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Neurological impairment during long-term intrathecal infusion of bupivacaine in cancer patients: a sign of spinal cord compression

Robert T.M. van Dongen, Rob van Ee, Ben J.P. Crul

Abstract

Adequate pain relief in patients with far advanced cancer sometimes requires intrathecal (IT) administration of a combination of opioids and local anesthetics. Tumor progression as well as the IT administration of local anesthetics can lead to neurologic dysfunction during treatment. Five patients showed symptoms of compression of the cauda equina or spinal cord shortly after the start of combined IT administration of morphine and bupivacaine in a dosage usually not associated with neurologic symptoms. Unexpectedly, neurologic evaluation suggested compression of the cauda equina and spinal cord, which was confirmed radiographically. Manifestation of new neurologic symptoms during low dose bupivacaine infusion intrathecally might therefore be an early indicator of space-occupying processes within the spinal canal in cancer patients.

Keywords: Intrathecal morphine/bupivacaine; Metastatic cancer; Neurologic dysfunction; Spinal cord and cauda equina compression

1. Introduction

In about 15% of cancer patients, neurologic symptoms can be present during the course of the disease (Posner, 1995). Compression of the spinal cord or cauda equina manifests clinically in about 5% of cancer patients (Gilbert et al., 1978; Schiff et al., 1995) and is usually accompanied by pain complaints in the back, with or without radiation into an extremity. Frequently, sensory disturbances, motor weakness ultimately leading to paralysis, and problems with fecal and urinary continence can follow if left untreated (Portenoy, 1987).

In some of these patients, pain relief can either remain inadequate despite the administration of various analgesics including opioids or can be accompanied by intolerable side-effects. Spinal (i.e., epidural, intrathecal (IT)) administration of morphine may then be considered (Krames et al., 1985; Onofrio and Yaksh, 1990) although neurogenic pain components do not always respond favourably (Arnér and Arnér, 1985; Max et al., 1985). Recently a combination of intrathecally administered morphine and bupivacaine (an amide-type local anesthetic) was proposed as a step forward toward the solution of these intractable pain problems (van Dongen et al., 1993; Sjöberg et al., 1994). Usually a wide dosage range of IT bupivacaine is tolerated without severe side-effects below a bupivacaine dosage of 45 mg day⁻¹ (Sjöberg et al., 1994), but individual titration remains mandatory to prevent neurologic dysfunction. We report five cancer patients who developed unexpected, severe, neurologic disturbances during continuous, low-dose, IT morphine/bupivacaine infusions. The clinical signs, differential diagnosis and management are described.

2. Case histories

2.1. Patient no. 1

A 63-year-old man suffered from increasing back pain, radiating into the anterior side of both legs despite high oral morphine (480 mg day⁻¹) intake. The pain was related to widespread bone metastases of a prostatic carcinoma. Diffuse vertebral metastases were shown previously on...
bone scan. Neurologic function was normal. A lumbar IT catheter was inserted. As an initial IT infusion of morphine (9.6 mg day\(^{-1}\)) did not result in adequate pain relief, bupivacaine (15 mg day\(^{-1}\)) was added to the infusion. Pain relief improved but was accompanied by complete motor and sensory block of the left leg below the L2 dermatome and urinary incontinence. CT scanning performed thereafter was suspicious for epidural compression of the spinal cord and cauda equina at the level of Th12-L3 (Fig. 1).

Systemic corticosteroids and radiotherapy resulted in relief of the pain and partial restoration of motor function thereafter. The IT infusion was continued until death, due to respiratory insufficiency, two weeks later, without progression of motor weakness in the legs.

2.2. Patient no. 2

A 45-year-old woman presented with vertebral metastases, nine years after primary resection and radiotherapy of an adenocystic carcinoma of the parotid gland. One year before the start of the IT infusion for pain relief, radiotherapy to the vertebral column was started for complete destruction of the body of the L1 vertebra. At that time, a pathological fracture of L1 with compression of the cauda equina and the spinal cord with weakness of both legs was present.

