Effect of sotalol on haemodynamics and renin–angiotensin–aldosterone system in hypertensive patients

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(Received 24 November 1975)

Summary

1. Twenty-three hypertensive patients were treated by sotalol, a pure beta-adrenergic receptor blocking agent. The drug produced a significant decrease of blood pressure in nineteen patients.

2. On average, cardiac index decreased but not significantly; heart rate decreased and stroke index increased significantly. Total peripheral resistance varied in both directions.

3. Sotalol determined a fall in plasma renin concentration (only significant in the high-renin group), a fall in plasma angiotensin II concentration and in urinary excretion rate of aldosterone accompanied by a rise in plasma potassium concentration.

4. The fall of blood pressure was not correlated with the decreases of renin and angiotensin II concentrations or excretion rate of aldosterone. However, in the placebo period plasma angiotensin II concentration was significantly correlated with total peripheral resistance; during sotalol treatment the variations of these two parameters seemed also to be correlated.

5. There was a poor correlation between decreases of cardiac output and of blood pressure; it was impossible to foresee the magnitude of the lowering of the blood pressure from the initial cardiac index.

6. The association of a diuretic with sotalol enhanced the hypotensive effect of the beta-receptor blocking drug, without significant increase of plasma renin and angiotensin II concentrations.

Key words: adrenergic beta-receptor blockade, aldosterone, angiotensin II, cardiac output, diuretics, haemodynamics, hypertension, renin, sotalol.

Introduction

Beta-adrenergic receptor blocking drugs have been used in the treatment of arterial hypertension for several years. Propranolol was found to reduce significantly the arterial blood pressure in hypertensive patients (Prichard & Gillam, 1964, 1969; Zacharias & Cowen, 1970). The same therapeutic effect was obtained with sotalol (Prichard & Boakes, 1974; Verniory, Staroukine, Telerman & Delwiche, 1974) and with other beta-receptor blocking agents.

Sotalol is deprived of agonist activity and of membrane stabilizing effect, it is free of depressant action in isolated cardiac muscle (Levy & Richards, 1966), it does not affect myocardial contractility in dogs and has no adverse haemodynamic effect in cardiac patients (Brooks, Banas, Meister, Szucs, Dalen & Dexter, 1970) and it blocks cardiac as well as vascular beta receptors. This pure beta-receptor blocking effect of sotalol led us to investigate its action on haemodynamics and the renin–angiotensin system in a group of hypertensive patients.

Materials and methods

The study was planned as a single blind trial. The total observation had a span of 24 weeks divided into four periods:
Period 1. After withdrawal of all drugs, a placebo was given during 3 weeks, except in the most severe cases, where this period was shortened.

Period 2. During the second period (titration phase), sotalol was given orally starting from three tablets of 0.26 mmol (80 mg)/day; this dose was increased stepwise until the blood pressure was reduced to the normal range or until the heart rate fell below 50 beats/min.

Period 3. The same dose, which varied between patients from 0.78 to 3.88 mmol (230–1200 mg)/day was generally maintained for 13 weeks, except for minor adjustments (maintenance phase). The mean daily dose (±SEM) during the titration phase was 1.39 ± 0.09 mmol (429 ± 29 mg) and during the maintenance phase 2.44 ± 0.26 mmol (754 ± 79 mg). When the hypotensive effect obtained was unsatisfactory and when the heart rate prevented further increase of the dose, chlorthalidone [0.296 mmol (100 mg), two or three times a week] or frusemide [0-121 mmol (40 mg) per day] was given as well.

Period 4. In patients in whom the severity of hypertension allowed it, the drugs were withdrawn for a second placebo period of 3 weeks' duration.

The study was started in twenty-eight patients. Informed consent was obtained from all patients. The treatment was interrupted after a few days in four patients: for lack of co-operation in three and for drug intolerance with severe bradycardia in one. In one patient, the severity of hypertension, which was not alleviated by a week of treatment with sotalol, obliged us to add diuretics to the treatment. Therefore we have useful data for only twenty-three patients. Sixteen of them went through the whole group of patients was tested by paired comparisons with Student’s t-test for unpaired data.

