HAEMODYNAMIC EFFECTS OF MIDAZOLAM AND THIOPENTONE DURING INDUCTION OF ANAESTHESIA FOR CORONARY ARTERY SURGERY


SUMMARY
The cardiovascular effects of thiopentone 3 mg kg\(^{-1}\) and midazolam 0.3 mg kg\(^{-1}\) were observed during induction of anaesthesia in 16 premedicated patients about to undergo myocardial revascularisation. There were no significant changes in either group in cardiac output or central venous pressure. The heart rate in both groups showed an increase at 3 min and thereafter returned to control values. After 3 min, there was a significant decrease in both arterial pressure and peripheral resistance by 12% and 15% (mean values) respectively from control values in the group receiving midazolam, whereas after thiopentone the peripheral resistance increased by approximately 13% and was not affected by a further dose of thiopentone 1 mg kg\(^{-1}\).

Midazolam maleate, a relatively new water-soluble benzodiazepine has been administered i.v. either to produce sedation or to induce anaesthesia (Conner et al., 1978; Fragen, Crahl and Caldwell, 1978; Reeves, Corssen and Halcomb, 1978; Reeves et al., 1979). Reeves, Samuelson and Lewis (1979) studied the haemodynamic effects of this drug during induction of anaesthesia in 10 patients undergoing myocardial revascularisation. Since then the drug has been reformulated as the hydrochloride and the study reported here compares the acute haemodynamic effects of thiopentone and midazolam hydrochloride when they were used to induce anaesthesia in patients undergoing coronary artery bypass surgery.

METHODS
Sixteen patients (14 male, two female) undergoing elective surgery for coronary artery disease consented to the investigation after the nature and purpose of the study had been explained to them. Relevant data are shown in table I. The patients were allocated to each group using a series of random numbers.

The doses of β-blockers required to minimize symptoms and cause resting heart rates around 70 beat min\(^{-1}\) vary widely in different patients with coronary disease: 40 mg to more than 500 mg daily for propanolol and 50 mg to more than 400 mg daily for atenolol. In the thiopentone group two patients were receiving propanolol (dose range 80–200 mg) and four received atenolol (dose range 100–200 mg daily). In the midazolam group, four had received atenolol (dose range 100–200 mg daily) and three propanolol (dose range 80–160 mg daily).

All patients received papaveretum 10–20 mg, hyoscine 0.2–0.4 mg and droperidol 5 mg i.m. approximately 60 min before induction of anaesthesia. In none of these patients was the ventricular function sufficiently impaired to justify pulmonary artery catheterization (Lowenstein and Teplick, 1980; Mangano, 1980) and measurements were restricted to those which can be obtained using conventional monitoring: heart rate, arterial pressure, central venous pressure and cardiac output (fig. 1).

When the patients arrived in the induction area a conventional four lead e.c.g. was recorded. I.v., radial artery and superior vena caval (via the right jugular vein) cannulae were introduced under local anaesthesia with 1% lignocaine. Mean and dynamic

**Table I Relevant patient data Where appropriate, values are mean ± SEM**

<table>
<thead>
<tr>
<th></th>
<th>Thiopentone</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.5 ± 1.88</td>
<td>57.2 ± 2.02</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.0 ± 2.77</td>
<td>76.0 ± 4.44</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.0 ± 2.42</td>
<td>172.0 ± 3.27</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/0</td>
<td>6/2</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
FIG. 1. Values (mean ± SEM) for cardiac output, central venous pressure, heart rate and mean arterial pressure during induction of anaesthesia. 0 = Control after preoxygenation, •—• = midazolam (n = 8); •—•—• thiopentone (n = 8). Only the following changes were statistically significant: (1) The increase in heart rate 2–3 min after both thiopentone and midazolam (P < 0.01); (2) The decrease in mean arterial pressure at 2–3 min after thiopentone (P < 0.01) and after midazolam at 5 min (P < 0.01) and at 10 min (P < 0.05).

arterial and central venous pressures and the e.c.g. were displayed on an oscilloscope or a pen-recorder, and the beat-by-beat heart rate using a digital display.

