Sedation caused by clonidine in patients with spinal cord injury

J.-M. Malinovsky*, M. Malinge, J.-Y. Lepage and M. Pinaud

Department of Anaesthesia and Intensive Care, Hôtel-Dieu, 44093 Nantes Cedex 1, France
*Corresponding author. E-mail: jeanmarc.malinovsky@chu-nantes.fr

Background. In patients with spinal cord injury, cephalad spread of intrathecal (i.t.) medication could be delayed.

Methods. We used bispectral index and an observer scale to assess sedation after two different doses of i.t. clonidine in patients with or without spinal cord injury. Twelve patients with neurological deficit caused by trauma (Spinal Cord Injury, SCI) were compared with patients without neurological disease. They received 10 mg of i.t. bupivacaine with clonidine, with either 50 mg (low dose, n=6) or 150 mg (high dose, n=6) at L2–L3. A further 12 patients, six with spinal trauma lesion and six healthy, received i.t. bupivacaine and 150 µg of i.m. clonidine.

Results. Sedation and a decrease in BIS occurred only in patients receiving 150 µg of clonidine. Onset of sedation and the decrease in BIS was delayed in most spinal cord injured patients whatever the route of administration (P<0.001). Duration of sedation was not different between the groups. Delayed sedation and decrease of BIS after i.t. clonidine in patients with spinal cord injury are similar than those observed after i.m. clonidine.

Conclusion. A systemic effect is likely to be the main reason for sedation.

Br J Anaesth 2003; 90: 742–5

Keywords: anaesthetic techniques, subarachnoid; complications, spinal injury; monitoring, bispectral index; sympathetic nervous system, clonidine

Accepted for publication: February 14, 2003

Clonidine, an alpha2 adrenergic agonist, acts on neurons in the superficial laminae of the spinal cord, and also within numerous brainstem nuclei.1 After intrathecal (i.t.) injection clonidine reaches nervous tissues by diffusion in the cerebrospinal fluid (CSF), providing segmental analgesia.2 The concentration of clonidine in CSF correlates with pain score in humans.2 I.t. clonidine used alone provides postoperative analgesia3 but not reliable anaesthesia for surgery in humans.

In addition to analgesia, clonidine causes sedation regardless of the route of administration. I.t. and epidural clonidine cause dose-dependent sedation, over doses ranging from 50 to 450 µg intrathecally and up to 900 µg epidurally, usually rapidly. Sedation is mainly caused by clonidine action at the locus coeruleus, with inhibition of the regulation of sleep and wakefulness.4 However, it is not clear how clonidine reaches cerebral sites after spinal lumbar injection. It may be by vascular absorption and systemic effect of clonidine, a local spinal cord effect, or by rostral migration of clonidine within CSF. A systemic effect from vascular absorption may partly explain the sedation observed after epidural clonidine.5 A local effect seems possible since Marwaha and colleagues demonstrated that neural firing in the locus coeruleus was inhibited by spinal clonidine in rats.6 The rostral spread of clonidine is also suggested, as observed with i.t. fentanyl7 and sufentanil.8 If rostral diffusion is the main route by which clonidine reaches cerebral centres, patients with slow CSF circulation would have delayed sedation, compared with normal CSF circulation. To answer these questions we studied sedation in patients receiving clonidine, who had spinal cord injury.

Materials and methods

After ethical committee approval and informed consent, we studied 36 patients (21–73 yr old) about to have lower urinary tract surgery under spinal anaesthesia. Patients with paraplegia or tetraplegia after traumatic spinal cord injury more than 1 yr before were allocated to a Spinal Cord Injury (SCI) group. They had permanent and complete deficit in the lower body below the spinal lesion. They were randomly assigned to receive a low or high dose of i.t. clonidine, and
were matched for age, weight, and height with patients in a normal group (N), who were of ASA physical status 1 and 2, without spinal cord injury, and without any known neurological disease. Twelve further patients, six with traumatic spinal cord injury and six healthy, received i.t. bupivacaine and clonidine intramuscularly. All but four of the SCI patients were taking the γ-amino butyric acid agonist baclofen, in daily oral doses.

