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Case Report

High-Dose Use of Parenteral Diazepam in Tetanus: A Clinical Pharmacology Perspective

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Abstract: Tetanus, a vaccine-preventable disease, remains a life-threatening condition in low- and middle-income countries. It is characterised by muscle spasms and rigidity, driven by the tetanospasmin toxin, and is associated with a high mortality. Benzodiazepines, particularly diazepam, are the cornerstone of spasm control due to their GABA-A receptor agonism, which counteracts the toxin's disinhibition of motor neurons. Diazepam can be administered at higher doses than those typically used in the average patient population. We report the successful clinical management of a 67-year-old male with severe generalised tetanus using high-dose intravenous diazepam (up to 210 mg/day initially as boluses and short infusions), highlighting pharmacokinetic and pharmacodynamic considerations, propylene glycol toxicity risks, and the need for careful titration. From a clinical pharmacology perspective, high-dose parenteral diazepam provides rapid spasm control but requires monitoring for accumulation of the active metabolite (N-desmethyldiazepam) and solvent-related complications. This case underscores the balance between therapeutic efficacy and safety in the management of tetanus.

Keywords: Benzodiazepines, Diazepam, High Dose, Pharmacokinetics, Propylene Glycol, Tetanus.

INTRODUCTION

Tetanus, caused by *Clostridium tetani* and with an incubation period of 3-21 days, produces tetanospasmin (GSTG, 2017), which blocks the release of the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine in the central nervous system, resulting in unopposed motor neuron excitation, rigidity, and spasms (Karnad, D. R., & Gupta, V., 2021). Controlling spasms and muscle rigidity is critical to prevent complications such as aspiration pneumonia, rhabdomyolysis, respiratory failure, autonomic dysfunction, and fractures (Karnad, D. R., & Gupta, V., 2021; Sudarshan, R. *et al*., 2025). Benzodiazepines enhance GABA-A receptor activity (Yen, L. M., & Thwaites, C. L., 2019), restoring inhibitory tone and providing sedation, muscle relaxation, and anticonvulsant effects (Kumar, A. *et al.,* 2025). Diazepam is a widely used benzodiazepine in tetanus because of its availability, multiple routes of administration, and extensive clinical experience in tetanus, often requiring doses far exceeding standard anxiolytic or anticonvulsant regimens. The dose of diazepam in tetanus can sometimes exceed 1 mg/kg/day or reach up to 1000 mg/day in extreme cases (Karnad, D. R., & Gupta, V., 2021). However, parenteral formulations contain about 40% propylene glycol as a solvent, raising concerns about hyperosmolar lactic acidosis with prolonged high-dose infusions (Yen, L. M., & Thwaites, C. L., 2019). This case report discusses the pharmacological rationale, dosing strategy, monitoring, and pitfalls from a clinical pharmacology perspective.

CASE PRESENTATION

A 67-year-old male was in his usual state of health until a week before presentation, when he developed sudden-onset back stiffness. He initially managed it with an over-the-counter analgesic (the name of which was not specified), but the symptoms did not resolve. A day after onset, the symptoms progressed to include neck stiffness, jaw and neck trismus, and back pain associated with backward arching. The patient initially presented to a peripheral medical centre, where

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he was managed as an inpatient for 9 days with intravenous (IV) diazepam 10 mg 12 hourly, IV metronidazole 500 mg 8 hourly, IV amoxicillin/clavulanic acid 1.2 g 8 hourly, and oral baclofen 10 mg 12 hourly for seven days. He was subsequently referred to the emergency centre of our facility for further assessment and management.

The patient had no clear history of injury or animal bite to any part of the body. After admission and on examination, there was upper muscle stiffness, including the back, neck, and anterior abdominal wall, without drooling or loss of consciousness. Our patient was in a tetanic position but was not in respiratory distress, with oxygen saturation (SpO_2) consistently ≥95% throughout his hospital stay. All vital signs were within range (Table 1), except for pallor and fever (body temperature of 37°C), and bowel sounds were present. Other systemic examinations were essentially normal. There was no focal neurological deficit, and the patient's Glasgow Coma Scale (GCS) on arrival was 15/15 (motor-6, verbal-5, eye-opening-4). A urethral catheter was passed to monitor urine output.

