Efficacy of Intrathecal Bupivacaine: How Important Is the Flow Rate?

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ABSTRACT

We present two cases of cancer patients with intractable mechanical and visceral pain that was unrelied with either comprehensive medical management or intrathecal morphine who received intrathecal bupivacaine. While the continuous administration of a seemingly significant daily dose neither relieved pain nor caused measurable clinical changes, the addition of small, presumably negligible bolus doses on top of the continuous infusion resulted in spectacular pain control, clear thermolagemic suspended block, and in one of the patients, significant hypotension. To the best of our knowledge, such an observation has neither been reported before nor can we provide a satisfactory explanation for it. However, we believe it may have significant implications for the treatment of some patients, in particular, cancer patients with mechanical pain that cannot be adequately relieved with morphine whatever the route of administration.

Key Words. Intrathecal; Chronic Pain; Local Anesthetics

Introduction

The administration of drugs directly into the cerebrospinal fluid (CSF) has become increasingly popular in the last two decades [1]. The intrathecal (IT) route has clear advantages that include the delivery of a drug close to its site of action, resulting in increased efficacy, and the possibility of using drugs, such as local anesthetics, that cannot be administered systemically.

While morphine (and baclofen) are the only two drugs that are approved for long-term IT administration, a recent survey [2] has suggested that, in routine clinical practice, more than half of patients receive other IT drugs. The primary reasons for switching to drugs other than morphine are the lack of efficacy or intolerable side effects. Hydromorphone seems to be the opiate that is most frequently used instead of morphine and clonidine has become commonly added, generally in combination with other drugs. Yet, lack of efficacy remains a problem, particularly in patients with mechanical pain, whatever the cause, and the adjunct of bupivacaine to either opiate or clonidine or both is a logical option.

In contrast to its relatively widespread use, there is little knowledge regarding the basic science of IT drug delivery, including pharmacokinetics, neurotoxicity, and stability of a large number of drugs, let alone drug combinations, that are used in routine clinical practice [3]. Intrathecal morphine is considered very safe (at least at low concentrations) and has been used extensively in patients suffering from chronic pain, whether or not it is associated with cancer. Hydromorphone, which seems to be the primary opiate used instead of morphine, seems to be safe, although the compound has been poorly studied. Clonidine, which is mostly used in combination with opiates, seems to be devoid of neurotoxicity [4] and chemically stable [5], although the study was not performed with implanted pumps and at 37°C.

While neurotoxicity has been clearly established for a number of local anesthetics, bupivacaine has had a very good safety record so far,
although one serious complication has been observed [6]. The rationale behind the use of intrathecal bupivacaine relies on the fact that it is the only currently available drug that results in an “all or none” response on neural conduction. Provided the drug is delivered to the appropriate location with a reliable and precisely adjustable device, it may be possible to control the most refractory pain conditions in an elegant and relatively simple way.

Several authors have reported excellent results with IT bupivacaine, either alone or in combination, in patients with chronic intractable pain associated with both cancer and benign disorders, and the clinical experience has been reviewed recently [7]. Although most authors reported improved pain relief as a result of the addition of bupivacaine, all but one study were uncontrolled and nonrandomized case series. A recent multicenter, double-blinded randomized study [8] suggested that the addition of bupivacaine (up to 8 mg/day) did not provide better pain relief than opiate alone. We report a clinical observation that may contribute to improve the effectiveness of IT bupivacaine administration.

Case No. 1
A 71-year-old woman (73 kg/175 cm) was referred for the treatment of intractable pain in her lower back and sacrum due to metastatic breast carcinoma. She experienced severe mixed neurogenic and mechanical pain that was poorly controlled, despite optimal conventional management. The efficacy of IT morphine and clonidine administration was tested on two separate occasions with single shot IT boluses of 1 mg of morphine and 50 mg of clonidine. On both instances, the pain decreased by 80%, and it was decided to implant a pump (SynchroMed® 8627EL; Medtronic Inc.; Minneapolis, MN). The catheter (Indura® 8709; Medtronic Inc.) was inserted at the L2–L3 level and advanced in the subarachnoid space. Postoperative X-rays confirmed the satisfactory placement of the catheter in the posterior intrathecal space, extending up to the level of Th9. A continuous IT infusion of 2 mg of morphine and 100 µg of clonidine per day was started but failed to achieve appropriate pain control, in particular on movement and in the sitting and standing positions. The daily doses of morphine and clonidine were progressively increased to 4 mg and 240 µg, respectively, over the next 6 days, but the pain on movement remained unchanged. It was felt that the mechanical component of the pain syndrome was a predominant factor, and a daily dose of 8 mg of bupivacaine was added to the continuous infusion (0.7 mL/day) 6 days after the implant. The drug preparations that were used and their true concentrations in the pump reservoir are summarized in Table 1. Except for a slight drowsiness that was attributed to clonidine or morphine or both, no side effects occurred, and the vital signs remained within the normal range. Pain on movement was not significantly decreased and no sensory or motor changes could be demonstrated on neurological examination.