Cardiac output was measured using dye dilution (indocyanin green, Guilford Instrument Laboratories Model 140). Duplicate readings were taken after preoxygenation before induction of anaesthesia, and thereafter starting at 2, 5 and 10 min after completing the injection of each drug. The coefficient of variation of duplicate readings was 3.5%. Samples of arterial blood were collected anaerobically in heparinized syringes for the measurement of pH, PaO₂ and PaCO₂ (Radiometer ABL 1).

After preoxygenation for 3 min using a Magill breathing system control values for cardiac output were measured and anaesthesia was induced either with midazolam 0.3 mg kg⁻¹ or thiopentone 3 mg kg⁻¹. Each drug was administered during a period of 30 s. Oxygen 100% was administered throughout each study from a Magill system. Seven of the eight patients who received thiopentone required an additional dose (1 mg kg⁻¹), one by 3 min and six between 5 and 10 min in order to complete the study. Once the last cardiac output measurement was made, anaesthesia was continued in a manner appropriate for these patients.

Statistical analysis was performed using analysis of variance and t tests where applicable.

RESULTS

The mean induction time for midazolam was 30 s (range 12–45 s) and for thiopentone 16 s (range 10–30 s). The patients receiving midazolam did not become apnoeic, they tolerated an airway, inflation was not required and they remained asleep throughout the period of measurement.

In contrast, those receiving thiopentone all became apnoeic for a period of 20–45 s. Ventilation of the lungs was assisted using a Magill system until regular satisfactory spontaneous ventilation had returned. One patient started to recover at 3 min and six at 5 min. An additional dose of thiopentone 1 mg kg⁻¹ caused no obvious haemodynamic or respiratory effects, and allowed observations to be made for a period comparable to that in the midazolam group.

The haemodynamic data are shown in figures 1 and 2. The following observations can be made.

Neither drug caused any significant change in cardiac output and there were no significant differences between the two groups of patients.

The mean resting heart rate was 7 beats slower in the midazolam group, but this difference was not statistically significant. The pattern of change was the same for both drugs. There was an initial increase in rate, but by 5 min values returned to control and remained so for the duration of the period of observation.

In those receiving thiopentone the mean arterial pressure decreased initially from 83 mm Hg to 74 mm Hg; thereafter it returned to control values. With midazolam the mean pressure did not change immediately, but by 5 min it had decreased from 75 to 68 mm Hg after which it appeared stable and at 10 min the value was 66 mm Hg, a reduction of approximately 12%.

Although the trends observed for central venous pressure appeared to be different for the two drugs
HAEMODYNAMIC EFFECTS OF MIDAZOLAM AND THIOPENTONE

(fig. 1), none of the changes observed was statistically significant.

The changes in peripheral vascular resistance are illustrated in figure 2. In the patients receiving midazolam resistance decreased progressively from 17.4 units to 14.9 at 5 min (approximately 15%; \( P<0.05 \)); thereafter there was little further change. Although there was, in the patients receiving thiopentone, a transient initial decrease in mean peripheral vascular resistance (approximately 11%) which was not statistically different from that obtaining in the midazolam group (fig. 2), resistance subsequently increased to slightly greater than control values and was not affected by the additional dose of thiopentone (1 mg kg\(^{-1}\)) which was given to seven of the patients during this period (fig. 2). By 5 min, the difference between midazolam and thiopentone has become significant (\( P<0.05 \)).

The mean heart rate—systolic pressure products (mean ± SEM) for thiopentone were: control 7539 ± 584; at 2.5 min 8359 ± 783; at 5 min 8010 ± 718; at 10 min 7819 ± 974. For midazolam these values were 7312 ± 542, 7584 ± 645, 6327 ± 573 and 6474 ± 772 respectively. None of the changes was statistically significant, either within each group or between groups.

Blood-gas data are shown in table II. The ease of maintaining the airway in the patients receiving midazolam and the absence of apnoea compared with those receiving thiopentone has already received comment. After the administration of the drug \( P_{\text{aCO}}_2 \) in the group receiving midazolam increased slightly from a mean value of 5.9 kPa to 6.2 kPa. After preoxygenation, none of the changes in \( P_{\text{aCO}}_2 \), \( P_{\text{aO}}_2 \) and pH was statistically significant in either group.

