseline period. Histories obtained from the patients indicated that the mean number of attacks per week was 11. During the baseline period the mean attack rate remained fairly steady from one week to the next at between 11 and 13 attacks per week, with an over-all mean of 11.8 for all patients. This decreased to 7.2 during the titration period (on sotalol), decreased further to 3.6 attacks per week during the sotalol treatment period and increased during the placebo period to 8.0. The difference in the number of attacks during the drug, baseline and placebo periods is statistically significant with 99% confidence levels.

Because of the apparent increasing effect of sotalol with time, the mean values for the last 2 weeks of sotalol and placebo treatment were also compared; these were 2.7 and 10.4 respectively. Comparison of these results by Student's t test shows that the differences are highly significant with confidence levels of 99% ($t = 6.1$).

The mean number of attacks decreased by 50% or more in 24 patients (80%) while taking sotalol, and by 40% or more in 28 patients (93%), compared with the attacks which occurred while taking placebo.

Eighteen patients reported at least 1 week free of attacks during sotalol treatment but there were no attack-free periods during the baseline and placebo periods.

The TNT consumption ran parallel to the decreased number of attacks during sotalol treatment (Fig. 1). Seventeen patients (57%) reported at least 1 week during which no nitroglycerine tablets were taken while on sotalol, compared with one nitroglycerine-free week in the placebo period.

![Fig. 1. Effect of sotalol compared with placebo on 30 patients.](image)

Heart Rate and Blood Pressure

The systolic and diastolic pressures were somewhat lower during sotalol administration but the differences

| TABLE I. EFFECT OF SOTALOL ON MEAN NUMBER (SD) OF ATTACKS AND NUMBER OF TNT TABLETS CONSUMED |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Period                                        | First visit     | Baseline        | Titration       | Drug            | Placebo         | Last 2 weeks of drug |
| Attacks (per week)                           | 11.0 ± 7.7     | 11.8 ± 9.2      | 7.2 ± 7.4       | 3.6 ± 3.4       | 8.0 ± 5.1       | 2.7 ± 3.1         |
| Tablets (per week)                           | 11.7 ± 9.5     | 10.9 ± 9.3      | 6.5 ± 7.5       | 3.3 ± 3.3       | 7.7 ± 4.7       | 2.5 ± 3.0         |
|                                                |                 |                 |                 |                 |                 |                 |
are not statistically significant. However, it was noted that the blood pressure tended to remain lower after withdrawal of the sotalol.

Exercise Tests

All patients underwent a suboptimal exercise test before and every 3 weeks during the study. The results at the end of the baseline period, after 6 weeks of sotalol and after 6 weeks of placebo, are shown in Table II. During sotalol treatment, compared with the placebo period, there was an increase of 32% in the number of trips which the patients could perform, and the heart rate before and after exercise was reduced by 20% and 16%, respectively. The mean of the heart rate response to exercise increased by 37% on sotalol and 31% on placebo. Sotalol, therefore, did not have an adverse effect on the response of the heart rate to effort. The total time of the effort test was 22% greater in the sotalol group and the time taken for the pain to subside after exercise was 59% less on sotalol than on placebo.

The patients did not develop anginal pain at all in at least one test while taking sotalol.

Electrocardiographic Response (Table III)

Five of the 30 patients had iso-electric ST segments in every ECG taken. Two patients showed improvement in the ST segments of pre-exercise ECGs while they were taking sotalol as compared with ST segments while they were on placebo. Twenty-four patients (96% of those with ST segment abnormalities before exercise) showed improvement in the ST segments during and after exercise while they were taking sotalol.

Side-Effects

There was a notable lack of side-effects; the only one of possible significance was dyspnoea, which was reported by 3 patients taking sotalol; there was no evidence of cardiac failure or bronchospasm in these patients. The significance of this side-effect is difficult to evaluate, since all patients in this study had severe cardiac disease.

Laboratory Tests

No significant changes were found in the haemoglobin, haematocrit, red cell count, white cell count, blood urea nitrogen, serum glutamic oxalo-acetic transaminase and serum cholesterol values when these were measured during the study.

DISCUSSION

All the patients included in this study were well-motivated, took their medication in the prescribed manner and kept careful records. This is essential in an outpatient trial. The mean number of attacks remained remarkably constant during the 6-week baseline period, when patients were receiving placebo. All patients subsequently reported fewer attacks during the sotalol treatment period, although there had been no vital changes in their lifestyle. The extent of the clinical improvement is indicated by the fact that 90% of the patients experienced a 50% or greater reduction in the number of attacks during the sotalol period, compared with the baseline period, and in comparison with the placebo period, 80% of the

