THE EFFECT OF METHOHEXITONE ON MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION IN THE DOG

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SUMMARY

Methohexitone in doses of 2 mg/kg and 4 mg/kg was administered via a right atrial catheter to mechanically ventilated dogs lightly anaesthetized with trichloroethylene. The drug caused a significant initial increase in heart rate and a decrease in mean arterial pressure with both doses and a decrease in cardiac output. There was a significant reduction in myocardial blood flow, and myocardial oxygen availability and consumption following both doses. Neither dose caused any change in myocardial oxygen extraction.

Since the introduction of methohexitone to clinical practice in 1956, there have been many studies of its haemodynamic effects. Consistent findings include a reduction in arterial pressure and an increase in heart rate (Dobkin and Wyant, 1957; Sankawa, 1965; Conway, Ellis and King, 1968; Rowlands et al., 1967) whilst variable changes have been reported in cardiac output and total peripheral resistance (Dobkin and Wyant, 1957; Sankawa, 1965; Rowlands et al., 1967). The present study was designed to repeat these measurements and to examine the effect of methohexitone on myocardial blood flow, myocardial vascular resistance and myocardial oxygen consumption and extraction.

METHODS

Ten healthy adult greyhounds (weight range 20–30 kg) were anaesthetized by an inhalational technique using 30% oxygen, 70% nitrous oxide and halothane vaporized from a Boyle bottle. Suxamethonium 100 mg was given intravenously and endotracheal intubation performed. The dogs were then ventilated using a Palmer pump and anaesthesia was maintained with 0.5–1.0% trichloroethylene, thecarrier gas being a mixture of nitrogen and oxygen. Intermittent doses of suxamethonium were given intramuscularly and the minute ventilation and inspired oxygen concentration were adjusted to maintain the PaCO₂ at about 40 mm Hg and the PaO₂ at about 100 mm Hg.

Catheters were positioned, under radiographic control, just within the orifice of the left coronary artery, and several centimetres into the coronary sinus. Other catheters were positioned in the descending aorta, and the right atrium. Arterial, right atrial and coronary sinus pH, PO₂ and PCO₂ were measured using Radiometer electrodes. Aortic and right atrial pressures were measured continuously using Elema-Schönander transducers and recorded during flow measurements on a Mingograf 81 ink-jet recorder together with the standard limb lead II electrocardiogram. Cardiac output was measured by the dye dilution technique using indocyanine green withdrawn through a Waters cuvette densitometer after injection of the dye into the right atrium. Stroke volume (ml) was calculated by dividing the cardiac output (ml/min) by heart rate (beat/min). Myocardial blood flow was measured using the inert gas clearance technique (xenon-133) as described by Ross et al. (1964). The methods used in our laboratory have been described in previous publications (Ledingham et al., 1970; Vance, Brown and Smith, 1973).

The following derived data were obtained as described previously (Ledingham et al., 1970; Vance, Brown and Smith, 1973): myocardial oxygen consumption, myocardial oxygen availability and myocardial oxygen extraction.

In addition, the following data were derived:
Before measurements were commenced, at least 1 hour was allowed to elapse after induction of anaesthesia and catheterization of the vessels.

Two dose levels of methohexitone were studied—2 mg/kg and 4 mg/kg given as a 1% solution, the order of administration of the two doses being randomized. One to two hours was allowed to elapse between injections so that stable haemodynamic, myocardial blood flow and blood gas readings were obtained before injection of the second dose. Complete sets of measurements were made immediately after and at 5 and 15 min after injection of the drug.

RESULTS

These are presented in the tables which give the mean control value for each variable ± standard error of the mean (SEM) accompanied by the mean differences (±SEM) from control levels immediately after and at 5 and 15 min after injection.

Following the 2 mg/kg dose of methohexitone, there was a gradual decrease in cardiac output accompanied by an initial tachycardia and decrease in stroke volume (table I). Myocardial blood flow decreased significantly at 5 and 15 min and there was an initial increase in right atrial pressure.

Myocardial vascular resistance showed an initial decrease followed by an increase which was significant at 15 min. Total peripheral resistance showed a similar pattern, although the changes were small and were not statistically significant.