Laboratory investigations showed 80 *Plasmodium falciparum* trophozoites on malaria testing, whereas retro-screening for HIV I and HIV II, hepatitis C virus, and hepatitis B surface antigen (HBsAg) was non-reactive. All full blood count parameters were within the normal range, except the mean corpuscular haemoglobin concentration (MCHC), which was low. Renal function tests were also normal, but liver function tests showed low total protein and albumin levels, with elevated aspartate aminotransferase (AST). His erythrocyte sedimentation rate was 47 mm/hour (normal: 0-15 mm/hour). Serum magnesium, phosphate, and calcium (adjusted) were all within normal ranges, except for calcium (total), which was low (Table 2).

On the first day of admission, the patient was diagnosed with tetanus, and pharmacological management with IV diazepam 10 mg 12 hourly, IV amoxicillin/clavulanic acid 1.2 g 8 hourly, IV metronidazole 500 mg 8 hourly, IV paracetamol 1 g 8 hourly, IV Ringer's lactate 1 litre, subcutaneous (SC) heparin 5000 IU 12 hourly, and oral baclofen 20 mg 12 hourly was initiated. Before that, 1500 IU of anti-tetanus serum and 0.5 ml of tetanus toxoid were given intramuscularly as stat doses. The patient was admitted to an isolation ward to avoid bright lights and sounds in the ward and unnecessary physical examination to prevent worsening of the condition, and was nursed on a ripple mattress.

On the second day of admission, IV diazepam was perfused at a dose of 8.75 mg/hour (210 mg in 24 hours) and was continued till the fifth day of admission. IV morphine 5 mg 8 hourly was also added to the therapy and switched to oral morphine 20 mg in 10 ml on the fourth day of admission, and IV amoxicillin/clavulanic acid was held. Oral artemether/lumefantrine 80/480 mg at 0, 8, 12, 36, 48, and 60 hours was given for uncomplicated malaria treatment.

On the sixth day of admission, the IV diazepam perfusion rate was increased to 350 mg/hour in 500 ml of 0.9% sodium chloride. Also, IV dextrose 5% in sodium chloride 0.9%, 2 litres was initiated for parenteral nutrition.

On the thirteenth day of admission, our patient showed improvement in mouth opening and speech, and physiotherapy commenced. IV diazepam was discontinued, and oral diazepam was continued at 20 mg 8 hourly until the twenty-fourth day of admission. Our patient was discharged on the twenty-fifth day on oral diazepam 20 mg 8-hourly for 14 days, oral baclofen 20 mg 8-hourly for 14 days, oral morphine 10 mg 6-hourly for 14 days, oral celebrex 200 mg 12-hourly for 30 days, and oral omeprazole 40 mg daily for 14 days.

On a 7-day review after discharge, our patient had no focal neurological deficits, and power was 4/5 in both upper and lower limbs. The neck was less rigid than on admission, and the patient could flex and extend the neck to about 45 degrees. Our patient was to continue his discharge medications and to continue physiotherapy.

Table 1: Relevant vital signs

Vital sign	AD 1	AD 5	AD 10	AD 15	AD 20	AD 25
Body temperature (^{0}C)	37.0	36.5	36.8	37.5	37.1	36.1
Blood pressure (mmHg)	131/87	129/67	139/78	140/84	121/83	134/70
Respiratory rate (cpm)	20	20	20	20	20	20
Heart rate (bpm)	60	67	81	85	72	90
SpO2	98%	96%	95%	95%	97%	99%
Glasgow Coma Scale	15/15	13/15	14/15	14/15	15/15	15/15

AD, admission day; SpO2, saturated oxygen pressure.

