Acute Cardiovascular Effects of Ro5-4200: A New Anaesthetic Induction Agent


SUMMARY

Anaesthesia was induced in 12 patients by intravenous injection of Ro5-4200, a benzodiazepine. Consciousness was lost following injection of 2 - 3 mg, given at a rate of 1 mg per minute.

Respiratory minute volumes were well maintained, but arterial oxygen saturation fell significantly, by 1,5%. There was a 17% increase in heart rate; a 26% fall in mean arterial blood pressure; a 31% fall in stroke volume and a 24% drop in peripheral vascular resistance.

Cardiac output was well maintained at control levels. The drug appeared to be compatible with ancillary drugs commonly used in anaesthetic practice. Post-operative recovery was uneventful.


Ro5-4200 is a tranquilizer of the benzodiazepine group. In animal experiments it possesses marked sedative, muscle relaxant and spasmolytic properties. Use of the drug as a muscle relaxant and anticonvulsant in man was complicated by a high incidence of drowsiness, muscle weakness and ataxia. The hypnotic qualities suggested a place for the drug as a sedative before anaesthesia, and as an intravenous anaesthetic induction agent. Diazepam, another member of this group of drugs, already has an established place in anaesthetic practice.

In this communication, we report the immediate cardiopulmonary effects of Ro5-4200 when given by intravenous injection for induction of anaesthesia.

METHODS

Twelve male patients, aged 20 - 40 years, who gave their consent, were investigated before elective minor surgery. The patients' weights ranged from 50 to 70 kg, and heights from 160 to 170 cm. No clinical evidence of cardiopulmonary disease was found in any case. All patients were given, one hour before commencement of the study, 15 mg papaveretum and 0,4 mg hyoscine.

Upon arrival in theatre, plastic catheters were inserted percutaneously, under local analgesia, into the radial artery, and into the right atrium from a right antecubital vein. Pressures were measured by Statham gauge transducers, supported 7,5 cm above the surface of the operating table, and recorded continuously on a Philips 3T recorder. Heart rate was measured using a SAN-E12D16 pulse meter and a finger photo cell.

Cardiac output was measured by dye dilution using indocyanine green and a Philips XO-1000 combined oximeter/densitometer cuvette. Arterial oxygen saturation and haemoglobin were measured during the cardiac output estimation. A lead I ECG was recorded continuously during the study.

Exhaled carbon dioxide levels were measured, using the Beckman LB-1 infrared gas analyser, sampling continuously from a point 2 cm within the external nares. The output of the analyser was displayed upon a panel meter and recorded continuously on a 25 cm Beckman potentiometric recorder. At the conclusion of each experiment, the cardiac output densitometer was calibrated, using each patient's own blood and known doses of cardiac green. Cardiac output was calculated using the method of Williams et al. to prepare an appropriate programme for an Olivetti digital computer. Total peripheral vascular resistance (PVR) was calculated from the formula of Aperia:

\[
PVR = \frac{mean \text{ arterial pressure (mmHg)}}{\text{Cardiac output (litre/min)}} \times 80 \text{ dynes/sec cm}^{-2}
\]

Tests of statistical significance were applied to the mean differences in measurement made in the control periods before induction of anaesthesia with Ro5-4200, and afterwards by applying Student's t-test to the paired comparisons.

Patients were left undisturbed following introduction of the catheters, until heart rates and arterial pressures were steady. Cardiac output, arterial oxygen saturation and haemoglobin estimations were then made at about 3-minute intervals, till the areas of at least two dye dilution curves appeared to agree within 10%, and the arterial oxygen saturation was steady to within 1%. Blood pressures and heart rates at this moment were noted, and served as the control measurements. Anaesthesia was induced by injecting Ro5-4200 into the tubing of an intravenous infusion containing Ringer's lactate. The drug was given at a rate of 1 mg/min until the patient failed to respond to an auditory stimulus and the lash reflex disappeared. Control measurements were repeated 2 and 5 minutes after loss of consciousness.

*Date received: 18 September 1972.
RESULTS

Ro5-4200 2 - 3 mg were required to produce loss of consciousness. Usually, therefore, the induction period lasted for a period of 2 - 3 minutes. Induction of anaesthesia with this agent appeared to be pleasant and was not accompanied by excitatory phenomena.

Respiratory Effects

Respiratory frequency, as indicated by the capnographic record, was unchanged. The end-expired carbon dioxide level fell insignificantly (Fig. 1), indicating that alveolar ventilation was well maintained.

Arterial Oxygen Level

The arterial oxygen level fell significantly from a mean value of 91.9% in the control period to 89.2% and 89.7% 2 and 5 minutes after loss of consciousness ($P < 0.05$).

Cardiovascular Effects

The cardiovascular effects of Ro5-4200 are shown in Table I.

