The treatment of autonomic dysfunction in tetanus

G L Maryke Spruyt, MB ChB, MMed (Surg); **T van den Heever,** MB ChB, MMedSc (Crit Care)

Department of Critical Care, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Corresponding author: *T van den Heever (theavdheever@gmail.com)*

We report a case of generalised tetanus in a 50-year-old female patient after sustaining a wound to her right lower leg. She developed autonomic dysfunction, which included labile hypertension alternating with hypotension and sweating. The autonomic dysfunction was treated successfully with a combination of morphine sulphate infusion, magnesium sulphate, and clonidine. She also received adrenaline and phenylephrine infusions as needed for hypotension. We then discuss the pathophysiology, clinical features and treatment options of autonomic dysfunction.

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Despite extensive vaccination programmes worldwide that have resulted in a significant decline in the incidence of tetanus, this preventable disease remains a challenge, especially in developing regions of the world. In 2013, a total of 103 cases of tetanus were reported in Europe and 457 cases in the Americas, compared twith 4 153 cases in South-East Asia and 6 508 cases in Africa.[1] In South Africa (SA), the incidence of tetanus has decreased from a total of 356 cases in 1980 to 38 in 2002 and only 2 cases in 2014.[2] Although it could be regarded as a rare disease in SA, patients presenting with tetanus are still seen occasionally. Tetanus is a notifiable disease in SA. According to the National Health Act No. 61 of 2003, it has to be reported to appropriate local, provincial and national health authorities. However, notification from the public sector is often lacking due to uncertainty of the channels to be followed to report notifiable diseases,[3] probably more so in rural areas. It is therefore not an overstatement to suggest that tetanus may have a higher incidence in SA than reflected by official statistics.

Case description

A 50-year-old female presented to our intensive care unit (ICU) at the Universitas Academic Hospital Complex in Bloemfontein, South Africa (SA), with generalised tetanus after sustaining a wound to her right lower leg. On day 11 she developed autonomic dysfunction, which included labile hypertension alternating with hypotension and sweating. The autonomic dysfunction was treated successfully with a combination of morphine sulphate infusion (27 mg/day as constant infusion), magnesium sulphate (16.8 - 40.8 g/day as constant infusion titrated to maintain a level of 2 - 4 mmol/L) and oral clonidine (75 µg in three divided doses per day). She also received adrenaline and phenylephrine infusions as needed for hypotension. The tetanus was complicated by rhabdomyolysis, which responded to aggressive fluid management. The duration of autonomic instability was 18 days. On day 39 after admission she was discharged to the ward. Informed consent was obtained from the patient to use her information for a case study. Ethical approval (ref. no. ECUFS 226/2014) to report this case was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State in Bloemfontein, SA.

Discussion

Pathophysiology

The spores of *Clostridium tetani* are found in soil, faeces and street dust. Entry into the body is usually through lacerations, minor cuts and wounds, or injections.[4,5] Cases have resulted from wounds that were considered too trivial to warrant medical attention.[6] Two toxins are produced by the tetanus bacillus, namely tetanospasmin and tetanolysin.[7] Tetanospasmin is extremely potent and as little as 240 g is sufficient to obliterate the entire world population.[4,5] For the purpose of this case study, we looked at the pathophysiology and treatment of autonomic dysfunction in tetanus.

Autonomic dysfunction

The pathogenesis of autonomic dysfunction in tetanus is unclear. Several theories have been proposed, including damage to brain stem and hypothalamic nuclei, and direct disturbances in autonomic nerves (by tetanospasmin).[8]

Autonomic dysfunction is characterised by sympathetic overdrive as well as a parasympathetic component.[9,10] Tetanospasmin blocks the inhibitory transmitter release from the presynaptic terminal of inhibitory spinal interneurons, resulting in sympathetic overdrive.[4,9] There is selective inhibition of the inhibitory reflex in the central nervous system (CNS). The resulting motor neuron overactivity causes excessive secretion of acetylcholine.[11] This cholinergic effect causes parasympathetic overactivity.

The development of sympathetic overdrive presents between 7 and 14 days after the onset of muscle spasms,[12,13] and is characterised by tachycardia and precipitous systolic arterial pressure changes from minute to minute.[9] During autonomic instability there is an increase in noradrenaline and adrenaline levels indicative of both adrenal medullary and neuronal involvement.[13] Urinary catecholamine excretion in tetanus has been found to exceed that in other critically ill patients.[14]

The systemic vascular resistance (SVR) may initially be low, but rises as the disease progresses. This high SVR then becomes labile and can vary widely within minutes. As a result of this high and widely variable SVR, perfusion may become dependent on adequate myocardial contractility. The use of beta-adrenergic blockers in this situation, with the negative inotropic effect, may precipitate cardiovascular collapse by reducing cardiac output.[7,9]

Clinical features

Tetanus is characterised by rigidity, muscle spasms and increased urinary excretion of catecholamines. Tonic muscular spasms may

be confused with tonic-clonic convulsions. These muscular spasms may either be spontaneous or triggered by touch, visual, auditory or emotional stimuli.[7] Autonomic dysfunction may occur, and does not necessarily correlate with the severity of tetanus. Wassay *et al.*[8] reported autonomic dysfunction in a third of tetanus cases.