Following radiotherapy and corticosteroids, an initial deterioration in neurologic function, with progressive motor weakness of the legs and problems with micturition, was present but these symptoms gradually disappeared with minimal radiation of pain into the right leg in the

Fig. 1. CT-scan (transverse plane) at the level of Th12 of patient I showing pathologic changes in the posterolateral border of the corpus of the vertebra, lining the spinal canal (asterisk). Disappearance of the epidural fat is highly suggestive for epidural metastasis here. The white dot (arrow) in the anterior part of the spinal canal is the IT catheter.

weeks thereafter. On readmission one year later, a "belt-like" pain in the lower back and legs had returned despite high doses of oral morphine, dextromoramide, carbamazepine and tricyclic antidepressants. Slight paraesthesiae were present in the right leg without signs of motor weakness. A lumbar IT catheter was inserted and as morphine only (7.2 mg day\(^{-1}\)) did not result in adequate pain relief, a mixture of morphine/bupivacaine was infused continuously thereafter. At a dosage of 7.2 mg morphine and 21.6 mg bupivacaine per day, the patient experienced severe muscular weakness in both legs and inability to walk alone. Diminishing the daily IT bupivacaine to 7.2 mg, adding clonidine (150 \(\mu\)g day\(^{-1}\)) and increasing the morphine (14.4 mg day\(^{-1}\)), resulted in improved motor performance and adequate pain relief. During palliative treatment at home, paraplegia probably due to ongoing spinal cord compression presented before death.

2.3. Patient no. 3

A 67-year-old woman presented with severe low back pain radiating to the thoracic region as well as the back and sides of both legs despite oral morphine (260 mg day\(^{-1}\)). Global hypesthesia was present from the groin down to the feet in both legs. Five years previously, a Grawitz tumor with local-regional spread was resected. A year before start of IT treatment, multiple pathological fractures in both humeri and left femur developed, all treated palliatively by osteosynthesis and radiotherapy. Because of persistent, severe back pain, a lumbar IT catheter was inserted, delivering a combination of morphine and bupivacaine and resulting in significant decrease in pain. Following a gradual increase of the infusion rate during the three days thereafter, motor blockade in both legs and loss of bladder control developed at a bupivacaine dosage of 36 mg day\(^{-1}\). The bupivacaine dosage was reduced to 15 mg day\(^{-1}\) while morphine remained at around 15 mg day\(^{-1}\). Epidural compression or lumbar plexopathy was suspected. On MRI scanning (see Fig. 2) a large mass could be seen eroding the posterior side of the body of L4 with extension into the epidural space, completely occluding the spinal subarachnoid space.

Oral dexamethasone 16 mg day\(^{-1}\) was started and despite a slight increase of the bupivacaine to 24 mg day\(^{-1}\) neurological improvement with restoration of assisted walking could be attained. The patient died at home free of pain with slight motor weakness at day 42 without further increase in IT infusion rate.

