CASE REPORT

Rocuronium for control of muscle spasms in a tetanus patient with chronic methamphetamine use disorder

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SUMMARY

This is a case of a 31-year-old Filipino man with chronic methamphetamine use disorder who developed tetanus from a necrotic skin graft over his left calcaneus, which was fractured after a motor vehicular accident. During the course of his illness, the patient's muscle spasms were unusually refractory to benzodiazepine, which is the first-line drug used in the management of muscle spasms. The muscle spasms were successfully controlled on the seventh day of illness with rocuronium at a dose of 10 µg/kg/min and midazolam at 0.30 mg/kg/hour. Both infusions were tapered off until the 23rd day of illness. The patient was discharged on the 30th day of illness, improved and stable.

BACKGROUND

Substance abuse results in impaired judgement and increased risk-taking behaviours, associated with fatigue, somnolence and depression. These are all contributors to unsafe driving. Motor vehicular accident is one of the more common causes of tetanus infection. This is because injuries sustained are tetanus-prone, being exposed to dirt or soil, where spores are usually found.¹

Tetanus is a disease of the nervous system that presents with tonic spasms, caused by *Clostridium tetani*, which produces tetanospasmin that causes violent spastic paralysis by blocking the release of γ-aminobutyric acid (GABA). This leads to dangerous overactivity in the muscles from the smallest stimulus, leading to generalised contractions of the agonist and antagonist musculature, termed a tetanic spasm. The treatment of tetanic spasms and rigidity is one of the most important aspects in the management of tetanus, as it is very crucial to the outcome. Uncontrolled tetanic spasms are life-threatening because they can cause respiratory failure, leading to aspiration, and induce generalised exhaustion. Several drugs may be used to control these spasms, including sedatives such as diazepam and midazolam, as well as neuromuscular blockers such as vecuronium and pancuronium.^{2,3}

The first-line drug used for the prevention and control of muscle spasms and convulsions is benzodiazepines—diazepam and midazolam. Benzodiazepines have been reported to have significant benefits, attributed to their combined anticonvulsant and muscle relaxation actions on tetanus muscle spasms and rigidity, together with their sedative and anxiolytic effects.⁴

However, it has been cited that drug users are commonly difficult to sedate. Chronic methamphetamine use may cause tolerance to commonly used sedatives such as benzodiazepines. In general, they require higher dose of sedatives. As such, the same struggle is encountered in the management of muscle spasms in patients with tetanus who are chronic substance users. Hence, the use of neuromuscular junction blockers, acting on an entirely different mechanism, comes into play.⁵

CASE PRESENTATION

This is a case of a 31-year-old Filipino man who came to the emergency room for lockjaw. He has been a methamphetamine user for the past 5 years, inhaling it two to three times daily. He was driving a motorcycle under the influence of methamphetamine and alcohol when he crashed against a post and sustained multiple injuries including a left calcaneal fracture. He came in with a positive urine methamphetamine test and a negative cannabinoid test. He underwent detoxification with activated charcoal. He was given antitetanus serum and tetanus toxoid injection on admission, and underwent a series of debridement and open reduction with screw fixation and cerclage wiring of the left calcaneus, with superficial thickness skin graft over the left heel. He was on close follow-up with the orthopaedic surgery clinic, where the wound graft was checked and debrided monthly.

The patient was brought to the emergency department 2 months later for progressive lockjaw and stiffening of the tongue. At this time, there were no spasms, no seizures, no dyspnoea, no profuse sweating and no irritability. He arrived awake and comfortable, not in cardiorespiratory distress, with stable vital signs. He had trismus of 1 finger-breadth and risus sardonicus. No nuchal, thoracic, abdominal and limb rigidity were noted at this time. The wound on the left heel was noted to be dry and gangrenous with eschar formation (figure 1). Neurological examination showed hyper-reflexia on all extremities. The rest was unremarkable.

TREATMENT

The patient was managed as a case of tetanus stage II and was immediately given antitetanus serum 10 000 units intramuscularly and tetanus toxoid 0.5 mL intramuscularly near the site of the wound. He was hooked to 24 g MgSO₄ drip given over 12 hours, and was started on metronidazole

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Figure 1 Open necrotic wound graft, left heel.

500 mg intravenously every 6 hours and diazepam 5 mg tablets, one tablet every 8 hours. Ciprofloxacin 400 mg was given intravenously every 12 hours for wound infection. He underwent emergency tracheostomy immediately on admission.

The patient had an onset of generalised spasms (5 spasms in 24 hours) on the second day of illness. Diazepam was then increased to a maximum dose (40 mg/day), and he was started on midazolam drip at 0.15 mg/kg/hour, which was titrated up to a maximum of 0.30 mg/kg/hour as needed for spasms. He was then hooked to a mechanical ventilator.

On the third day of illness, there was progression of trismus to half a fingerbreadth. Increase in the frequency of generalised spasms was also noted, now occurring once every hour despite maximum dose of diazepam and midazolam drip. The patient was then hooked to propofol infusion at 50 µg/kg/min given for 48 hours. Diazepam tablet was discontinued and was shifted to diazepam 5 mg intravenously as needed for frank spasms. On the same day, the patient underwent escharotomy and removal of implants, with superficial thickness skin graft.