Table 2: Laboratory investigations

Test	Result	Reference range	Unit	Comment
Calcium (total)	2.19	2.20-2.55	mmol/L	Slightly low
Calcium (adjusted)	2.33	2.20-2.55	mmol/L	Normal
Magnesium	0.89	0.66-0.99	mmol/L	Normal

Test	Result	Reference range	Unit	Comment
Phosphate	1.30	0.81-1.45	mmol/L	Normal
AST	80.0	0-35	mmol/L	Markedly elevated
Total proteins	53.1	66-83	-	Markedly low
Albumin	32.5	38-55	g/L	Slightly low
MCHC	30	32-35	g/dL	Slightly low

AST, aspartate aminotransferase; MCHC, mean corpuscular haemoglobin concentration.

DISCUSSION

Tetanus has no confirmatory diagnostic test and is diagnosed based on the clinical presentation of relevant signs and symptoms (GSTG, 2017). This case of a 67-year-old hypertensive male with generalised tetanus of unknown portal of entry illustrates the challenges and pharmacological nuances of managing severe muscle spasms with high-dose parenteral diazepam in low- and middle-income countries (LMICs). The patient presented with classic features of tetanus (trismus, neck and back stiffness, and opisthotonos) that progressed despite initial treatment at a peripheral facility (Chouksey, S.S. *et al*., 2025; Li, J. *et al.,* 2023). On admission, he exhibited upper-body rigidity without respiratory distress, with SpO_2 > 95% and no loss of consciousness (GCS 15/15), consistent with moderate-to-severe tetanus (Ablett grade II–III) (Karnad, D. R., & Gupta, V., 2021). Management of our patient included standard care: anti-tetanus serum, tetanus toxoid, metronidazole, isolation, and supportive care, combined with escalating doses of diazepam therapy while maintaining safety (Abubakar, B. *et al*., 2022). More importantly, anti-tetanus serum and tetanus toxoid were injected at different sites to prevent drug-drug interaction (GSTG, 2017; Brayfield, A., 2014). As an anaerobic Gram-positive bacillus, *Clostridium tetani* is highly susceptible to metronidazole (Karnad, D. R., & Gupta, V., 2021), making it the first-line antibiotic for the treatment of tetanus (GSTG, 2017).

From a clinical pharmacology standpoint, diazepam remains a cornerstone for spasm control in tetanus because it is a positive allosteric modulator of GABA-A receptors, enhancing chloride influx and counteracting tetanospasmin-mediated blockade of inhibitory (GABA/glycine) neurotransmission in the spinal cord and brainstem (Karnad, D. R., & Gupta, V., 2021; Yen, L. M., & Thwaites, C. L., 2019). This diazepam activity restores the inhibitory tone, reduces rigidity and reflex spasms, and provides sedation and anxiolysis. Due to significant central disinhibition, the use of diazepam in tetanus frequently necessitates much higher dosages than typical anxiolytic or anticonvulsant dosing (2-10 mg). This is because the neurotoxic tetanospasmin reduces GABA release from inhibitory interneurons. As a result, high doses of benzodiazepines are required to adequately relax muscles and prevent spasms (Karnad, D. R., & Gupta, V., 2021). In this patient, initial intermittent IV diazepam 10 mg every 12 hours was escalated on day 2 to a continuous infusion of 8.75 mg/hour (210 mg/24 hours), then further increased on day 6 to a markedly high rate (350 mg/hour), indicating aggressive dose escalation to achieve spasm control. Transition to oral diazepam 20 mg every 8 hours (60 mg/day) by day 13 allowed successful de-escalation, with discharge on day 25 and continued outpatient tapering.

High-dose parenteral diazepam is effective, relatively affordable, and widely accessible, particularly in LMICs, but requires careful pharmacokinetic and pharmacodynamic (PKPD) consideration (Karnad, D. R., & Gupta, V., 2021; Kumar, A. *et al.,* 2025). Diazepam is highly lipophilic, with a large volume of distribution, a rapid onset of action (1-5 minutes IV), and prolonged action due to active metabolites, especially N-desmethyldiazepam, which has a half-life of 50-100 hours. Temazepam is also an active metabolite of diazepam, which, together with N-desmethyldiazepam, is further metabolised to oxazepam, which in turn is largely eliminated by glucuronidation (Figure 1) (Brayfield, A., 2014; Karnad, D. R., & Gupta, V., 2021). Accumulation of the active metabolite, N-desmethyldiazepam, is more pronounced in the elderly and in those with hepatic impairment (since diazepam is metabolised by the hepatic P450 enzymes CYP2C19 and CYP3A4), as suggested by our patient's low serum albumin and total protein levels and elevated AST, or during prolonged autonomic instability. Adjunctive baclofen, a GABA-B agonist, and morphine provided multimodal spasm and pain (Karnad, D. R., & Gupta, V., 2021), facilitating gradual weaning and initiation of physiotherapy on day 13.

