Case reports

Tetanus Managed in a Peripheral Hospital - A Case Report and a Review of Management

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ABSTRACT

Tetanus has become increasingly uncommon. However, with many people failing to maintain adequate levels of immunisation it will continue to present sporadically, with patients who are affected frequently requiring intensive care management. A case of tetanus, and its management in a peripheral hospital in New Zealand, is described. Current treatment options are reviewed. (**Critical Care and Resuscitation 2001; 3: 163-169**)

Key words: Tetanus, intensive care unit, dysautonomia

Tetanus is a disease that has been recorded throughout human history, with the clinical syndrome being mentioned in medical papyri, in ancient Greek writings and by the English surgeon John of Arderne (1307-1380), who made the connection between a gardening injury and the development of the syndrome 11 days later. Neuromuscular paralysis and artificial ventilation were proposed in the early 19th century and immunisation was shown to be feasible late in 1890. However, it was not until the polio epidemic in Denmark in the 1950's that artificial ventilation and neuromuscular blockade became acceptable modalities of treatment and that such therapy for tetanus became available.[1]

CASE REPORT

An 80 year old woman with a past history of aplastic anaemia, osteoporosis and hypertension presented to her general practitioner (GP) three days after a calf injury caused by a garden rake. As she had not been immunised for tetanus previously, the wound was debrided and dressed and intramuscular tetanus toxoid (0.5 mL) and oral flucloxacillin (1 g) were administered.

The wound was redressed on each of the following two days. Nine days following the injury she saw her GP again, complaining of neck stiffness, difficulty in opening her mouth, nocturnal dyspnoea and sweating, and was referred to hospital with a diagnosis of tetanus.

On admission she appeared unwell with respiratory distress and stridor. Her blood pressure was 170/85 mmHg, heart rate 100 beats per minute, respiratory rate 24 per minute and temperature 36.8ºC. Pulse oximetry revealed a saturation of 97% breathing air. Her neck was stiff and immobile, her jaw was 'locked' and her abdomen was rigid, although there were no episodes of generalised muscle spasms.

She was admitted to the intensive care unit (ICU) for further management where 750 units of tetanus immunoglobulin was administered intramuscularly and intravenous metronidazole (500 mg 12-hourly) and flucloxacillin (1 g 6-hourly) were given.

Four hours after admission she had a respiratory arrest and was intubated and ventilated. Ongoing sedation and neuro-muscular blockade were achieved using morphine with midazolam and pancuronium, respectively. The wound was debrided, a central venous catheter and arterial cannula were inserted and an infusion of dopamine commenced. A second dose of intramuscular tetanus immunoglobulin (750 units) was also given.

The initial investigations revealed a haemoglobin of

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89 g/L, a white blood cell count of 4.2 x 10^9/L, blood urea of 9.3 mmol/L and serum albumin of 24 g/L.

The blood pressure became labile, increasing initially when the patient was stimulated by nursing and medical interventions, and subsequently, hyper- and hypotensive episodes began to occur spontaneously. This resulted in the dopamine infusion being frequently altered and at times being discontinued. Intravenous fluid boluses were also administered depending upon the changes in central venous pressure. A blood transfusion was also given during the first 24 hours when the haemoglobin decreased to 65 g/L. On the fifth day, intravenous nutrition was commenced and a tracheostomy was performed.

After 24 days, the muscle spasms were controlled with boluses of midazolam without additional pancuronium. Dopamine was discontinued by the 26th day, morphine was ceased on the 32nd day and midazolam was discontinued on the 34th day, by which time weaning from the mechanical ventilation began. By the 41st day the patient began eating and by the 48th day the tracheostomy was fenestrated and 'capped'. The following day the tracheostomy tube was removed and she was discharged to the ward. The patient was discharged from hospital 2 weeks later. She was reviewed six weeks later at an outpatient clinic and while she was still generally weak she had continued to recover.