![Fig. 1. Typical capnographic record of exhaled air following induction of anaesthesia with Ro5-4200.](image)

**TABLE I. THE CARDIOPULMONARY EFFECTS OF RO5-4200**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Control</th>
<th>Minutes after loss of consciousness</th>
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<tbody>
<tr>
<td></td>
<td>+2</td>
<td>+5</td>
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<tr>
<td>Heart rate (beats/min) (SD)</td>
<td>75 (22.71)</td>
<td>90 (19.06)$^+$</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg) (SD)</td>
<td>96 (13.88)</td>
<td>71 (15.8)$^+$</td>
</tr>
<tr>
<td>Mean central venous pressure (mmHg) (SD)</td>
<td>2.89 (1.83)</td>
<td>1.49 (2.6)$^*$</td>
</tr>
<tr>
<td>Cardiac output (litre/min) (SD)</td>
<td>7.8 (2.49)</td>
<td>7.4 (2.14)</td>
</tr>
<tr>
<td>Stroke volume (ml) (SD)</td>
<td>104 (21.98)</td>
<td>83 (22.72)$^+$</td>
</tr>
<tr>
<td>Peripheral vascular resistance (dynes/sec cm$^{-2}$) (SD)</td>
<td>1 042 (306.37)</td>
<td>802 (196.95)$^+$</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%) (SD)</td>
<td>91.9 (1.74)</td>
<td>89.2 (3.59)$^+$</td>
</tr>
</tbody>
</table>

Levels of significance: *$P<0.05$; †$P<0.025$; ‡$P<0.001$; ¶$P<0.005$; §§$P<0.001$.

Changes in heart rate and blood pressures commenced within 30 seconds of commencement of injection. Heart rate increased significantly by 15 beats a minute, from a control level of 75 ($P < 0.005$). There was a significant fall in the mean arterial blood pressure of 20 - 30 mm Hg ($P < 0.001$). Mean central venous pressure also fell by about 1.5 mmHg ($P < 0.05$). Cardiac output was well maintained at the control level of about 7 litres per minute. There was a significant fall in the stroke volume of 20 - 25 ml ($P < 0.01$). Peripheral vascular resistance fell significantly at each period of measurement by about 200 dynes ($P < 0.005$) (Fig. 2).

Subsequent Operative and Postoperative Course

The study of the immediate cardiovascular effects of Ro5-4200 was considered complete 5½ minutes after loss of consciousness, and 20 mg alcuronium (a non-depolarizing muscle relaxant) was given to all patients to facilitate endotracheal intubation. Patients were connected to a Manley respirator delivering an expired minute volume of about 5 litres (70% nitrous oxide and 30% oxygen). Minute volumes were adjusted to maintain end-expired carbon dioxide levels between 4% and 5%. No further doses of muscle relaxant drugs were given, and surgery was complete in all instances within 2½ hours of induction of anaesthesia.

No difficulty was experienced in reversing the residual effects of muscle relaxant drugs with neostigmine. All patients, although drowsy, were capable of obeying simple commands on the table at the end of surgery. No nausea or vomiting occurred within 1 hour of completion of surgery.

DISCUSSION

Thiopentone, propanidid and althesin will produce loss of consciousness within 1 minute of injection, and are therefore classified as rapid-acting intravenous anaesthetic induction agents. Ro5-4200 cannot strictly be classed with these drugs because induction of anaesthesia was protracted in this study for periods ranging from 120 to 180 seconds.

Respiratory effects of the drug compare favourably with thiopentone or althesin. In this study, the mean
fall in arterial oxygen saturation, following induction of anaesthesia with Ro5-4200, was about 1.5%; the mean falls, after sleep doses of althesin or thiopentone, were about 7% and 4%, respectively. The respiratory minute volume was maintained at control levels after induction of anaesthesia, indicating that the drop in arterial oxygen saturation was due to increased physiological shunt.

The cardiovascular effects of Ro5-4200 were similar in most respects to those occurring after sleep doses of either thiopentone or althesin. In a comparable study performed on unpremedicated subjects in this laboratory, thiopentone and althesin were associated with an increase in heart rate of about 25%, a fall in mean arterial blood pressure of about 22%, and a fall in peripheral vascular resistance of the order of 24%. There was no significant change in cardiac output following induction of anaesthesia with thiopentone or althesin. In this study, administration of Ro5-4200 was associated with a 17% increase in heart rate, a fall in mean arterial blood pressure of 26%, a fall in stroke volume of 31% and a fall in peripheral vascular resistance of 24%. The exact mechanism of the changes in cardiovascular status following induction of anaesthesia with Ro5-4200 is uncertain, although the pattern appears to resemble that which follows injection of thiopentone or althesin; peripheral vascular resistance and blood pressure falls, heart rate increases and the cardiac output either increases or is unchanged. These changes suggest a peripheral site of action, with hypotension due to peripheral vasodilatation producing a reflex tachycardia, with maintenance of cardiac output.

In view of the above observations Ro5-4200 appears to be worthy of further clinical trials.

REFERENCES