Journal of Biology, Agriculture and Healthcare
ISSN 2224-3208 (Paper) ISSN 2225-093X (Online)
Vol.5, No.8, 2015

Adjunctive Use of Ceftriaxone and Sodium Valproate in the Management of Tetanus: A Case Report and Literature Review

Stephen Oriaifo[1*] Nicholas Oriaifo[2] Maris Oriaifo[3] Esther Okogbenin[4] Eric Omogbai[5]
1 Dept of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria
2 Dept of Obstetrics and Gynaecology, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria
3 Dept of Radiology, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria
4 Dept of Psychiatry, Ambrose Alli University and Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria
5 Dept of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin-City, Edo State, Nigeria
*Stephen.oriaifo@yahoo.com

Abstract
Since the introduction of active immunisation against tetanus in 1923, there has been a dramatic decline in cases of tetanus all over the world. However, cases of tetanus are still being reported in developing and developed economies; with more cases reported from Africa than from Europe. The three planks in the management of tetanus are the elimination of toxin production, neutralisation of unbound toxin and control of spasms. In this report of a fifteen-year old Nigerian female patient with Ablett II tetanus, elimination of toxin production was by the combination of metronidazole and the glutamate transporter I (GLT I) enhancer, ceftriaxone. Neutralisation of unbound toxin was by the use of anti-tetanus serum due to the non-availability of human tetanus immune globulin. Control of spasms was mainly by the use of the GABAergic-enhancing drugs diazepam and sodium valproate combined with the use of the anti-excitotoxics magnesium sulphate and ketamine. The introduction of valproate hastened the disappearance of opisthotonus and residual rigidity and deserves to be added to drug combination regimens for tetanus.
Keywords: tetanus, ceftriaxone, diazepam, sodium valproate, magnesium sulphate, ketamine

1.0 Introduction

Tetanus is characterised by the acute onset of hypertonia and muscle spasms which begin initially in the jaw muscles. This is the cause of the trismus (lockjaw) which may be an early diagnostic hall-mark of tetanus. This lockjaw is due to spasms of the masseter muscles. Spasms progressively extend to the facial muscles causing the typical facial expression, 'risus sardonicus', and muscles of swallowing causing dysphagia. Generalised muscle rigidity and tonic contractions of agonist and antagonist muscles cause opisthotonus. During this, patients have an intact sensorium and feel severe pain (emedicine.medscape.com). The spasms can cause fractures and respiratory failure. As the disease progresses, mild stimuli may trigger generalised tetanic seizure-like activity which contributes to serious complications and eventually death unless supportive treatment is given (www.who.int).

1.1 Epidemiology

Despite the availability of passive immunisation since 1893 and an effective active vaccination since 1923, tetanus remains a major health problem in the developing world and is still encountered in the developed world. There are between 800,000 and I million deaths due to tetanus each year, of which about 400,000 are due to neonatal tetanus. Eighty percent of these deaths occur in Africa and South-East Asia and tetanus remains endemic in 90 countries worldwide (Farrar *et al.* 2000) in spite of the WHO's efforts, such as the Maternal and Neonatal Tetanus Elimination Initiative (MNTE) (Owusu-Darko *et al.* 2012). It has now been realised that it is not possible to eradicate the disease tetanus, due to its nature (WHO.int/immunisation, monitoring/MNTE Strategic plan) and so the goal is to eliminate maternal and neonatal tetanus (MNT) as a public health problem as called for by the 42nd World Health Assembly in 1989 and endorsed by the World Summit for Children in 1990 and later reinforced by the relaunch of the MNTE initiative in 1999. The year 2015 is the global target by WHO for reaching MNTE in all countries.

1.2 Microbiology

Tetanus is caused by a Gram-positive bacillus, *Clostridium tetani*, a natural habitat of soil which can also be isolated from stools of domestic animals and humans. It is a motile, spore-forming obligate anaerobe. The spore is incompletely destroyed by boiling but eliminated by autoclaving at I atmosphere pressure and 120°C for 15 min. It is rarely cultured, as the diagnosis of tetanus is clinical (Cook *et al.* 2001). *Clostridium tetani* produces its clinical effects via a powerful exotoxin, tetanospasmin. The DNA for this toxin is contained in a plasmid which is not present in all strains of clostridia.

Binding of this spasmogenic toxin to neurons is irreversible and nerve function can only be returned by the growth of new terminals and synapses (Farrar *et al.* 2000). And because anti-tetanus serum or tetanus immune globulin can neutralise toxin in circulation but not toxin bound to neurons, patients with tetanus are likely be in critical care for the 2-3 weeks it may take for the toxin bound to neurons to be depleted.
Extent of adequate antitetanus immunity in the adult population tends to wane (Bleck 1991) and physicians become less comfortable with tetanus diagnosis and management as new cases drop (Schon *et al.* 1994) consequent upon the introduction of active immunisation with tetanus toxoid which is remarkably safe and effective.

1.3 Pathophysiology
The tetanus bacillus secretes two toxins, tetanospasmin and tetanolysin. Tetanolysin optimises the conditions for bacterial multiplication by its haemolysins. Tetanospasmin leads to the clinical syndrome of tetanus (Rodrigo *et al.* 2014).