On the fifth day of illness, the patient was still having spasms at least once every 3 hours at a maximum dose of midazolam (0.30 mg/kg/hour) and after 48 hours of propofol infusion. This prompted us to start another neuromuscular relaxant with a different mechanism of action, which is a neuromuscular junction blocker. In our resource-limited setting, the neuromuscular junction blockers available were atracurium and rocuronium, both of which were not the recommended neuromuscular junction blockers for tetanus. We started the patient on rocuronium due to better cardiovascular profile compared with atracurium at a dose of 5 µg/kg/hour, which was titrated up to a maximum of 10 µg/kg/min as needed for spasms.

At a maximum dose of midazolam and rocuronium infusion, the patient was spasm-free for 72 hours from the seventh day of illness to the tenth day. Midazolam was maintained at a maximum dose, while trials of turning off of rocuronium infusion was done starting on the 10th day of illness, every other day, to check for occurrence of spasm. Rocuronium infusion was successfully discontinued on the 13th day of illness. Midazolam was then maintained at the lowest possible dose. Stimulation-induced spasms occurred once every 3 days, for which the patient was given diazepam 5 mg/SIVP for each episode of spasm. Midazolam was gradually titrated down on the 17th day of illness and was discontinued on the 23rd day of illness. The patient was then awake and spasm-free, with improved mouth opening of 2 fingerbreadths, with no nuchal, thoracic, abdominal or limb rigidity. The patient was discharged on the 30th day of illness, off mechanical ventilator and off benzodiazepines (figure 2).

OUTCOME AND FOLLOW-UP

On follow-up care, the patient significantly lost weight while admitted. He reported myalgia for the first month after discharge, which was tolerable. He was able to feed per ore immediately on discharge. He underwent a series of physical therapy thereafter. He was successfully decannulated 3 months after and was

Figure 2 Timeline of pharmacological management of muscle spasms. ATS, Antitetanus serum; DZP, diazepam; IM, intramuscularly; MDL, midazolam; PRO, propofol; ROC, rocuronium; TeANA, tetanus toxoid.

Table 1 Case reports on the use of rocuronium in tetanus

	Anandaciva <i>et al</i>	Iff <i>et al</i>	Case
Subject	Man	Dog	Man with substance use disorder
Monitoring of degree of blockade using train-of-four	Done	Done	Not done
Rocuronium bolus dose	8 µg/kg	600 µg/kg	None
Rocuronium infusion dose	8–10 µg/kg/min	1–1.2 mg/kg/hour (16.67–20 µg/kg/min)	5–10 µg/kg/min
Outcome	Poorly controlled spasms, shifted to alcuronium	Spasms controlled on the third day but the dog died 2 days after of unknown aetiology	Spasms controlled after 48 hours Adverse effect: myalgia

ambulatory and independent of all activities of daily living after 6 months. The prolonged recovery of ambulation can also be attributed to the healing skin graft of the left heel. The patient was seen 2 years later, methamphetamine-free since the day of his accident and back to work as a driver.

DISCUSSION

Local guidelines in the management of tetanus include the following goals: to neutralise the unbound toxin, to eliminate exotoxin production, to prevent and control muscle spasms, and supportive measures to prevent complications of the disease. Tetanus immunoglobulin is given at 500 IU intramuscularly, along with antitetanus serum 10 000 units intramuscularly. Elimination of the source of infection is done by wound debridement or removal of other possible sources such as implants. Metronidazole is given at 500 mg intravenously every 6 hours for 10 days. Penicillin G is no longer recommended due to its antagonistic effect on GABA receptors. The standard of therapy for controlling muscle spasms is benzodiazepines due to their combined relaxant, anticonvulsant, sedative and anxiolytic effects. The most commonly used is diazepam because it is cheap and readily available in a resource-limited setting such as ours. Midazolam, a shorter acting benzodiazepine, is another option, usually given as an infusion. Despite the lack of published evidence on the use of benzodiazepines, they still remain the backbone of treatment regimens for tetanus. In cases where benzodiazepines may be insufficient to control muscle spasms, a muscle relaxant with an entirely different mechanism of action is required. These are the non-depolarising neuromuscular blockers.^{4 6}

There are no published randomised controlled trials to assess the effects of neuromuscular blockers in patients with tetanus. Relevant articles available are case reports or case series of patients with tetanus managed in the intensive care unit setting. The most commonly used neuromuscular blocker was pancuronium, followed by vecuronium, atracurium and rocuronium. This is attributable to the year the drug was introduced, with pancuronium being introduced in the early 1940s and rocuronium in the late 1990s. Rocuronium was one of the newer non-depolarising neuromuscular blockers; hence, there are only two case reports, one on human and one on a dog, on the use of this neuromuscular junction blocker for tetanus.⁷

