EFFECT OF BOLUS DOSES OF MIDAZOLAM ON INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE IN PATIENTS WITH SEVERE HEAD INJURY

L. PAPAZIAN, J. ALBANESE, X. THIRION, G. PERRIN, O. DURBEC AND C. MARTIN

SUMMARY

We have studied the effects of bolus doses of midazolam 0.15 mg kg\(^{-1}\) i.v. on intracranial pressure (ICP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) in 12 patients with severe head injury (Glasgow Coma Scale score \(\leq 6\)). The study was performed in patients aged 17-44 yr who were sedated (phenoperidine 20μg kg\(^{-1}\) h\(^{-1}\)) and paralysed (vecuronium 2 mg h\(^{-1}\)). Midazolam reduced MAP from 89.0 mm Hg to 75.0 mm Hg (\(P < 0.0001\), while CPP decreased from 71.0 mm Hg to 55.8 mm Hg (\(P < 0.0001\)). During the study, CPP decreased to less than 50 mm Hg in four patients. Midazolam induced small, non-significant changes in ICP. However, when control ICP was less than 18 mm Hg (\(n = 7\) patients), an increase in ICP was observed. The remaining five patients (control ICP \(\geq 18\) mm Hg) exhibited a slight decrease in ICP. These findings suggest that bolus administration of midazolam should be performed with great caution in patients with severe head injury, especially when ICP is less than 18 mm Hg. (Br. J. Anaesth. 1993; 71: 267-271)

KEY WORDS


The aim of intensive medical treatment in patients with severe head injury is to prevent secondary cerebral damage with the maintenance of an adequate cerebral perfusion pressure (CPP). This may be undertaken by controlling intracranial pressure (ICP) and maintaining adequate mean arterial pressure (MAP), blood-gas tensions, temperature, blood glucose and electrolyte concentrations and serum osmolarity. Nocteptive stimulation may induce an increase in ICP, and thereby decrease CPP, which may induce cerebral ischaemia. Muscle paralysis, adequate analgesia and sedation are usually used to prevent such undesirable increases in ICP [1].

The introduction of infusions of hypnotic drugs for the treatment of post-traumatic ICP increases, as a measure to minimize secondary brain damage, has led to a search for agents with a shorter duration of action and fewer side effects than barbiturates. Midazolam is a water-soluble, short-acting benzodiazepine that has been recommended as an effective i.v. agent for induction of anaesthesia [2]. Its effects on ICP and CPP are not known in patients with severe head injury and have been studied only in neurosurgical patients [3, 4]. However, these findings may not be applicable to head-injured patients, as they were performed on patients with focal intracranial lesions before elective neurosurgical procedures. In many of these patients, ICP was normal and intracranial compliance may have been sufficient to allow some increase in intracranial volume without change in ICP. The aim of this work was to study, in patients with head injury, the effects of an i.v. bolus injection of midazolam on ICP, MAP and the resulting CPP.

PATIENTS AND METHODS

After approval by our local Committee for the Protection of Human Subjects, informed consent was obtained from members of the patients' families.

Patients

The study was performed in 12 patients (11 male) admitted to the Intensive Care Unit (ICU) with severe head injury (Glasgow Coma Scale score \(\leq 6\)). Intracranial pathologies are shown in table I, which also lists age, diagnosis, initial GCS score, associated injuries and outcome of the study patients. The mean weight of the patients was 69.5 (±9.6) kg. Throughout the study, the patients were lying in the horizontal position with 15° of head elevation.

Monitoring

A radial artery was cannulated to measure MAP continuously and to allow blood sampling (Merlin 1092-A, Hewlett Packard, Andover, MA). The zero reference for the arterial transducer was the mid-axillary line.\(P_{A_{\text{O}_2}}\) and \(P_{A_{\text{CO}_2}}\) were measured before and 10 min after injection of midazolam (Ciba Corning B 288, Ciba Corning diagnostics corp., Medfield, MA). Intracranial pressure was measured with a digital pressure monitor (mod. 420, Camino...
Laboratories, San Diego, CA) which utilizes an intracranial bolt and sterile miniature intraparanchymal pressure transducer [5]. The study was performed less than 48 h after insertion of the device. Cerebral perfusion pressure was calculated automatically by the monitor as CPP = MAP - ICP and displayed continuously. Continuous records of MAP and ICP were stored on computer (Vectra, Hewlett-Packard, Andover, MA).