Tetanospasmin is a two-chain polypeptide of 150,000 Da which is initially inactive. The heavy chain (100,000 Da) and the light chain (50,000 Da) are linked by a protease sensitive loop that is cleaved by tissue proteases leaving a disulphide bridge linking the two chains. Binding to the polysialoganglioside receptor is by means of the Hc fragment of the heavy or B chain. It is recently reported that tetanospasmin may be more specific for the glycosylphosphatidylinositol (GPI)-anchored protein receptor (Munro *et al.* 2001). The light or A-chain, a zinc endopeptidase attacks the vesicle-associated membrane protein (VAMP), synaptobrevin and selectively acts to prevent inhibitory neurotransmitter release from spinal cord interneurons (Kanda and Takano 1983), leaving the alpha-motoneurones with unopposed excitatory actions. Cleavage of synaptobrevin affects the stability of the soluble N-ethylmaleimide sensitive fusion attachment protein receptor complex (SNARE) core by restricting it from entering the low energy conformation which is the target of N-ethylmaleimide sensitive fusion (NSF) protein binding (Pellegrini *et al.* 1995).
1.3.1 Mechanism of tetanospasmin: 6 steps
a): specific binding to the peripheral neurons
b): selective retrograde transsynaptic transfer subsequent to its retrograde axonal transport to the CNS inhibitory interneurons by means of the molecular motors, dyneins (Schwab *et al.* 1979; Lalli *et al.* 2003) that move on microtubules to effect cargo transport.
c): transcytosis from the axon into the inhibitory neurons presynaptic nerve endings
d): temperature and acidic pH mediated traslocation of the light chain into the cytosol
e): reduction of the disulphide bond between the light and heavy chains (mediated by the H_N fragment of the B chain); thus freeing the light chain for attack on synaptobrevin.
f): cleavage of synaptobrevin (Schiavo *et al.* 1992) and subsequent differential blockade of release of the inhibitory neurotransmitters, glycine and gamma-amino-butyric acid (GABA).

Further retrograde intraneural transport may occur in severe cases with toxin spreading to the brainstem and midbrain (Cook *et al.* 2001). Blood-brain-barrier (BBB) normally prevents direct entry of toxin to the CNS. Tetanospasmin has a convulsant effect in animal models (Altenmuller *et al.* 2013; Anderson *et al.* 1997).

Hyperglutamatergic excitotoxicity is implicated in the mechanisms of neuronal degeneration and neuronal loss produced by intrahippocampal tetanus toxin in rat (Baggeta and Nistico 1992). Intrahippocampal tetanus toxin produces generalised convulsions and neurodegeneration antagonised by NMDA receptor blockers (Bowery *et al.* 1992).

1.4 Clinical Features
Tetanus usually follows a recognised injury (Cook *et al.* 2001). Contamination of wound with soil, manure, or rusty metal can lead to tetanus. Tetanus can complicate burns, ulcers, gangrene, necrotic snakebites, middle ear infections, septic abortion, childbirth, intramuscular injections and surgery. In 15-25% of patients, there is no evidence of a recent wound or there may be a wound not considered serious enough to seek medical treatment (Edmondson and Flowers 1979).

There is a clinical triad of rigidity, muscle spasms and, if severe, autonomic dysfunction. Neck stiffness, sore throat and difficulty opening the mouth are often early symptoms (Alfery and Rauscher 1979). Interneuronal dysfunction with hyperactivity of gamma-motoneurons contributes to the rigidity in an early stage of the disease (Bratzlavsky and Vander-Eecken 1980)

Masseter spasm causes trismus, an early diagnostic feature of tetanus. Spasms of facial muscles cause risus sardonicus. Spasms of muscles of swallowing cause dysphagia. Rigidity of the neck muscles leads to retraction of the head while truncal rigidity may lead to opisthotonus and respiratory difficulty with decreased chest wall compliance.

These spasms may be spontaneous or triggered by touch, visual, auditory or emotional stimuli. Spasms

may be almost continual leading to respiratory failure (Kokal *et al.* 1984). Pharyngeal spasms are often followed by laryngeal spasms and are associated with aspiration and life-threatening acute airways obstruction.

In generalised tetanus, muscles throughout the body are affected. This is the commonest form of tetanus. With lower toxin loads and peripheral injuries, local tetanus is seen. Cephalic tetanus results when localised tetanus from a head wound affects the cranial nerves III, IV, VI, VII and XII but especially VII (facial nerve) and paralysis predominates (Seo *et al.* 2012). Cephalic tetanus may progress to generalised tetanus and mortality is high. Tetanus neonatorum causes more than 50% of deaths from tetanus worldwide (Galazka and Gasse 1995). Before the introduction of artificial ventilation, many patients with severe tetanus died from acute respiratory failure (Trujillo *et al.* 1987).

