# Once daily sotalol in the treatment of hypertension

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SUMMARY. In a small group of hypertensive patients studied at home, once daily early morning sotalol therapy effectively decreased lying, standing, and post-exercise blood pressure and pulse rate. A dose-response relationship was seen. Adverse effects were mild and transient. The once daily regimen is easy to administer and appears to give precision in blood pressure reduction. Providing there is no subsequent escape from control, once daily beta-blocking therapy should aid long-term hypertension treatment in general practice.

## Introduction

THE beta-adrenergic blocking drugs were introduced into antihypertensive therapy more than ten years ago (Prichard and Gillam, 1964) and, though considerable investigational and theoretical work has been carried out since that time, the mode of action of these agents is still not fully elucidated and the exact reasons for their usefulness are not yet clear (Simpson, 1974).

A large number of beta-blockers are currently available and, provided that equipotent doses are given, they appear at first sight to be equally effective. Membrane-stabilizing and partial agonist activity may be unimportant at normal oral dose levels and cardioselective action should not be misinterpreted as a cardiospecific effect when considering patients at risk (*British Medical Journal*, 1977).

With the withdrawal of practolol from domiciliary use after recognition of the associated oculomucocutaneous syndrome (Brown *et al.*, 1974; Felix *et al.*, 1974; Wright, 1975), the general practitioner has eight beta-blockers available for the treatment of hypertension, namely acebutolol, atenolol, metoprolol, oxprenolol, pindolol, propranolol, sotalol, and timolol. The desirable attributes of the ideal antihypertensive drug have been summarized (Gross, 1974).



Sotalol was chosen for this study since it is devoid of intrinsic sympathomimetic, membrane-stabilizing, and local anaesthetic activity (Lish *et al.*, 1965), and its 13-hour mean plasma half-life (Shanks *et al.*, 1974) is the longest of the agents listed above. Though a long half-life *in itself* may not necessarily imply that a drug can be given at long dose intervals, it has been suggested (Shanks *et al.*, 1974) that sotalol should be administered once daily.

## Patients and methods

Eight patients, five men and three women, were studied. The men were aged 30 to 67 years (mean age 51 years) and the women were between 37 and 64 years (mean age 54 years). The mean age of the group was 52 years. The known duration of their hypertension ranged from less than one year to 13 years. No patient was suffering from obstructive lung disease, recent myocardial disease, renal failure, diabetes mellitus, hepatic disease, malignant or accelerating hypertension. None had eye ground changes of more than grade 2.

On entry to the study patients were physically examined and had the following investigations: chest x-ray, electrocardiogram, serum electrolytes, urea and uric acid, liver function tests, and 24-hour urinary catecholamines. Previous antihypertensive therapy was then withdrawn and after a three-week washout period all had diastolic blood pressures above 100 mm Hg.

The study consisted of a four-day control period subsequent to the washout period and was followed by a treatment period. During the control period, patients had lying, standing, and post-exercise blood pressure and pulse rate measured three times a day on each of the four days. The treatment period was then started, sotalol being administered once daily in the early morning.

The initial dose of sotalol was 80 mg and this was increased daily in increments of 80 mg, the objective being to reduce the diastolic blood pressure below 100 mm Hg, that is to at least 10 mm Hg below that level which is accepted as giving rise to severe morbid events (Petrie, 1976; Dollery, 1977). This first phase of

the treatment period lasted up to one week, during which time daily measurements of blood pressure and pulse rate were continued as for the control period. When satisfactory pressure levels were reached, the current dose level was maintained and patients were assessed three times a day on a weekly basis for a further six weeks.

All assessments, whether daily or weekly, were carried out to a standard pattern. Readings of blood pressure and pulse rate were made in the patients' homes at 07.00, 19.00, and 23.00 hours. Measurements were taken after a standing period of two minutes; after a lying period of five minutes; and after four minutes of two-step exercising. A standard mercury sphygmomanometer was employed and all readings were taken by the investigator.

Group mean blood pressures and pulse rates for the control and maintenance periods were calculated for each of the three daily assessment times. Student's paired t-test was employed to assess the significance of change.

Dosage of sotalol ranged from 80 mg to 640 mg and was taken as a single daily dose after the 07.00 hour recordings.

## Results

The analysis is based on the seven patients who completed the study.

Standing, lying, and post-exercise blood pressures, pulse rates, and the effect of treatment on these measurements are shown in Table 1. All readings were judged to be clinically significantly reduced from pre-treatment values and no clinically significant differences were seen in the treatment readings between the 07.00, 19.00, and 23.00 hour assessments. The minor variations in treatment results between the three assessments were not statistically significant.

As expected, all treatment values were statistically significant compared with pre-treatment levels.

The percentage reduction in standing diastolic blood pressure and post-exercise pulse rate for the dose of sotalol used is shown in Figure 1. Within the stated dose range there is a dose-related response.

