EFFECTS OF MIDAZOLAM ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS

T. B. SLOAN, M. L. FUGINA AND J. R. TOLEIKIS

SUMMARY

We have studied the effect of i.v. midazolam on median nerve somatosensory evoked potentials (SSEP) in 10 unpremedicated adults. Anaesthesia was induced with midazolam by bolus administration (0.2 mg kg\(^{-1}\)) followed by infusion (5 mg h\(^{-1}\)). The latency and amplitudes of the SSEP responses over the second cervical vertebrae (SC2) and sensory cortex (P17, N20, P25) were recorded before and for 10 min after induction. Data were analysed over that period for time-related alterations. Small but statistically significant increases in latency of the cortical N20 (P < 0.005) and P25 (P < 0.001) waves and interwave conduction times of SC2 to P25 (P < 0.005) and N20 to P25 (P < 0.021) were observed. Cortical amplitude (N20–P25) decreased significantly (P < 0.012), to approximately 60% of baseline. These results demonstrated that midazolam produced a depression of cortical SSEP amplitude without clinically significant alterations in latency.

KEY WORDS: Hypnotics, benzodiazepines: midazolam. Monitoring: somatosensory evoked potentials.

Several studies have examined the effects of various anaesthetic agents on median nerve somatosensory evoked potentials (SSEP). An opioid-based anaesthetic technique is often chosen for spinal procedures, and adjuvant drugs should be chosen carefully to ensure lack of awareness.

Midazolam, a water-soluble imidazo-benzodiazepine, has sedative and amnesic properties, and is a suitable adjuvant drug for opioid-based anaesthesia. In studies comparing it with thiopentone, midazolam required fewer adjuvant drugs for maintenance of anaesthesia, produced greater amnesia and was associated with fewer emergence complications [1, 2]. Furthermore, its pharmacokinetics make it suitable for administration by infusion [3].

We have found that total i.v. anaesthesia can be produced in adults for surgical procedures requiring SSEP monitoring with a midazolam-opioid technique. It is important to identify the anticipated alterations in the SSEP caused by midazolam. However, few studies have examined the effects of midazolam on the SSEP. The present study was designed to examine the time-related alterations in median nerve SSEP when unpremedicated adults were given an induction dose of midazolam followed by a continuous infusion.

PATIENTS AND METHODS

Ten ASA Class I and II adult patients scheduled to undergo lumbar spinal surgery with SSEP monitoring gave written informed consent to participate in this study, which was approved by the Institutional Review Boards. Patients with possible neurological abnormalities in the median nerve pathway or intracranial pathology were excluded.

Unpremedicated patients came to the operating room, where a catheter was inserted i.v. and the overnight fluid deficit replaced over 30 min using 5% glucose in lactated Ringer's solution. Routine
monitoring included a precordial stethoscope, spirometer, continuous electrocardiogram, automated oscillotonometry, pulse oximeter, temperature and end-tidal carbon dioxide measurement.

SSEP were recorded using techniques described previously [4]. Active recording electrodes were placed over the spinal cord at the inion (SC2) and over the sensory cortex for the hand. Using the International 10–20 System, the cortical electrodes were located at C3' and C4'. A reference electrode was placed at Fz and a silver–silver chloride grounding electrode placed on the shoulder. All electrode impedances were less than 3000 Ω, and interelectrode impedance differences were less than 1000 Ω. Using a bipolar bar electrode, median nerve SSEP were generated from a single arm using stimulation of the median nerve at the wrist. Stimulation at 5.7 Hz was with constant current, 300-μs duration, square-wave pulses at intensities 1 mA greater than the motor threshold.

Each averaged waveform consisted of 250 artefact-free responses acquired using a Nicolet CA-1000/DC-2000 signal averager (Nicolet Bio-medical, Madison, Wisconsin) with bandpass filtration of 5–250 Hz (60-Hz notch filtration was not used) and an analysis window of 50 ms. All data were stored on magnetic discs for later analysis.