DISCUSSION

Despite tetanus being one of the first diseases prevented by immunisation, it is still commonly found in third world countries, with neonatal tetanus, which has a high mortality, accounting for almost half the cases.[2] Immunisation of the United Kingdom armed forces from 1938 was the first opportunity to test the tetanus vaccine on a large scale.[3]

In 1987, a survey in New Zealand revealed decreasing levels of tetanus immunity with increasing age, with only 57% of those who were aged more than 60 - 65 years being immune.[4] In the United States of America, for the period between 1988 - 1991, while 80% of 10 - 16 year old subjects had adequate immunity, only 27.8 % of individuals who were greater than 70 years of age had effective antibody levels.[5] One hundred and twenty four cases of tetanus were reported to the centre for disease control (CDC) in the United States between 1995 and 1997 with only 13% having received a primary course of tetanus toxoid. Although mortality has declined from 91% to 11% since CDC records began in 1947,[6] declining levels of immunity in some population groups provide a continued source of intensive care involvement with this condition.[7-10]

Tetanus is caused by a Gram-positive anaerobic bacillus known as *Clostridium tetani*. Spores for the bacillus are ubiquitous and the lesion causing an inoculation may be minor. The spores germinate in regions of low oxygen tension, producing two endotoxins, tetanospasmin and tetanolysin. Tetanolysin's role in the disease is unknown, but tetanospasmin inhibits neurotransmitter release at cholinergic neurones. The toxin gains entry into the nervous system mainly via the neuromuscular junction (NMJ) and travels in a retrograde fashion to the cell body and thence to other neurones.[11]

Tetanospasmin has three predominant effects:

a) Central motor effect, where it inhibits the release of glycine (at the spinal level) and gamma amino butyric acid (at the brain stem) from inhibitory neuron-es, causing motor neurones to respond to stimulation with sustained activity causing sustained skeletal muscle contractions and rigidity.

b) Autonomic nervous system effect, causing a loss of inhibitory control by the spinal cord sympathetic tracts on the adrenal medulla, leading to adrenal sympathomimetic hypersecretion. The parasympathetic nervous system may also be affected.

c) Neuromuscular junction (NMJ) effect, causing a defect in presynaptic release of acetylcholine, with the junction being permanently affected and requiring the motor neurone to develop new synapses to recover.

Clinical features

Four clinical presentations of tetanus have been described.

Generalised tetanus. This is the commonest form which often presents after a short incubation period following inoculation. Rigidity of the masseter muscles (trismus) causing 'lockjaw' is the commonest presentation. Risus sardonicus (a sneering grin, said to resemble the contorted face of those who eat a Sardinian plant of the genus *Ranunculus*) may be difficult to discern other than by those who are familiar with the patient. Abdominal rigidity will also be present. Generalised tetanic spasms consist of a tonic contraction of skeletal muscles which may lead to opisthotonus (the head and heels are bent backward, the abdomen is arched forward, the legs are extended and the fists are clenched on the abdomen). During muscle spasms (which are usually painful), the patient will remain conscious, distinguishing it from epileptiform seizures. The upper airway may become compromised and ventilation may be difficult due to intercostal muscle and diaphragmatic dysfunction.

Local tetanus. This is usually a forerunner of generalised disease and may not be observed prior to presentation. There is pain and rigidity at or near the

injury site that may persist for several months.

Cephalic tetanus. This is a form of local tetanus affecting the cranial nerves.

Neonatal tetanus. This occurs if there is no maternal immunity as this confers protection to the foetus. The usual route of entry is the umbilical stump and this is made more likely in human cultures that have traditional methods of dressing the area with soil or animal dung.[1]

Diagnosis

Tetanus is diagnosed clinically, with laboratory tests often being performed to exclude strychnine poisoning, maxillofacial infections or meningitis. Dystonic reactions to dopamine antagonists may give a similar clinical picture although the facial characteristic of risus sardonicus is absent.