### *Adverse effects*

Three patients experienced adverse effects. One patient complained of tiredness, which was noted on the maximum dose given (240 mg daily) 20 minutes after taking medication and which reached a peak at 13.00 hours. Another patient felt loss of energy on 320 mg daily; the dose of sotalol was lowered to 240 mg daily and no further adverse effects were noted during the subsequent five weeks. The third patient felt cold when on 400 mg daily. This symptom remitted after three days and therapy was continued without further incident at the same dose level for a further four weeks.

### *Withdrawals*

One patient was withdrawn from the study. This patient, a man aged 65 years, proved impossible to control on single therapy. Before entry to the study he had a standing blood pressure of 175/135 mm Hg and was taking debrisoquine 20 mg tds. He proved unresponsive to sotalol 560 mg daily. His blood pressure has been lowered to 155/125 mm Hg on a combination of debrisoquine 20 mg bd and sotalol 240 mg bd.

**Table 1.** Group mean blood pressure and pulse rate (± SE) before and after treatment.

| | Readings taken at: | | | | | |
|---|---|---|---|---|---|---|
| | 07.00 hours | | 19.00 hours | | 23.00 hours | |
| Lying blood pressure (mm Hg): | Before | After | Before | After | Before | After |
| Systolic | 168.2 ± 8.3 | 155.4 ± 6.9 | 180.3 ± 7.0 | 152.0 ± 8.0 | 174.9 ± 7.4 | 157.8 ± 8.0 |
| Diastolic | 107.4 ± 5.1 | 96.6 ± 4.8 | 110.2 ± 2.6 | 96.2 ± 4.3 | 113.1 ± 6.5 | 95.4 ± 4.0 |
| Standing blood pressure (mm Hg): | | | | | | |
| Systolic | 162.8 ± 7.4 | 150.5 ± 6.5 | 173.5 ± 6.4 | 153.2 ± 6.1 | 172.8 ± 8.1 | 155.6 ± 7.3 |
| Diastolic | 112.3 ± 4.9 | 101.1 ± 4.0 | 115.9 ± 3.9 | 98.2 ± 2.4 | 117.4 ± 5.6 | 101.7 ± 3.3 |
| Post-exercise blood pressure (mm Hg): | | | | | | |
| Systolic | 186.1 ± 10.5 | 167.9 ± 7.7 | 199.1 ± 9.4 | 172.4 ± 7.2 | 189.4 ± 9.5 | 166.0 ± 7.9 |
| Diastolic | 108.0 ± 4.6 | 96.1 ± 5.0 | 109.1 ± 6.7 | 98.4 ± 2.9 | 110.0 ± 6.0 | 96.9 ± 4.2 |
| Pulse rate (beats/min.): | | | | | | |
| Lying | 84.2 ± 3.3 | 66.7 ± 1.9 | 87.1 ± 3.0 | 66.7 ± 1.8 | 80.9 ± 3.9 | 67.6 ± 2.0 |
| Standing | 92.0 ± 3.1 | 66.7 ± 2.2 | 94.3 ± 3.7 | 67.7 ± 2.0 | 86.3 ± 4.0 | 70.3 ± 4.0 |
| Post exercise | 114.0 ± 9.3 | 87.6 ± 7.8 | 114.3 ± 6.9 | 80.2 ± 3.3 | 108.8 ± 7.2 | 81.5 ± 5.2 |

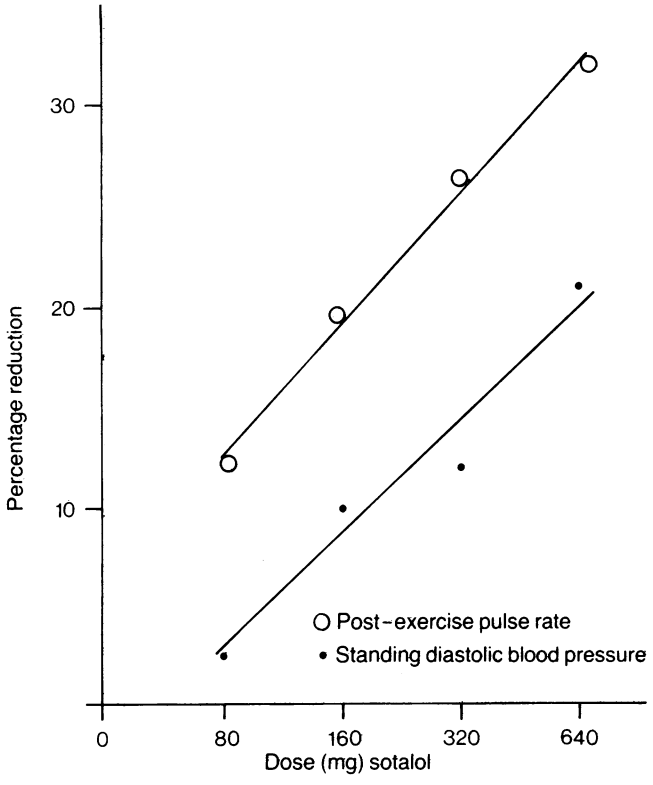
## Discussion

In general practice, patient compliance is an important consideration. It is known that the fewer the doses of drug per day, the greater is the reliability in taking medication (Gatley, 1968; Blackwell, 1973). Most patients receiving treatment for hypertension will be ambulant and performing normal daily activities. A once daily therapy, if effective, has obvious advantages in acceptability for such people.