After acquisition of duplicate baseline recordings, midazolam 0.2 mg kg⁻¹ was given i.v. over 30 s, followed by an i.v. infusion of midazolam 5 mg h⁻¹. The midazolam was administered in lactated Ringer’s solution with 5% glucose. At 1-min intervals for 10 min after administration, the SSEP, arterial pressure (AP) and heart rate (HR) were recorded and ventilation was assisted manually as necessary with a facemask using 40% oxygen in air to maintain an end-tidal carbon dioxide partial pressure of 4.7–6.0 kPa. All patients had rectal temperatures > 36.5 °C. At the conclusion of the study, the patients were given hyoscine 0.4 mg i.v. and the midazolam infusion continued. Sufentanil and pancuronium were administered, the trachea intubated and the surgery performed. Posterior tibial nerve SSEP responses recorded from the appropriate recording location were used for monitoring during operation.

The waveforms of stored averages were recalled after the study. The post-stimulus peak latency of the major cervical negative wave (SC2) (approximately 15 ms) and the peak latencies of the primary cortical response waves (P17, N20 and P25) were measured and recorded. Conduction times (CT) were calculated as the time interval between various peaks. Wave amplitudes were calculated as the voltage difference between the positive or negative peak and the following peak of opposite polarity.

SSEP latencies, conduction times, amplitudes and arterial pressure (systolic and diastolic) and heart rate were compared from 0 to 10 min using a Friedman two-way analysis of variance. Differences were confirmed with the Wilcoxon matched pairs signed rank test. Data were considered statistically significant when P < 0.05.

RESULTS

We studied six women and four men aged 24–64 yr (mean 45 yr). The average height was 170 cm (range 162–187 cm) and weight 77 kg.
TABLE I. Effects of midazolam on SSEP latency and amplitude and cardiovascular variables (mean (sd)). * P < 0.05 compared with baseline

<table>
<thead>
<tr>
<th>Latency (ms)</th>
<th>Latency (ms)</th>
<th>Latency (ms)</th>
<th>Latency (ms)</th>
<th>Latency (ms)</th>
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</thead>
<tbody>
<tr>
<td>SC</td>
<td>14.8 (1.0)</td>
<td>16.1 (1.6)</td>
<td>14.9 (1.2)</td>
<td>15.1 (1.4)</td>
</tr>
<tr>
<td>P15</td>
<td>17.4 (0.9)</td>
<td>17.7 (1.9)</td>
<td>17.6 (1.2)</td>
<td>17.7 (1.5)</td>
</tr>
<tr>
<td>N20</td>
<td>20.6 (1.8)</td>
<td>20.3 (1.6)*</td>
<td>20.2 (1.6)*</td>
<td>20.6 (1.5)</td>
</tr>
<tr>
<td>P25</td>
<td>25.1 (2.9)</td>
<td>23.9 (2.8)*</td>
<td>24.1 (2.6)*</td>
<td>24.7 (2.8)</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td></td>
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</tr>
<tr>
<td>SC</td>
<td>1.94 (0.93)</td>
<td>2.66 (1.04)</td>
<td>2.01 (1.05)</td>
<td>2.12 (1.15)</td>
</tr>
<tr>
<td>P15</td>
<td>1.04 (0.88)</td>
<td>0.76 (0.57)</td>
<td>0.59 (0.33)</td>
<td>0.66 (0.41)</td>
</tr>
<tr>
<td>N20</td>
<td>2.22 (1.25)</td>
<td>1.77 (1.24)</td>
<td>1.79 (1.21)</td>
<td>1.80 (0.77)</td>
</tr>
<tr>
<td>P25</td>
<td>2.35 (2.21)</td>
<td>2.16 (1.78)</td>
<td>1.96 (1.84)</td>
<td>1.49 (0.92)</td>
</tr>
<tr>
<td>N20–P25 change</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Cardiovascular variables</td>
<td></td>
<td></td>
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<tr>
<td>SAP (mm Hg)</td>
<td>129 (15)</td>
<td>126 (14)</td>
<td>121 (16)</td>
<td>117 (13)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>80 (9)</td>
<td>77 (11)*</td>
<td>76 (11)*</td>
<td>72 (11)*</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>80 (17)</td>
<td>88 (14)*</td>
<td>88 (14)*</td>
<td>83 (14)</td>
</tr>
</tbody>
</table>

(range 57–109 kg). All patients were unrousable during the study and tolerated it well. Upon questioning, none recalled the study or intra-operative period.