Investigation of the possible aetiologies of hypertension was completed in each patient by intravenous pyelogram, isotopic nephrogram and, in ten patients, by renal arteriography. The diagnosis of each case and the degree of severity of the hypertension are reported in Table 1. The severity of hypertension was estimated according to the criteria of Goodman & Gilman (1970).

Patients were examined weekly in the out-patient department, where heart rate and blood pressure were measured supine and after standing for 3 min. Plasma renin and angiotensin II concentrations were determined after the patients had been ambulatory for 2 or 3 h, twice in the first placebo period and thereafter at intervals of about 3 weeks. Routine blood examinations were performed at the same time as well as urinalyses including catecholamines and aldosterone excretion rate. Patients followed the same diet throughout the whole study, with moderate salt restriction in most cases. Cardiac index was also determined in twenty-three patients during the placebo period; the measurement was repeated in fifteen patients during administration of sotalol.

Initially we used the dye-dilution technique of Stewart & Hamilton, detailed by Wood & Swan (1954), with Cardiogreen, but it became evident that the prospect of repeated arterial catheterization was unacceptable for most hypertensive outpatients. Therefore we changed to the classical Fick method, which calculates the cardiac output by dividing oxygen consumption by arteriovenous oxygen difference, mixed venous blood being taken from the pulmonary artery and arterial blood from the femoral artery (Cournand, Riley, Breed, Baldwin & Richards, 1945).

Plasma renin concentration was determined by the method of Brown, Davies, Lever, Robertson & Tree (1964) and angiotensin II concentration by that of Düsterdieck & McElwee (1971). The urinary excretion rate of aldosterone was measured by the method of Salokangas & Adlercreutz (1968) and catecholamines excretion rate by the method of De Schaepdryver (1958).

The effect of sotalol on several variables in the whole group of patients was tested by paired comparisons with the Student’s t-test. Differences between various periods in the same patient or between groups of patients were tested by Student’s t-test for unpaired data.