At the time of writing, the beta-blocking drugs are officially recommended for use in divided daily doses with the exceptions of atenolol, metoprolol, sotalol, and a recently introduced sustained-release preparation of oxprenolol.

Once daily atenolol treatment was reported last year (Douglas-Jones and Cruickshank, 1976; Harris *et al.*, 1976). These studies can be criticized on the grounds that blood pressure was measured on only one occasion in each assessment period and no post-exercise readings were taken. Thus adequate 24-hour control could not be said to have been demonstrated. An interim report on another trial (Woolfson and Knapp, 1976) suggests that full 24-hour control may be achieved using atenolol once daily.

**Figure 1.** *Percentage reduction in blood pressure and pulse rate with sotalol.*




| Dose sotalol | 80 mg | 160 mg | 320 mg | 640 mg |
|---|---|---|---|---|
| Percentage reduction | | | | |
| Pulse rate | 12.0 | 19.5 | 26.2 | 32.4 |
| Blood pressure | 2.5 | 9.7 | 12.0 | 21.0 |

Regression line for pulse rate is:
$\Delta\%\ PR = 9.8 \log_e \text{dose} - 30.6$
and passes through the points dose 80 reduction 12.3
dose 640

Regression line for blood pressure is:
$\Delta\%\ BP = 8.3 \log_e \text{dose} - 33.9$
and passes through the points dose 80 reduction 2.6
dose 640 reduction 20.0

There is as yet no published evidence on the use of metoprolol therapy once daily as a treatment for hypertension. Published evidence on the efficacy of sustained-release oxprenolol is not available in the UK at the time of writing. Sustained-release preparations, by introducing yet another variable in the mechanism of drug absorption, are open to criticisms (Rawlins, 1975).

In spite of the present paucity of available evidence, there seems little doubt that once daily therapy for hypertension is increasing in popularity, and beta-blocking agents commonly used in multiple daily dose schedules have been used as once daily treatments, as, for example, with propranolol (Westerlund and Hansson, 1976) and pindolol (Frithz, 1976).

This study was designed to assess as accurately as possible the true blood pressure at home. Since home recordings of blood pressure are consistently lower than clinic recordings and may therefore be more pertinent in identification of truly raised blood pressure (*Lancet*, 1975), the frequency and timing of assessments employed in this investigation is probably the closest the family practitioner can attain to the ideal. The 07.00 hour readings are a final measure of the previous day's therapy; the 19.00 hour figures record the effect of morning medication at the end of the working day; and the 23.00 hour assessments are in practice the latest readings that can be taken without interfering with patients' sleep patterns.

This study shows that sotalol is an effective antihypertensive when administered in once daily doses. Not only are lying and standing blood pressures and pulse rates controlled for 24 hours but post-exercise values are similarly controlled, an important finding regarding ambulant patients who may well have to exert themselves physically in the course of their normal daily routine. Additionally, there has been documented a dose-response relationship with sotalol which implies that the practitioner can titrate the dosage employed to achieve the desired effect. The drug was well tolerated in the group studied, as shown by the minimal adverse effects elicited.

Further investigation is required to establish the full significance of these findings. Meanwhile it is postulated that for patients on once daily sotalol therapy an evening blood pressure reading combined with a post-exercise pulse rate measurement will give a good prediction of both hypertension control and beta-blockade the following morning.

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## Drugs and driving

However well aware the public may be of the detriments of 'drugs' they tend not to understand that the medicines they receive may not be wholly curative but may have additional deleterious adverse effects. The situation may, however, be changing. People are, perhaps, becoming more cautious in relation to medicines. Possibly the phenomenon of non-compliance in the taking of medicines is a sign of mistrust of what has been prescribed. One can be certain that, as with all human problems, the public's attitude to medicine will be complex and will no doubt contain contradictions.

So far as drugs and driving are concerned, it was made clear at the symposium that a driver whose performance is impaired by drugs will be liable under the law. So, the onus is on the individual to judge whether he feels fit enough to take charge or to continue in charge of a vehicle. But what is the individual's responsibility when the untoward effect of a medicine is sudden in onset? That is why advance warnings by pharmacists and doctors are so important. Whatever in law may be the liability of the individual member of the public, it seems clear that there must also be a professional responsibility to warn the patient against potential effects. For that reason alone, this year's symposium session ought to merit the close attention of pharmacists.

**Reference**

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