**DISCUSSION**

The 16 patients in this study were all suffering from symptomatic coronary artery disease and all received either three or four coronary artery vein grafts. In such patients any substantial increase in heart rate or arterial pressure during the period of induction of anaesthesia (increase in the rate—pressure product) is to be avoided (Nelson et al., 1974).

The data presented here suggest that the haemodynamic and respiratory effects of midazolam are compatible with this aim since it has relatively minor effects on the circulation. This confirms the view expressed about this drug by Reeves, Samuelson and Lewis (1979) who made haemodynamic observations on 10 similar patients, who were premedicated with morphine sulphate 0.1 mg kg\(^{-1}\) and hyoscine 6–8 \( \mu \)g kg\(^{-1}\) up to 10–15 min in the present study, after the injection of midazolam in a dose of only 0.2 mg kg\(^{-1}\). The long and more variable induction time (mean 44 s; range 30–90 s) in their study, compared with the present one (mean 30 s; range 12–45 s), is probably a result of the heavier premedication and the larger dose of midazolam (0.3 mg kg\(^{-1}\)) reported here.

In the present study there were no significant

<table>
<thead>
<tr>
<th>Time</th>
<th>Thiopentone (( P_{\text{aO}}_2 )) (kPa)</th>
<th>Midazolam (( P_{\text{aO}}_2 )) (kPa)</th>
<th>Thiopentone (( P_{\text{aCO}}_2 )) (kPa)</th>
<th>Midazolam (( P_{\text{aCO}}_2 )) (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before ( O_2 )</td>
<td>7.40 ± 0.01</td>
<td>7.38 ± 0</td>
<td>10.2 ± 0.29</td>
<td>9.4 ± 0.50</td>
</tr>
<tr>
<td>After ( O_2 )</td>
<td>7.38 ± 0.01</td>
<td>7.37 ± 0.01</td>
<td>48.0 ± 4.72</td>
<td>49.5 ± 3.09</td>
</tr>
<tr>
<td>2–3 min</td>
<td>7.37 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>57.4 ± 1.23</td>
<td>47.9 ± 3.33</td>
</tr>
<tr>
<td>5 min</td>
<td>7.37 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>56.0 ± 2.10</td>
<td>51.2 ± 3.03</td>
</tr>
<tr>
<td>10–15 min</td>
<td>7.36 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>48.6 ± 6.39</td>
<td>48.5 ± 5.34</td>
</tr>
</tbody>
</table>
changes in cardiac output in patients in whom anaesthesia was induced with either thiopentone or midazolam, confirming the findings of Reeves, Samuelson and Lewis (1979) for midazolam. Following both drugs there was an initial increase in heart rate, seen by 3 min, which then returned to control values.

Differences between thiopentone and midazolam were seen in the changes in mean arterial pressure and systemic vascular resistance. After an initial decrease in both values at 3 min in the patients who received thiopentone, both the mean arterial pressure and the peripheral resistance returned to control values, during the period 5–10 min after injection of the drug. This result was not changed by an additional dose of 1 mg kg\(^{-1}\) in seven of the eight patients who required such a dose to maintain hypnosis for 10–15 min. In contrast, in the patients who received midazolam the arterial pressure and peripheral vascular resistance both showed a significant decrease which, after 5 min, continued unchanged for the duration of the study. Changes in the rate–pressure product were not statistically significant in the present study which is in agreement with Reeves, Samuelson and Lewis (1979).

Reeves and his associates (1979) related the tachycardia after the injection of midazolam to an observed increase in \(P_{aCO_2}\) from 5.32 kPa to 6.12 kPa. However, in the present study, although there was a tendency for \(P_{aCO_2}\) to increase in the patients who received midazolam, these changes were much smaller than those observed by Reeves, Samuelson and Lewis (1979) and did not reach statistical significance. Moreover the tachycardia was transient, maximal within 2–3 min and had returned to control values by 5 min when the \(P_{aCO_2}\) was maximal. Also, in artificially ventilated, anaesthetized animals with the blood-gases maintained constant, the onset of action of midazolam is associated with marked tachycardia (Whitwam et al., 1980) and it would be reasonable to assume that this transient increase in heart rate is a result of the haemodynamic effects of the drug, and not secondary to blood-gas changes.