Based on previous clinical experience, we decided to administer a bolus of 0.5 mg of bupivacaine, and the patient was closely monitored over the next 2 hours. Given the mixture that was used, 0.25 mg of morphine and 15 µg of clonidine were coadministered in a volume of 44 µL during a period of 120 seconds. Within 15 minutes following the bolus dose, the pain during movement (measured on a 100-mm visual analogue scale [VAS]) decreased from 70 mm to less than 20 mm, and the patient could sit and stand with only minimal pain. Neurological examination revealed a thermal anesthesia extending from Th8 to Th12 on both sides, with neither subjective nor objective motor weakness. The vital signs, in particular

<table>
<thead>
<tr>
<th>Case</th>
<th>Drug Mixture Preparation*</th>
<th>True Concentration in Pump Reservoir</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>morphine 40 mg/mL</td>
<td>2.9 mL</td>
<td>5.7 mg/mL</td>
</tr>
<tr>
<td></td>
<td>clonidine 1,200 µg/mL</td>
<td>11.4 mL</td>
<td>342.9 µg/mL</td>
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<tr>
<td></td>
<td>bupivacaine 40 mg/mL</td>
<td>5.7 mL</td>
<td>11.4 mg/mL</td>
</tr>
<tr>
<td>Case 2</td>
<td>morphine 40 mg/mL</td>
<td>3.5 mL</td>
<td>6.9 mg/mL</td>
</tr>
<tr>
<td></td>
<td>clonidine 1,200 µg/mL</td>
<td>2.9 mL</td>
<td>171.4 µg/mL</td>
</tr>
<tr>
<td></td>
<td>bupivacaine 40 mg/mL</td>
<td>13.6 mL</td>
<td>27.4 mg/mL</td>
</tr>
</tbody>
</table>

* A total of 20 mL of mixture was prepared, but only 18 mL was injected into the pump reservoir.
the blood pressure (BP), remained essentially unchanged and no orthostatic hypotension occurred. The sensory block gradually faded off over the next 2 hours, but the pain did not recur for at least 4–5 hours. The same test was repeated on three occasions with similar results, and the patient was given a hand-held device providing patient-controlled capabilities with implanted SynchroMed® pumps [9] that was programmed to allow the delivery of a maximum of one bolus every 4 hours. The patient was discharged from hospital and has had an uneventful clinical course with excellent pain control for the last 5 months.

Case No. 2

A 60-year-old woman (48 kg/168 cm) was referred because of intractable abdominal pain due to a retroperitoneal metastasis of a pulmonary carcinoma. The pain was localized in the lower thoracic and upper abdominal region and was thought to be of visceral and neuropathic origin. A well-conducted and comprehensive conservative management failed to provide adequate symptom control. An intrathecal (L2–L3) single-shot trial injection of 2 mg of morphine and 50 μg of clonidine resulted in much better, yet incomplete, pain relief for 12 hours. A pump (SynchroMed® 8627EL; Medtronic Inc.) was implanted and the catheter (Indura® 8709; Medtronic Inc.) was advanced in the intrathecal space up to the level of Th7. Because it was felt that optimal analgesia would not be obtained without local anesthetics, the pump was started with a continuous infusion (0.22 mL/day) of morphine (2 mg/day), clonidine (50 μg/day), and bupivacaine (5 mg/day) (Table 1). Although pain relief was much improved (VAS score decreased from 80 mm to 20 mm), position- and movement-related pain (VAS score of 65 mm) still persisted. Neither motor nor sensory block was found, and the BP was 100/60 mmHg. A bolus dose (44 μL) of 1 mg of bupivacaine associated with 0.25 mg of morphine and 15 μg of clonidine was administered over 120 seconds (Table 2). A bilateral thermoanalgesic block extending from Th4 to L1 without evidence of motor block developed within 15 minutes, and the patient could move without pain although her mobility was limited by arterial hypotension (BP 75/35 mmHg) that required initial treatment with intravenous fluid and two 5-mg doses of ephedrine. The block faded off over the next 90 minutes, and 2 hours after the bolus injection, the sensory and circulatory changes had disappeared but the pain relief persisted (VAS score of 30 mm). One day later, a bolus of half the first dose was administered in 62 seconds (Table 2) and resulted in similar pain control with a less extensive, slightly asymmetrical sensory block (Th4 to Th8–Th12) and less pronounced arterial hypotension. However, symptomatic orthostatic arterial hypotension persisted and it was decided not to use patient-controlled analgesia bolus doses and the patient was discharged with a continuous flow.