Arterial, right atrial and coronary sinus \(P_{O_2}\), \(P_{CO_2}\) and pH remained unchanged throughout. Changes in myocardial oxygen availability accompanied the changes in myocardial blood flow. Myocardial oxygen consumption decreased throughout the 15-min period, the change being significant at 5 min and 15 min. Myocardial oxygen extraction was unchanged.

The pattern of results following 4 mg/kg of methohexitone was similar to that of the smaller dose with the changes in mean blood pressure (21%) and cardiac output (15%) being considerably greater (table II). Cardiac output was significantly reduced at 5 and 15 min. The trend in heart rate followed the same pattern as with the 2 mg/kg dose but the changes were not significant. Stroke volume decreased throughout the experiment. Myocardial blood flow was again unchanged immediately following injection but was significantly reduced at 15 min while right atrial pressure decreased initially but tended to return towards the control value after 5 min. Arterial \(P_{O_2}\), \(P_{CO_2}\) and pH were unaltered although myocardial oxygen availability and consumption decreased and myocardial oxygen extraction was unchanged.

### Table I. Methohexitone 2 mg/kg body weight.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Immediately postinjection</th>
<th>5 min</th>
<th>15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>207 ±14</td>
<td>+13 ±5.4*</td>
<td>+3 ±3.7</td>
<td>−6 ±7.7</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>160 ±5</td>
<td>−13 ±4.6†</td>
<td>−7.7 ±2.3†</td>
<td>−7.5 ±2.3*</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>0.6 ±0.9</td>
<td>+0.6 ±0.3*</td>
<td>+0.4 ±0.3</td>
<td>+0.4 ±0.3</td>
</tr>
<tr>
<td>Cardiac output (l./min)</td>
<td>4.04 ±0.41</td>
<td>−0.18 ±0.09</td>
<td>−0.30 ±0.13*</td>
<td>−0.30 ±0.13*</td>
</tr>
<tr>
<td>Myocardial blood flow (ml min(^{-1}) 100g(^{-1}))</td>
<td>127 ±14</td>
<td>−0.4 ±3.17</td>
<td>−8.6 ±3.7*</td>
<td>−15.8 ±3.2†</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>19.9 ±1.8</td>
<td>−1.9 ±0.5†</td>
<td>−1.6 ±0.7*</td>
<td>−1.0 ±0.8</td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
<td>44.2 ±5.9</td>
<td>−2.4 ±1.5</td>
<td>+0.25 ±1.5</td>
<td>+1.4 ±0.8</td>
</tr>
<tr>
<td>Myocardial vascular resistance (units)</td>
<td>139 ±13.3</td>
<td>−12.7 ±6.1*</td>
<td>+5.3 ±2.9</td>
<td>+12.7 ±2.8†</td>
</tr>
<tr>
<td>Myocardial (O_2) availability (ml min(^{-1}) 100g(^{-1}))</td>
<td>34 ±3.9</td>
<td>−0.7 ±0.8</td>
<td>−2.7 ±0.9*</td>
<td>−4.4 ±1.07†</td>
</tr>
<tr>
<td>Myocardial (O_2) consumption (ml min(^{-1}) 100g(^{-1}))</td>
<td>16.9 ±1.6</td>
<td>−0.6 ±0.5</td>
<td>−1.9 ±0.5†</td>
<td>−2.3 ±0.6†</td>
</tr>
<tr>
<td>Myocardial (O_2) extraction (%)</td>
<td>49.9 ±3.7</td>
<td>−0.6 ±1.1</td>
<td>−1.5 ±0.9</td>
<td>−0.45 ±1.1</td>
</tr>
</tbody>
</table>

Mean control value (±SEM) of each variable is presented along with the mean difference (±SEM) immediately after and at 5 and 15 min after injection of a dose of 2 mg/kg of methohexitone.

*Significantly different from control (P <0.05). †Significantly different from control (P <0.01).
Mean control value (± SEM) of each variable is presented along with the mean difference (± SEM) immediately after and at 5 and 15 min after injection of a dose of 4 mg/kg of methohexitone.

* Significantly different from control (P < 0.05). † Significantly different from control (P < 0.01).