Response to neuromuscular blockers is unpredictable in critically ill patients. The degree of blockade is ideally monitored with peripheral nerve stimulation using train-of-four

Patient's perspective

In Filipino

"Hindi ko mabuksan ang bibig ko kaya ako dinala sa emergency room. May tetano daw ako. Naninigas ang buong katawan ko. Pagkatapos nun, pinatulong nila ako ng ilang araw. Nagising na lang ako na mahina ang katawan ko. Naninigas ako pag sinusuction nila ang plema ko. Tinanggal nila ang ventilator tapos nakauwi na ako. Nung mga unang linggo sa bahay, masakit ang katawan ko pero hindi ko naman kinailangan uminom ng gamot. Namayat din ako kasi lumuwag ang mga damit ko. Nagtherapy ako at nakatulong yun para bumalik ang lakas ko. Nakapagtrabaho na ako bilang driver matapos ang anim na buwan at nagkaroon pa ako ng bagong anak matapos ng isang taon."

Translated to English (via Google Translate)

"I could not open my mouth so I was brought to the emergency room. I have Tetanus. I had uncontrolled stiffening. After that, they put me to sleep for a few days. I woke up with my body generally weak. I had spasms when they suction my secretions. Eventually, I was off the ventilator and I was sent home. During the first weeks at home, my body was painful but I didn't have to take medicine. I also lost weight and noticed that my clothes were loose. Physical therapy helped me gained my strength back. I went back to work as a driver after six months and had a daughter a year after I was discharged."

(TOF) stimulation. TOF involves stimulation of a peripheral motor nerve with four sequential stimuli over a 2 s period. The response of a muscle innervated by the nerve is observed. The neuromuscular blocker dose is generally titrated to achieve two visible twitches in response to each TOF. The depth of neuromuscular blockade is assessed every 2–3 hours until the dose is stable, then every 8–12 hours. If no or one twitch is present, the dose is reduced by 10%, and if there are three or four twitches present the dose is increased by 10%. The ulnar nerve is the most commonly stimulated motor nerve on the wrist to observe the response of adductor pollicis.^{8 9}

Patients with tetanus commonly present with autonomic dysfunction as a complication, making their cardiovascular function unstable. Hence, the choice of neuromuscular junction blocker for tetanus is one with the least cardiovascular adverse effect. Given this, the best options would be vecuronium, pipercuronium and rocuronium.¹⁰

Rocuronium has an intermediate duration of action and a very rapid onset. It can be given as a bolus dose of 0.6–1.0 mg/kg, with neuromuscular blockade achieved within 3 min. Continuous infusions are given at a rate of 10 µg/kg/min. Two studies reviewed the dose requirements, recovery times and pharmacokinetics of rocuronium in critically ill patients. Most were given intermittent bolus doses, while a few received continuous infusion. The mean dose required to maintain 80% blockade was 0.34 mg/kg, and the median infusion rate required to maintain one twitch in the peripheral nerve stimulator was 0.54 mg/kg/hour. The median time from the last bolus dose to the appearance of twitch was 100 min. In the infusion group, the twitch returned 60 min after the infusion was stopped.¹¹

There are two published case reports on the use of rocuronium infusion to control muscle spasms in tetanus, one on human and one on a dog. The use of rocuronium in a human patient was unsuccessful. It was given at a rate of 8 µg/kg/min and then increased to a rate of 10 µg/kg/min. The muscle spasms

Learning points

- ▶ In tetanus patients with muscle spasms refractory to benzodiazepines, a neuromuscular junction blocker may be used.
- ▶ Rocuronium is a good choice of neuromuscular blocking agent because of its good cardiovascular profile. Adverse effects include short-term myalgia.
- ▶ Methamphetamine toxicity may downregulate the -aminobutyric acid receptors, leading to tolerance to benzodiazepines.

were poorly controlled in this case, and the patient was shifted to a different neuromuscular junction blocker. The use of rocuronium in a dog was successful in controlling the muscle spasms. The first dose was given at 0.6 mg bolus, with 100% blockade noted in TOF within 45 s. Subsequently, a continuous infusion was started. The dose was titrated according to TOF responses. Spasms were successfully controlled on the third day at a dose of 1.6 mg/kg/hour, but the dog died 2 days after discontinuation of the drug (table 1).^{12 13}

The explanation for the incidentally poor response of chronic substance users to benzodiazepines is likely related to the effect of methamphetamine toxicity on GABA receptors. A rat study on the effect of methamphetamine toxicity on GABA receptors showed downregulation of receptors in the nucleus accumbens core and shell. In effect, GABA transmission is decreased. This study opens the potential for further studies exploring the effects of methamphetamine on GABA receptors in other parts of the brain.¹⁴

Contributors CAGE was the primary author who wrote the manuscript. She was the resident in charge of the patient. JEEA was the senior neurology resident supervising the management of the patient. He proof-read the manuscript. PAR was the consultant supervising CAGE and JEEA. CPDM is a neurotoxicologist who advised on the possible relationship of methamphetamine toxicity to benzodiazepine tolerance.

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