Ketanserin in the treatment of hypertension following coronary artery bypass surgery

A preliminary study

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Summary

The possible role of 5-hydroxytryptamine (serotonin) in patients developing hypertension following coronary artery bypass surgery was investigated by intravenous administration of ketanserin, a specific 5-hydroxytryptamine-receptor antagonist. Our findings in the preliminary study indicate that 5-hydroxytryptamine might not play a role in the hypertension seen after coronary artery bypass surgery.

Hypertension is known to be a common complication after open-heart surgery, particularly after coronary artery bypass surgery. It has been estimated to occur in 30 - 50% of cases. Many causes of this complication have been described, including elevation of plasma levels of adrenaline, noradrenaline, antidiuretic hormone and angiotensin, as well as factors such as haemodilution and activation of reflex pressor mechanisms. It is possible that 5-hydroxytryptamine (5-HT) (serotonin) may play a role in the hypertension seen after coronary artery bypass surgery because this compound can be released from platelets. We decided to conduct a study to investigate whether the postoperative hypertension seen in patients submitted to coronary artery bypass surgery could be treated effectively and safely with ketanserin, a specific 5-hydroxytryptamine-receptor antagonist.

Patients and methods

Twenty patients varying in age from 32 to 67 years (5 were aged 32-40 years, 6 41-50 years, and 9 51-67 years) and weighing between 51 and 120 kg (2 weighed 51-60 kg, 1 61-70 kg, 6 71-80 kg, 4 81-90 kg, 4 91-100 kg, and 3 111-120 kg) were entered into the study. All patients gave informed consent to participation in the study.

The patients underwent bypass procedures varying from 130 to 360 minutes in duration; anaesthesia lasted between 150 and 390 minutes. Five patients received one bypass graft, 5 patients two grafts, 8 patients three grafts and 2 patients four grafts. Recognizing the large number of patient variables and intra- and postoperative variations we tried to standardize anaesthesia and postoperative care.

Anaesthetic technique

Patients received lorazepam 2.5 mg the night before the operation. As premedication intramuscular papaveretum 0.3 mg/kg, with a maximum of 15 mg, was given 60 minutes before induction. The same anaesthetic technique was used in all cases. Anaesthesia was induced with etomidate 0.3 mg/kg, fentanyl 10 μg/kg and pancuronium 0.1 mg/kg. The patients were mechanically ventilated with a mixture of 50% nitrous oxide and 50% oxygen. Ventilation was guided by monitoring the blood gas values in arterial blood samples.

Before median sternotomy, during cardiopulmonary bypass and before closure of the sternum incremental doses of fentanyl 5 μg/kg and pancuronium were given.

Intra-operative monitoring

A Swan-Ganz flow-directed thermodilution catheter (model 93A-131-7F) was placed in the pulmonary artery for registration of pulmonary artery and pulmonary capillary wedge pressures and a cardiac output computer (model 9520) was used to monitor cardiac output and core temperature. A radial artery cannula (Teflon Abbocath-T 20-gauge cannula) was inserted before induction of anaesthesia. On arrival in the operating theatre ECG leads II and V5 were connected, temperature (rectal, nasopharyngeal and pulmonary arterial), urine output, blood loss, blood gas and electrolyte values and the haematocrit were monitored, and the amount of intravenous fluids given was recorded.

Postoperative care

Artificial ventilation was continued during transfer to the intensive care unit and for 12 hours postoperatively, aiming at an arterial carbon dioxide pressure of 35-40 mmHg and an arterial oxygen pressure of 90 - 100 mmHg.

Care was taken that sedation and analgesia were adequate in all cases and that the patients were free of respiratory difficulties. On arrival in the intensive care unit each patient received clo thiapine (40 mg) and morphine sulphate (15 mg) for sedation and analgesia. This was repeated when necessary. Each patient received transcutaneous nitroglycerin ointment (40 mg) every 3 hours.

A hypertensive episode was defined as a period of sustained raised mean blood pressure (over 90 mmHg), provided that this rise was not reversed by sedation or analgesia and that there was no evidence of hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube.
Patients with hypertension were treated with an intravenous dose of 10 mg ketanserin injected over a period of 3 minutes. A continuous infusion of ketanserin 20 mg/h was also started. A further 10 mg dose of ketanserin was given intravenously after 30 minutes if necessary to control the blood pressure.

Systolic, mean and diastolic blood pressures and the heart rate were recorded at and 1, 2, 3, 4, 5, 10, 15, 30, 60, 120 and 360 minutes after the start of treatment. Systolic, mean and diastolic pulmonary arterial pressures, pulmonary capillary wedge pressure, cardiac output, central venous pressure and temperature were recorded at and 5, 15, 30, 60, 120 and 360 minutes after the start of treatment. Total peripheral vascular resistance, pulmonary vascular resistance, stroke volume and the rate pressure product and triple index were calculated.

