EFFECT OF KETANSERIN ON SODIUM NITROPRUSSIDE REQUIREMENTS, ARTERIAL PRESSURE CONTROL AND HEART RATE FOLLOWING CORONARY ARTERY BYPASS SURGERY

N. B. A. HODSMAN, J. R. COLVIN AND G. N. C. KENNY

Between 30 and 60\(^\circ\) of patients develop early hypertension following cardiac bypass surgery and require the administration of short-acting vasodilator agents [1,2]. This early hypertension develops within the first 4–6 h after cardiopulmonary bypass, and is associated with many factors, including patient arousal, pain and tracheal suction. The presence of increased concentrations of circulating catecholamines, serotonin and activation of the renin–angiotensin system also may contribute [3,4]. Close control of arterial pressure is necessary to reduce the incidence of bleeding from suture lines and protect the myocardium from ischaemia [1,3]. Sodium nitroprusside (SNP) is one of the most commonly used agents; however, it can cause reflex tachycardia and, by reducing diastole, can lead to a decrease in coronary blood flow, especially to the endocardium.

Ketanserin is a serotonin S\(_2\) receptor antagonist with weak alpha-1 blocking properties. It has been shown to reduce systemic arterial pressure by decreasing peripheral vascular resistance without causing reflex tachycardia [5]. It causes peripheral arteriolar dilatation, thereby decreasing left ventricular afterload, and may reduce right atrial pressure by venodilatation or indirectly by an improvement in left ventricular function [6]. Ketanserin has been shown also to prolong the duration of the cardiac action potential and has properties similar to Class III antiarrhythmic drugs [7]. These features should make ketanserin a useful vasodilator after cardiac surgery, reducing myocardial work and oxygen consumption. Several studies have shown ketanserin to be effective in reducing arterial pressure [5–8], but a wide range of infusion rates has been used and the optimum dose for the acutely hypertensive patient has not been determined.

A double-blind, placebo-controlled study was undertaken to determine the efficacy of ketanserin in patients who had undergone elective coronary artery bypass surgery and who required antihypertensive therapy. SNP was used as escape medication and was delivered by a computer-controlled closed-loop system which has been shown in previous studies to provide better control of arterial pressure than that provided with manual alteration of vasodilators by nursing staff [9,10].

SUMMARY

In a double-blind, placebo controlled study ketanserin, a serotonin S\(_2\) antagonist, was administered to hypertensive patients who had undergone coronary artery bypass surgery. Patients were allocated randomly to receive placebo or ketanserin at an infusion rate of 0.05, 1 or 2 mg kg\(^{-1}\) h\(^{-1}\). Sodium nitroprusside was used as escape medication. Ketanserin reduced the nitroprusside requirements and improved the quality of arterial pressure control in all groups, and this was significant in the low- and high-dose groups. There was a significant decrease in heart rate in the low- and high-dose groups compared with placebo, and no effect in patients who received the medium dose of ketanserin. Ketanserin may be a useful treatment for hypertension following coronary artery surgery as it reduced arterial pressure without reflex tachycardia.


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PATIENTS AND METHODS

We studied patients undergoing elective coronary artery bypass grafting (CABG) following their informed consent. Patients were not included if they were aged less than 30 or more than 70 yr, weighed less than 45 kg or more than 100 kg, lost more than 1 litre of blood after operation or had severe hepatic, renal or respiratory disease.

All patients received an opioid-midazolam based anaesthetic and all underwent elective ventilation to normocapnia in the cardiac intensive care unit after operation. Monitoring consisted of continuous measurement of ECG, direct arterial pressure and core temperature, with intermittent recordings of central venous pressure and urine output. Arterial blood-gas values, haematocrit and potassium concentrations were measured at the discretion of the cardiac surgeons and also at the start and end of the study.

Patients who had given informed consent and who required vasodilator therapy for post-surgical hypertension were entered into the study and connected to a closed-loop arterial pressure controller which consisted of an Atari 1040 ST microcomputer interfaced to a computer-controlled IMED 929 infusion pump. Sodium nitroprusside, in a dilution of 100 mg in 5%, dextrose 250 ml was used as escape medication in all patients initially, but this concentration was doubled if the SNP requirements were high and there was concern over the volume of fluid administered. The cardiac surgeons prescribed the desired target systolic arterial pressure for each patient.

Ketanserin may prolong the Q–T interval [11] and there have been reports of ventricular arrhythmias [12]. As hypokalaemia also prolongs QTcorr (corrected Q–T interval) and is a risk factor for arrhythmia, patients with a serum potassium concentration of less than 3.5 mmol litre⁻¹ were not included in the study until administration of potassium had increased the serum concentration to a value greater than 3.5 mmol litre⁻¹. The ECG for each patient was examined before operation and during the infusion of test drug to determine the effect of ketanserin on the Q–T interval.