Severe tetanus is associated with marked autonomic instability with periods of severe hypertension and tachycardia alternating with periods of profound hypotension, bradycardia or recurrent cardiac arrest. During these 'storms', plasma catecholamine levels may be raised up to 10-fold, similar to levels seen in phaeochromocytoma (Domenighetti *et al.* 1984). This hyperadrenergic syndrome that occurs in severe tetanus is characterised by hypertension, tachycardia and increased systemic arteriolar resistance and is responsive to the combined beta- and alpha-adrenergic receptor blocker, labetalol (Domenighetti *et al.* 1984; Alagbe-Briggs and Tinubu 2012); and may be responsible for the unexpected cardiac arrests which is the commonest cause of deaths of patients in intensive care under artificial ventilation (Trujillo *et al.* 1987). Neuronal hyperactivity rather than adrenal medullary hyperactivity appears to predominate (Toothill *et al.* 1970).

1.5 Natural history

The incubation period is the time from injury to first symptoms and averages 7-10 days with a range of 1-60 days. The onset time is time of first symptoms to first spasm and varies between 1-7 days. Shorter incubation and onset times are associated with more severe illness. Spasms reduce after 2-3 weeks but stiffness may persist considerably longer. Recovery from tetanus occurs because of re-growth of axon terminals (Bleck 1987; Dunchen and Tonge 1973) and by toxin destruction (Dance and Lipman 1994).

1.6 Severity grading

The grading system reported by Ablett is most widely used (Phillips 1967):

Table 1: ABLETT CLASSIFICATION OF SEVERITY OF TETANUS

Grade: Clinical features
I Mild: mild to moderate trismus; general spasticity; no respiratory embarrassment; no spasms; little or no dysphagia.
II Moderate: moderate trismus; well-marked rigidity; mild to moderate but short spasms; moderate respiratory embarrassment with an increased respiratory rate greater than 30; mild dysphagia.
III Severe: severe trismus; generalized spasticity; reflex prolonged spasms; increased respiratory rate greater than 40; apnoeic spells; severe dysphagia; tachycardia greater than 120.
IV Very severe: grade III and violent autonomic disturbances involving the cardiovascular system. Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent.

1.7 Systemic effects of tetanus

Severe uncomplicated tetanus is marked by a hyperkinetic circulation (James and Manson 1985). Apart from the effects on the circulatory system in severe tetanus, the restrictive defect as a result of spasms of chest, diaphragmatic and abdominal musculatures impact negatively on respiratory physiology.

Hypoxia is a uniform finding in moderate or severe tetanus even when the chest wall is radiologically clear (Udwadia 1994). And acute respiratory distress syndrome may occur as a specific complication of tetanus.

In mild tetanus, renal function is preserved. In severe disease, reduced glomerular filtration rate and impaired renal tubular function are frequent. Contributory causes of renal failure include dehydration, sepsis and rhabdomyolysis (Seedat *et al.* 1981) and alterations in renal blood flow secondary to catecholamine surges.

1.8 Prognosis

Prognosis of tetanus is dependent on:

a) incubation period
b) time from spore inoculation to first symptom
c) time from first symptom to first tetanic spasm (onset)

Shorter intervals indicate more severe disease and a poorer prognosis.

Table II Prognostic Scoring in Tetanus:		**Dakar Score**
Prognostic factor	Score (1)	Score (0)
Incubation period	< 7 days	> 7 days or unknown
Period of onset	< 2 days	> 2 days
Entering site	umbilicus, burn, uterine, open fracture, surgical wound, IM injection	All others plus unknown
Spasms	Present	Absent
Fever	> 38.4°C	< 38.4°C
Tachycardia	Adults > 120 beats/min Neonates > 150 beats/min	Adults < 120 beats/min Neonates < 150 beats/min

Table II: The Dakar Score is a prognostic scoring system proposed by a team from Dakar, Senegal in 1975 which can be established after the third day following the first clinical signs. The prognosis is bleaker as the clinical score increases (Ogunrin 2009)

Table III	**Predictive value of Dakar Score**	
0-1:	mild tetanus,	mortality below 15%
2-3:	moderate tetanus,	mortality 10-20%
4 :	severe tetanus,	mortality 20-40%
5 or 6:	very severe tetanus,	mortality above 50%

1.9 Complications of tetanus

These include asphyxia, sudden cardiac death, nosocomial infection, fractures of long bones, aspiration pneumonia, peripheral thromboembolism, hypertension and arrhythmias. Others are paralytic ileus, pressure sores, urinary retention, stress ulcers, coma, nerve paralysis and flexion contractures.

1.10 Differential diagnosis of tetanus

1) strychnine poisoning
2) dental infection causing trismus
3) local oral infection causing trismus
4) hysteria (especially nowadays disease is not common)
5) neoplasm
6) malignant hyperthermia
7) stimulant use
8) intracranial haemorrhage
9) dystonic drug reaction from neuroleptic use
10) acute abdomen
11) seizure disorder
12) serotonin syndrome
13) stroke
14) ischaemia

2.0 Management

The management of tetanus rests on three planks: a) prevention of further toxin production and release, b) neutralisation of unbound toxin, c) control of rigidity and spasms.