It was concluded that induction of anaesthesia with midazolam in patients with coronary artery disease is accompanied by a relatively stable cardiovascular system with a modest reduction in peripheral vascular resistance. The absence of apnoea in the present study could be regarded as advantageous compared with thiopentone. Such is the smoothness and stability of the induction period with midazolam that it could well become an important agent for the induction of anaesthesia by the i.v. route.

ACKNOWLEDGEMENTS

This work was supported by Roche Products Ltd. Dr D. Al-Khudhairi is supported by Roche Products Ltd, and Dr H Askriotopoulou by the Onassis Foundation.

We thank Professor H. H. Bentall and Mr R. Sapsford in the department of Cardiothoracic Surgery for permission to study their patients and Mrs Shirley Richens for assistance with preparation of the manuscript.

REFERENCES


Lowenstein, E., and Tepplek, R. (1980). To (PA) catheterise or not to (PA) catheterise—That is the question Anesthesiology, 53, 361.


EFFETS HEMODYNAMIQUES DU MIDAZOLAM ET DU THIOPENTONE PENDANT L'INDUCTION DE L'ANESTHESIE POUR UNE INTERVENTION CHIRURGICALE SUR L'ARTERE CORONAIRE

RESUME

Les effets cardiovasculaires du thiopentone administré à raison de 3 mg/kg\(^{-1}\) et du midazolam administré à raison de 0.3 mg/kg\(^{-1}\), ont été observés pendant l'induction de l'anesthésie sur des malades ayant déjà reçu une prémédication en attendant de subir une revascularisation myocardique. Il n'y a eu aucun changement significatif dans le débit cardiaque ou dans la pression veineuse centrale, dans l'un ou l'autre groupe. On a constaté, après trois minutes, dans ces deux groupes, une augmentation de la fréquence cardiaque, mais celle-ci est ensuite retournée aux valeurs témoin. Après trois minutes, il y a eu une baisse importante de la pression artérielle et de la résistance périphérique, respectivement de 12 et de 15% (valeurs moyennes) par rapport aux valeurs témoin, dans le groupe auquel on avait administré du midazolam, alors qu'on a constaté dans le groupe ayant reçu du thiopentone une augmentation d'approximativement 13% de la résistance périphérique et que celle-ci n'a pas été autrement affectée par une dose supplémentaire de thiopentone de 1 mg/kg\(^{-1}\).
ZUSAMMENFASSUNG
Die Kreislaufwirkungen von Thiopental iv 3 mg kg⁻¹ und Midazolam 0,3 mg kg⁻¹ wurden während der Narkoseeinleitung bei 60 prämedizierten Patienten beobachtet, die sich einer koronaren Bypass-Operation unterziehen mussten. Es traten in beiden Gruppen keine signifikanten Änderungen des Minutenvolumens und des zentralen Venendruckes auf. Die Herzfrequenz stieg in beiden Gruppen um 3 min⁻¹ an und kehrte danach zu den Kontrollwerten zurück. Nach 3 Minuten fiel sowohl der arterielle Druck als auch der periphere Gefäßwiderstand um 12% und 15% (Mittelwert) gegenüber den Kontrollwerten in der Midazolam-Gruppe ab, während nach Thiopental der periphere Gefäßwiderstand um ungefähr 13% zunahm und durch eine weitere Dosis von Thiopental (1 mg kg⁻¹) i.v. nicht mehr beeinflusst wurde.

SUMARIO
Se observaron los efectos cardiovasculares de 3 mg kg⁻¹ de tiopentona y de 0,3 mg kg⁻¹ de midazolam durante la inducción de anestesia en 16 pacientes premedicados que iban a ser sometidos a una revascularización miocárdica. No hubo cambio significativo alguno en la producción cardíaca ni en la presión venosa central de ninguno de los dos grupos. El ritmo cardíaco de ambos grupos mostró un incremento a los 3 minutos y, posteriormente, volvió a los valores de control. Hubo una disminución significativa después de transcurridos 3 minutos, tanto en la presión arterial como en la resistencia periférica, del 12% y del 15% (valores medios) respectivamente con respecto a los valores de control del grupo sometido a midazolam, mientras que después de la tiopentona la resistencia periférica aumentó en el 13% aproximadamente y no quedó afectada por una dosis complementaria de de 1 mg kg⁻¹ de tiopentona.