EFFECT OF DIFFERENT KINDS OF PREMEDICATION ON THE INDUCTION PROPERTIES OF MIDAZOLAM

J. KANTO, S. SJOVALL AND A. VUORI

The effects of different premedication (i.m. and i.v.) on the usefulness of midazolam or thiopentone as induction agents for minor surgery was studied in 194 women undergoing either dilatation and curettage or explorative fractionate curettage. Midazolam appeared to produce light sedation which required powerful premedication (i.m. atropine + pethidine and i.v. fentanyl or fentanyl + dehydrobenzperidol) when used as an induction agent for minor surgery. The clinically useful dose of midazolam is about 0.30 mg kg\(^{-1}\) i.v. There was greater variability in onset and duration of action among patients receiving midazolam than among those receiving thiopentone. Midazolam caused less respiratory depression, but there were no clinically significant differences between midazolam and thiopentone with respect to cardiovascular variables. Muscular movements were found more often, and postoperative sedation lasted longer in patients receiving midazolam. Midazolam as an induction agent appears more suited for major than for minor surgery.

Midazolam hydrochloride (Ro 21-3981), is a 1,4-benzodiazepine derivative currently being evaluated as an induction agent in anaesthesia. It differs from other benzodiazepines in that it is water-soluble, has a half-life of about 2 h (about one-tenth that of diazepam and flunitrazepam), and does not cause significant thrombophlebitis. In addition, while anterograde amnesia seems to be more marked it is of shorter duration than with other benzodiazepines (Conner et al., 1978; Brown et al., 1979; Reves et al., 1979; Dundee and Wilson, 1980). Midazolam, like other benzodiazepines, effectively maintains haemodynamic and respiratory variables even in poor-risk patients (Forster et al., 1979; Fragen and Caldwell, 1980; Samuelson et al., 1980). Its onset of action is quicker, and there is less individual variation in response than after the administration of diazepam (Reves, Corssen and Holcomb, 1978). In this open study we compared the effect of different premedicants on the onset of action of midazolam hydrochloride, on the maintenance of anaesthesia induced with midazolam hydrochloride, and on recovery from such anaesthesia, for minor gynaecological operations. The results were compared with those produced with thiopentone.

PATIENTS AND METHODS

A total of 194 women participated in this study (table I). All were undergoing either dilatation and curettage or explorative fractionate curettage. Each patient received atropine 0.5 mg and pethidine 50 mg i.m. about 1 h before the surgical intervention. In group 1 (fig. 1), 44 patients received midazolam hydrochloride (Ro 21-3981) as an induction agent in increasing dose (from 0.15 to 0.5 mg kg\(^{-1}\) i.v.) over 30 s to determine the clinically useful dose for minor surgery. If there were involuntary muscular movements or other disturbing sequela, thiopentone was given i.v., in addition, in increments of 50 mg. The results in group 1 were compared with those produced in 30 patients receiving thiopentone sufficient to affect loss of the eye lash reflex. In group 2, fentanyl 50 µg was injected i.v. 1 min before the beginning of anaesthesia induced either with midazolam 0.30 ± 0.01 mg kg\(^{-1}\) (n = 30) or thiopentone 6.6 ± 0.3 mg kg\(^{-1}\) 6.0 ± 0.3 mg kg\(^{-1}\) (n = 30) in 30 s. In group 3, the patients received both fentanyl 50 µg and dehydrobenzperidol 2.5 mg 1 min before the induction of anaesthesia with either midazolam 0.37 ± 0.02 mg kg\(^{-1}\) (n = 30) or 6.6 ± 0.3 mg kg\(^{-1}\) thiopentone (n = 30). Anaesthesia was supplemented with 70% nitrous oxide in oxygen in all patients. No i.v. infusion was used.