Therapy

Antibiotics

Clostridium tetani is sensitive to a broad range of antibiotics, although metronidazole is probably the drug of choice. While the toxin has already been produced and introduced into the neural tissue by the time of clinical presentation, an antibiotic will prevent further propagation of the bacterial infection. Surgical debridement will also help to reduce the toxin producing source and prevent secondary infection. Penicillins are GABA antagonists and theoretically may worsen hypertonicity.[11]

Immunotherapy

Tetanus antitoxin is required whatever the immune status of the patient as it will neutralise any circulating toxin that is not within the nervous system. Previously, equine anti-tetanus serum (ATS) was used but this carries a risk of anaphylaxis. Human tetanus immune globulin (HTIG) is now currently available and can be given in a dose of 250units intramuscularly or up to 5000 units intravenously. The doses recommended are quite variable but 250 units intramuscularly for prophylaxis and 500 units intramuscularly as part of the treatment of a tetanus infection appears to be acceptable.[12]

Intrathecal antitoxin has also been used at a dose of 250 units in adults, taking care to avoid preparations containing a preservative. This has been shown to improve survival if given in the early stages, reducing mortality from 21% to 2%, although administration before the onset of spasms appears to be more beneficial.[13] Singh *et al*, also showed a reduction in mortality in children with tetanus from 68% to 37% with intrathecal horse antitetanus serum (ATS 50 or 100 units) and dexamethasone.[14] They believed that this was both economical and feasible in their circumstances. Similarly, Sanders *et al*, with a large series of adult patients, showed that 200 units of intrathecal equine antitetanus serum (proving more effective than 1500 units) as well as diazepam and steroids reduced mortality from 14% to 4.5%.[15] However, a recent meta-analysis failed to show any benefit with intrathecal therapy in neonatal tetanus and cautioned against accepting its perceived benefit in adults.[16] The authors also reiterated the concern regarding the presence of preservative in some formulations and also of a lack of follow-up studies concerning the possible complications.[16]

As only small amounts of tetanus toxin are produced (insufficient to elicit an immune response), the patient must still be actively immunised, because in the absence of antitoxin the disease will continue as long as the source of tetanospasmin persists. Recurrent tetanus has also been reported when immunisation is not performed.[17]

Glucocorticoids

Glucocorticoids have been used as an adjunctive treatment in the management of tetanus, usually to avoid sequelae of other therapies (e.g. anaphylaxis associated with equine antitetanus serum).[14,15] However, in a study from Turkey of 63 patients with severe tetanus who received normal care and who were randomised to receive either 0 or 40 mg of prednis-olone, a non significant reduction in mortality from 55% in the control group to 31% in the steroid group was reported.[18] In a double-blind randomised study of intravenous betamethasone in tetanus patients managed with intrathecal antitetanus therapy, a marked (but once again non-significant) improvement in mortality was recorded.[19]

Therapy for muscle spasm

Dantrolene

Dantrolene is a direct acting muscle relaxant that has been used in the treatment of malignant hyperthermia and muscle spasticity. In tetanus it has been used intravenously in the post-acute period to treat muscle spasms that may have returned after neuromuscular blocking agents were discontinued. It has also been used to aid weaning from mechanical ventilation and to establish enteral feeding.[20]

In one study where a group of children treated with dantrolene was compared with an historical control group, a reduction in mortality from 73% to 33% in the dantrolene group using doses of 6mg/kg/day was reported.[21] The authors concluded that as respiratory depression was not induced, dantrolene may have a place where sophisticated treatment modalities such as mechanical ventilation are unavailable. Treatment

usually begins either intravenously or orally at 1mg/kg/hr for 3 hours and is reduced to 1 mg/kg for an hour every 4-6 hours. Further reductions are then made according to spasm resolution.[22] However, as intravenous infusions of dantrolene require large volumes of fluid, enteral administration may be required when fluid retention is a problem. Hepatotoxicity is also a potential adverse effect and liver function must be closely monitored and treatment duration should be limited to 60 days.[11]

