

Case Report

## Remifentanyl in the management of severe tetanus

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A 61-yr-old woman presented with severe tetanus. Her intensive care management was complicated by severe generalized tetanic spasms despite the use of propofol, midazolam, alfentanil, magnesium sulphate, and atracurium. We describe the management of this problem with a variable dose remifentanyl infusion.

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Despite widespread immunization programmes since 1961, there are still an average of 10 cases of tetanus reported per year in the UK.<sup>1</sup> Tetanus causes muscle rigidity and weakness, muscle spasms, and autonomic instability. When severe, the muscle spasms can lead to respiratory compromise. The mainstay of the management of tetanus is supportive care with sedation, airway protection, and controlled ventilation routinely required. Many different drugs have been used to suppress and control tetanic spasms. We present a case of generalized tetanus complicated by severe tetanic spasms managed with a variable dose remifentanyl infusion.

### Case report

A 61-yr-old woman sustained a 5-cm wound to the right temple following a fall in the garden. The wound was cleaned and sutured in the accident and emergency department. A tetanus booster was not given as the patient had received one 6 yr earlier. Before that injection, she had not had a booster vaccination for 20 yr.

Nine days later she presented with a right upper motor neurone facial nerve palsy and, with a presumed diagnosis of Bell's palsy, was prescribed a course of steroids. Following treatment, she developed a local infection around the original wound with severe trismus. She was admitted for rehydration, i.v. antibiotics (co-fluampicil 250 mg/250 mg qds) and investigated further. Thirteen days following the initial injury, whilst still an in-patient, she collapsed and suffered a 15-s period of apnoea. She restarted breathing after use of basic airway manoeuvres and suction. A diagnosis of cephalic tetanus progressing to generalized tetanus was made.

The patient was taken to an anaesthetic room for stabilization before transfer to the intensive care unit

(ICU). Following insertion of a radial arterial catheter, she was electively intubated using a rapid sequence induction technique. The patient was then sedated with propofol (0–5 mg kg<sup>-1</sup> h<sup>-1</sup>) and alfentanil (0–2.5 mg h<sup>-1</sup>) infusions, given boluses of midazolam (0.1–0.2 mg kg<sup>-1</sup>) to control the spasms, and paralysed with boluses of the non-depolarizing neuromuscular blocking agent atracurium (0.5 mg kg<sup>-1</sup>), while further invasive monitoring was established. During this period, she suffered a period of fast atrial fibrillation at a rate of 170–200 beat min<sup>-1</sup>, and a mean arterial pressure of 30 mm Hg. This spontaneously reverted to sinus rhythm after 90 s, and once stable the patient was transferred to the ICU. Here she was given a bolus of tetanus immune globulin (150 u kg<sup>-1</sup> i.m.), and a magnesium sulphate infusion was commenced (0–10 mmol h<sup>-1</sup>, titrated to maintain plasma magnesium at 2–4 mmol litre<sup>-1</sup>). She was also prescribed i.v. metronidazole (500 mg tds) for 7 days. The wound on the right temple was surgically debrided following transfer to the ICU.

The patient remained haemodynamically stable during her ICU admission with no signs of autonomic instability. However, she continued to have severe generalized spasms occurring spontaneously and triggered by the most minor stimuli. She was ventilated using a pressure control mode with tidal volumes of 5–7 ml kg<sup>-1</sup>. Between spasms, artificial ventilation was achieved satisfactorily. However, during a spasm, tidal volumes dropped to less than 1 ml kg<sup>-1</sup>, and manual bagging was impossible because of chest wall rigidity. With frequent and often prolonged spasms, this caused major problems in administering basic intensive care, and made physiotherapy almost impossible. Gas exchange worsened and oxygen requirements increased.

Initially the spasms were managed with propofol, alfentanil, midazolam (0–10 mg h<sup>-1</sup>), and magnesium

sulphate infusions along with boluses of atracurium when required. However, even with maximum doses of this therapy, the spasms remained problematical. On day 2, the alfentanil and midazolam infusions were discontinued along with the atracurium boluses, and a remifentanyl infusion was started at a rate of  $0.05\text{--}0.1\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$  as an adjunct to sedation and for analgesia. The infusion rate was increased 1 min before any therapy, and titrated to effect ( $0.3\text{--}0.6\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ ). This controlled spasms sufficiently to allow therapy to continue without the need for neuromuscular block or the use of benzodiazepines, and allowed the propofol to be reduced to  $0.5\text{--}2.0\text{ mg kg}^{-1}\text{ h}^{-1}$ . The patient remained haemodynamically stable with this infusion regimen. When the remifentanyl infusion was in progress and the spasms were controlled, the magnesium sulphate infusion was also stopped. The spasms did not worsen after stopping the magnesium. On day 2, an elective percutaneous tracheostomy was performed with propofol sedation, remifentanyl, and local anaesthetic infiltration of the skin (lidocaine 2% with 1:200 000 epinephrine).