2.1 Prevention of further toxin production and release

Where present, obvious wounds should be surgically debrided (Owusu-Darko *et al.* 2012) after patients have been started on antibiotics. Metronidazole is the antibiotic of choice (Ahmadsyah and Salim 1985) in preference to penicillin which is a GABA antagonist and pro-convulsant. Other antibiotics that may be used against this anaerobic Gram-positive bacillus include doxycycline, erythromycin, chloramphenicol and vancomycin. It is now known that selected β-lactam antibiotics, to which *Clostridia tetani* is sensitive to (www.globalrph.com), such as ceftriaxone may offer neuroprotection by increasing glutamate transporter I or excitatory amino acid transporter 2 (EAAT 2) expression (Rothstein *et al.* 2005).

2.2 Neutralisation of unbound toxin

Use of human tetanus immune globulin (5,000-8,000 i.u) is safer and more effective the anti-tetanus serum (500-1,000 i.u/kg) in neutralisation of unbound toxin and both can be given intra-thecally, intravenously or intra-muscularly (Farrar *et al.* 2000). Human tetanus immune globulin may not be readily available in emerging economies. The combination of intra-thecal anti-tetanus serum and parenteral betamethasone have been found beneficial (Thomas *et al.* 1982). Higher doses of anti-tetanus serum may be associated with hypersensitivity reactions.

2.3 Control of rigidity and spasms

The ideal therapeutic regimen should abolish spasmodic activity without causing oversedation and hypoventilation (Ogunrin 2009). Drug combinations may be a method to reduce toxicity as it allows doses of individual drugs to be reduced.

2.3.1 Use of drugs that enhance GABAergic neurotransmission

In tetanus, there is antagonism of release of the main inhibitory neurotransmitter in the central nervous system, GABA. Therefore, drugs that enhance GABAergic neurotransmission may be indispensable for the management of tetanus, especially Ablett I and II:

a) The benzodiazepines: These have emerged as the mainstay of symptomatic therapy for tetanus. Diazepam, which is easily available, is a prototype of the benzodiazepines. Doses of diazepam (3-8 mg/kg/day) required to adequately control spasms are associated with respiratory depression, coma and medullary depression. Therefore, its combination with other drugs such as the neuroleptic, chlorpromazine may be mandatory. Diazepam enhances GABAergic neurotransmission by increasing the frequency of channel opening (Twyman *et al.* 1989) to cause sedation.
b) Valproate: Animal experimentations have revealed a significant role for the anti-epileptic valproate in attenuation or abrogation of spasms due to tetanus toxin (Altenmuller *et al.* 2013; Foca *et al.* 1984). Moreover, valproate may help with the cognitive decline after tetanus (Anlar *et al.* 1989). Valproate inhibits GABA-aminotransferase, thereby inhibiting GABA breakdown.
c) Pyridoxine: Pyridoxine is a coenzyme with glutamic decarboxylase in production of GABA from glutamic acid and has been tried (Godel 1982) and found to decrease mortality and spasms in neonatal tetanus.
d) Baclofen: The GABA B agonist may be used in severe tetanus by intra-thecal administration in artificially ventilated patients (Rodrigo *et al.* 2014). Facilities for prolonged periods of ventilation are limited in many developing countries where tetanus may still pose a major threat (Rodrigo *et al.* 2014).

2.3.2 Use of anti-excitotoxics in tetanus

Tetanus may be a hyperglutamatergic state that may respond to anti-excitotoxics (Bowery *et al.* 1992):

a) Magnesium sulphate: Magnesium sulphate has been used both in ventilated patients to reduce autonomic disturbance and in non-ventilated patients to control spasms. Magnesium sulphate, by lowering intracellular and serum calcium, reduces Ca^{2+}-induced excitotoxicity and muscular contractions. In overdose, it causes sedation or even paralysis. Given for 7 days, it reduces incidence of sympathetic over-activity (Thwaites *et al.* 2006) and autonomic instability (Rodrigo *et al.* 2014). It is usually given as a loading dose of 75 mg/kg or 5 gms., then infused at a rate of 2-3 gm/hr (Hinfey 2014). It has been found adequate in Ablett II where it controls the spasms and allows fluid intake, without need for heavy sedation and artificial ventilation, useful attributes especially in poor-resource settings. It helps to avoid the risks of prolonged periods of intubation and ventilation which includes ventilator-associated pneumonia, tracheal stenosis, difficulty in weaning and adult respiratory distress syndrome.
b) Ketamine: Ketamine, a dissociative anaesthetic agent, remarkably inhibits calcium currents (Tan *et al.* 2010; Sun *et al.* 2004; Hatekeyama *et al.* 2001) to provide neuroprotection and muscle relaxation in tetanus (Obanor *et al.* 2008).
c) $Alpha_2$-adrenoceptor agonists: Clonidine and dexmedetomidine are examples of α_2-adrenoceptor agonists that inhibit Ca^{2+}-mediated excitotoxicity to provide neuroprotection and muscle relaxation (Ma *et al.* 2005) and have been used in tetanus care for their sedative effects (Cook *et al.* 2001).
d) Dantrolene: The ryanodine receptor blocker, dantrolene, protects motoneurons against Ca^{2+}-mediated excitotoxicity (Haastert *et al.* 2006) mediated by AMPA receptors and can cause muscle relaxation. Its use may obviate the need for neuromuscular blockers in severe tetanus.

