

## Profound central depression during treatment of tetanus with combined magnesium, midazolam, morphine and fentanyl

\**RMMKN Ratnayaka*<sup>1</sup>, *J Ranaweera*<sup>2</sup>, *P Palihakkara*<sup>2</sup>, *PEAN Ranathunga*<sup>4</sup>

*Trainee in Medical Toxicology*<sup>1</sup>, *Consultant Anaesthetist*<sup>2</sup>, *Medical Officer, Emergency Treatment Unit*<sup>3</sup>,  
*Provincial General Hospital, Ratnapura, Sri Lanka*

*Corresponding author: namalrath10@yahoo.com*

A 61 year old male patient with generalized tetanus developed central depression due to combined use of magnesium sulphate, midazolam, morphine and fentanyl. He was successfully treated with magnesium sulphate (MgSO<sub>4</sub>) infusion with the minimal usage of sedatives and paralytic agents. Lowering of GCS occurred on day 6, 7 and 8 indicating central depression.

**Keywords:** generalized tetanus, magnesium sulphate, central depression, midazolam, morphine, fentanyl

### Introduction

Tetanus is an infective disease of the central nervous system (CNS) caused by an anaerobic gram positive bacillus, *Clostridium tetani*. It produces a neurotoxin which blocks the neurotransmitter release from inhibitory pathways of the motor and autonomic nervous systems.<sup>1</sup> This results in muscle spasms, increased muscle tone and autonomic dysfunction (sympathetic over activity). We report a case of generalized tetanus successfully treated with magnesium sulphate (MgSO<sub>4</sub>), in combination with midazolam, morphine and fentanyl, where profound CNS depression occurred probably due to synergistic effect of the combination of drugs.

### Case report

A 61 year old male patient was transferred from a local hospital for further management of tetanus. On admission to emergency treatment unit he had shortness of breath and dysphagia of 3 days duration and gradual onset of weakness and stiffness of lower limbs for one day. He had taken treatment for sore throat 3 days back. His past medical history was not significant but he had sustained a wound over his right foot one week back which had not been treated.

On examination he was afebrile; Glasgow Coma Score (GCS) was 15/15 with pupils equal and reacting to light. He had neck stiffness and trismus. Blood pressure was 170/100mmHg, pulse

rate was 66/min, respiratory rate was 32/min, bilateral lung fields were clear and SpO<sub>2</sub> was 100% on room air. He had increased muscle tone and exaggerated reflexes. According to Ablett classification of severity of tetanus the patient belonged to grade II (moderate) of disease severity.

He was given tetanus toxoid and then tetanus immunoglobulin stat doses intramuscularly. MgSO<sub>4</sub> infusion was started with a loading dose of 5g in 5% dextrose 100ml over 30min and a maintenance dose of 1g/hour in 5% dextrose 100ml. Intravenous metronidazole 500mg thrice a day was started and as the sensitivity test was positive, crystalline penicillin was not given.

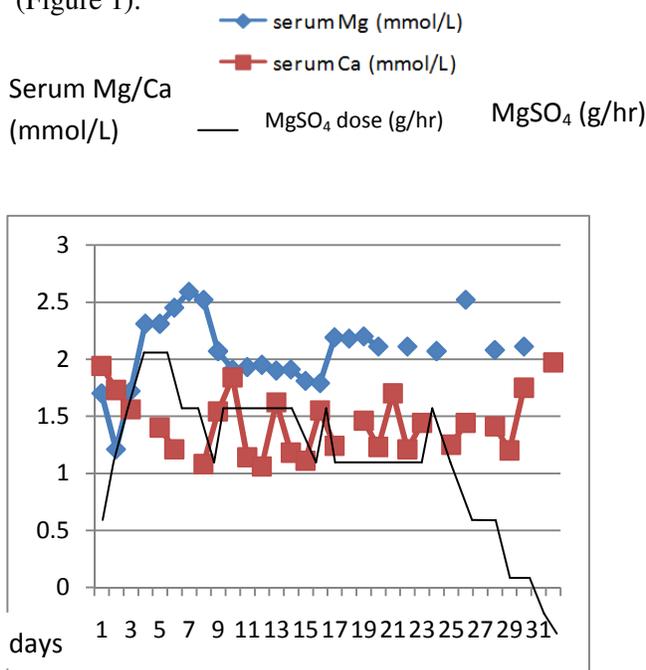
On admission investigations showed a white blood cell count  $7.4 \times 10^3/\mu\text{L}$ , neutrophils 88.3%, lymphocytes 7.1%, platelets  $217 \times 10^3/\mu\text{L}$ , Hb 11.1g/dL, Na<sup>+</sup> 144mmol/L, K<sup>+</sup> 4mmol/L, serum creatinine 96 $\mu\text{mol/L}$ , blood urea 5.2 $\mu\text{mol/L}$ , SGOT 118U/L, SGPT 35U/L, ALP 111U/L, total bilirubin 15.5  $\mu\text{mol/L}$ , PT 13.7/12.5, INR 0.89, APTT 28/25sec and serum calcium 1.94mmol/L. Arterial blood gas analysis on air was pH 7.406, Pco<sub>2</sub> 33.8mmHg, Po<sub>2</sub> 74.3mmHg, BEecf 3.4mmol/L, HCO<sub>3</sub> 21.5mmol/L, SO<sub>2</sub> 95%. ECG and chest x-ray findings were normal.