All patients received 5 mg of oral midazolam and prophylactic antibiotics as pre-medication. On arrival in the operating room a standard electrocardiogram, non-invasive automatic arterial pressure cuff, and pulse oximetry were applied. After cannulation of a vein in the forearm, Ringer lactate solution was infused slowly. EEG electrodes were applied to the scalp, ensuring that skin impedance was less than 5 kOhm for each electrode. The Fp1 and Fp2 leads were recorded using CZ as the reference. The EEG was continuously monitored using an Aspect A-1000 EEG monitor (Spacelab Instruments) and recorded on a personal computer using 4D software database. After a 15-min resting period, EEG monitoring began and the BIS values were recorded every minute before and up to 180 min after the spinal injection.

All patients were given 10 mg of isobaric bupivacaine at L2–L3 level using a 27G-spinal needle, while placed in the lateral position. For i.t. treatment, patients received either 50 (low dose) or 150 μg (high dose) of clonidine added to 10 mg of bupivacaine. The other patients received 150 μg of i.m. clonidine, and 10 mg of bupivacaine intrathecally. The volume of i.t. injection (5 ml) was always given over 30 s.

Sedation was scored using the Observer Assessment of Alertness and Sedation, every 5 min after spinal injection. Patients were considered sedated when they had a score of 3 or less on the OAAS scale. Data from the BIS recording were averaged over 5 min periods. The time between injection and reaching a score of 3 on OAAS scale was taken as the onset time for sedation. The total duration of sedation was the time between onset of score of 3 on OAAS scale and complete recovery from sedation.

Sensory block in patients without spinal injury was assessed by loss of pinprick sensation in the midclavicular line on both sides, and motor block at the knee using a modified Bromage scale. The level of sensory and motor block was recorded every 5 min up to complete recovery from anaesthesia. Hypotension was defined as a decrease of mean arterial pressure by more than 25% of the baseline. Either ephedrine and/or atropine were given for correction of arterial pressure and heart rate.

Results are presented as median and range. Times of sedation were compared with the Mann–Whitney test between SCI and N groups, and sensory and motor block were compared by using the Kruskall–Wallis test within groups. The values of BIS were compared using ANOVA for repeated measures. The level of significance was set at \( P<0.05 \).

<table>
<thead>
<tr>
<th>Spinal injury</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of clonidine</td>
<td>50 μg</td>
</tr>
<tr>
<td>Number of patients</td>
<td>6</td>
</tr>
<tr>
<td>Level of lesion</td>
<td>T8 (C7–T3)</td>
</tr>
<tr>
<td>Onset of sensory block (min)</td>
<td>–</td>
</tr>
<tr>
<td>Duration of L2–L3 anaesthesia (min)</td>
<td>–</td>
</tr>
<tr>
<td>Number of dermatomes blocked</td>
<td>–</td>
</tr>
<tr>
<td>Onset of complete motor block</td>
<td>–</td>
</tr>
<tr>
<td>Paralysis of knee (min)</td>
<td>–</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>15 (12–21)</td>
</tr>
<tr>
<td>Onset of sedation (min)</td>
<td>50 (35–120)</td>
</tr>
<tr>
<td>Duration of sedation (min)</td>
<td>75 (50–185)</td>
</tr>
</tbody>
</table>

Results

Eighteen patients with spinal cord injury and eighteen normal patients were studied. Details are reported in Table 1. After i.t. bupivacaine and clonidine, patients with spinal injury had uneventful surgery. All patients without neurological disease had complete sensory and motor block (Table 1), and one patient became hypotensive after 150 μg of clonidine. He received ephedrine 15 mg of i.v.. No sedation occurred after 50 μg clonidine in N and SCI groups (Table 1). Sedation was observed in all patients given 150 μg of i.t. or i.m. clonidine. The onset of sedation was delayed in the patients with spinal injury whatever the route of administration (50 min after i.t. and 100 min after i.m. clonidine in SCI groups, 25 min after i.t. and 30 min after i.m. in N groups; \( P<0.01 \)). The duration of sedation was not different in the groups (75 and 70 min after i.t. and i.m. in SCI groups, and 58 and 60 min, respectively, in N group; NS).
A decrease in BIS occurred earlier in normal patients ($P<0.001$), and greater inter-individual variations of BIS occurred with time in patients with spinal injury (Fig. 1). No relationship between the onset of sedation and the level of spinal cord lesion was found in SCI groups.

**Discussion**

We found that sedation and a decrease in BIS occurred in patients given 150 μg of clonidine regardless of the route of administration. However, sedation was delayed in some SCI patients, so that decreases in BIS scattered more in this group than in healthy patients.