Results

Effect of sotalol on haemodynamics

Blood pressure. This did not vary systematically during the whole period of sotalol treatment. In a group of eleven patients, who were treated during 3 months with sotalol alone, the decreases of blood pressure were not statistically different from month to month. Systolic blood pressure supine was 204 ± 7 mmHg (mean ± SEM) during the placebo period,
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Table 1. Details of patients studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis(1)</th>
<th>Severity</th>
<th>Duration(2) (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.E.W.</td>
<td>73</td>
<td>M</td>
<td>Essential hypertension</td>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>S.C.</td>
<td>35</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Mild</td>
<td>12</td>
</tr>
<tr>
<td>M.I.</td>
<td>78</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Mild</td>
<td>36</td>
</tr>
<tr>
<td>F.E.</td>
<td>63</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Moderate</td>
<td>12</td>
</tr>
<tr>
<td>S.A.</td>
<td>50</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Moderate</td>
<td>51</td>
</tr>
<tr>
<td>D.E.F.</td>
<td>57</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Moderate</td>
<td>60</td>
</tr>
<tr>
<td>D.E.R.</td>
<td>44</td>
<td>M</td>
<td>Essential hypertension</td>
<td>Severe</td>
<td>21</td>
</tr>
<tr>
<td>C.O.</td>
<td>51</td>
<td>F</td>
<td>Essential hypertension</td>
<td>Severe</td>
<td>36</td>
</tr>
<tr>
<td>S.T.</td>
<td>44</td>
<td>M</td>
<td>Essential hypertension; atrial fibrillation</td>
<td>Severe</td>
<td>60</td>
</tr>
<tr>
<td>H.I.</td>
<td>40</td>
<td>M</td>
<td>Essential hypertension</td>
<td>Severe</td>
<td>74</td>
</tr>
<tr>
<td>B.E.</td>
<td>56</td>
<td>M</td>
<td>Malignant hypertension</td>
<td>Severe</td>
<td>18</td>
</tr>
<tr>
<td>N.A.</td>
<td>65</td>
<td>M</td>
<td>Malignant hypertension; atrial fibrillation</td>
<td>Severe</td>
<td>30</td>
</tr>
<tr>
<td>B.A.</td>
<td>42</td>
<td>M</td>
<td>Malignant hypertension</td>
<td>Severe</td>
<td>72</td>
</tr>
<tr>
<td>D.E.C.</td>
<td>67</td>
<td>F</td>
<td>Chronic pyelonephritis</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>D.E.K.</td>
<td>69</td>
<td>F</td>
<td>Chronic pyelonephritis</td>
<td>Moderate</td>
<td>240</td>
</tr>
<tr>
<td>L.E.</td>
<td>41</td>
<td>F</td>
<td>Chronic pyelonephritis</td>
<td>Moderate</td>
<td>240</td>
</tr>
<tr>
<td>P.I.</td>
<td>41</td>
<td>F</td>
<td>Chronic pyelonephritis</td>
<td>Severe</td>
<td>0-5</td>
</tr>
<tr>
<td>V.E.R.</td>
<td>62</td>
<td>M</td>
<td>Renovascular hypertension</td>
<td>Moderate</td>
<td>17</td>
</tr>
<tr>
<td>G.E.</td>
<td>46</td>
<td>M</td>
<td>Renovascular hypertension</td>
<td>Severe</td>
<td>36</td>
</tr>
<tr>
<td>B.O.</td>
<td>62</td>
<td>M</td>
<td>Renovascular hypertension</td>
<td>Severe</td>
<td>48</td>
</tr>
<tr>
<td>V.A.N.</td>
<td>51</td>
<td>F</td>
<td>Renovascular hypertension; atrial fibrillation</td>
<td>Severe</td>
<td>120</td>
</tr>
<tr>
<td>D.A.</td>
<td>54</td>
<td>M</td>
<td>Renovascular hypertension not cured by previous surgery</td>
<td>Moderate</td>
<td>36</td>
</tr>
<tr>
<td>V.A.S.</td>
<td>54</td>
<td>F</td>
<td>Renovascular hypertension not cured by previous surgery</td>
<td>Severe</td>
<td>120</td>
</tr>
</tbody>
</table>

(1) 'Malignant hypertension' is used to qualify an essential hypertension with retinopathy grade IV or grade III+renal insufficiency [plasma creatinine > 0.177 mmol/l (20 mg/l)]. 'Renovascular hypertension' means hypertension associated with a stenosis of a renal artery; no surgery was so far performed. 'Renovascular hypertension not cured by previous surgery' meets the same criteria concerning the stenosis; surgery, although technically satisfactory, did not cure the hypertension.

(2) 'Duration of hypertension' means the delay since the discovery of high blood pressure.

172 ± 6 mmHg during the first month of treatment, 179 ± 8 mmHg during the second month and 179 ± 10 mmHg during the third month. This has been previously reported (Verniory et al., 1974). In addition, the hypotensive effect of sotalol was not statistically different between titration and maintenance phases and it therefore seemed reasonable to evaluate the hypotensive effect of sotalol by pooling the results for each patient and comparing the average blood pressure of this patient during placebo period and sotalol treatment.

In nineteen out of twenty-three patients there was a significant lowering (P < 0.05) of at least one of the four measurements of blood pressure: systolic, diastolic supine, systolic, diastolic standing blood pressure.
For the whole group of twenty-three patients, the mean decrease of blood pressure was highly significant: 23/15 mmHg supine and 29/19 mmHg standing (Table 2).

**Heart rate.** Sotalol reduced the heart rate in all patients. On average, the heart rate decreased by 25 beats/min supine and by 26 beats/min standing. The slowing of the heart rate was more marked during the maintenance phase (−29 ± 3 beats/min). The difference, statistically significant ($P < 0.001$), seemed to be due to the difference of dose. Three patients had atrial fibrillation during the placebo period, which reverted to normal sinus rhythm during sotalol treatment.