Patients were allocated randomly to one of four groups:
(a) Group P received placebo: a bolus dose of 10 ml followed by an i.v. infusion.
Each patient allocated to receive ketanserin was given a loading i.v. dose of 10 mg in saline 10 ml followed by an infusion:
(b) Group L (low dose) received 0.05 mg kg⁻¹ h⁻¹
(c) Group M (medium dose) received 0.1 mg kg⁻¹ h⁻¹
(d) Group H (high dose) received 0.2 mg kg⁻¹ h⁻¹
The infusion was given for a maximum of 8 h or until the SNP requirements had been zero for 30 min.

The arterial pressure, heart rate, quality of arterial pressure control as assessed by variation from the prescribed target pressure, SNP infusion rate and total volume of SNP infused were recorded for each patient on to computer disk every 1 min during the administration of the trial drug and for 1 h after the infusion had been discontinued. The patients received midazolam and morphine at the discretion of the nursing or medical staff. No addition vasodilator or anti-hypertensive therapy was permitted.

Demographic data were analysed using Student's t test. Non-parametric data were analysed by a two-tailed Mann–Whitney U test or Chi-square test.

RESULTS

Forty-four patients were entered into the study; three were excluded from subsequent analysis: two because of errors in data collection and one after receiving propranolol for persistent tachycardia. There were 10 patients in groups P, L and M, and 11 patients in group H.

There was no significant difference between the group for age, weight or sex (table I). There was a small (0.6 °C) but statistically

| Table I. Comparison of age, weight, sex and initial temperature (mean (SD)). *P < 0.05 |
|-----------------|-------|-------|-------|-------|-------|
|                | Group P | Group L | Group M | Group H |
| Age (yr)       | 54.4 (7.7) | 53.9 (8.9) | 56.7 (6.5) | 53.1 (9.1) |
| Sex (M:F)      | 7:3 | 9:1 | 9:1 | 10:1 |
| Weight (kg)    | 77.5 (6.5) | 79.6 (9.9) | 76.3 (4.7) | 77.7 (11) |
| Temperature at start (°C) | 35.1 (1.5) | 35.5 (0.5)* | 35.2 (1.1) | 34.7 (0.6) |
significant difference between groups L and H for core temperature at the start of the study ($P < 0.05$). There were no significant differences between the groups for target pressure assigned by the surgeon or for blood loss during the study.

There were no significant differences between the groups for the numbers of patients treated before operation with beta-blockers, or for the numbers treated with the longer acting drug, atenolol.

**Duration of test infusions**

The test infusions were discontinued after 8 h or when the SNP requirements had been zero for 30 min. The durations of infusions of the trial drug were analysed for each patient (table II). The median times during which the trial drugs were infused were significantly less for all patients receiving ketanserin compared with those receiving placebo.

**Nitroprusside requirements**

The sodium nitroprusside requirements at various periods for the four groups are shown in table III. At 30 min from the start of the test infusion, and for the entire duration of the study, patients receiving ketanserin required less SNP than those who received placebo, although the difference was not significant for those in group M. As the durations of test infusions were significantly different, the mean hourly requirements of SNP during the infusions were analysed for each group. The patients who received ketanserin required less SNP per hour during ketanserin infusion, and this was significant in group L ($P < 0.05$) and group H ($P < 0.001$). When the infusions had been discontinued, the SNP requirements for the next 1 h were such that those patients who received medium and high doses of ketanserin needed less SNP than group L ($P < 0.05$, $P < 0.05$, respectively) although the differences were not significant compared with group P.

The median SNP requirements from the time of arrival in the intensive care unit until entry into the study (administration of trial drug) were significantly different (table IV): group P required less SNP than groups M and H ($P < 0.05$), and group L required less than group M ($P < 0.01$) and group H ($P < 0.05$).

**Quality of arterial pressure control**

The quality of control arterial pressure was assessed as a percentage of the time spent outside the target pressure ±10 mm Hg (table V). There was no significant difference between the groups for percentage time spent at pressures more than 10 mm Hg below the target, or for pressure

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**Table II. Median (range) duration of test infusions. *P < 0.05; **P < 0.01; ***P < 0.001**

<table>
<thead>
<tr>
<th></th>
<th>Group P</th>
<th>Group L</th>
<th>Group M</th>
<th>Group H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (h)</td>
<td>7.2 (1.7-8.0)</td>
<td>3.0 (0.5-8.0)*</td>
<td>3.0 (0.5-7.3)*</td>
<td>2.1 (0.6-7.8)***</td>
</tr>
</tbody>
</table>

**Table III. SNP requirements (median (range)). *P < 0.05; **P < 0.01; ***P < 0.001**

<table>
<thead>
<tr>
<th>Volume of SNP infused (ml)</th>
<th>Group P</th>
<th>Group L</th>
<th>Group M</th>
<th>Group H</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 30 min after bolus of trial drug</td>
<td>12 (2-44)</td>
<td>3 (0-10)**</td>
<td>8 (0-36)</td>
<td>3 (0-15)***</td>
</tr>
<tr>
<td>While trial drug infused</td>
<td>111 (9-780)</td>
<td>17 (0-333)*</td>
<td>54 (0-204)</td>
<td>11 (1-168)***</td>
</tr>
<tr>
<td>Per hour of study</td>
<td>22 (5-95)</td>
<td>6 (0-42)*</td>
<td>11 (0-33)</td>
<td>7 (1-22)***</td>
</tr>
<tr>
<td>First 1 h after infusion</td>
<td>5 (0-98)</td>
<td>4 (0-43)</td>
<td>1 (0-5)*</td>
<td>0 (0-20)*</td>
</tr>
</tbody>
</table>