On the following day the patient was transferred to intensive care unit (ICU). He was intubated on day

2 due to respiratory difficulty, a tracheostomy done and ventilatory support given on spontaneous mode. Midazolam 2mg i.v. boluses were given for the control of spasms until day 11. On day 4 he had repeated uncontrolled spasms and a single dose of atracurium 25mg i.v. was given for controlled ventilation. Pain was managed with subcutaneous morphine 4.5mg/6hrly and fentanyl 50µg i.v. (as required). Accordingly midazolam 20mg i.v., subcutaneous morphine 18mg and fentanyl 200µg i.v. were used daily.

As broncho-alveolar lavage culture was positive for gram-negative enteric organisms, meropenem 1g i.v. thrice a day was started on day 8.

MgSO<sub>4</sub> infusion was continued throughout adjusted in the range of 0.25-2.5g/hour according to the clinical features, serum Mg and Ca levels (Figure 1).



**Figure 1:** Daily serum Mg and Ca levels related to MgSO<sub>4</sub> dose

On ICU day 6, 7 and 8, the patient's GCS was 3/15 with dilatation of pupils' to size 4. But when the Mg infusion was stopped for 5 hours in mornings of those days, the GCS gradually improved to 15/15. 10% w/v Ca gluconate one vial (2.3mmol) was given after receiving the serum Ca

levels. But before Ca was replaced his GCS improved to 15/15. Investigations on those days were as follows,

	normal range	day 6	day 7	Day 8
Mg dose (g/hour)	Therapeutic range 2-5g/hr	2	2	1.5
Serum Mg level (mmol/L)	therapeutic range 2-3.5mmo/L	2.45	2.59	2.52
Serum Ca level(mmol/L)	2.10-2.55	1.21	not done	1.08
Na <sup>+</sup> (mmol/L)	135-145	138.3	142	141
K <sup>+</sup> (mmol/L)	3.5-5.1	2.6	4	3.5
Blood urea (µmol/L)	2.2-8.2	7.7	not done	10.7
s.creatinine (µmol/L)	60-115	100	not done	71

Throughout the ICU stay patient had hypocalcaemia and calcium supplements were given when Ca level was less than 1.5mmol/L. But on days 6, 7 and 8 before giving Ca, GCS improved when MgSO<sub>4</sub> infusion was turned off for 5 hours. Potassium (KCl) 35mmol was given on lay 6 and then 30mmol twice a day regular dose was started and continued till day 11. Our patient also had carpopedal spasm on day 20.

**Discussion**

MgSO<sub>4</sub> has previously been used for the treatment of tetanus and found to control the features of sympathetic over activity such as hypertension, tachycardia etc., minimize the ventilator support as well as usage of sedatives and paralytic agents.<sup>2,3</sup> The important observation made in our patient was the profound suppression of CNS with the continuation of MgSO<sub>4</sub> infusion with synergistic depressants such as midazolam, morphine and fentanyl. Other authors<sup>4</sup> have used Mg in combination with benzodiazepines and narcotics, and indeed the current WHO recommendation is large dose diazepam for the control of spasms and Mg and morphine for the control of sympathetic overaction.<sup>5</sup> Thwaites et al., in a randomized controlled trial, showed that MgSO<sub>4</sub> therapy reduces the requirement for other drugs to control muscle spasms and cardiovascular instability in adults with severe tetanus but does not reduce the need for mechanical ventilation. The midazolam requirement was reduced from 7.1 to 1.4mg/kg/day.<sup>4</sup> But it was shown in a meta-

analysis that MgSO<sub>4</sub> does not change the mortality of patients with tetanus.<sup>6</sup>

Another important observation was that the patient responded quickly to stopping the Mg infusion (as Mg undergoes rapid renal excretion and our patient had normal renal function), and the synergistic effect was reversed in a few hours. Reversal with calcium gluconate would have been immediate. It is noteworthy that midazolam and opiates could also have been reversed promptly with flumazenil and naloxone, and may have had the same effect.

Mg toxicity per se is extremely rare and cases have been reported only with accidental overdose. Mg also does not cause sedation at serum concentrations less than 8mmol/l as long as ventilation is adequate, as it does not easily cross the blood brain barrier. Severe drowsiness may occur as a side effect of Mg therapy<sup>7</sup> in higher doses. Here we encountered a great difficulty in treating hypocalcaemia because there is no cut off value in guidelines and Ca supplements may lead to soft tissue calcification and renal failure too in the presence of high Mg.<sup>8</sup>

The lesson learnt is that although drugs with short context sensitive half lives and specific reversal agents provide a safety net, dosages should always be individualized with close monitoring, and titrated to clinical endpoints.

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