TABLE II. MODIFIED MASTER'S 2-STEP TEST RESULTS IN LAST WEEK OF EACH PERIOD — MEAN VALUES (±SD) OF 30 PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sotalol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trips</td>
<td>32.5 ± 10.9</td>
<td>42.5 ± 6.6</td>
<td>32.2 ± 8.7</td>
</tr>
<tr>
<td>Heart rate before exercise (beats/min)</td>
<td>73.2 ± 4.8</td>
<td>58.0 ± 5.5</td>
<td>72.6 ± 6.9</td>
</tr>
<tr>
<td>Heart rate after exercise (beats/min)</td>
<td>95.8 ± 11.2</td>
<td>79.5 ± 8.2</td>
<td>95.9 ± 10.4</td>
</tr>
<tr>
<td>Heart rate when pain ends* (beats/min)</td>
<td>87.3 ± 9.5</td>
<td>75.4 ± 9.2</td>
<td>86.5 ± 11.4</td>
</tr>
<tr>
<td>Heart rate when ECG returns to pre-exercise pattern (beats/min)</td>
<td>79.6 ± 6.6</td>
<td>68.5 ± 8.1</td>
<td>78.3 ± 8.8</td>
</tr>
<tr>
<td>Total time of test (s)</td>
<td>127.1 ± 42.1</td>
<td>153.9 ± 27.8</td>
<td>125.8 ± 36.6</td>
</tr>
<tr>
<td>Time post-exercise when chest* pain ends (s)</td>
<td>209.6 ± 106.8</td>
<td>83.0 ± 44.2</td>
<td>203.3 ± 83.8</td>
</tr>
<tr>
<td>Time post-exercise when the ECG returns to pre-exercise pattern (s)</td>
<td>509.9 ± 209.3</td>
<td>282.8 ± 142.2</td>
<td>547.5 ± 181.1</td>
</tr>
<tr>
<td>Time post-exercise when heart rate reaches resting plateau (s)</td>
<td>662.5 ± 237.5</td>
<td>511.0 ± 208.7</td>
<td>715.9 ± 242.1</td>
</tr>
</tbody>
</table>

* Ten patients did not develop pain on at least one occasion while taking sotalol, 1 while taking sotalol and placebo and 1 on one occasion while taking placebo only.
patients showed such a reduction. This decrease in the number of attacks is confirmed by the decreased consumption of TNT tablets, a criterion which is acceptable in patients who experience many attacks of angina every day — as in the present study. These very satisfactory results have been achieved with relatively moderate dosages of sotalol — 80% of the patients received a dosage of 320 mg per day for most of the study. In most cases the maintenance dosage of sotalol was reached within 2 or 3 weeks. Occasionally the dosage had to be increased or decreased slightly later.

Sotalol reduced the mean supine pulse rate by 19% from 73,1 per minute during the baseline period to 59.2 during the sotalol period, the pulse rate returned to a mean of 67.1 during the placebo period. The pulse rate fell below 50 per minute in 2 patients, both of whom were receiving a dose of 320 mg per day. No change was made in the dosage and no ill-effects occurred. The systolic and diastolic blood pressures showed slight reductions during the sotalol period and only partial return towards baseline levels during the subsequent placebo treatment. The reason for this is not clear. A prolonged action of sotalol is unlikely, since the drug is not metabolised and is virtually completely cleared from the plasma after 72 hours. The same prolongation of effect on the blood pressure after withdrawal of the drug has been noted with other β-adrenergic blocking drugs and has been attributed to resetting of the baroreceptors. However, Fröhlich does not regard this as the likely explanation, since the initial changes are those of blood flow, not pressure. A central effect cannot be excluded.

The effectiveness of sotalol in preventing attacks of angina is shown by the reduction in the mean number of attacks per week during the baseline and placebo periods (11.8 and 8.0 respectively) to 3.6 per week during the sotalol periods. Because transfer from an active agent to placebo might allow a carry-over effect, the results of the last 2 weeks were compared and were even more impressive — the mean number of attacks per week was 10.4 on placebo and 2.7 on sotalol.

With regard to exercise tolerance, sotalol increased the number of trips performed by the patients by 22% and reduced the heart rate after effort by 16%. The increase in heart rate from the resting level was not affected by sotalol but the drug did allow a 22% increase in the time elapsed before angina pain occurred on effort and caused a more rapid return of the heart rate to the pre-exercise levels. More significant was the improvement in ST-segment changes during and after exercise while patients were on sotalol. This occurred in 96% of the patients who showed such changes during the pre-drug assessment. Digitalis can cause false positive results, but only 2 patients in the present series were receiving digoxin, and both showed an improvement in the effort ECG while they were on sotalol.

The incidence of side-effects was low and of no significance. There were no signs of cardiac failure attributable to drug therapy.

CONCLUSION

Sotalol has been shown to be safe and highly effective in reducing the frequency of attacks of angina pectoris, with very few side-effects. It has also been shown to improve exercise tolerance and to improve the ECG after effort, while reducing the duration of anginal pain. The findings reported here are similar to those of trials elsewhere.

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REFERENCES