Autonomic dysfunction presents as labile hypertension, tachycardia and vasoconstriction, as well as sweating, bradycardia, cardiac arrhythmias, fever, hypotension and hypercarbia.[4,7,15,16] Autonomic dysfunction, irrespective of ventilation requirement or severity of tetanus, predicts a poor outcome.[8]

A high-output hyperdynamic circulatory state has been observed in severe uncomplicated tetanus patients,[10] which was postulated to be mainly due to excessive muscular contractions, increased sympathetic tone, and a rise in the core temperature. Increased tissue metabolism and oxygen demand result from frequent convulsive seizures and increased muscle tone.[10] Oxygen supply and consumption are increased through peripheral vasodilatation, increased venous return and an increased cardiac output.

Treatment of autonomic dysfunction

Treatment of autonomic dysfunction entails a treatment plan that will keep the patient comfortable and stabilise the cardiovascular system, while maintaining compensatory mechanisms and avoiding sudden cardiovascular collapse.[9] A combination treatment plan is recommended in the treatment of autonomic dysfunction.

Sedation

Deep analgosedation has been found to be important in overcoming autonomic dysfunction.[17] This should be combined with boluses of sedation before unavoidable stimuli. Sedation on its own does not control sympathetic overdrive and a combination of medication is therefore advised.[9]

The drug of choice for sedation may be a benzodiazepine.[9] Benzodiazepines increase gamma amino butyric acid (GABA) via the inhibition of an endogenous inhibitor at the $GABA_A$ receptor.[13,15] The two most commonly used benzodiazepines are diazepam and midazolam, and both are also used for the control of spasms.[15]

Propofol has also been used as an adjunct to sedation.[4] Propofol has a short duration of action, but it may cause dose-dependent hypotension and bradycardia.[18] With prolonged duration of treatment, severe adverse effects may occur due to accumulation of the drug.[18]

Magnesium sulphate

The use of magnesium in the treatment of tetanus was described in the beginning of the last century.[19-21] Magnesium acts as a muscle relaxant, blocks neuronal and adrenal catecholamine release, and causes antagonism of calcium with subsequent cardiovascular effects such as vasodilatation.[9,15]

In a prospective observational study of magnesium sulphate in 40 patients with tetanus, Attygalle and Rodrigo[22] found that spasms were controlled in 38 out of 40 patients, and sympathetic overdrive was controlled without supplementary sedation. Autonomic dysfunction was reported in 6 patients, and in 4 of them, it stabilised on introducing magnesium sulphate. No deaths due to cardiovascular instability occurred.

Magnesium levels should be kept at 2 - 4 mmol/L, with the upper limit of safety being lower in elderly patients.[22] Magnesium sulphate in overdose can cause hypotension, arrhythmias and paralysis with respiratory depression. Clinical evidence of magnesium overdose is assessed by the loss of patellar reflex, respiratory depression, hypotension and hypocalcaemia.[23]

Magnesium has been proven to act as a neuromuscular blocking agent because it leads to the reduction of acetylcholine release and diminishes motor end-plate sensitivity to acetylcholine. It reduces the amplitude of the motor end-plate potential,[9] and also inhibits the release of catecholamines from the adrenal medulla and peripheral adrenergic nerve terminals.[9,15,16]

In a randomised, controlled study, Thwaites *et al.*[24] found that magnesium infusion did not reduce the need for mechanical ventilation, but reduced the requirement for other drugs, such as sedation and neuromuscular blockade to control muscle spasms and verapamil to control cardiovascular instability.[24] Magnesium infusions did not cause substantial respiratory depression and had few cardiovascular side-effects.

Opiates

In 1972, Rie and Wilson[25] reported the successful use of morphine to control autonomic dysfunction in a case of tetanus. It does not appear to act as a peripheral α-adrenergic antagonist but rather attenuates sympathetic efferent discharge within the central nervous system.

Buchanan *et al.*[26] reported in 1979 that morphine had a significant effect on reducing spontaneous sympathetic overactivity in tetanus, though it had little effect on spasms.