SSEP tracings were acquired from all the patients during the study period. Figure 1 shows the cervical and cortical recordings from one patient. The measured peaks are marked (SC2, P17, N20, P25). The mean data and SD are shown in table I.

Statistically significant reductions occurred in the latency of the later cortical peaks N20 (P < 0.005) and P25 (P < 0.001) at 1–2 min after administration of midazolam, with small absolute changes in latency. The conduction times (inter-wave latencies) showed similar small reductions and were statistically significant for SC2 to P25 (P < 0.005) and P17 to P25 (P < 0.021).

The major waveform alterations consisted of reductions in amplitude (fig. 1). The cervical spinal amplitude (SC2) tended to increase (13%), whereas the cortical peak amplitudes tended to decrease to about 51–63% of baseline values. Only the change in N20 to P25 amplitude was significant (P < 0.012).

The systolic and diastolic arterial pressures decreased slightly and heart rate increased initially then decreased toward baseline (table I).

**DISCUSSION**

Midazolam is useful as an i.v. adjunct during general anaesthesia for procedures utilizing evoked potential monitoring. The effects of midazolam on median nerve SSEP were determined so that they might be differentiated from neural alterations resulting from positioning, spine manipulations and adverse alterations in intracranial dynamics.

The major effects of midazolam were a reduction in amplitude of the cortical peaks, which were reduced to approximately 60% of baseline values after 2–3 min. These varied somewhat for individual patients with the maximal amplitude reductions being to 10–12% of baseline values. No apparent relationship was seen between effect and patient weight.

Unlike the amplitude changes, the latencies of the spinal cord and cortical peaks, in addition to the inter-wave latencies (conduction times) were not affected to a marked degree. Although statistical significance was achieved for some latencies, the clinical significance of these observed changes is questionable. Those latency changes which did occur appeared to be resolved largely by 4–5 min after injection.

These changes in amplitude and latency are similar to those seen by Suzuki and colleagues in rats with cortical SSEP from upper lip stimulation [5]. They observed a dose-related reduction in cortical amplitude which ranged from 57.4% to 24.6% of baseline. Even with the larger reductions, latency changes could not be detected.

The amplitude changes observed in this study and by Suzuki and colleagues differ from those seen by Koht and colleagues [6]. They examined the effect of a larger dose of midazolam (0.3 mg kg⁻¹), followed by an infusion of...
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0.2 mg kg\(^{-1}\) h\(^{-1}\) in 10 adult patients. They noted an approximate 27% decrease in amplitude of the N20–P25 wave which did not achieve statistical significance and an increase in the N20 latency and the SC2–N20 inter-wave conduction time. However, conduction times and cortical latency were not stated for the initial time period, so a direct comparison cannot be made with this study during the time of maximal change. These differences may be caused by the different doses of midazolam and by the fact that the data of Koht were pooled over three 8-min periods. This may have masked the observation of significant changes occurring within these time periods, such as the transient changes in latency seen in the current study. Alternatively, differences may have resulted from differing patient populations or techniques of evoked potential stimulating and recording.

The small changes in latency observed with a dose of midazolam suitable for induction of anaesthesia, suggest that major latency changes are unlikely. Thus latency changes following administration of midazolam may be indicative of other deleterious factors (e.g., positioning). This is in contrast to amplitude changes, in which a reduction of 50–60% of baseline values may be anticipated for the cortical components. In the case of initially small amplitudes, midazolam may not be as suitable for SSEP monitoring as drugs such as etomidate that may enhance cortical responses [7].

REFERENCES