2.3.4 Use of neuromuscular blockers in severe tetanus

Neuromuscular blockers such as pancuronium (Dance and Lipman 1994) may be deployed when GABAergic agents and anti-excitotoxics fail to control the spasms. Their use is combined with intermittent positive pressure ventilation and is expensive.

3.0 Case Report

A fifteen-year old Nigerian female, residing in Ekpoma, presented in Oseghale Oriaifo Medical Centre, Idumebo-Ekpoma on 15th of January, 2015 with a diagnosis of hysteria from another clinic which had not responded to usual medications. On examination, she was not pale and not dehydrated. Respiratory rate was regular, 28/min and blood pressure was 110/70 mm.Hg, regular pulse at 98 beats/min. There was an injury on left great toe which was sustained in the farm. According to relations, injury had been there for up to 2 weeks. There was moderate trismus, neck stiffness and board-like rigidity of the abdomen. There was moderate dysphagia and moderate spasms on provocation. There were no apnoeic spells. Diagnosis of Ablett II tetanus was made. Dakar prognostic score was put at 2 since there was a surgical wound and there were spasms already. Incubation period was more than 2 weeks and time of onset was more than 2 days.

3.1 Pharmacologic treatment

Metronidazole (200 mg in infusion fluid every 8 hours) and ceftriaxone (one gram intravenously every 12 hours) were given to accelerate wound healing and stop production of toxin. The wound healed completely after 3 days. Anti-tetanus serum (ATS) was given intra-muscularly in divided doses to counter the toxin in circulation. Up to 26, 000 units of ATS was given. Prophylactic tetanus toxoid injection was started.

Sedation was started with low doses of intravenous diazepam (20 mg every 6 hours) and intravenous chlorpromazine (100 mg every 6 hours). This proved inadequate as spasms got prolonged and the dreaded opisthotonus ensued. Low dose of magnesium sulphate was commenced starting with a bolus of 5 grams and then 1 gram in intravenous fluid hourly. This was reduced to 5 grams intramuscularly after ketamine was added to the drug combination therapy. Institution of magnesium sulphate therapy lessened the severity of the trismus, allowing the patient to take sips of fluid orally after 36 hours. Ketamine was given in doses of 20 mg intravenously every 6 hours.

Above proved inadequate to stop or reduce the opisthotonus. Sodium valproate was then added to the drug combination therapy as a loading dose of 20 mg/kg in infusion fluid; and continued for another 24 hours at 15 mg/kg in divided doses in infusion fluid. This was then changed to valproate tablets which was continued at a dose of 500 mg twice daily given after grinding. The addition of valproate stopped the opisthotonus and also allowed patient to swallow better. Pyridoxine tablets was also given at a dose of 100 mg/day. With this combination therapy, spasms and the board-like rigidity of the abdomen stopped after 11 days of admission when swallowing got freer but residual rigidity continued for another week. Injections were tapered off after 3 weeks.

Patient was discharged after 3 weeks in hospital, and when she was seen at 4 weeks for her second tetanus toxoid injection, she was able to be on a motor-bike!

4.0 Discussion

Present report shows that there may be delay in diagnosis of tetanus now it has become a rare disease in Nigeria since the advent of active immunisation. This is similar to what may obtain elsewhere (Bleck 1991; Schon *et al.* 1994). Medical practitioners should be aware that a differential diagnosis of tetanus is hysterical conversion and acute abdomen!

The addition of ceftriaxone to metronidazole is synergistic and could have accelerated the attenuation of toxin production, and wound healing in this patient. Ceftriaxone is anti-excitotoxic and increases glutamate uptake by effect on glutamate transporter-I and cysteine/glutamate exchanger transporter (Zeng *et al.* 2010; Goodrich *et al.* 2013; Alhaddad and Sujan 2014). By its anti-depressant effects (Mineur *et al.* 2007), it stands to aid in the upregulation of GABAergic mechanisms and eventual patient recovery. Additionally, the institution of metronidazole + ceftriaxone combination is in good stead to prevent sepsis and pneumonia in tetanus patients. This is the first report of the use of ceftriaxone to aid recovery in tetanus patients.

The combination therapy of sedatives and anti-excitotoxics in this patient allowed doses of individual drugs to be reduced, thus minimizing toxicity. Magnesium sulphate is known to prevent autonomic instability in tetanus patients (Rodrigo *et al.* 2014). In this patient, there was no autonomic instability. Rodrigo et al (2014) also noted that magnesium sulphate allowed the earlier institution of oral intake and obviated the need for nutritional support especially in Ablett II tetanus. Our report agrees with this observation. Low-dose magnesium sulphate has also been reported to be suitable for management of eclampsia where excitotoxicity is coupled to seizures (Shilva *et al.* 2007). The anti-excitotoxic and anti-depressant, ketamine, is reported to help suppress the spasms of tetanus when other drugs prove inadequate (Obanor *et al.* 2008). Ketamine is known to suppress calcium currents (Tan *et al.* 2010).