2.4. Patient no. 4

A 45-year-old man underwent sigmoid resection because of adenocarcinoma one year before the start of IT treatment. As a child, he contracted poliomyelitis and meningitis. However, neither had any deleterious long-term effect on motor function in his legs. Subsequent che-
motherapy (5 FU, methotrexate) to treat liver metastases during the year following the operation, did not result in remission of the disease. Unbearable, lancinating pain attacks radiating from the groin into his left leg and foot were accompanied by sensory loss and paraesthesiae in a skin area in the left lumbosacral region. Clinically, a lumbar-sacral plexopathy due to tumor invasion or compression were suspected. Other neurologic signs were limited to slight difficulty with micturition without signs of motor impairment. A plain X-ray of the lumbar vertebral column one month previously did not show abnormalities. Further radiologic examination was not performed. Slow release oral morphine (MS contin®; 30 mg bd), amitriptyline and carbamezapine, did not result in adequate pain relief and severe neuropathic pain attacks persisted in combination with bothersome sedative effects. A lumbar subcutaneously tunnelled IT catheter was inserted. A solution containing morphine HCl 0.5 mg.ml⁻¹ and bupivacaine 3 mg.ml⁻¹ was started and gradually increased to a rate of 0.3 ml.hr⁻¹ (3.6 mg morphine and 21.6 mg bupivacaine per day respectively). Progressive neurological dysfunction with proximal and distal motor weakness in the left leg and global hypesthesia of the dermatomes L5 to S5 with inability to void developed at this dosage within 48 hours, with adequate analgesia. Although bupivacaine-induced side-effects were suspected, cauda equina compression due to epidural tumor spread was also considered. On MRI scanning, a large tumor mass eroding the sacral area from the left and extending to the pelvic cavity was observed.

The sacral canal was compressed due to epidural tumor growth. Palliative radiotherapy and oral dexamethasone were started. The IT infusion was not diminished due to the patient’s severe anxiety that the pain would return. The paralysis of the left leg did not subside. The patient was discharged with continuation of the IT treatment and died at home, free of pain, without additional analgesics, four weeks later.

2.5. Patient no. 5

A 67-year-old man was treated by radiotherapy to the right lung and mediastinum for squamous cell bronchial carcinoma three years before admission. Due to progressive tumor growth with invasion of the thoracic vertebrae (Th11–12) and spinal canal with imminent spinal cord compression, palliative radiotherapy was started. As conventional pain relief was inadequate and accompanied by severe constipation, an IT catheter was inserted at a lumbar (L2-L3) interspace initially delivering morphine 4 mg day⁻¹. As pain persisted, bupivacaine was added IT at a dosage of 2.5 mg day⁻¹. Despite adequate pain relief, 10 days after catheter insertion, paraplegia developed with suspicion of ongoing compression of the cord. However, cessation of the IT bupivacaine and increase of morphine IT (6 mg day⁻¹) resulted in complete restoration of motor function of the legs with adequate pain relief thereafter. No neurological symptoms recurred before death.

3. Discussion

In progressive cancer syndromes, severe back pain in combination with motor and sensory disturbances in a leg and problems with micturition can be caused by compression of the spinal cord or cauda equina as well as by tumor infiltration of the nerve roots or plexus (Jaekle et al., 1985; Portenoy et al., 1987). In these situations, increasing the dosage of analgesics, including morphine, is usually considered first. Also co-administration of anticonvulsants, antidepressant drugs or corticosteroids can be beneficial (Portenoy, 1991; Cherry and Portenoy, 1993).

Even when morphine is administered intrathecally, pain relief can still be insufficient especially when neurogenic pain components are present. Co-administration of bupivacaine IT has been advocated to improve pain relief substantially in these situations and we used this technique in our patients (Sjöberg et al., 1991). Morphine IT does not give rise to motor or sensory impairment and IT bupivacaine below a dosage of 45 mg day⁻¹, by continuous infusion has been reported not to produce neurological side-effects either (Sjöberg et al., 1994). We did not observe neurological deficits below a bupivacaine dosage of 30 mg day⁻¹ IT in a study of patients with an undisturbed neurologic history (van Dongen et al., 1993), and thus we did not expect to be confronted with such profound neurologic changes with these low IT bupivacaine dosages.

Severe pain complaints usually precede the clinical manifestation of compression of the spinal cord or plexus invasion during a variable period (Gilbert et al., 1978) in which the patient is usually just able to compensate for the impaired neurological function. Moreover, estimation of normal activity is severely impeded by the pain com-
plaints. Subsequent effective pain treatment with a combination of IT morphine/bupivacaine might lead to ‘unmasking’ of the subtle neurological deficits, which would otherwise stay undetected for a further period. One might argue therefore that the neurological deficits found were merely the result of ongoing compression. On the other hand, in all patients, neurologic symptoms were related to the start of IT bupivacaine infusion or improved following the diminution of the IT dose. This is highly suggestive of a bupivacaine-related effect in these patients. Early diagnosis and adequate treatment of compression is important as the outcome is closely related to the duration of the compression and the neurologic deficits at the moment of diagnosis (Portenoy et al., 1987; Schiff et al., 1995).