## DISCUSSION

In this study, methohexitone caused an immediate decrease in mean arterial pressure accompanied, in the case of the smaller dose, by an increase in heart rate. A reduction in cardiac output also occurred but this was of slower onset and became increasingly more evident during the later observations, at which time the arterial pressure and heart rate were returning towards control levels.

Comparison of the effects of methohexitone on the cardiovascular system of man and animals is complicated by variations in the method of basal anaesthetic employed in other investigations. In this study, an attempt has been made to minimize the effects of background anaesthesia by using inhalational methods for induction and maintenance and avoiding the use of other barbiturates. The haemodynamic changes found in the present investigation, however, do not vary greatly from those described by previous workers. Sankawa (1965) using doses of 5 mg/kg body weight and 9 mg/kg in dogs found a reduction in arterial pressure of 20–50% and, after the larger dose, a significant reduction in cardiac output. Conway, Ellis and King (1968) using doses of 2 mg/kg and 4 mg/kg found that methohexitone produced a reduction of 9–20% in arterial pressure in anaesthetized dogs but no significant change in cardiac output. In man, Dobkin and Wyant (1957) using a dose of approximately 3 mg/kg found a 9% decrease in mean arterial pressure and a 15% reduction in cardiac output during induction of anaesthesia. Dormandy and Bullough (1969) found a mean decrease of 18% in arterial systolic pressure in eight patients with healthy cardiovascular systems using repeated doses of methohexitone to maintain light anaesthesia.

There is not the same uniformity in previous estimates of the effect of methohexitone on total peripheral resistance. Sankawa (1965) found a reduction of 50% in dogs, but in man, Dobkin and Wyant (1957) and Rowlands et al. (1967) found no significant change. In the present study, we also found no significant change in total peripheral resistance.

The maximum decrease in arterial pressure occurred immediately after injection of the methohexitone and possibly resulted from the combination of a reduction in total peripheral resistance and in cardiac output, although neither of these changes was in itself significant at this time. By 5 min, the total peripheral resistance had increased above the control level but because of the decrease in cardiac output, the mean arterial pressure was still significantly less than the control value. The reduction in cardiac output accompanied by a relatively stable total peripheral resistance suggests that methohexitone exerts its effects on systemic pressure, at least in part, by a direct depressant action on the myocardium. This suggestion is supported by the finding of a reduction in myocardial oxygen consumption.

Barbiturates have been shown to cause myocardial depression. This has been demonstrated by Gordh (1964) in rabbits, using a pneumopericardium to measure changes in heart size, and in intact dogs by Cotten and Bay (1956) using a strain gauge to measure the contractile force of the left ventricle. In a study of the effect of several drugs on myocardial contractility, assessed by the duration of the preinjection period, Blackburn et al. (1971) found that methohexitone caused a marked initial decrease in myocardial contractility followed by a rapid recovery.
In the present study, the maximum decrease in myocardial blood flow occurred at 15 min although the maximum changes in heart rate and systemic arterial pressure occurred within 1 min. In spite of the decrease in arterial pressure immediately after injection, the myocardial blood flow was maintained by a decrease in myocardial vascular resistance. Thereafter, there was a steady diminution in myocardial blood flow accompanied by an increase in myocardial vascular resistance. The initial reduction in myocardial vascular resistance may have been caused by a reflex increase in adrenergic discharge resulting from the hypotension, as suggested by Ganong (1969). The subsequent reduction in myocardial blood flow was undoubtedly caused by a variety of factors, including a reduction in perfusion pressure, cardiac work, and myocardial oxygen requirements.

As a result of the gradual reduction in oxygen consumption after the injection of methohexitone, the reduction in myocardial oxygen availability was not accompanied by any change in oxygen extraction. It has been shown that under certain conditions of decreased oxygen availability, the myocardium will increase its oxygen extraction to meet requirements (Vance, Parratt and Ledingham, 1971; Vance, Brown and Smith, 1973). From this, it would seem that the myocardium was not compromised by the haemodynamic changes induced by methohexitone. Although the systemic haemodynamic effects of methohexitone are of short duration, its myocardial vascular and metabolic effects appear to last considerably longer.

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REFERENCES