Clinical management

All patients received the same standard management, including immediate neurological assessment by Glasgow Coma Scale score, early diagnosis and treatment of mass lesions, followed by intensive treatment and monitoring. Computerized tomography was performed on admission, 2-4 days later and whenever indicated. All patients received intermittent positive pressure ventilation to maintain \( P_{a\text{CO}_2} \) in the range 3.3-4.3 kPa. Inspired oxygen concentration was adjusted to maintain \( P_{a\text{O}_2} \) in the range 10.0-20.0 kPa.

Patients were sedated using a continuous i.v. infusion of phenoperidine 20 \( \mu \text{g kg}^{-1} \text{h}^{-1} \) and paralyzed with a continuous infusion of vecuronium 2 mg h\(^{-1}\). Fluid intake was restricted to 5 % glucose 1 ml kg\(^{-1}\) h\(^{-1}\). No colloidal solutions, vasoactive agents, steroids or prophylactic anticonvulsants were administered before or during the study. Measurements were performed in stable patients, at least 12 h after the last infusion of mannitol or frusemide.

The effects of an i.v. bolus dose of midazolam 0.15 mg kg\(^{-1}\) over a 1-min period on MAP, ICP and CPP were investigated. Midazolam was administered by manual injection into an infusion given continuously via a peripheral i.v. cannula. From the computer recordings, the following measurements were made: MAP, ICP and CPP in the 5 min before injection of midazolam (control values for MAP, ICP and CPP); MAP, ICP and CPP at 1-min intervals for 15 min after administration of midazolam; MAP, ICP and CPP at 5-min intervals for the next 15 min.

Statistical analysis

Statistical calculations were performed using the Statistical Analysis System software package (SAS Institute, Cary, NC) [6]. Two-way analysis of
EFFECTS OF MIDAZOLAM ON ICP AND CPP

![Graph showing changes in MAP, CPP, and ICP before and after midazolam administration.](image)

FIG. 1. Mean (SEM) MAP, CPP and ICP before (time 0, control) and after administration of midazolam 0.15 mg kg⁻¹ i.v. Changes from control values statistically significant for MAP and CPP.

![Graph showing changes in ICP before and after midazolam administration.](image)

FIG. 2. Mean (SEM) change in ICP before (time 0, control) and after administration of midazolam to patients with control ICP < 18 mm Hg (○) and those with control ICP ≥ 18 mm Hg (●).

### Table II. $P_{CO_2}$ and $P_{CO_2}$ values at the time of injection of midazolam 0.15 mg kg⁻¹ i.v. (Initial) and 10 min after injection (Final)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial $P_{CO_2}$ (kPa)</th>
<th>Final $P_{CO_2}$ (kPa)</th>
<th>Initial $P_{CO_2}$ (kPa)</th>
<th>Final $P_{CO_2}$ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.6</td>
<td>10.7</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>18.9</td>
<td>19.9</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>15.9</td>
<td>13.0</td>
<td>3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>9.5</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>16.1</td>
<td>15.2</td>
<td>3.9</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>16.1</td>
<td>16.5</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>7</td>
<td>16.8</td>
<td>16.0</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td>8</td>
<td>13.9</td>
<td>17.5</td>
<td>4.3</td>
<td>3.6</td>
</tr>
<tr>
<td>9</td>
<td>10.0</td>
<td>10.4</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>10</td>
<td>15.9</td>
<td>15.2</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>11</td>
<td>13.7</td>
<td>14.0</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>12</td>
<td>16.9</td>
<td>15.3</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Mean</td>
<td>14.7</td>
<td>14.5</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>sd</td>
<td>2.8</td>
<td>3.1</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### RESULTS

Changes in ICP, MAP and CPP are presented in figure 1. The bolus dose of midazolam induced a significant decrease in MAP ($P < 0.0001$). MAP decreased nine of 12 times after midazolam injection; in six patients this decrease was 10–20% of MAP control and in two other patients the maximal decrease was 20–30%. In the remaining patient, the maximal decrease in MAP reached 50% of control value. Despite these decreases in MAP, ICP increased slightly (not significant). Four of 12 bolus doses of midazolam were followed by a sustained increase in ICP greater than 5 mm Hg.