The following were recorded by the anaesthetist during and after anaesthesia: time of spontaneous closing of the eyes after commencing i.v. injection of midazolam or thiopentone, disappearance of the
TABLE I. Characteristics of the patients (mean ± SEM)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Midazolam</th>
<th>Thiopentone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.8±1.9</td>
<td>43.5±2.2</td>
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<tr>
<td>Weight (kg)</td>
<td>64.2±1.6</td>
<td>66.7±1.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.3±0.9</td>
<td>162.4±1.1</td>
</tr>
<tr>
<td>ASA class 1</td>
<td>n = 37</td>
<td>n = 24</td>
</tr>
<tr>
<td>ASA class 2</td>
<td>n = 7</td>
<td>n = 6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>Midazolam</th>
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<td>36.5±2.2</td>
</tr>
<tr>
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<td>64.7±1.7</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>163.9±0.9</td>
</tr>
<tr>
<td>ASA class 1</td>
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<td>n = 27</td>
</tr>
<tr>
<td>ASA class 2</td>
<td>n = 2</td>
<td>n = 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3</th>
<th>Midazolam</th>
<th>Thiopentone</th>
</tr>
</thead>
<tbody>
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<td>Age (yr)</td>
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</tr>
<tr>
<td>Weight (kg)</td>
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<tr>
<td>Height (cm)</td>
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<td>163.3±1.0</td>
</tr>
<tr>
<td>ASA class 1</td>
<td>n = 29</td>
<td>n = 28</td>
</tr>
<tr>
<td>ASA class 2</td>
<td>n = 1</td>
<td>n = 2</td>
</tr>
</tbody>
</table>

eyelash reflex; respiratory rate; appearance and duration of apnoea (absence of respiration for longer than 10 s); heart rate and arterial pressure; hiccup, cough, involuntary muscular movements and related unwanted effects during surgical intervention; sleeping time; state of vigilance in the recovery room (about 30 min): alert, fairly alert or sedated; lower abdominal muscular relaxation during gynaecological examination (gynaecologist): good, fair or poor.

In addition, following anaesthesia in group 3, the following were recorded by nurses in the ward: degree of sedation when coming to the ward: alert, fairly alert or sedated; time for return to full consciousness (patient able to take care of herself) < 1 h, 1-3 h, > 3 h; postoperative nausea and vomiting; psychic state in the evening: clear, moderately clear or tired; patients' opinion of the anaesthetic, when asked by the nurse on the following day: good, fair or unacceptable.

Statistical analyses of the results were carried out by Student's t test (parametric data) or by the χ²-test (non-parametric data).

RESULTS

The ability of midazolam to induce sleep was slower in onset, with a wider interindividual variability than that of thiopentone (fig. 1). Three patients (two receiving diazepam and one carbamazepine therapy) were excluded from the study, because they were

![Figure 1](https://example.com/figure1.png)

**Fig. 1.** Effect of increasing doses of midazolam (M) i.v. on time to spontaneous closing of the eyes (O), disappearance of palpebral reflex (D), and duration of sleep (A) (mean ± SEM). In group 1, a fixed dose of midazolam was injected i.v. in 30 s and bolus doses (50 mg) of thiopentone (T) given if needed. In group 2, fentanyl 50 μg and in group 3, fentanyl 50 μg with dehydrobenzperidol 2.5 mg was injected i.v. 1 min before the administration of midazolam over 30 s (according to the response of the patient). Results in each of the three patient groups were compared with those produced by thiopentone 5 mg kg⁻¹ i.v. in 30 s. As can be seen, many patients fell asleep less than 30 s after commencing the administration of thiopentone, and some additional doses were needed later.
still awake 5 min after the administration of up to 0.5 mg kg\(^{-1}\) of midazolam. Each dose of midazolam, or of midazolam plus a small dose of thiopentone caused a sleeping time distinctly longer than the usual dose of thiopentone. This difference was significant in each of the three groups of patients (\(P<0.001\)).

In contrast, respiratory depression after the administration of thiopentone was clearly more marked than after the administration of midazolam (fig. 2). In addition, apnoea lasting more than 10 s was recorded in 12–67% of patients in whom anaesthesia was induced with thiopentone, but in only 2–10% of those receiving midazolam. In both instances, the previous administration of fentanyl and, more especially, fentanyl with dehydrobenzperidol increased the frequency of apnoea. The mean total period of apnoea varied between 36.6 and 59.8 s in thiopentone-induced patients and between 14.2 and 17.8 s in patients receiving midazolam (\(P<0.001\) in each of the three groups of patients).