Morphine sulphate maintains cardiac stability, decreasing blood pressure and heart rate without deleterious effects on cardiac performance.[7,15,27] It replaces endogenous opioids and reduces reflex sympathetic activity and the release of histamine.[7] In commonly used doses, it blocks sympathetically mediated peripheral vasoconstriction,[28] and causes peripheral and arterial vasodilatation by antagonising the sympathetic α-adrenergic tone.[16,29] The effects of morphine are reversible should paroxysmal hypotension arise.[25]

Fentanyl has been reported in a case study[30] to have the same effect as morphine in tetanus. Similar to morphine, fentanyl blocks sympathetically mediated constriction of peripheral veins. It induces peripheral arterial dilatation by reflex reduction in sympathetic α-adrenergic tone through alteration of the sympathetic efferent discharge in the central nervous system.[30] Fentanyl has also been shown in animal studies to have a cardioprotective and anti-arrhythmic effect in sympathetic overactivity, independent of its haemodynamic effects.[31]

The use of remifentanil in tetanus has also been reported, but was used for spasms only and could cause hypotension and bradycardia in an already cardiovascularly unstable patient.[32]

Epidural blockade

Bhagwanjee *et al.*[33] assessed the role of epidural blockade with bupivacaine and sufentanil in controlling sympathetic hyperactivity in 11 patients with severe tetanus. Blood pressure fluctuations reduced significantly with a non-significant decrease in heart rate fluctuations.[33]

Clonidine

Clonidine is an α-2 agonist which works centrally in the brain stem.[13] It decreases sympathetic outflow, inducing peripheral vasodilatation, thus reducing arterial pressure. It increases vagal tone, acts as a sedative and also decreases motor activity.[7,9] It also has a peripheral effect by preventing the release of noradrenaline from the pre-junctional nerve endings.[7] Since synthesis, storage, re-uptake and metabolism of adrenergic neurotransmitters are not affected, and adrenergic receptors are not blocked, reflex control of capacitance remains intact.[9] Compensatory changes of blood pressure are preserved,

and postural hypotension is less likely than with α- and ß-adrenergic blockers. In the event of hypotension and bradycardia, vasoactive drugs also remain effective.

Clonidine was first used by Metz *et al.*,[34] who demonstrated that it lowers the basal plasma catecholamine levels in healthy adult males. In 1989, Sutton *et al.*[9] described the first reported use of clonidine to control sympathetic overactivity in tetanus. They reported a decrease in plasma noradrenaline after administration of clonidine, matched by an improvement in cardiovascular stability. In this case it was used in combination with magnesium, sedation and neuromuscular blockade. It should not cause rebound hypertension if withdrawn carefully.[9]

Dexmedetomidine

Dexmedetomidine use has been reported in cases with paroxysmal autonomic instability with dystonia and in tetanus.[35,36] Dexmedetomidine is highly lipophilic and has an affinity for α-2 receptors, with analgesic, anxiolytic, sedative and anti-sympathetic effects.[18,37] It has a α2:α1 adrenoreceptor ratio >7 times greater than that of clonidine.[38] Presynaptic α-2 receptor stimulation blocks noradrenaline release and post-synaptic α-2 stimulation decreases sympathetic activity.[39] It reduces plasma levels of catecholamines, maintaining haemodynamic stability through its anti-sympathetic properties. Dexmedetomidine also reduces the frequency of spasms and may be used as an adjunct with sedation.[37]

Due to its vasodilatory effects it may blunt the adrenergic tone and thereby maintain haemodynamic stability.[18,37] Hypotension and bradycardia are not observed with the administration of a maintenance dose (0.2 - 0.7 μg/kg/hour) titrated every 30 minutes instead of using a bolus dose.[18,37] Hypertension is experienced with higher doses.[18] It may be used longer than 24 hours and it has been proven to be safe.[37] In a study of six patients reported by Girgin *et al.*,[37] dexmedetomidine infusion was started with a loading dose of 1 μg/kg over more than 10 minutes, followed by a maintenance infusion rate of 0.2 - 0.7 μg/kg/hour.

β-blockers

β-blockers such as propranolol were used in the past but can cause hypotension and sudden death; only esmolol is currently recommended.[6] Buchanan *et al.*[40] described a fatality in tetanus with autonomic instability, apparently due to the use of propranolol.

One of the earliest drugs attempted in the treatment of sympathetic overdrive in tetanus was labetalol.[41] This α- and β-blocker reduces blood pressure and tachycardia, but does not improve heart rate and blood pressure variability.

Successful use of esmolol has been described in a case report.[42] Because of its short duration of action, the effects are more easily reversible in the event of hypotension and bradycardia.

Atropine infusion

It has been postulated that tetanus is acetylcholine poisoning causing parasympathetic overactivity.[11,43] Dolar[11] suggested that atropine has a sedative effect due to its central depressive action and that acetylcholine accumulation in the CNS causes autonomic instability and anxiety in tetanus. He found in a study of four patients that their anxiety and agitation disappeared with a single dose of atropine and they fell asleep.[11]

Conclusion

Several drugs have been investigated or reported in case studies for the treatment of autonomic instability in tetanus. As yet there is no single drug that will control autonomic instability on its own, therefore combination therapy is advocated. Dexmedetomidine holds promise for the treatment of autonomic instability, although more studies are needed. Treatment of autonomic instability in tetanus should be individualised.

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