Benzodiazepines

Benzodiazepines are gamma amino butyric acid (GABA) receptor agonists, acting as indirect antagonists to the effect of tetanospasmin on inhibitory neurons, thus reducing or relieving muscular spasm.[23] Diazepam has been used with effect since the early 1960's, both in mechanically ventilated and unventilated patients.[24,25] As large doses may be required, the propylene glycol in intravenous formulations can cause a metabolic acidosis so either enteral administration or using a non-propylene glycol benzodiazepine formulation may be required. Tachyphylaxis and withdrawal symptoms may occur after long periods of administration.

Baclofen

Baclofen directly stimulates postsynaptic GABA receptors blocked by tetanus toxin and may decrease the need for sedation and ventilatory support. As baclofen does not cross the blood-brain barrier readily, it may be given by intravenous bolus (i.e. 50-1500 μg) or continuous infusion via an intrathecal catheter (usually at the lower thoracic level), at doses of up to 1500 μg/day. This may make it useful in areas where tetanus is common and mechanical ventilation is not readily available.

Intrathecal administration should be started early to avoid other respiratory depressant drugs being required. Lower thoracic intrathecal administration results in a decreased cephalad concentration thereby reducing the possibility of baclofen-induced respiratory failure. However, this also means that spasms in the upper limbs may not be as well controlled as those that occur in the lower limbs.

Baclofen has also been reported to improve blood pressure control, although doses above 2000μg/day may lead to over-suppression. Sedation and respiratory depression are also other possible adverse effects, although these may be reversed with flumazenil.[26,27]

Magnesium sulphate

At serum levels ranging from 2 - 4 mmol/L, magnesium sulphate has been used to control tetanus spasms. Using the clinical criteria of preservation of tendon reflexes as a guide to therapeutic levels, the need for ventilation with its attendant risks may be reduced, although tracheostomy may be required for airway access and sputum removal.[28,29,30] Magnesium also improves cardiovascular stability by inhibiting neuronal and adrenal catecholamine release reducing circulating catecholamine levels[31] and reducing adrenergic receptor sensitivity.[32] It also reduces acetylcholine release and NMJ end plate sensitivity to acetylcholine,[33] reducing skeletal muscular spasms.

While magnesium sulphate may not be adequate by itself for the management of muscle spasms or autonomic dysfunction, it is often helpful in combination with other agents.

Clonidine

Clonidine, is a central α_2 adrenergic agonist which reduces sympathetic outflow from the brainstem while maintaining reflex peripheral control, thereby decreasing the incidence of hypotension.[29,34] In one randomised prospective study of patients with tetanus who were otherwise managed by conventional means, it significantly reduced mortality.[34] However, another report failed to find it useful in blood pressure control or in modifying catecholamine release.[35]

Morphine

By providing sedation and pain relief from muscle spasm, morphine reduces sympathetic overactivity[36,37] and by a central effect it decreases sympathetic outflow.[38] Fentanyl also been found to be useful in the management of patients with tetanus.[39]

Neuromuscular blockade

When adequate sedation has been achieved without relief of muscle spasm then neuromuscular paralysis and mechanical ventilation are usually required. Concomitant sedation is mandatory. In patients with tetanus, many studies have reported that artificial ventilation and neuromuscular blockade have had a significant beneficial effect on survival.[40,41] The neuromuscular blockade should be stopped at intervals to review its need and to ensure the background sedation is adequate.

