INTRAVENTRICULAR DIAMORPHINE VIA AN OMMAYA SHUNT FOR INTRACTABLE CANCER PAIN

W. G. REEVE AND J. G. TODD

SUMMARY
We describe two patients in whom diamorphine was administered into the intraventricular space via an Ommaya reservoir, producing excellent pain relief. The use of this technique for long term administration of analgesia is reviewed.

KEY WORDS

The Ommaya reservoir, described first in 1963 [1], was developed to allow the repeated introduction into the CSF of drugs such as antibiotics or cancer chemotherapy agents [2]. In 1982 Leavens and colleagues reported the administration of intraventricular morphine via an Ommaya shunt [3], but intraventricular administration of diamorphine has not been described previously. We report its use in two patients. Despite excellent pain relief, the technique failed to prevent a withdrawal syndrome when systemic opioids were stopped.

CASE REPORTS

Patient 1
A 52-yr-old man presented in October 1986 with a 2-yr history of progressive weakness and painful paraesthesiae in both legs. He had a past history of removal of right cerebellar haemangioblastoma in 1955, from which he had made a good recovery. Spinal magnetic resonance imaging (MRI) showed an extensive intramedullary lesion extending from C5 to T9. The patient underwent a midline dorsal myelotomy and removal of an intermediate grade astrocytoma. In July 1987, a new left cerebellar haemangioblastoma was diagnosed and subsequently excised. Later a repeat MRI scan showed a cystic recurrence of the astrocytoma, but further surgery was not considered.

By October, the patient’s main problem was bilateral leg pain, neuropathic in nature and more severe on the right. This was associated with objective sensory loss from T1 to L5 on the right side, increased tone and leg weakness. However, he was able to walk with a stick and was continent. By January 1988 his symptoms had progressed to bilateral leg, neck, upper back and shoulder pain which prevented sleep. The pain was relieved only partially by morphine sulphate (MST Continus tablets) 60 mg 8-hourly, codeine phosphate 60 mg 4-hourly, dexamethasone 4 mg 12-hourly, diazepam 5 mg 8-hourly and mianserin 60 mg at night. Neither transcutaneous nerve stimulation nor guanethidine block produced lasting benefit.

A lumbar intrathecal test dose of diamorphine 2 mg brought good relief of his leg pain but, as expected, no relief of interscapular pain. An Ommaya reservoir (Heyer-Schulte, silicone, burr hole design) was inserted via a right frontal burr hole. A subsequent CT scan showed the tip of the catheter in the third ventricle. Instillation of diamorphine 5 mg produced good pain relief. Over the next few days oral opioids were stopped. Two days later he developed a withdrawal reaction with severe abdominal cramps, diarrhoea, sweating, tachycardia, hypertension, anxiety and restlessness. This was relieved by parenteral administration of opioids, followed by MST Continus 30 mg 12-hourly. Intraventricular diamorphine resulted in improved analgesia and a
smaller dose of oral opioids, with his previously distressing constipation controlled. The duration of pain relief was up to 4 weeks. Repeated injections into the reservoir were made on a monthly outpatient basis. As a result of progression of the disease and analgesic tolerance, his opioid requirements increased steadily until November, when he received a monthly bolus of diamorphine 17 mg in water 0.5 ml into the reservoir, together with MST Continus 90 mg 8-hourly. Six months later the increasing requirement for oral opioids caused doubt as to the benefit of intraventricular opioids, so administration was stopped. This was followed by return of intolerable pain, relieved only by intraventricular diamorphine.

The patient suffered no complications from the reservoir and only minor, short-lived side effects after top-ups. These were vomiting and drowsiness commencing 30 min after injection and lasting for 4 h. There was no respiratory depression and the reservoir was still in situ 21 months after insertion.

**Patient 2**

A 13-yr-old girl was diagnosed as having nodular sclerosing Hodgkins lymphoma, stage 2a, in June 1986. Despite repeated courses of chemotherapy and radiotherapy, her disease remained active. By April 1988 a mass in her left axilla, extending to the side of the neck, had invaded the brachial plexus. She was suffering from severe pain in the fingers of her left hand, arm and scapular region. By June 1988 she had developed bilateral ankle clonus caused by spread of disease to the cervical vertebrae and spinal cord. Despite MST Continus 180 mg 12-hourly, combined with dextromoramide 5 mg during periods of activity, her pain was relieved only partially and she was commenced on a continuous subcutaneous infusion of diamorphine 12 mg h⁻¹. An Ommaya reservoir was inserted via a right frontal burr hole under general anaesthesia. After the instillation of diamorphine 3 mg she was pain free. After weaning from the diamorphine infusion she was discharged from hospital. The next day she developed diarrhoea, vomiting and insomnia. She was readmitted 4 days later "feeling suicidal", but still pain free. A diagnosis of opioid withdrawal syndrome was made and her sleep pattern improved only after recommencement of systemic opioids. She was discharged with oral morphine sulphate 30 mg twice daily plus haloperidol. Her pain control was excellent for 4 weeks after the initial intraventricular injection; her quality of life improved and she was able to resume horse riding. After 4 weeks she received further top-ups of diamorphine 2–3 mg every 10 days. Each administration produced complete pain relief, but the duration of action decreased. During the terminal phase of the illness, her condition became too poor to warrant frequent hospital attendance, so intraventricular administration ceased. Subcutaneous diamorphine was recommenced and she eventually died in December 1988.