Changes induced by the injection of ketanserin were evaluated for statistical significance using the BMDP 1R linear regression analysis model for 0-15, 0-120 and 0-360 minutes. A paired t test was used as the control for 0-5, 0-15, 0-30, 0-60, 0-120 and 0-360 minutes.

Seventeen patients (85%) developed hypertension in the postoperative period.

Systolic arterial pressures before administration of ketanserin varied from 107 to 180 mmHg (median 133 mmHg). Diastolic pressures varied from 70 to 87 mmHg (median 79 mmHg) and mean pressures from 92 to 121 mmHg (median 98 mmHg). The effect of ketanserin on arterial blood pressure is illustrated in Fig. 1. The decrease in systolic blood pressure was statistically significant over a period of 0-120 minutes after the start of treatment (P < 0.01). Diastolic and mean blood pressures were significantly (P < 0.001) decreased over a period of 0-360 minutes. No statistically significant decrease in arterial blood pressure occurred during the first 30-60 minutes after the start of treatment.

No statistically significant regression of the systolic, diastolic and mean pulmonary arterial pressures or of pulmonary capillary wedge pressure was noted over the 0-360-minute period (Figs 2 and 3). The decrease in pulmonary capillary wedge pressure was significant according to the paired t test over periods of 0-5, 0-15, 0-30, 0-60 and 0-120 minutes after the start of treatment (P < 0.05).

The increases in central venous pressure and heart rate were significant over a period of 0-360 minutes after the start of treatment (P < 0.05) but not over the periods of 0-15 or 0-120 minutes (Fig. 3).

Cardiac output did not increase to a statistically significant extent over a period of 0-360 minutes (Fig. 4). However, according to the paired t test, the decrease in cardiac output was significant (0-15 minutes P < 0.01, 0-30 minutes P < 0.05, and 0-60 minutes P < 0.01). The increase in temperature was significant (P < 0.001).

The decrease in total peripheral vascular resistance was significant (P < 0.01) over a period of 0-360 minutes (Fig. 5). According to the paired t test there was a statistically significant rise in total peripheral vascular resistance over a period of 0-15 minutes (P < 0.05). Pulmonary vascular resistance, stroke...
volume and the rate/pressure product and triple index did not change significantly.

No untoward effects were noticed during or after administration of ketanserin.

Discussion

Sodium nitroprusside, nitroglycerin and other vasodilating agents are often used to treat postoperative hypertension after coronary artery surgery. The main disadvantage of these compounds is that they can cause reflex tachycardia.

Some clinicians consider that these agents produce an improvement in left ventricular function and myocardial oxygenation.5 6 Others claim that sodium nitroprusside may cause subendocardial ischaemia by lowering the diastolic arterial pressure and causing reflex tachycardia.7

It is believed that ketanserin is capable of lowering the pre- and afterload of the heart by decreasing peripheral vascular resistance.8 11 Ketanserin is a quinazoline derivative and a specific serotonin antagonist.12

The endocardial viability ratio (EVR) may be indicative of myocardial ischaemia.13 The EVR is calculated as follows:

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EVR = \frac{MDP - LVDP}{DT} \times \text{MSP} \times ST
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where MDP = mean diastolic arterial pressure, LVDP = left ventricular diastolic pressure, DT = diastolic time, MSP = mean systolic arterial pressure, and ST = systolic time. The EVR takes into account both oxygen supply and demand. Since the relation of diastolic to systolic time stays constant for a heart rate below 150/min we found a decrease in the EVR during treatment with ketanserin. When using this drug one should be aware of the possibility that it can cause subendocardial ischaemia.

The rate/pressure product is seen as a good indication of myocardial oxygen demand.11 Although no statistically significant change was noted, the rate/presure product showed a decreasing inclination over the period of 0 - 120 minutes. Thereafter it tended to rise again. This rise may be due to the fact that some patients had low blood levels of ketanserin at that stage. Our results show that ketanserin may cause an increase in myocardial oxygen demand. An advantageous finding is the significant lowering of total peripheral resistance, but this is unfortunately not associated with a decrease in pulmonary vascular resistance and a significant increase in cardiac output. Pre- and afterload therefore did not decrease significantly, while diastolic pressure did decrease significantly — all factors that may be disadvantageous to the heart's oxygen balance. The drug also did not produce a dramatic reduction in blood pressure.

Conclusion

The findings in the preliminary study indicate that 5-HT might not play a role in the hypertension seen after coronary artery bypass surgery. Other factors will have to be considered. In view of favourable findings elsewhere when ketanserin has been used in the treatment of hypertension, it should be investigated further.

REFERENCES