The anti-epileptic, valproate, enhances GABA neurogenesis (Laeng *et al.* 2004) and GABAergic neurotransmission, an attribute that already makes it useful for generalised convulsive status epilepticus (Chen *et al.* 2011). Moreover, valproate attenuates Ca^{2+}-mediated excitotoxicity (Chen *et al.* 2007), a property that could make it synergise with magnesium sulphate to help quench excitotoxicity coupled to seizures as happens in

tetanus. A beneficial effect of this combination has previously been reported (Barbosa *et al.* 2011). Valproate does not easily cause respiratory depression and hypotension when compared to diazepam (Chen *et al.* 2011). The addition of valproate to the combination therapy in this patient hastened the disappearance of opisthotonus and accelerated recovery of deglutition. Valproate has previously been demonstrated in animal models to enhance survival from tetanus seizures (Altenmuller *et al.* 2013; Foca *et al.* 1984). We report here for the first time the safety and tolerability of adjunctive low-dose valproate in tetanus; a drug that could also attenuate the cognitive decline after tetanus (Hashimoto *et al.* 2002; Laeng *et al.* 2004; Tsai *et al.* 2010; Chiu *et al.* 2013).

5.0 Conclusion

In conclusion, adjunctive use of low-dose valproate appears to synergise with low-dose magnesium sulphate, diazepam, chlorpromazine and ketamine in the management of Ablett II tetanus in a young Nigerian girl. Also, the combination of metronidazole and ceftriaxone may synergise potently in accelerating healing of and stopping toxin production from the infected wounds of tetanus patients.

References

Ahmadsyah, I., Salim, A. (1985), "Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole", *British Medical Journal* 291: 648-50

Alagbe-Briggs, O.T., Tinubu, S.A. (2012), "Tetanus-a case report with severe autonomic instability and a review of the literature", *Nigerian Journal of Medicine* 21(3): 353-6

Alfery, D.D., Rauscher, A. (1979), "Tetanus: a review", *Critical Care Medicine* 4: 176-81

Alhaddad, H., Sujan, S.Y. (2014), "Effects of ceftriaxone on ethanol intake: a possible role for XCT and GLT-I isoforms modulation of glutamate levels in rats", *Psychopharmacology* 231(2): 40-49

Altenmuller, D-M., Hebel, J.M., Ressner, M.P., Volz, S., Freiman, T.M., Feuerstein, T.J., *et al.* (2013), "Locally applied valproate enhances survival in rats after neocortical treatment with tetanus toxin and cobalt chloride", *Biomed Research International* 2013: 49785

Anderson, A.E., Hrachow, R.A., Swann, J.W. (1997), "Increased susceptibility to tetanus toxin-induced seizures in immature rats", *Epilepsy Research* 26(3): 433-42

Anlar, B., Yalaz, K., Dizmen, R. (1989), "Long-term prognosis after neonatal tetanus", *Developmental Medicine and Child Neurology* 31: 76-80

Bagetta, G., Nistico, G. (1992), "Glutamate transmission is involved in the mechanisms of neuronal degeneration produced by intrahippocampal tetanus toxin in rats", *Toxicology Letters* 63-64: 447-53

Barbosa, F.J., Hesse, B., de Almeida, R.B., Baretta, I.P., Borrngen-Lacerda, R., Andreatini, R. (2011), "Magnesium sulphate and sodium valproate blocks methylphenidate-induced hyperlocomotion, an animal model of mania'', *Pharmacology Reports* 63: 64-70

Bleck, T.P. (1987), "Tetanus: dealing with the continuing clinical challenge", *Journal of Critical Care* 2: 41-52

Bleck, T.P. (1991), "Tetanus: pathophysiology, management and prophylaxis'', *Disease. Monday* 37(9): 545-603

Bowery, N.G., Baggetta, G., Nistico, G., Britton, P., Whitton, P. (1992), "Intrahippocampal tetanus toxin produces generalised convulsions and neurodegeneration in rats: antagonism by NMDA receptor blockers", *Epilepsy Research Supplement* 9: 249-56

Bratzlavsky, M., Vander-Eecken, H. (1980), "Pathophysiology of tetanus rigidity", *Revue Neurologique (Paris)* 136(12): 815-23

Chen, P.S., Wang, C.L., Bortner, C.D., Peng, G.S., Wu, X., Pang, H., *et al.* (2007), "Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity'', *Neuroscience* 149: 203-212

Chen, W.B., Gao, R., Su, Y.Y., Zhao, J.W., Zhang, Y.Z., Wang, L. *et al.* (2011), "Valproate versus diazepam for generalised convulsive status epilepticus: a pilot study", *European Journal of Neurology* 18(12): 1391-6

Chiu, C-T., Wang, Z., Hunsberger, J.G., Chuang, D-M. (2013), "Therapeutic potential of mood stabilisers, lithium and valproic acid: beyond bipolar disorder'', *Pharmacological Reviews* 65(1): 105-142

Cook, T.M., Protheroe, R.T., Handel, J.M. (2001), "Tetanus: a review of the literature", British *Journal of Anaesthesia* 87(3): 477-487

Dance, M., Lipman, J. (1994), "Tetanus: an internsivist's view", *International Journal of Intensive Care* 1: 56-60

Domenighetti, G.M., Savary, G., Stricker, H. (1984), "Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol", *British Medical Journal* 288: 1483-1488