As a result of these changes in ICP and MAP, CPP was significantly reduced from the second 1 min after injection to the end of the study period ($P < 0.0001$). The decrease in CPP was observed in all patients, and was occasionally severe; it decreased to less than 50 mm Hg for 4 min in two patients and for 28 min in two others. One of the 12 patients had a CPP less than 50 mm Hg before administration of midazolam; CPP remained stable after the injection of midazolam. The magnitude of variation in the different variables (MAP, ICP, CPP) was evaluated according to the control value of ICP. We divided the patients into two groups: group 1 ($n = seven$) with a control ICP less than 18 mm Hg; group 2 ($n = five$) with an ICP greater than or equal to 18 mm Hg. Although baseline values of MAP were not different between the two groups, analysis of variance showed that in group 1 the decrease in MAP was more pronounced than in group 2 ($P < 0.0001$). CPP was decreased significantly in both groups, with the change more pronounced in group 1 than in group 2.
(P < 0.0001). This was related probably to the increase in ICP observed in group 1, compared with the slight decrease observed in group 2 (P < 0.0001) (fig. 2). Table II shows PaO₂ and PaCO₂ measurements obtained before and 10 min after the injection. There were no significant changes over the period of the study.

**DISCUSSION**

In managing patients with severe head injury, it is essential to use techniques and pharmacological agents which do not modify ICP and CPP unfavourably. Etomidate has been studied in patients with intracranial lesions [7] and in patients with severe head injury [8, 9]. ICP decreased, but CPP decreased slightly because of the effect of etomidate on MAP. Propofol has also been studied in such patients [10]: ICP was reduced, but CPP decreased because of its effects on MAP. Because of their profound cerebral vasoconstrictive and metabolic depressant effects, barbiturates have been used widely as the drugs of choice for induction of anaesthesia or sedation in patients with intracranial hypertension. The ability of thiopentone to reduce cerebral blood flow (CBF), cerebral metabolic rate and ICP has been demonstrated by Nordström and colleagues [11]. These actions are not entirely dependent of the action of thiopentone on CPP. Shapiro and colleagues [12] reported that ICP has been shown to decrease significantly in patients with intracranial hypertension, but not in patients with normal ICP.

There have been several reports of the effects of benzodiazepines on ICP and CPP. Tateishi and colleagues [13] have shown that diazepam causes a decrease in MAP and CPP. ICP was maintained when baseline values of ICP were greater than 15 mm Hg, but when baseline values were less than 15 mm Hg, ICP decreased. However, this study was conducted in neurosurgical, but non-injured patients. Midazolam may offer some advantages compared with other benzodiazepines because it is a short-acting, water-soluble agent associated with cardiovascular stability [14]. In humans, induction of anaesthesia with midazolam results in a slight decrease in arterial pressure and an increase in heart rate to a degree similar to those after hypnogenic doses of thiopentone [15]. Some experimental studies have concluded that midazolam causes a decrease in cerebral oxygen consumption (CMRO₂) and CBF [16–19]. In healthy volunteers, Forster and colleagues [20] have shown a decrease in CBF and an increase in cerebrovascular resistance after a bolus injection of midazolam 0.15 mg kg⁻¹, but there are conflicting data: Wolf [21] found that the decrease in CBF was a result of cerebral metabolic depression, rather than a direct vasoconstrictive effect of midazolam. However, in contrast with these experimental studies, midazolam has been found to cause minimal changes in CBF and CMRO₂ when administered to patients anaesthetized with nitrous oxide–fentanyl [22]. However, midazolam-induced decreases in CBF and CMRO₂ are dose-dependent only to a certain degree, until a plateau effect has been established [19]. It is assumed that the onset of this plateau effect reflects a saturation of the benzodiazepine receptors. Fleisher and colleagues did not note an effect of midazolam on ICP in dogs without intracranial hypertension [19].