There were no clinically significant differences in cardiovascular parameters between midazolam (M) and thiopentone (T). The faster heart rates in M + T patients (group 1) were caused by the small bolus doses of thiopentone 50 mg which were injected only if the action of midazolam was unacceptable. In group 1, the significantly higher heart rates in patients receiving midazolam (plus a small additional dose of thiopentone) were apparently a result of the design of the study: thiopentone was given only when the effect of midazolam had worn off.

Hiccup, cough, disturbing involuntary muscular movements and related unwanted effects were recorded more often after midazolam (group 1: 57% \(\text{vs.} 37\%\); group 2: 46% \(\text{vs.} 23\%\); group 3: 43% \(\text{vs.} 10\%\)). Lower abdominal relaxation, as assessed by the gynaecologist, was similar after both induction agents.
In the recovery room, patients in whom anaesthesia was induced with midazolam were clearly more sedated than those induced with thiopentone (table II). The opinions formed by the nurses when the patients returned to the ward, were similar (assessed in group 3 only). However, as regards time for return to full consciousness, postoperative nausea and vomiting, psychological state in the evening and patients’ opinion of anaesthesia, there were no significant differences between the patients receiving midazolam or thiopentone (group 3 only).

**DISCUSSION**

We found midazolam to be a mild hypnotic which requires powerful premedication when used alone as an anaesthetic agent for minor surgery. After the administration of fentanyl or fentanyl plus dehydrobenzperidol anaesthesia could be induced easily. Similar experiences have been obtained in patients undergoing major surgery (to be published). Generally, a distinctly wider interindividual variability, both in onset and duration of action, was found with midazolam as compared with thiopentone. The slow onset of anaesthesia was assessed as subjectively pleasant by some patients who had received thiopentone on a previous occasion. However, the longest of the induction times and durations of action observed in this study are clinically unacceptable in minor surgery. Thus, this new benzodiazepine derivative appears to be useful either as an induction agent for major surgery or as a general basal sedative before surgery.

The sedative effect lasted longer after operation in the patients receiving midazolam. This is a drawback in hospitals like ours where there are only a few recovery rooms. On the other hand, this property of an induction agent appears to be subjectively pleasant and decreases the amount of analgesic needed following surgery. After the return to the ward, the difference in the sedative effect disappeared in a short time and the subjective and objective psychic state was, thereafter, comparable in patients in whom anaesthesia was induced with midazolam or thiopentone.

The dose of midazolam which is clinically useful in minor surgery appears to be greater than that suggested by the manufacturer (0.15 mg kg⁻¹). In this respect, we agree with Dundee and Gamble (1981): at least 0.30 mg kg⁻¹ i.v. should be administered to induce clinically acceptable anaesthesia.

In our relatively healthy patients there were no clinically significant differences in cardiovascular variables between patients receiving midazolam or thiopentone. In contrast, midazolam caused clearly a less respiratory sequelae, being comparable to diazepam in this respect (Fragen, Gahl and Caldwell, 1978). On account of these effects on respiration and circulation, midazolam has been recommended for poor-risk patients (Reves and Samuelson, 1979).

Although benzodiazepine derivatives have a central muscle relaxant effect there was no difference in this respect between midazolam and thiopentone. The reason may lie in the deeper anaesthesia caused by the barbiturate. This is further supported by the greater prevalence of disturbing muscular movements during surgical intervention in the patients receiving midazolam.