All of the currently available NMJ blocking agents have been used. Pancuronium, however, may not be ideal due to its sympathomimetic effects. Because of its hypotensive effects, d-tubocurarine may be useful if hypertension is the predominant feature.[42]

Therapy for autonomic dysfunction

Invasive haemodynamic studies have shown that in severe uncomplicated tetanus, systemic vascular resistance (SVR) often increases markedly and that the hypotensive episodes are usually due to sudden decreases in SVR even though the myocardium usually

responds normally with a rise in cardiac index.[42,43] The combined α and β adrenergic receptor antagonist, labetalol, has long been the drug of choice in management of tetanus autonomic dysfunction.[23] The α-adrenergic receptor blockade alleviates the vasoconstriction caused by the excess noradrenaline. However, during periods when the SVR suddenly diminishes, as it does frequently and unpredictably, the myocardium may be unable to respond with increased contractility (an effect which may be exacerbated by the β-adrenergic receptor blockade) to maintain the arterial pressure.[29,44,45]

Atropine infusions have been used to counteract the cholinergic activity of tetanus and when high doses are used in combination with sedative agents it may provide cardiovascular stability and facilitate artificial ventilation without requiring neuromuscular paralysis.[46]

Continuous subarachnoid and epidural analgesia have also been used to provide sympathetic (epidural) and combined sympathetic and parasympathetic (subarachnoid) blockade to contribute to cardiovascular stability,[47,48] although catecholamine infusions were required in the subarachnoid group to maintain blood pressure. In a retrospective review of 11 cases of tetanus managed with epidural bupivacaine and sufentanil and intravenous midazolam it was believed that better control of the sympathetic overactivity was achieved and less sedation was required without increasing the morbidity and mortality.[49]

Nutrition

Nutritional requirements may be increased due to muscular overactivity and catecholamine excess.[23] Gastric emptying may be impaired due to the use of opiates and neuromuscular blockade, necessitating nasojejunal feeding or parenteral nutrition.

Complications

Hypoxic brain damage due to respiratory or cardiac arrest, especially where facilities for artificial ventilation and intensive care monitoring are limited, is the commonest adverse outcome in third world countries. In areas where intensive care units are available, sympathetic overactivity leading to cardiomyopathy, cardiac failure and cardiac arrest have been reported. Skeletal muscle overactivity may cause rhabdomyolysis and acute renal failure. Forty per cent of patients may also suffer psychological sequelae.[23]

In a follow-up study of 50 survivors of tetanus in the United Kingdom, morbidity amongst survivors was found to be significant. Tracheal stricture was common and psychological disturbance, particularly associated with the memory of spasm pain, fear of ventilator disconnection and physiotherapy were reported. Nevertheless, the majority of patients had returned to full-time employment.[50]

Prevention

Active immunisation with tetanus toxoid is one of the most effective preventive measures in medicine. Three intramuscular injections at monthly intervals for adults provides complete immunity for at least 5 years. Booster doses are required every 10 years. Immunodeficient patients should receive passive immunisation with HTIG after a tetanus prone injury.

If a patient has a tetanus prone injury (e.g. contaminated with animal faeces, dirt, unsterile needles, burns) and 5 or more years have elapsed since the last immunisation, a booster dose should be administered. If the immunisation history is not known or is incomplete, then active immunisation should be given as well as passive immunisation with 250IU HTIG, if the wound is tetanus prone.[11]

CONCLUSION

The case reported highlights some of the difficulties one may face in treating a case of tetanus and how it was managed in a small peripheral hospital. It is a condition that we see rarely but will continue to encounter with less than perfect immunisation rates in the general population. It will most likely involve the intensive care specialist early on in the patients management and some or all of the various treatment options presented may be required.

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REFERENCES

1. Bleck TP, Brauner JS. Tetanus. In: Infections of the central nervous system, 2nd ed. Scheld WM, Whitley RJ, Durack DT. eds. Lippincott-Raven, Philadelphia 1997.
2. Thayaparan B, Nicoll A. Prevention and control of tetanus in childhood. Curr Opin Pediatr 1998;10:4-8.
3. Immunisation against Infectious Diseases 1992 Edition. Department of Health, Welsh Office, Scottish Office and Health Department, DHSS (Northern Ireland). HMSO, London.
4. Lau RCH. Diptheria, tetanus, pertussis: antibody detection in New Zealand. N Z Med J 1987;100:481-483.

5. Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med 1995;332:761-766.
6. Bardenheier B, Prevots DR, Khetsuriani N, Wharton M. Tetanus surveillance-United States,1995-1997. MMWR CDC Surveill Summ 1998;47:1-13.
7. Murphy SM, Hegarty DM, Feighery CS, Walsh JB, Williams Y, Coakley DP. Tetanus immunity in elderly people. Age and Aging 1995:24;99-102.
8. Cumberland NS, Kidd AG, Karalliedde L. Immunity to tetanus in United Kingdom populations. J Infect 1993;27:255-260.
9. Reid PM, Brown D, Coni N, Sama A, Waters M. Tetanus immunisation in the elderly population. J Accid Emerg Med 1996;13:184-185.
10. Khajehdehi P, Rezaian G-R. Tetanus in the elderly: is it different from that in younger age groups? Gerontology 1998;44:172-175.
11. Ernst ME, Klepser ME, Fouts M, Marangos MN. Tetanus: Pathophysiology and management. Ann Pharmacother 1997;31:1507-1513.
12. Blake PA, Feldman RA, Buchanan TM, Brooks GF, Bennett JV. Serological therapy of tetanus in the United States. JAMA 1976;235:42-44.
13. Gupta PS, Kapoor R, Goyal S, Batra VK, Jain BK. Intrathecal human tetanus immunoglobulin in early tetanus. Lancet 1980;2:439-440.
14. Singh AK, Bansal A, Goel SP, Agarwal VK. Intrathecal antitetanus serum (horse) with steroid in the treatment of neonatal tetanus. Arch Dis Child 1980;55:527-531.
15. Sanders RKM, Joseph R, Martyn B, Peacock ML. Intrathecal antitetanus serum (horse) in the treatment of tetanus. Lancet 1977;1:974-977.
16. Abrutyn E, Berlin JA. Intrathecal therapy in tetanus. A meta-analysis. JAMA 1991;266:2262-2267.
17. Sahadevan MG. Recurrent tetanus. Br Med J 1968;2:492-493.
18. Paydas S, Akoglu TF, Akkiz H, Ozer FL, Burgut R. Mortality-lowering effect of systemic corticosteroid therapy in severe tetanus. Clin Ther 1988;10:276-280.
19. Chandy ST, Peter JV, John L, Nayyar V, Mathai D, Dayal AK et al . Betamethasone in tetanus patients: an evaluation of its effect on the mortality and morbidity. J Assoc Physicians India 1992;40:373-376.
20. Tidyman M, Prichard JG, Deamer RL, Mac N. Adjunctive use of dantrolene in severe tetanus. Anesth Analg 1985;64:538-540.
21. Aguilar Bernal OR, Bender MA, Lacy ME. Efficacy of dantrolene sodium in management of tetanus in children. J R Soc Med 1986;79:277-281.
22. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. Anaesthesia 1993;48:969-971.
23. Bleck TP. Tetanus: pathophysiology, management and prophylaxis. Dis Mon 1991;37:545-603.
24. Lockwood WR, Allison F. Injectable Diazepam: A new drug for the treatment of tetanus. J Miss State Med Assoc 1967;8:66-70.
25. Okuonghae HO, Airede AI. Neonatal tetanus: Incidence and improved outcome with diazepam. Dev Med Child Neurol 1992;34:448-453.
26. Engrand N, Guerot E, Rouamba A, Vilain G. The efficacy of intrathecal baclofen in severe tetanus. Anesthesiology 1999;90:1773-1776.
27. Dressnandt J, Konstanzer A, Weinzierl FX, Pfab R, Klingelhöfer. Intrathecal baclofen in tetanus: four cases and a review of reported cases. Intensive Care Med 1997;23:896-902.
28. Attygalle D, Rodrigo N. Magnesium sulphate for control of spasms in severe tetanus. Anaesthesia 1997;52:956-962.
29. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. Intensive Care Med 1990;16:75-80.
30. Ho HS, Lim SH, Loo S. The use of magnesium sulphate in the intensive care management of an Asian patient with tetanus. Ann Acad Med Singapore. 1999;28:586-589.
31. Lipman J, James MFM, Erskine J, Plit ML, Eidelman J, Esser JD. Autonomic dysfunction in severe tetanus: Magnesium sulfate as an adjunct to deep sedation. Crit Care Med 1987;15:987-988.
32. James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. Intensive Care Med 1985;11:5-12.
33. Mudge GH, Weiner IM. Agents affecting volume and composition of body fluids. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. The Pharmacological Basis of Therapeutics. 8th edition. Singapore: McGraw-Hill; 1991:704-707.
34. Gregorakos L, Kerezoudi E, Dimopoulos G, Thomaides T. Management of blood pressure instability in severe tetanus: the use of clonidine. Intensive Care Med 1997;23:893-895.
35. Brown JL, Sinding H, Mathias CJ. Autonomic disturbance in severe tetanus: failure of parenteral clonidine to control blood pressure. J Infect 1994;29:67-71.
36. Buchanan N, Cane RD, Wolfson G, De Andrade M. Autonomic Dysfunction in Tetanus: The effects of a variety of therapeutic agents, with special reference to morphine. Intensive Care Med 1979;5:65-68.
37. Rie MA, Wilson RS. Morphine therapy controls autonomic hyperactivity in tetanus. Ann Intern Med 1978;88:653-654.
38. Feldberg W, Wei E. The central origin and mechanism of cardiovascular effects of morphine as revealed by naloxone in cats. J Physiol 1977;272:99-100.
39. Moughabghab AV, Prevost G, Socolovsky C. Fentanyl therapy controls autonomic hyperactivity in tetanus. Br J Clin Pract 1996;50:477-478.
40. Trujillo MH, Castillo A, España J, Manzo A, Zerpa R. Impact of intensive care management on the prognosis of tetanus. Chest 1987;92:63-65.
41. Jolliet P, Magnenat J-L, Kobel T, Chevrolet J-C. Aggressive intensive care treatment of very elderly