Few studies have been conducted on the effects of midazolam on ICP and CPP [3, 4, 23]. Moreover, these studies included patients without head injury. After a bolus injection of midazolam 0.2 mg kg⁻¹, Mastronardi and colleagues [3] found a decrease in ICP associated with a slight decrease in MAP in spontaneously breathing patients with various intracranial lesions. Rosa and colleagues [4] did not find significant changes in ICP, MAP or CPP after a bolus injection of midazolam 0.2 mg kg⁻¹ in patients with intracranial space-occupying lesions and undergoing artificial ventilation. Giffin and colleagues [23] showed that, in patients undergoing elective surgery and with initial small ICP (12 (sd 1) mm Hg), there was no difference between thiopentone and midazolam in their effects on MAP, CPP and ICP. In our study, we have shown that in head-injured patients, midazolam produced little change in ICP, but a significant decrease in CPP, caused mainly by a decrease in MAP. These effects were more pronounced in patients with ICP < 18 mm Hg and could be related to better preservation of the autoregulatory response of the brain. When pressure autoregulation is maintained, a sudden reduction in MAP is likely to induce cerebral vasodilatation and consequently an increase in ICP. Although the critical value of CPP after administration of midazolam has not been determined, CPP was less than 50 mm Hg in five patients in the present study. This is considered the lower limit of autoregulation of CBF in hypertensive patients. It has been reported that a decrease in CPP to this lower limit could be tolerated well in terms of flow–metabolism coupling and intracranial pressure in head trauma patients [24]. However, after severe brain injury, the critical value of CPP could be significantly greater than that of normal patients and a value of 70 mm Hg has been suggested [25]. At values smaller than this threshold, CBF velocity is impaired markedly.

**REFERENCES**

8. Dearden NM, McDowall DG. Comparison of etomidate and Althesin in the reduction of increased intracranial pressure
9. Few studies have been conducted on the effects of midazolam on ICP and CPP [3, 4, 23]. Moreover, these studies included patients without head injury. After a bolus injection of midazolam 0.2 mg kg⁻¹, Mastronardi and colleagues [3] found a decrease in ICP associated with a slight decrease in MAP in spontaneously breathing patients with various intracranial lesions. Rosa and colleagues [4] did not find significant changes in ICP, MAP or CPP after a bolus injection of midazolam 0.2 mg kg⁻¹ in patients with intracranial space-occupying lesions and undergoing artificial ventilation. Giffin and colleagues [23] showed that, in patients undergoing elective surgery and with initial small ICP (12 (sd 1) mm Hg), there was no difference between thiopentone and midazolam in their effects on MAP, CPP and ICP. In our study, we have shown that in head-injured patients, midazolam produced little change in ICP, but a significant decrease in CPP, caused mainly by a decrease in MAP. These effects were more pronounced in patients with ICP < 18 mm Hg and could be related to better preservation of the autoregulatory response of the brain. When pressure autoregulation is maintained, a sudden reduction in MAP is likely to induce cerebral vasodilatation and consequently an increase in ICP. Although the critical value of CPP after administration of midazolam has not been determined, CPP was less than 50 mm Hg in five patients in the present study. This is considered the lower limit of autoregulation of CBF in hypertensive patients. It has been reported that a decrease in CPP to this lower limit could be tolerated well in terms of flow–metabolism coupling and intracranial pressure in head trauma patients [24]. However, after severe brain injury, the critical value of CPP could be significantly greater than that of normal patients and a value of 70 mm Hg has been suggested [25]. At values smaller than this threshold, CBF velocity is impaired markedly.

**REFERENCES**

8. Dearden NM, McDowall DG. Comparison of etomidate and Althesin in the reduction of increased intracranial pressure
EFFECTS OF MIDAZOLAM ON ICP AND CPP