The propofol and remifentanyl infusions were stopped on a regular basis to ensure optimal sedation levels and to monitor progress of the disease. The spasms gradually reduced both in frequency and severity, allowing the propofol and remifentanyl infusion rates to be reduced. After 2 weeks of intensive care, the tetanic spasms had ceased and the propofol and remifentanyl infusions were successfully discontinued. However, with cessation of sedation, the patient showed no conscious response to stimuli and decerebrate posturing. There was also spontaneous facial twitching. She could not be weaned from ventilatory support. An EEG performed on day 8, whilst the patient was sedated, had shown alternating slow wave activity and periods of suppression, attributable to her sedated state. No epileptiform activity was seen. However, with the history of a respiratory arrest and a period of haemodynamic compromise shortly before transfer to the ICU, we were concerned that the patient may have sustained a hypoxic brain injury. On day 17, cerebral function monitoring was commenced, which showed epileptiform activity. After a loading dose of phenytoin (1 g as an i.v. infusion over 20 min) both the seizure activity seen on the cerebral function monitor and the facial twitching stopped. At this time, the patient also developed severe bronchopneumonia, and in view of this and the cerebral function findings, treatment was not increased. The patient died on day 18. Subsequent post-mortem examination showed evidence of hypoxic brain injury.

## Discussion

Tetanus is caused by the toxin tetanospasmin, which is released by the germinated spore of the tetanus bacillus. This toxin primarily affects inhibitory neurones, preventing the release of the neurotransmitters glycine and gamma-aminobutyric acid, and leading to failure of inhibition of motor reflex responses to sensory stimulation. This

causes the muscle rigidity and the characteristic generalized contractions of a tetanic spasm, along with autonomic instability.

Since the widespread immunization programme introduced in 1961, tetanus has become a rare disease in the UK. Vaccination guidelines are widely available.<sup>2</sup> Omission of the tetanus booster in this case follows current guidelines for the management of tetanus-prone wounds, but with no booster having been given for 20 yr, the patient's immunity should have been considered further. In this case, the diagnosis was delayed. This was because the patient initially presented with a facial nerve palsy. This was treated and, when she then developed trismus, more common causes of this were investigated first. Cephalic tetanus, when a cranial nerve is affected leading to a localized motor weakness (in this case, the facial nerve) is a rare form of tetanus and is associated with a poor prognosis, especially if it progresses to generalized tetanus.

A review article<sup>3</sup> comprehensively discussed the presentation and management of tetanus, which has traditionally been with sedation, anticonvulsants, neuromuscular blocking agents, and intermittent positive pressure ventilation. However, this approach is associated with a degree of morbidity and mortality,<sup>4,5</sup> and different methods to control the spasms have been sought including magnesium sulphate infusions,<sup>6</sup> dantrolene infusions,<sup>7</sup> and intrathecal administration of baclofen.<sup>8,9</sup> The mainstay of control of rigidity and spasms is sedation with a benzodiazepine,<sup>3</sup> and in this case midazolam was used. Anticonvulsants are also used for additional sedation, particularly phenobarbitone.<sup>3</sup> There were supply problems with phenobarbitone in this case and whilst waiting for the drug to arrive, and in the face of worsening spasms, the remifentanyl was started. When an EEG on day 8 did not show any epileptiform activity, anticonvulsants were not added as spasms were being controlled.

Remifentanyl, a phenylpiperidine derivative, is a selective mu-opioid receptor agonist, which has recently been licensed for use in critical care. It has an established role in neurosurgical intensive care,<sup>10</sup> and is becoming established within cardiac and general intensive care.<sup>11</sup> Remifentanyl has a rapid onset of action and is metabolized by non-specific ester hydrolysis in the blood and tissues. It has a short clinical duration of action (3–5 min) independent of the duration of infusion.<sup>12</sup> As such, its half time is context-insensitive, allowing precise titration of infusion rates.

In this case, a maintenance infusion dose of remifentanyl was sufficient to provide analgesia and tolerance of artificial ventilation. Increasing the infusion rate 1 min before therapy proved successful in controlling spasms and with titration of the dose, procedures such as physiotherapy could be performed. There was also a rapid fall in oxygen requirements (from  $FI_{O_2}$  0.6 to 0.3). On day 2 of the remifentanyl infusion, we successfully performed a percutaneous tracheostomy using propofol sedation and an increase in the infusion rate of remifentanyl ( $0.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ ) with local anaesthetic infiltration of the skin. Gupta and colleagues<sup>13</sup> report

the routine use of this technique in general intensive care, and note excellent haemodynamic stability during procedures.

