Inadvertent intrathecal injection of tramadol

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The present case report describes the observed sequelae following an inadvertent intrathecal injection of tramadol in a patient with metastatic malignancy. The contributing circumstances before the injection are discussed, as is the potential aetiology of the observed sequelae.

Keywords: analgesic opioids, tramadol; complications, cancer; complications, intrathecal catheters

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Case report

Mrs MF, a 57-yr-old female, was admitted to our institution for palliative management of a widely metastatic squamous cell carcinoma of unknown primary. She had a life expectancy of only a few weeks. Her principal problem was pain management for right iliac metastases that were fungating through the skin of her inguinal region causing severe neuropathic and bony pain. She also had pain from other metastatic deposits. She had no other medical problems.

Analgesia was primarily via an intrathecal catheter placed on day 2 of her admission, through which was running morphine 24 mg and bupivacaine 90 mg over a 24-h period. Additional agents included a fentanyl patch (150 µg h⁻¹), s.c. ketamine (5 mg h⁻¹), paracetamol (500 mg every 6 h), gabapentin (300 mg every 6 h) and tramadol (50 mg orally or i.v. every 6 h). She also received s.c. morphine and midazolam as required, and had received a total of morphine 600 mg and midazolam 100 mg in the 24 h leading up to the events described in this report. Despite the massive doses of morphine (equivalent to oral morphine ~5000 mg per day) she gained symptomatic benefit from both the fentanyl patch and the tramadol.

An inadvertent intrathecal injection of tramadol ~25 mg was given on day 21 of her admission.Within 10 min of the injection it was noted that she was diaphoretic and hypotensive, with a systolic blood pressure of 70–80 mm Hg. In the preceding days her systolic blood pressure was approximately 110–130 mm Hg. Her heart rate was unchanged at 110–130 beats min⁻¹ in a regular rhythm. Other observations were normal. She developed severe central back pain associated with back arching spasms and myoclonic jerks in both lower limbs. Her sensorium was unchanged.

To control the myoclonus, intrathecal baclofen 0.5 mg was given without effect. However, the myoclonus was controlled by phenobarbitone 200 mg s.c., which was given as required. The myoclonus and hypotension persisted until her death 48 h later.

Discussion

The intrathecal injection of tramadol has not been previously reported in humans. Tramadol has been used extensively by the oral, i.v. and epidural routes but has not been reported to have the sequelae presented here.¹⁻⁴ Intrathecal tramadol has been used in pharmacodynamic studies in rats, in which it provided demonstrable analgesia without reported toxicity.⁵⁻⁷ Intrathecal tramadol has also been used in dogs in doses of up to 100 mg without reported toxicity.⁸ We do not know what caused the constellation of signs and symptoms that followed the intrathecal injection of tramadol in the present case. However, given the temporal relationship between injection and patient symptoms, a potential causal relationship should be considered. There are a number of possible mechanisms that deserve consideration.

Tramadol is presented in a sterile i.v. preparation with water for injection and sodium acetate as a buffering agent. Significant neurotoxicity has never been reported related to the use of sodium acetate. Tramadol is an agonist at the mu opioid receptor and inhibits the uptake of monoamines in the serotonergic synapse.⁵ Tramadol may have caused these symptoms and signs by virtue of its serotonergic effects. It is known to cause seizures and the serotonin syndrome, especially when coadministered with other inhibitors of monoamine reuptake.⁹⁻¹² The serotonin syndrome can present with a variety of features, including myoclonus.
diaphoresis and hypotension.\textsuperscript{13} The M1 metabolite of tramadol (mono-O-desmethyltramadol) has also been demonstrated to cause seizure activity.\textsuperscript{14} However, given the short time between injection and onset of symptoms, the likelihood of the M1 metabolite being responsible seems remote. The amount of intrathecal and s.c. morphine which this patient was receiving has been reported to cause myoclonus, as have other opioids (methadone and hydromorphone).\textsuperscript{15,16} However, the myoclonus is thought to be secondary to the accumulation of 3-glucuronide metabolites rather than a mu receptor effect.\textsuperscript{15} Consequently, it is unlikely that tramadol acted in a synergistic manner with the morphine to produce the syndrome. Given the relationship between giving the tramadol and the onset of the symptoms, it is also unlikely, although not impossible, that the clinical presentation was solely one of morphine neurotoxicity. Another potential mechanism is via an alteration in the CSF pH. It is known that intrathecal injections of morphine do lower the pH of the CSF,\textsuperscript{17} and it is possible that the addition of tramadol compounded this, although there is no evidence for this.

Our management of the patient after the injection of tramadol was not particularly successful. Baclofen did not assist in control of the symptoms despite its usefulness as an antispasmodic. We were able to control the symptoms for short periods of time using phenobarbitone. However, this resulted in the patient being drowsy in her last days and probably contributed to the persisting hypotension. Our focus at this point, however, was to allow her to remain comfortable.

Within our institution the pain service, consisting of an anaesthetic/pain consultant, anaesthetic registrar and pain clinical nurse consultant, is involved in the management of all patients with intrathecal and epidural catheters. There are also written protocols for nursing staff involved in the daily care of patients with these catheters \textit{in situ}. These cover all aspects of management of the catheter. Despite these safeguards, this incident happened. The primary error was the connection of an i.v. giving set to the intrathecal catheter, which is against hospital protocol. Although there were labels on the infusion device and on the intrathecal catheter itself, the giving set was unlabelled. The change in giving set occurred over the weekend. Hence, the circumstances were in place for the inadvertent injection on Monday morning by an agency-registered nurse unfamiliar with intrathecal catheters and the hospital protocols. Since this error, re-education of nursing staff regarding the management of neuraxial catheters has taken place. Greater recognition of the problems faced by wards with ever-increasing numbers of agency nursing staff has also occurred.

Preventing inadvertent injection of drugs is a recurring problem.\textsuperscript{18–22} Errors in the drawing up and handling of drugs occur within operating theatres and on the wards. Although many changes have been introduced over the years, such as checking drugs with other staff, labelling of syringes and different-coloured syringes, which may have reduced the incidence of inadvertent drug administration, errors still occur. A recent review of the epidural literature has highlighted inadvertent administration of drugs into neuraxial catheters.\textsuperscript{18} The authors suggested education, labelling, separation of intravenous and epidural infusion devices and avoidance of injection ports in neuraxial lines. Despite all of these systems being implemented in our hospital as part of the pain management protocols, this error still occurred. Part of the solution is ongoing education of staff and ensuring that casual and agency staff are included in such education or suitably supervised by regular ward nursing staff. However, human errors do occur and a system needs to be in place that minimizes the potential for errors.\textsuperscript{18–22}

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