A critical safety concern with prolonged high-dose IV diazepam is propylene glycol solvent toxicity (Yen, L. M., & Thwaites, C. L., 2019). Commercial IV formulations of diazepam contain approximately 40% propylene glycol, which can accumulate with high cumulative exposure, leading to hyperosmolar anion-gap metabolic acidosis, an elevated osmolar gap, lactic acidosis, renal impairment, hypotension, seizures, and arrhythmias (Kapoor, W. *et al.,* 1981). The risk of toxicity rises significantly with daily doses exceeding 900 mg or with prolonged infusions, though it has been reported at lower thresholds in high-risk patients (Karnad, D. R., & Gupta, V., 2021). In our patient, no overt propylene glycol toxicity, such as unexplained acidosis (although arterial blood gases could not be performed in our facility) or renal deterioration, was observed, possibly due to the patient's relatively preserved renal function, an initial intermittent rather than purely continuous high-rate infusion, and eventual

switching to enteral diazepam. However, escalation to very high infusion rates underscores the need for pharmacovigilance through serial arterial blood gas measurements, anion gap, osmolar gap, lactate, renal and liver function tests, and sedation depth (Ng, T. *et al.,* 2025). Recent case reports emphasise switching to enteral diazepam or alternative benzodiazepines, such as midazolam (which is water-soluble), as soon as spasms are controlled to limit exposure to propylene glycol (Pitton Rissardo *et al*., 2025; Karnad, D. R., & Gupta, V., 2021). It is recommended that prophylactic airway management, including tracheostomy or intubation, be considered when infusion rates exceed 10-12 mg/hour due to the risk of respiratory depression (Pitton Rissardo, J. *et al*., 2025).

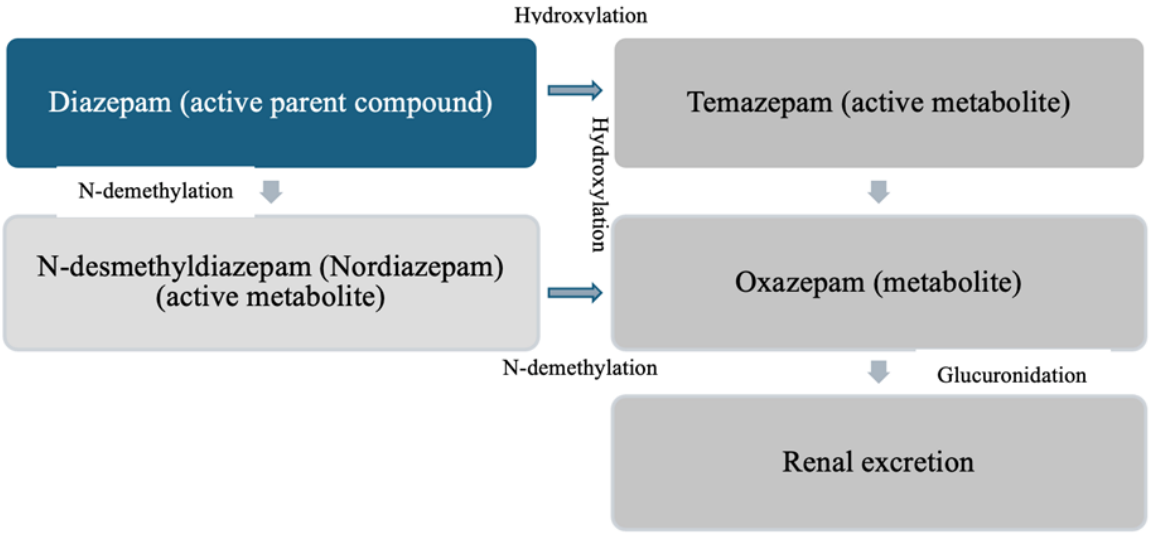

Figure 1: Metabolic pathways of diazepam adapted from Brayfield (2014)