Dunchen, L.W., Tonge, D.A. (1973), "The effects of tetanus toxin on neuromuscular transmission and on the morphology of motor end plates in slow and fast skeletal muscle of the mouse", *Journal of Physiology (London)* 228: 157-72

Edmondson, R.S., Flowers, M.W. (1979), "Intensive care in tetanus: management, complications and mortality in 100 cases", *British Medical Journal* 1: 1401-4

Farrar, J., Yen, L., Cook, T., Fairweather, N., Binh, N., Parry, J., *et al.* (2000), "Neurological Aspects of Tropical Disease: Tetanus'', *Journal of Neurology. Neurosurgery and Psychiatry* 69(3): 292-209

Foca, A., Rotiroti, D., Mastroeni, P., Nistico, G. (1984), "Effects of tetanus toxin after intracerebral microinjection are antagonised by drugs enhancing GABAergic neurotransmission", *Neuropharmacology* 23(2A): 155-8

Galazka, A., Gasse, F. (1995), "The present state of tetanus and tetanus vaccination", *Current Topics in Microbiology and Immunology* 195: 31-53

Godel, J.C. (1982), "Trial of pyridoxine therapy for tetanus neonatorum", *Journal of Infectious Diseases* 145: 547-9

Goodrich, G.S., Kabakov, Y., Hameed, M.Q., Dhamne, S.C., Rosenberg, P.A., Rotenberg, A. (2013), "Ceftriaxone treatment after traumatic brain injury restores expression of the glutamate transporter, GLT-I, reduces regional gliosis, and reduces post-traumatic seizures in the rat'', *Journal of Neurotrauma* 30(16): 1434-1441

Haastert, I.C., Jahn, K., Dengler, R., Groth, C., Bufler, J., Grosskreutz, J. (2006), "Dantrolene protects motoneurons in culture against AMPAR-mediated excitotoxicity'', *Klinische Neurophysiologie* 37: A75 doi: 10.1055/s.2006-939158

Hashimoto, R., Taki, N., Shimazu, K., Christ, L., Lu, B., Chuang, D.M. (2002), "Lithium induces BDNF and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity'', *Neuroscience* 43:1173-1179

Hatekeyama, N., Yamazaki, M., Shibuya, N., Yamamura, S., Momose, Y. (2001), "Effects of ketamine on voltage-dependent calcium currents and membrane potentials in single bullfrog atrial cells", *Journal of Anaesthesia* 15(3): 149-153

Hinfey, P.B. (2014), "Management of tetanus", Emedicine.medscape.com

James, M.F.M., Manson, E.D.M. (1985), "The use of magnesium sulphate infusions in the management of very severe tetanus", *Intensive Care Medicine* 11: 5-12

Kanda, K., Takano, K. (1983), "Effect of tetanus toxin on the excitatory and the inhibitory post-synaptic potentials in the cat motoneurone", *Journal of Physiology* 335: 319-333

Kokal, K.C., Dastur, F.D., Mahasshur, A.A., Kolhatkar, V.P. (1984), "Disordered pulmonary function in tetanus", *Journal of Association of Physicians of India* 32: 691-5

Laeng, P., Pitts, R.L., Lemire, A.L., Drabik, C.E., Weiner, A., Tang, H., *et al.* (2004), "The mood stabiliser valproic acid stimulates GABA neurogenesis from rat forebrain stem cells'', *Journal of Neurochemistry* 91(1): 238-51

Lalli, G., Gschmeissner, S., Schiavo, G. (2003), "Myosin Va and microtubule-based motors are required for fast axonal retrograde transport of tetanus toxin in motor neurons", *Journal of Cell Science* 116: 4639-4630

Ma, D., Rajakumaraswamy, N., Maze, M. (2005), "Alpha 2-adrenoceptor agonists: shedding light on neuroprotection!, *British Medical Bulletin* 71(1): 77-92

Mineur, Y.S., Picciotto, M.R., Sanacora, G. (2007), "Antidepressant-like effects of ceftriaxone in male C57BL16J mice", *Biological Psychiatry* 61(2): 250-252

Munro, P., Kojima, H., Dupont, J.L., Bossu, J.L., Poutain, B., Boquet, P. (2001), "High sensitivity of mouse neuronal cells to tetanus toxin requires a GPI-anchored protein", *Biochemical and Biophysical Research Communications* 289(2): 623-9

Obanor, A., Osazuwa, H.O., Amadasun, J.E. (2008), "Ketamine in the management of generalised cephalic tetanus", *The Journal of Laryngology and Otology* 122(12): 1389-91

Ogunrin, O.A. (2009), "Tetanus: a review of current concepts in management", *Journal of Post-Graduate Medicine* 11(1): 46-61

Owusu-Darko, S., Diouf, K., Nour, N.M. (2012), "Elimination of maternal and neonatal tetanus: a 21st-century challenge", *Reviews of Obstetrics and Gynaecology* 5(3-4): e151-e157

Pellegrini, L.L., O'Connor, V., Lottspeich, F., Betz, H. (1995), "Clostridial neurotoxin compromises the stability of a low energy SNARE complex mediating NSF activation of synaptic vesicle fusion", The *Journal of European Molecular Biology Organization* 14(19): 4705-13