As a differential diagnosis for neurological deficits in cancer patients with pain and dysfunction in a leg, lumbo-sacral plexopathy should be considered (Jaeckle et al., 1985). Finally, infectious complications (meningitis, abscess formation), epidural hematoma formation both due to the presence of the IT catheter and late effects of radiation myelopathy may give rise to similar neurologic dysfunction (Warar and Larson, 1991; Table 1).

In these patients, however, these causes were excluded due to the absence of related clinical manifestations and the partial reversibility of the symptoms following the reduction of the bupivacaine administered.

It is unclear what is the exact mechanism of this increased ‘susceptibility’ for bupivacaine IT in these patients. We assume that the neurologic disturbances were caused primarily by the subclinical compression of the spinal cord and cauda equina, which can be easily overlooked during initial patient evaluation. Extreme neurogenic pain complaints can hinder ambulation and routine neurologic testing, whereas the unselective sensory and motor blocking effects of bupivacaine interfere with this compromised neurologic status.

A wide range of IT bupivacaine dosages seems to be tolerated (Sjöberg et al., 1994) suggesting differences in sensitivity, probably influenced also by pharmacological factors. Both pharmacokinetic (e.g., altered distribution of the drug in the CSF with locally increased concentrations due to obstruction of normal CSF flow; proximity of the catheter tip to a spinal root) as well as pharmacodynamic factors (e.g., increased toxicity of local anesthetics in the presence of neurologic dysfunction, changes in CSF com-

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<td>Differential diagnosis of neurologic symptoms in cancer patients</td>
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| Due to primary tumor/metastasis |
| Due to endocrine disturbances (e.g., ADH, glucose, Ca, electrolytes) |
| Cerebral and spinal vascular disease |
| Primary treatment related (chemotherapy, radiotherapy) |
| CNS infections |
| Paraneoplastic syndromes |

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<td>Dosages of bupivacaine IT and clinical signs during neurological deficit</td>
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<tr>
<th>Patient</th>
<th>Bupivacaine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Radiography</th>
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<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>compression Th12-L2</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>compression L1</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>compression L4</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>compression cauda</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>compression Th11-12</td>
</tr>
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<sup>a</sup>Dosage of bupivacaine in mg day<sup>-1</sup> by continuous IT infusion at moment of neurologic deficit.

position or pH), may be of importance (Jones and Healy, 1980).

In our view, the most striking observation in the patients reported here was that neurologic deterioration took place during a low dose IT administration of bupivacaine while other symptoms suggestive of spinal cord or cauda equina compression were clinically absent or unremarkable (Table 2).

The continuous IT co-administration of bupivacaine with morphine, necessitated by the pain syndrome, more or less ‘revealed’ the presence of compression. When this occurs in patients with previous relatively undisturbed neurology, one should consider this as additional diagnostic information. We recommend that besides the pain history and diagnosis of the pain syndrome (Arnér and Arnér, 1985), a neurological examination combined with radiographic evaluation of the vertebral column including CT or MRI is considered before the start of IT treatment. This may be even more important when the use of IT local anesthetics seems to be inevitable.

Specific attention should be given to those patients suspected of having compression of the spinal cord and cauda equina, as conventional radiologic examination may show no abnormalities and MRI scanning is not always available. Early diagnosis of the likely cause of neurological deterioration after initiation of IT morphine/bupivacaine administration is important, not only when there are still palliative treatment modalities available but also because neurological deterioration may have devastating functional and emotional consequences.

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**References**