**DISCUSSION**

These two patients highlight several aspects of long term intraventricular administration of opioids.

There is an acceptably low morbidity and mortality associated with insertion of the reservoir [2]. Strict aseptic precautions are taken each time the reservoir dome is punctured, because of the risk of meningitis. The risks are outweighed by the potential dangers and neurological deficits linked to major ablative procedures used in the management of diffuse pain caused by orofacial, neck and disseminated cancer [4].

The incidence of opioid side effects is acceptably low. Previously reported side effects include urinary retention, somnolence, visual hallucinations, pruritus and facial tingling lasting usually for a few hours [5, 6]. Patient 1 demonstrated the absence of gastrointestinal side effects.

Respiratory depression is uncommon after intraventricular morphine. Only two cases have been reported [4, 5], both antagonized easily by naloxone. To assess the likelihood of respiratory depression, together with the quality and duration of pain relief, a test dose of lumbar intrathecal opioid is advised. A suitable test dose comprises 1% of the patient's usual morphine requirement [6]. Because of the theoretical risk of respiratory depression, we avoided pumping the reservoir, to prevent a bolus dose being delivered into the ventricle. These patients had ECG and ventilatory frequency monitored in the ward for 2 h after intraventricular administration of drug (which was administered by one of the authors (J. G. T.)), and were allowed home 6 h later. However, other workers have trained the family of their patients to perform the technique at home [3, 6].

Diamorphine may have advantages over morphine. The white crystalline powder diamorphine
hydrochloride is highly soluble in water and is preservative free. The selected dose may be dissolved in 0.2–0.5 ml of water or saline immediately before injection into the reservoir.

In our two patients the long duration of pain relief exceeded the usual duration of up to 48 h reported for intraventricular morphine; this is difficult to explain. It takes some time for the drug to diffuse out of the reservoir, but the rate of diffusion is unknown. The action of diamorphine is continued by its active metabolites, monoaacetyl morphine and morphine [7]. Intraventricularly administered morphine probably acts at a supraspinal level, and the short latency of analgesia is consistent with this hypothesis. Analgesia may be continued by caudal diffusion resulting in a direct spinal action [4]. The interactions of endogenous and exogenous opioids with their different receptor populations are complex, but activation of endogenous opioid systems may be involved in analgesia of longer duration than predicted by pharmacokinetics [8]. "Permanent" analgesia produced by intraventricular morphine has been reported previously [4].

The duration of pain relief in both patients decreased with subsequent administration because of a combination of progression of disease and development of tolerance. It is possible that more effective long term analgesia may have been achieved by increasing the frequency of intraventricular top-ups, rather than by increasing systemic administration.

Most patients embarking on this therapy are already receiving opioid analgesics and there is cross tolerance between systemic and intraventricular opioids. For this reason, reduction or discontinuation of systemic opiates has been advised before initiation of intraventricular therapy [4]. Experience in our patients suggests that it is undesirable to stop systemic opioids, as intraventricular diamorphine, although providing excellent analgesia, does not necessarily prevent abstinence syndrome. In monkeys, opioid withdrawal symptoms are believed to be mediated by increased noradrenergic activity at the midbrain coeruleus [9]. The reduction of withdrawal symptoms by clonidine [10] suggests that the same mechanism occurs in man.

Glucose utilization in the limbic system increases during experimental withdrawal of opioids, with a distribution similar to naloxone binding site distribution [11]. This is consistent with the finding that neither spontaneous withdrawal in these patients, nor naloxone [4,5], antagonized the analgesia of intraventricular opioids. The development of withdrawal in these patients suggests that the concentration of active opioid at CNS receptors involved in physical dependence was insufficient to prevent withdrawal. Experimentally induced lesions of the fasciculus retroflexus in the interpeduncular nucleus increase the diarrhoea of opioid withdrawal, suggesting a central component of this symptom—probably an interaction between the limbic system and the dorsal motor nucleus of the vagus [12]. However, the characteristics of opioid dependence in isolated guineapig ileum closely resemble those of dependence in whole animals [13]. This supports the suggestion that lack of opioid at gut mu receptors contributed to the increased gut motility and gastrointestinal symptoms.

It is clear that the balance between analgesic and unwanted effects depends upon many factors. The opioid concentration at different central and peripheral receptor sites appears to be important and may be influenced by route of administration.

REFERENCES

10. Gossop M. Clonidine and the treatment of the opiate