Tetanic spasms are extremely painful and may be so severe as to cause fractures and tendon avulsions. Remifentanyl is known to be a highly effective analgesic with recent work suggesting it inhibits muscular pain to a greater degree than cutaneous pain in human volunteers.<sup>14</sup> It also has fewer of the side-effects seen with the agents commonly used for sedation in the ICU.<sup>15</sup> With its rapid metabolism it is non-cumulative even in patients with hepatic or renal failure,<sup>16,17</sup> a problem seen with other such agents and their metabolites.

Potential problems do exist with the use of remifentanyl. It is expensive but appears to have a sparing effect on other drugs. With tetanus being primarily a disease of the developing world, access to this new drug in the areas where the disease is more commonly seen may be limited by its cost. One of the side-effects of remifentanyl is muscle rigidity,<sup>12</sup> but this did not cause any problems with chest wall compliance or ventilation in this case. Remifentanyl by infusion is also associated with hypotension and bradycardia, both of which are undesirable in a patient already prone to cardiovascular instability by the nature of the disease. In this case, autonomic instability was not problematical either before or during the infusion. However, remifentanyl should be used with caution to avoid this side-effect. Tolerance is also a side-effect of the opiates. Evidence for the development of tolerance following a remifentanyl infusion is conflicting, and studies have only examined tolerance following short (less than 3 h) periods of use. One study<sup>18</sup> found a profound and rapid decline in the analgesic effect of remifentanyl and a corresponding increase in opioid requirements, but subsequent studies<sup>19,20</sup> found no clinical evidence of acute opioid tolerance.

## References

- 1 Data from Public Health Laboratory Service Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
- 2 *British National Formulary Number 47*. British Medical Association and Royal Pharmaceutical Society of Great Britain: Pharmaceutical Press, March 2004; 592–93
- 3 Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *Br J Anaesth* 2001; **87**: 477–87
- 4 Edmondson RS, Flowers MW. Intensive care in tetanus; management, complications, and mortality in 100 cases. *Br Med J* 1979; **1**: 1401–4
- 5 Appadu BL, Greiff JMC, Thompson JP. Postal survey on the long-term use of neuromuscular block in the intensive care. *Intensive Care Med* 1996; **22**: 862–66
- 6 Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; **57**: 778–817
- 7 Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia* 1993; **48**: 969–71
- 8 Dressnandt J, Konstanzer A, Weinzierl FX, Pfab R, Klingelhöfer J. Intrathecal baclofen in tetanus: four cases and a review of reported cases. *Intensive Care Med* 1997; **23**: 896–902
- 9 Saissy JM, Demaziere J, Vitris M, *et al.* Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; **18**: 241–4
- 10 Tipps LB, Coplin WM, Murry KR, Rhoney DH. Safety and feasibility of continuous infusion of remifentanyl in the neurosurgical intensive care unit. *Neurosurgery* 2000; **46**: 596–602
- 11 Cohen J, Royston D. Remifentanyl. *Curr Opin Crit Care* 2001; **7**: 227–31
- 12 Egan TD. Remifentanyl pharmacokinetics and pharmacodynamics. A preliminary appraisal. *Clin Pharmacokinet* 1995; **29**: 80–94
- 13 Gupta A, Ravalia A. Remifentanyl for percutaneous tracheostomies in ITU. *Anaesthesia* 2000; **55**: 491–92
- 14 Curatolo M, Petersen-Felix S, Gerber A, Arendt-Nielsen L. Remifentanyl inhibits muscular more than cutaneous pain in humans. *Br J Anaesth* 2000; **85**: 529–32
- 15 Murdoch S, Cohen A. Intensive care sedation: a review of current British practice. *Intensive Care Med* 2000; **26**: 922–28
- 16 Dershwitz M, Hoke JF, Rosow CE, *et al.* Pharmacokinetics and pharmacodynamics of remifentanyl in volunteer subjects with severe liver disease. *Anesthesiology* 1996; **84**: 812–20
- 17 Hoke JF, Shlugman D, Dershwitz M *et al.* Pharmacokinetics and pharmacodynamics of remifentanyl in persons with renal failure compared with healthy volunteers. *Anesthesiology* 1997; **87**: 533–41
- 18 Vinik HR, Kissin I. Rapid development of tolerance during remifentanyl infusion in humans. *Anesth Analg* 1998; **86**: 1307–11
- 19 Cortínez LI, Brandes V, Muñoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanyl-based anaesthesia. *Br J Anaesth* 2001; **87**: 866–9
- 20 Gustorff B, Nahlik G, Hoerauf K, Kress HG. No early tolerance during remifentanyl infusion in volunteers. *Eur J Anaesthesiol* 2001; **18** (Suppl 21): 138–138 (abstract A494)