Discussion

In neither of these cases did IT morphine and clonidine provide sufficient pain relief, and it was felt that the addition of bupivacaine was a reasonable option. Surprisingly, the continuous administration of a seemingly significant daily dose of bupivacaine neither significantly relieved pain nor did it cause measurable clinical changes. However, the addition of small, presumably negligible, bolus doses on top of the continuous infusion resulted in spectacular pain control, clear thermoanalgesic suspended block and, in one of the patients, significant hypotension.

The uncertainties regarding chemical stability, drug interactions, side effects, tolerance development, and neurotoxicity are fully acknowledged and were discussed with each patient before the treatment was started. The drug formulations that we use do not contain preservative and are prepared either by the hospital pharmacy (clonidine 1,200 μg/mL) or are commercially available (morphine sulphate 40 mg/mL; Bioren SA, Couvet, Switzerland and bupivacaine 4%; Sintetica SA, Mendrisio, Switzerland). Calculations regarding the preparation of the drug mixture, the true concentration of each drug in the pump reservoir, as well as the volume and drug content of the bolus doses were performed using the e-MICS® program available on the internet (http://www.emics.ch).

The two cases that are reported here represent one end of a spectrum of effect that we observed
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in several patients submitted to various small bolus doses of bupivacaine (never exceeding 1 mg) administered during a continuous infusion of bupivacaine with either morphine or clonidine or both. In other cases, a similar procedure resulted in either no response at all (pain, neurological examination, and vital signs unchanged) or a (usually) brief decrease in pain without any other clinical or neurological modification.

Although we cannot offer an explanation for this observation, we considered two factors that may be important. First, there is the issue of diffusion and mixing of drugs within the CSF. Common knowledge among clinical anesthetists suggests that, with spinal anesthesia, the rate of the injection does affect the spread of the block, particularly when hyperbaric solutions are used. This is presumably due to increased turbulence occurring at the tip of the needle, which results in improved diffusion and mixing of the local anesthetic. Recent studies in volunteers [10] suggested that, with morphine and fentanyl, the mixing is the primary determinant of the early concentrations in the CSF. In addition, the same work showed considerable variability among individuals, which could explain, at least in part, why some patients did not respond at all to bolus doses that, in other patients, caused extended blocks and significant hypotension. Preliminary and unpublished results from laboratory work involving a model designed to look at the distribution of drugs administered with a SynchroMed® pump suggest that, with continuous flow rates of less than 1 mL per day, there is very limited mixing occurring whether the milieu (i.e., the CSF) is immobile or pulsating. Mixing, however, increases when bolus doses, even small, are administered, in particular when oscillations (that mimic the arterial pulsations) are generated in the column of fluid that represents the CSF.

Another factor that might have played a role is the volume and flow of CSF in the region around the catheter tip. It has been shown that the pulsations and flow velocities of the CSF are not uniform throughout the subarachnoid space [11,12], and in the ventral thoracic region, the CSF is both relatively immobile and scarce. Coffey and Burchiel hypothesized that poor mixing (of morphine) in this region could lead to relatively high drug concentrations, triggering a nonspecific inflammatory reaction that in turn would further decrease mixing and result in even higher local drug concentration [13]. Although not directly related to this clinical observation, it should be pointed out that neurotoxicity is a major concern when the concentration of a drug increases in the vicinity of the spinal cord. Studies following the occurrence of both cauda equina syndrome and transient neurological symptoms after spinal anesthesia showed that most local anesthetics are neurotoxic in high concentrations. In particular, even clinically used concentrations of lidocaine [14] and tetracaine are associated with potentially severe neurotoxicity [4], although the long-term IT infusion of usual clinical concentrations of bupivacaine was not associated with obvious neurotoxicity [15]. Yet, recent evidence suggests caution, particularly with a higher concentration of any drug, even morphine, that is regarded as safe [16].

In conclusion, we believe that, despite unresolved issues regarding the chemical stability of drug mixtures, the tolerance to the effect of local anesthetics, and their potential neurotoxicity, the continuous administration of spinal bupivacaine remains a logical choice, particularly in cancer patients with intractable mechanical or visceral pain that is unrelieved by morphine. With bupivacaine, our experience suggests that the flow pattern of spinal administration should be evaluated carefully, since it seems to profoundly influence the clinical effect. When the administration of presumably significant doses of bupivacaine does not result in satisfactory pain relief nor cause neurological changes, small, seemingly insignificant bolus doses administered on top of the continuous infusion can produce spectacular pain relief with or without cardiovascular side effects.
References