**Cardiac index.** The effect of sotalol on cardiac index varied from patient to patient: it decreased in nine and increased in six (Fig. 1). On average, cardiac index decreased by 0.42 l/min$^{-1}$; this difference was not statistically significant (Table 3). Stroke index increased significantly from 34.4 to 46.6 ml beat$^{-1}$ m$^{-2}$, whereas total peripheral resistance was almost unchanged on average, although individual variations in both directions were observed.

**Effect of sotalol on the renin–angiotensin–aldosterone system**

**Plasma renin concentration.** In our laboratory, the normal range extends from 10.6 to 37.1 pmol/l (10.9–38.3 pg/ml), the mean (±SEM) being 18.7 ± 2.6 pmol/l (19.3 ± 2.7 pg/ml). For the same reason as for renin, statistical calculations were performed on logarithms of plasma angiotensin II concentrations. On the average, sotalol reduced plasma angiotensin II concentration by 46% ($P < 0.01$). When patients were divided into two groups (above or under the mean normal concentration), the decrease was much more pronounced (−72%; $P < 0.02$) in the high- than in the low-angiotensin II group (−15%; $P < 0.40$) (Fig. 3).

**Urinary aldosterone.** Urinary output of aldosterone was measured in fourteen patients during placebo and sotalol periods. Normal values are between 13.9 and 55.6 nmol/24 h (5–20 μg/24 h) with a mean value (±SEM) of 29.2 ± 2.8 nmol/24 h (10.5 ± 1.0 μg/24 h). In twelve patients out of fourteen, urinary output of aldosterone fell during sotalol treatment; for the whole group, the mean value decreased from 49.5 ± 9.5 during placebo period to 27.4 ± 4.2 nmol/24 h during sotalol treatment ($P < 0.01$).
**Sotalol and renin in hypertension**

**Table 3. Effect of sotalol on haemodynamics of patients**

Mean values±SEM are shown.

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Placebo</th>
<th>Sotalol</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (l min⁻¹ m⁻²)</td>
<td>15</td>
<td>3.15±0.28</td>
<td>2.73±0.22</td>
<td>&lt;0.30</td>
</tr>
<tr>
<td>Stroke index (ml beat⁻¹ m⁻²)</td>
<td>15</td>
<td>34.4±2.4</td>
<td>46.6±3.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>13</td>
<td>169±6</td>
<td>156±6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne s cm⁻⁵)</td>
<td>13</td>
<td>2644±278</td>
<td>2725±224</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total peripheral resistance corrected for body area (dyne s cm⁻⁵ m²)</td>
<td>13</td>
<td>4791±588</td>
<td>5102±404</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Fig. 1. Effect of sotalol on arterial blood pressure and cardiac index in fifteen hypertensive patients.** Patients are divided into two groups according to the initial cardiac index (respectively above or under the mean normal value). Initials of patients in Figs. 1-3 correspond to those of Table 1. B.P. = blood pressure; C.I. = cardiac index.

**Effect of sotalol on electrolytes, renal function and catecholamines**

**Electrolytes.** No significant change was observed in plasma sodium concentration (P < 0.001). Plasma potassium concentration increased very significantly (P < 0.001) from 3.95±0.07 to 4.32±0.07 mmol/l during sotalol treatment.

**Renal function.** No alteration of renal function was observed during sotalol treatment even in one patient with a severe renal failure.

**Catecholamines.** No significant variation was observed. Noradrenaline urinary excretion rate decreased slightly from 0.020±0.033 to 0.197±0.028 μmol/24 h (P < 0.001), whereas adrenaline output increased from 0.033±0.006 to 0.039±0.006 μmol/24 h (P < 0.05).

**Effects of the association of diuretics with sotalol**

**On blood pressure and heart rate.** In the twelve patients who were given diuretics associated with...
sotalol a further decrease of blood pressure was observed: 16 mmHg for the systolic (P<0.001) and 6 mmHg for the diastolic supine blood pressure (P<0.01), 18 mmHg for the systolic (P<0.02) and 4 mmHg for the diastolic standing blood pressure (P<0.20). The addition of diuretics to sotalol did not significantly modify the heart rate.