In conclusion, midazolam appears to be a mild hypnotic which needs relatively strong premedication to induce clinically acceptable anaesthesia in minor surgery. It is more suitable for major than for minor surgery. In comparison with our earlier studies with diazepam (Kanto and Iisalo, 1973) and flunitrazepam (Kangas, Kanto and Pakkanen, 1981; Kanto et al., 1981) the main novel property of midazolam is its distinctly shorter duration of action. However, it is not comparable to thiopentone in this respect. Our results are similar to other preliminary experiences with midazolam (Fragen, Gahl and Caldwell, 1978; Reves, Corssen and Holcomb, 1978; Fragen and Caldwell, 1980).
PREMEDICATION AND MIDAZOLAM

REFERENCES


EFFET DE DIFFERENTES SORTES DE PREMEDICATION SUR LES PROPRIETES D'INDUCTION DU MIDAZOLAM

RESUME

Nous avons étudié les effets de différentes prémédications i.m. et i.v. sur l'utilité du midazolam ou du thiopentale comme agents d'induction pour des actes de chirurgie mineure chez 194 femmes subissant soit une dilatation et un curetage, soit une curetage biopsique fractionné. Le midazolam est apparu comme inducant une sédation légère, qui nécessitait une prémédication puissante (atropine + pethidine i.m. et fentanyl i.v. ou fentanyl + droperidol) lorsqu'on l'utilisait comme agent d'induction pour des actes de chirurgie mineure. La dose de midazolam nécessaire en clinique est d'environ 0,30 mg kg⁻¹ i.v. Les variations de délai d'induction et de durée d'action sont plus importantes chez les patientes qui reçoivent du midazolam. Le midazolam apparaît convenir davantage comme agent d'induction pour les actes de chirurgie majeure que pour ceux de chirurgie mineure.

AUSWIRKUNG VON VERSCHIEDENEN PRÄMEDIKATIONEN AUF DIE EIGENSCHAFTEN VON MIDAZOLAM ALS EINLEITUNGSMITTEL

ZUSAMMENFASSUNG

Der Einfluß verschiedener Prämiedikationen — i.m. u. i.v. — bei der Verwendung von Midazolam oder Thiopental zur Einleitung für Kurzengriffe wurde an 194 Frauen studiert, die sich einer Dilatation mit Curetage oder einer diagnostischen Curetage unterzogen mußten. Midazolam schien nur eine leichte Sedierung zu bewirken, die dennoch eine starke Prämiedikation erforderlich machte (i.m. Atropin + Pethidin und i.v. Fentanyl oder Fentanyl + Deshydrobenzperidol), wenn es als Einleitungsmittel für Kurzengriffe verwendet wurde. Bei Midazolam ist eine Dosis von 0,3 mg kg⁻¹ erforderlich. Die Unterschiede in bezug auf Einsetzen und Dauer der Wirkung waren bei Midazolam größer als bei Thiopental. Midazolam rief weniger Atmdepression hervor, aber zwischen Midazolam und Thiopental bestanden keine signifikanten Unterschiede in der Kreislaufwirkung. Muskelbewegungen waren häufiger und die postoperative Sedierung dauerte länger bei Patienten, die Midazolam erhalten hatten. Midazolam scheint besser als Einleitungsmittel für große Operationen als für Kurzengriffe geeignet zu sein.

EFECTO DE DIFERENTES CLASES DE PREMEDICACION EN LAS PROPIEDADES DE INDUCCION DEL MIDAZOLAM

SUMARIO

Se estudiaron los efectos de diferente medición (intramuscular e intravenosa) en lo tocante a la utilidad del midazolam o de la tiopentona como agentes inductores conducentes a cirugía menor, en 194 mujeres sometidas a dilatación y curetaje o bien curetaje fraccional y explorativo. El midazolam pareció producir una ligera sedación, que necesitó una poderosa prémiedication (intramuscular atropina + petidina e intravenosa fentanilo o fentanalo + deshydrobenzperidol) cuando se usó como un agente de inducción para cirugía menor. La dosis de midazolam clínicamente útil es de unos 0,30 mg kg⁻¹ intravenosos. Hubo una mayor variabilidad en el comienzo de la actividad y en su duración en los pacientes que recibieron midazolam que entre los que recibieron tiopentona. El midazolam causó menos depresión respiratoria, pero no hubo diferencias de significación clínica entre el midazolam y la tiopentona con respecto a las variables cardiovascular. Los pacientes que recibieron midazolam presentaron movimientos musculares con más frecuencia y la sedación postoperatoria fue más duradera en estos pacientes. El midazolam, como agente de inducción, parece ser más adecuado para intervenciones mayores que para las menores.