Phillips, L.A. (1967), "A classification of tetanus", *Lancet* 1: 1216-7

Rodrigo, C., Fernando, D., Rajapakse, S. (2014), "Pharmacological management of tetanus: an evidence based review", *Critical Care* 18: 217 doi: 10.1180/cc13797

Rothstein, J.D., Patel, S., Regan, M.R., Haenggeli, C., Huang, Y.H., Bergles, D.S., *et al.* (2005), "B-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression", *Letters to Nature* (*Nature)* 433: 73-77

Schiavo, G., Benfenati, F., Poulain, B., Rossetto, O., Polverino de Laureto, P., DasGupta, B.R., *et al*. (1992),

"Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin", *Nature* 359(6398): 832-5

Schon, F., O'Dowd, L., White, J., Begg, N. (1994), "Tetanus: delay in diagnosis in England and Wales", *Journal of Neurology, Neurosurgery and Psychiatry* 57: 1006-7

Schwab, M.E., Suda, E.K., Thoener, H. (1979), "Selective retrograde transsynaptic transfer of a protein, tetanus toxin, subsequent to its retrograde axonal transport'', *Journal of Cell Biology* 82: 798-810

Seedat, Y.K., Omar, M.A.K., Seedat, M.A., Wesley, A., Pather, M. (1981), "Renal failure in tetanus", *British Medical Journal* 282: 360

Seo, D.H., Cho, D.K., Kwon, H.C., Kim, T.U. (2012), "A case of cephalic tetanus with unilateral ptosis and facial palsy", *Annals of Rehabilitation Medicine* 36(1): 167-170

Shilva, Kalra, J., Prasad, R., Saha, S.C. (2007), "Safety and efficacy of low-dose magnesium sulphate in the treatment of eclampsia", *International Journal of Obstetrics and Gynaecology* 97(2): 150-1

Sun, J., Zhou, Z.Q., Ly, R.R., Li, W.Y., Xu, J.G. (2004), "Ketamine inhibits LPS-induced calcium elevation and NF-kappa β activation in monocytes", *Inflammation Research* 53(7): 304-308

Tan, H.Y., Ma, S.P., Ye, T.H., Wang, X.L. (2010), "Effect of ketamine on high-voltage-activated calcium currents in rat hippocampal neurons", *Acta Academiae Medicinae Sinicae* 32(4): 441-444

Thomas, P.P., Crowell, E.B. Jr., Mathew, M. (1982), "Intrathecal ATS and parenteral betamethasone in the treatment of tetanus'', *Transactions of the Royal Society of Tropical Medicine and Hygiene* 76(5): 620-3

Thwaites, C.L., Yen, L.M., Loan, H.T., Thuy, T.T., Thwaites. G.E., Stepniewska, K., *et al.* (2006), "Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial", *Lancet* 368(9545): 1436-43

Toothill, C., Dykes, I.B.W., Ablett, J.J. (1970), "Urinary catecholamine metabolites concentrations in tetanus", *British Journal ofAnaesthesia* 42: 524-530

Trujillo, M.A., Castillo, A., Espana, J., Manzo, A., Zerpa, R. (1987), "Impact of intensive care management on the prognosis of tetanus. Analysis of 641 cases", *Chest* 92: 63-5

Tsai, L.K., Leng, Y., Wang, Z., Leeds, P., Chuang, D.M. (2010), "The mood stabilisers valproic acid and lithium enhance mesenchymal stem cell migration via distinct mechanisms, *Neuropsychopharmacology* 35: 2225-2237

Twyman, R.E., Rogers, C.J., Macdonald, R.L. (1989), "Differential regulation of GABA receptor channels by diazepam and phenobarbitone", *Annals of Neurology* 25(3): 213-20

Udwadia, F.E. (1994), "Pulmonary function in tetanus", In: Udwadia FE, ed., Tetanus. New York: Oxford University Press.

Zeng, L-H., Bero, A.W., Zhang, B., Holtzman, D.M., Wong, M. (2010), "Modulation of astrocyte glutamate transporters decreases seizures in a mouse model of tuberous sclerosis complex'', *Neurobiology of Disease* 37(3): 764-771

The IISTE is a pioneer in the Open-Access hosting service and academic event management. The aim of the firm is Accelerating Global Knowledge Sharing.

More information about the firm can be found on the homepage:
http://www.iiste.org

CALL FOR JOURNAL PAPERS

There are more than 30 peer-reviewed academic journals hosted under the hosting platform.

Prospective authors of journals can find the submission instruction on the following page: http://www.iiste.org/journals/ All the journals articles are available online to the readers all over the world without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. Paper version of the journals is also available upon request of readers and authors.

MORE RESOURCES

Book publication information: http://www.iiste.org/book/

Academic conference: http://www.iiste.org/conference/upcoming-conferences-call-for-paper/

IISTE Knowledge Sharing Partners

EBSCO, Index Copernicus, Ulrich's Periodicals Directory, JournalTOCS, PKP Open Archives Harvester, Bielefeld Academic Search Engine, Elektronische Zeitschriftenbibliothek EZB, Open J-Gate, OCLC WorldCat, Universe Digtial Library , NewJour, Google Scholar