Depth of sedation is difficult to measure clinically. In addition to clinical assessments, it is known that natural sleep, and sedation with midazolam or propofol can be assessed using EEG. To overcome the complexity of conventional EEG monitoring, a computerized EEG-derived phase coupling method (EEG-BI or BIS) has been developed. This index correlates with the depth of sedation caused by midazolam, propofol, and isoflurane. When these anaesthetics are used alone, values of BIS greater than 70 are associated with a high probability of response to verbal stimulus, both in volunteers and in surgical patients.

In the present study, patients sedated with clonidine had BIS values greater than 70, and all responded when their name was called loudly or repeatedly as in the study of Glass and colleagues, corresponding to a level of 3 on OAAS scale. The effects of midazolam as pre-meditation were small as baseline values of BIS were around 96 in all groups, but we cannot discount the potentiation of this agent by i.t. clonidine. This appeared to be dose-dependent as 50 μg of clonidine had no sedative effects and did not influence BIS values.

Several mechanisms may allow the effects of spinal clonidine to reach supraspinal sites: a local inhibition of neurotransmission, a cephalad spread within CSF, or a systemic effect.

The hypothesis of inhibition of neurotransmission is supported by the fact that i.t. clonidine reduces isoflurane requirements in anaesthetised rats. However, inhibition of neurotransmission at spinal cord level does not appear to be the major mechanism of sedation with clonidine. Sedation by spinal local anaesthetics has been reported previously, but the relationship with the extent of anaesthetic block remains controversial.

Loss of proprioceptive afferent information in patients with spinal injury make them less or more susceptible to sedative agents. Also, long-term treatment to prevent spasms from intact spinal reflexes below the level of spinal cord lesion may alter the efficacy of sedative agents such as clonidine. These influences could explain the range of onset degree and depth of sedation observed in our patients with spinal injury.

A delayed cephalad spread of clonidine within CSF could not be completely discounted. This hypothesis is supported by the high concentrations found in upper cervical spinal cord segments only 10 min after lumbar i.t. injection of clonidine in rats, and occurs with i.t. opioids of similar lipophilicity than clonidine. This may explain the extension of analgesia after continuous epidural clonidine. A rostral diffusion of local anaesthetics may explain late onset of sedation in volunteers with spinal anaesthesia.

---

**Fig 1** Individual changes of BIS after i.t. and i.m. clonidine. Interindividual variation was greater in patients with spinal cord injury than normal patients. A decrease in BIS occurred more quickly in normal patients than in patients with spinal cord injury whatever the routes of administration of clonidine ($P<0.001$).
expected delayed sedation, caused by abnormal kinetics of CSF, or altered mechanisms of sedation and awakening from the spinal cord lesion in SCI patients. Different levels of spinal cord lesion could partly explain differences in onset of sedation. However, abnormal bulk flow of clonidine appears to be of minor importance for clonidine to reach supraspinal centres, as sedation after intramuscular dosage was not different.

Despite i.t. administration, sedation is probably a systemic effect of clonidine as sedation was not different between patients receiving i.m. or i.t. clonidine. This confirms studies in animals: inhibition of locus coeruleus neuron activity occurs when rats have CSF bulk flow blocked by vaseline, suggesting a systemic redistribution of clonidine to supraspinal sites. Early peak concentrations in the plasma occur after i.t. clonidine in rat and sheep, but unfortunately no study is available in humans. To explain the difference observed in the onset of sedation after clonidine in spinal injury and normal patients it could be argued that paravertebral venous blood flow could be affected by spinal injury, so the disposition of clonidine could change in such patients. However, this is unlikely since the scatter range of BIS curves observed in SCI patients was similar after i.t. and i.m. clonidine.

We conclude that sedation after spinal clonidine is mainly a systemic effect. Delayed onset of sedation in patients with traumatic spinal cord injury could be related to several mechanisms including altered resorption from spinal cord sites, altered susceptibility to sedative agents especially in patients receiving treatment for spasticity, rather than a delayed cephalad spread of clonidine in the CSF.

References

2 Eisenach JC, Detweiler D, Hood D. Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 1993; 78: 277–87
3 Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. Anesthesiology 1992; 77: 267–74
7 Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ. Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. Pain 1989; 38: 253–9