Benzodiazepines can trigger a paradoxical excitatory reaction in approximately 10% of patients with tetanus. In addition to worsening spasms and autonomic overactivity, including tachycardia, hypertension, hypersalivation, and sweating, patients become agitated and restless. It is critical to recognise this syndrome and discontinue benzodiazepines. Combining phenobarbital, a long-acting barbiturate, with chlorpromazine, a phenothiazine with modest alpha-blocking and anticholinergic properties, is effective for patients who have been on prolonged, high-dose diazepam infusion to prevent agitation and restlessness (Karnad, D. R., & Gupta, V., 2021; Yen, L. M., & Thwaites, C. L., 2019).

The patient's comorbidities, including a possible mild hepatic dysfunction, anaemia, malaria co-infection, and low serum albumin, likely altered diazepam protein binding (normal:98%) and clearance, increasing free drug levels and metabolite (N-desmethyldiazepam) accumulation (Greenblatt, D.J. *et al*., 1978; Idasiak-Piechocka, I. *et al.,* 2025; Traeger, S. M., & Haug, M. T., 1986). Idasiak-Piechocka *et al*. (2025) reported that a patient with severe liver disease and hypoalbuminaemia developed coma after receiving diazepam, with total diazepam levels within the normal range, but N-desmethyldiazepam was elevated. This was attributed to higher unbound diazepam concentrations secondary to hypoalbuminaemia from liver disease, which contributed to clinical toxicity alongside altered metabolism.

Concurrent malaria treatment and low total calcium may have contributed to muscle irritability, though tetanus remained the dominant process. The successful clinical outcome at follow-up, with improved mouth opening, speech, and neck mobility, and only mild residual weakness (power 4/5), demonstrates that individualised high-dose diazepam, titrated to spasm control while avoiding oversedation, combined with multimodal therapy with baclofen, opioids, and magnesium if needed, can be life-saving even without advanced neuromuscular blockade or mandatory prolonged ventilation (Karnad, D. R., & Gupta, V., 2021; Kumar, A. *et al.,* 2025).

This case management approach for our patient aligns with current recommendations that benzodiazepines remain first-line for spasms (GSTG, 2017). Diazepam doses are titrated aggressively (infusions up to 900 mg/day in severe cases) but are limited by solvent toxicity risks (Karnad, D. R., & Gupta, V., 2021; Yen, L. M., & Thwaites, C. L., 2019). In LMICs, diazepam's low cost and familiarity make it practical, yet clinical pharmacologists advocate strict cumulative dose logging, early enteral transition, and readiness for haemodialysis if propylene glycol toxicity emerges. Slow tapering of diazepam over weeks prevents withdrawal-related rebound spasms or autonomic instability (Ng, T. *et al.,* 2026). Compared with neuromuscular blockers, which often require full ventilatory support, diazepam preserves some airway

reflexes at moderate doses and facilitates earlier mobilisation.

This case, therefore, highlights the therapeutic window for high-dose parenteral diazepam in tetanus and emphasises the need for PKPD monitoring for N-desmethyldiazepam accumulation and propylene glycol toxicity. In elderly patients with comorbidities, close monitoring, dose individualisation, and timely route transition optimise clinical outcomes (Kumar, A. *et al*., 2025). Notwithstanding, readily available human tetanus immunoglobulin and preventive vaccination remain paramount to reducing the incidence of tetanus infection.

CONCLUSION

High-dose parenteral diazepam can be life-saving in tetanus by providing effective control of spasm. Clinical pharmacologists play a key role in optimising dosing, anticipating metabolite accumulation, avoiding solvent toxicity, and facilitating safe de-escalation. In LMICs, this approach balances efficacy with practicality and highlights the need for ongoing education in benzodiazepine pharmacology for toxin-mediated disorders.

Consent: Informed patient consent was obtained from the patient for the publication of this case report.

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Conflict of Interest: There is none to declare.

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