On the renin–angiotensin–aldosterone system.
Plasma renin concentration was determined in nine patients during the treatment by the association of sotalol and diuretics. On average, plasma renin concentration was 22.2 ± 14.5 units/l during placebo period, 6.8 ± 2.9 units/l during sotalol treatment and 8.1 ± 2.4 units/l during the combined treatment of sotalol with diuretics.

Mean plasma angiotensin II concentration was 54.0 ± 31.1 during placebo period, 8.8 ± 1.7 during sotalol treatment and 15.9 ± 4.3 pmol/l during the association of sotalol and diuretics. The small rise observed in plasma renin and angiotensin II concentrations after the addition of diuretics was not statistically significant, respectively P < 0.20 and P < 0.10. Urinary excretion rate of aldosterone was also somewhat higher (35.8 ± 10.8 nmol/24 h) during the combined treatment of sotalol and diuretics than during the treatment by sotalol alone (25.6 ± 6.7 nmol/24 h) (P < 0.30), but lower than during the placebo period (52.8 ± 14.7 nmol/24 h) (P < 0.10).

Discussion
Hypotensive effect of sotalol
Sotalol shares, with other beta-adrenergic receptor blocking drugs, the property to lower blood pressure. As sotalol is a pure beta-receptor blocker, its hypotensive action can only be ascribed to this property. However, the mechanism of this anti-hypertensive effect is not clearly explained. We shall consider successively three possibilities: a decrease of activity of the renin–angiotensin–aldosterone system, a lowering of cardiac output; a decrease of activity of the autonomic sympathetic system.

Renin–angiotensin–aldosterone system. Our data clearly demonstrate a decrease of the plasma concentrations of renin and angiotensin II and of the urinary excretion rate of aldosterone during sotalol treatment. So we were able to confirm with sotalol the results obtained with other beta-receptor blocking drugs. As sotalol lacks a membrane-stabilizing effect, the lowering of plasma renin and angiotensin

**FIG. 2.** Effect of sotalol on arterial blood pressure and plasma renin concentration in twenty-two hypertensive patients. Patients are divided into two groups according to the initial plasma renin concentration being above or below the mean normal concentration.
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Fig. 3. Effect of sotalol on arterial blood pressure and plasma angiotensin II (A-II) concentration in twenty-two hypertensive patients. Patients are divided into two groups according to the initial plasma angiotensin II concentration being above or below the mean normal concentration.

II concentrations has to be ascribed to beta-receptor blocking properties. However, we could not find any significant relation between decrease of plasma renin or angiotensin II concentrations and decrease of arterial blood pressure ($P<0.05$ and $P<0.09$ respectively). Furthermore, if patients are divided into high- and low-renin or high- and low-angiotensin groups, the decreases of systolic blood pressure are not significantly different (Fig. 2 and Fig. 3). These observations differ from those of Bühler, Laragh, Baer, Vaughan & Brunner (1972), who used propranolol and divided their patients in high-, normal- and low-renin groups according to different criteria, taking into account the 24 h urinary output of sodium. Our results confirm results from several other studies (Birkenhager, Krauss & Schalekamp, 1971; Stokes, Weber & Thornell, 1974; Verniory et al., 1974; Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Bianchetti, Di Salle, Morselli & Chidsey, 1975).

It can be stressed that patients with renovascular hypertension showed a poor and often statistically insignificant fall of blood pressure under sotalol treatment, although the decreases of plasma renin and angiotensin II concentrations were generally very marked. For example, patient G.E. (Table 1) had the highest values of renin and angiotensin II during placebo period (first column on the left in Fig. 2 and Fig. 3), which were reduced almost to nothing by sotalol, but the decrease of blood pressure was statistically insignificant except for standing diastolic blood pressure ($P<0.005$). These results are similar to those of Michelakis & McAllister (1972) but conflict with those of Bühler, Laragh, Vaughan, Brunner, Gavras & Baer (1973); in both studies, propranolol was used as beta-receptor blocker.