**Table IV. Median (range) volume (ml) of SNP required in the 10 min before bolus dose given. *P < 0.05; **P < 0.01 compared with placebo; †P < 0.05 compared with low-dose group**

<table>
<thead>
<tr>
<th></th>
<th>Group P</th>
<th>Group L</th>
<th>Group M</th>
<th>Group H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>0.6 (0.3-4.3)</td>
<td>1.1 (0.4-2.1)</td>
<td>2.7 (0.9-9-10)***†</td>
<td>3.5 (0.5-7.2)*†</td>
</tr>
</tbody>
</table>
TABLE V. Quality of arterial pressure control: % time spent at pressures greater than 10 mm Hg above target pressure (median (range)). Compared with group P: \*P < 0.05; \**P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th>Time at target + 10 mm Hg (%)</th>
<th>Group P</th>
<th>Group L</th>
<th>Group M</th>
<th>Group H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 h</td>
<td>21 (3-37)</td>
<td>3 (0-45)*</td>
<td>12 (2-27)</td>
<td>7 (0-18)**</td>
</tr>
<tr>
<td>0-2 h</td>
<td>19 (4-33)</td>
<td>4 (0-41)*</td>
<td>10 (3-21)</td>
<td>4 (0-17)**</td>
</tr>
</tbody>
</table>

greater than target at times over 2 h. These results show that better quality of control of arterial pressure was achieved in all groups, although this did not reach significance in the medium dose group.

**Ketanserin and heart rate**

Previous studies have shown that ketanserin tends to reduce or have minimal effect on heart rate, whereas SNP tends to produce tachycardia [5,13,14]. Mean heart rate for each patient was analysed for 10 min before ketanserin was administered, and for the 10 min after the bolus dose was given. There was a significant increase in heart rate 10 min after the bolus dose of placebo had been given compared with the heart rate before administration (P < 0.05), but a significant decrease in heart rate in the low- and high-dose groups compared with the heart rate before ketanserin had been given (P < 0.05). These results (table VI) confirm that ketanserin does not cause tachycardia.

ECG recordings of all the patients were obtained before operation and also during the study to determine the effect of ketanserin on the corrected Q-T interval (QT\textsubscript{corr}). No significant differences were found between the groups for QT\textsubscript{corr} before or after the infusion of ketanserin, and there was no significant change in QT\textsubscript{corr} within each group.

**DISCUSSION**

We have shown that ketanserin controlled hypertension following coronary artery bypass surgery; this is in agreement with previous findings [15,16].

At the beginning of the study, the bolus dose of trial drug was given slowly but undiluted and this produced a marked, rapid decrease in systolic arterial pressure in two patients. Both these patients were found subsequently to have received the active drug and they also had relatively low central venous pressures. The arterial pressure returned to acceptable values with rapid i.v. infusion of fluid. All subsequent bolus doses were diluted thereafter and injected over a period of 10 min, without adverse effect on arterial pressure.

The effects of ketanserin and SNP were found to be additive and ketanserin infusion reduced the requirement for SNP, resulting in a reduced duration and volume of SNP infusion.

SNP requirements from the time of admission into the intensive care unit until the study commenced showed that patients in the medium- and high-dose groups required significantly more SNP than patients in either the placebo or the low-dose group. Analysis of SNP requirements during the period before the study suggested that the arterial pressure of patients in the medium- and high-dose groups was significantly more difficult to control. While the high dose of ketanserin appeared to be adequate in overcoming this difficulty, the medium dose was not.

The quality of arterial pressure control for patients who received ketanserin was better compared with those in the placebo group. There was no significant difference between the treated groups and placebo for the percentage time spent below the target pressure, indicating that although ketanserin reduced arterial pressure, it did not do so excessively.

Our data on the effect of ketanserin on heart rate support other studies [15], in that patients who received ketanserin did not exhibit reflex tachycardia. Analysis of the individual ECG records of each patient showed that in this study, in contrast with the small prolongation of QT\textsubscript{corr} reported previously after oral use [11], ketanserin had no effect on the corrected Q-T interval.

Several patients developed ECG abnormalities during treatment (two in the placebo group, two in the ketanserin low-dose group and two in the high-dose group); these were considered to be caused by patient arousal or, in one patient (ketanserin high dose), by a low concentration of potassium.
One patient, who had been allocated to receive the high dose of ketanserin, had short periods of ventricular bigemini and trigemini, alternating with intermittent bradycardia and 1st degree heart block for a few seconds. The arterial pressure remained stable throughout. However, the possibility of this response being related to the trial drug could not be excluded.

ACKNOWLEDGEMENT
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