patients with tetanus is justified. Chest 1990;97:702-705.
42. De Michele DJ, Taveira Da Silva AM. Cardiovascular findings in a patient with severe tetanus. Crit Care Med 1983;11:828-829.
43. Udwadia FE, Sunavala JD, Jain MC et al. Haemodynamic studies during the management of severe tetanus. Q J Med 1992;83:449-460.
44. Wesley AG, Hariparsad D, Pather M, Rocke DA. Labetalol in tetanus. Anaesthesia 1983;38:243-249.
45. Wright DK, Lalloo UG, Nayiager S, Govender P. Autonomic nervous dysfunction in severe tetanus: Current perspectives. Crit Care Med 1989;17:371-375.
46. Dolar D. The use of continuous atropine infusion in the management of severe tetanus. Intensive Care Med 1992;18:26-31.
47. Southorn PA, Blaise GA. Treatment of tetanus-induced autonomic nervous system dysfunction with continuous epidural blockade. Crit Care Med 1986;14:251-252.
48. Shibuya M, Sugimoto H, Sugimoto T, Shimazu T, Uenishi M, Yoshioka T. The Use of Continuous Spinal Anesthesia in Severe Tetanus with Autonomic Disturbance. J Trauma 1989;29:1423-1429.
49. Bhagwanjee S, Bösenberg AT, Muckart DJJ. Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: Experience with 11 patients. Crit Care Med 1999;27:1721-1725.
50. Flowers MW, Edmondson RS. Long-term recovery from tetanus: a study of 50 survivors. Br Med J 1980;280:303-305.