However, it is difficult to accept that the decrease of plasma renin and angiotensin II concentrations did not play any role in the decrease of blood pressure produced by sotalol. Indeed it is likely that, at least in certain forms of arterial hypertension, plasma angiotensin II concentration influences arterial blood pressure (Gavras, Brunner, Laragh, Gavras & Vukovich, 1975). We could demonstrate in the placebo period a significant correlation between plasma angiotensin II concentration and total peripheral resistance corrected for body area: $r=0.573$; $P<0.05$. During sotalol treatment the
individual variations of these two variables seem also to be correlated, although the correlation does not reach the level of significance ($r = 0.534; 0.05 < P < 0.1$). Similar results were reported by Tarazi (1975), who found a significant correlation between long-term changes in total peripheral resistance and reduction in plasma renin activity under the influence of propranolol. The decrease of aldosterone also to be correlated, although the correlation does not reach the level of significance.

Cardiac output. It is likely that, at least in some patients, the decrease of cardiac output was a factor lowering the arterial blood pressure. However, there was no significant correlation between decreases of cardiac output and of blood pressure ($P < 0.4$). When patients were divided into high- and low-cardiac index groups, with an initial cardiac index respectively higher or lower than the normal mean value ($3.1 \pm 1 \text{ min}^{-1} \text{ m}^{-2}$), there was no significant difference between the decreases of blood pressure observed in both groups (Fig. 1).

Sympathetic nervous system. Recent studies have shown the presence of beta-adrenergic receptors in the hypothalamus, in the brain stem, and in the spinal cord, whose stimulation facilitates sympathetic nervous outflow.

Electrical stimulation of the posterior hypothalamus elicits pressor responses, tachycardia and increase in adrenal catecholamines release, which are antagonized by intracerebroventricular injection of sotalol (Bhargava, 1975). Propranolol or sotalol, injected intraventricularly in cats, produces centrally mediated falls in blood pressure and heart rate (Day & Roach, 1975). However, a central mechanism can be implicated in the explanation of the hypotensive effect of beta-receptor blockers in man only if the drug crosses the blood–brain barrier, which is doubtful for sotalol, on account of its low lipid solubility. In our patients, excretion of catecholamines did not vary significantly during sotalol treatment but this does not exclude a decrease of the activity of the sympathetic nervous system.

Therapeutic use

High doses of beta-receptor blocking drugs are generally advised in the treatment of hypertension (Zacharias, Cowen, Prestt, Vickers & Wall, 1972). For sotalol, Prichard & Boakes (1974) emphasized the wide range of the useful doses, which varied between patients from 0.19 to 12.95 mmol (60–4000 mg) daily. In our experience, the maximal hypotensive effect was obtained with doses, which varied according to the patients, between 0.52 and 3.24 mmol (160–1000 mg) per day. However, the highest dosages were more frequently accompanied by severe bradycardia, with the risk of syncope and/or appearance of ectopic beats. Therefore it seems reasonable to maintain the patients with a heart rate above 55 beats/min. No other important side effect was observed in patients treated by sotalol. The renal function did not deteriorate during the treatment, even in cases of severe renal insufficiency. This finding conflicts with the observations of Warren, Swainson & Wright (1974), who found a rapid deterioration in renal function after beta-receptor blockade in patients with chronic renal failure and hypertension. However, in the experience of Kincaid-Smith, Fang & Laver (1973) this deterioration was temporary. Besides, the patients in the last-named report, as well as ours, with renal insufficiency, even severe, were given as high doses of propranolol or sotalol as patients with normal renal function without appearance of side effect.

Acknowledgments

This work was supported by a grant (no. 3.4547.75) from the Belgian Foundation for Medical Research and by the Lekime-Ropsy Foundation Brussels, Belgium. Sincere thanks are offered to Professor P. P. Lambert for encouragement and helpful criticism. We are also indebted to Dr H. M. Brems for aid and assistance. Renin and angiotensin II determinations were performed with the aid of Mr J. M. Giot and Mr W. Jacobs. Sotalol was supplied by Bristol–Myers International.

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