

# The Use of Magnesium Sulphate in the Intensive Care Management of an Asian Patient with Tetanus.

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## Abstract

*Tetanus, a potentially fatal but largely preventable disease through immunisation, is rare in Singapore. Timely diagnosis and appropriate intensive care management is essential to ensure survival. We aim to report the management of such a patient with magnesium sulphate. This has not been reported locally. By maintaining serum magnesium at 3 to 4 mmol/l we were able to control sympathetic overactivity by day 6, stop neuromuscular blockade by day 7 and wean off ventilator by day 11. Aminoglycoside-induced hypomagnesemia was also demonstrated, necessitating an increase in magnesium sulphate infusion rate to maintain serum magnesium at therapeutic level.*

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**Key words:** *Aminoglycoside-induced hypomagnesemia, Serum magnesium, Sympathetic overactivity*

## Case Report

A 29-year old Thai construction worker, previously well, was admitted to our Orthopaedic Department for sudden onset of lower back pain. Physical examination showed severe tenderness in the lumbar region, limited straight leg raising but no neurological deficit. A diagnosis of prolapsed intervertebral disc was made but despite treatment with analgesia, traction and hot packs, the patient's condition did not improve.

Four days later, he developed a fever (39°C), leukocytosis, profuse sweating and episodic generalised spasms with tendon tapping. Nuchal rigidity, limited mouth opening and guarded abdomen were also noted. A healed cut wound was found on the left big toe. A provisional diagnosis of tetanus was made but in view of possible acute abdomen, a general surgeon was consulted. Patient was found to be most tender in the right iliac fossa despite generalised guarded abdomen. An emergency appendectomy was scheduled.

Prior to induction of general anaesthesia, pulse oximetry read only 92% when patient was breathing room air. Physical examination showed reduced chest movement but breath sounds and chest X-ray were normal. An uncomplicated general anaesthesia with positive pressure ventilation was performed. There was transient hypertension and tachycardia whenever the surgeon manipulated the gut, despite maintaining an adequate

depth of anaesthesia. Operative findings included a grossly normal appendix, segmental loops of dilated bowel but no other abnormalities. However, histology of the appendix showed early acute appendicitis subsequently. With the preoperative clinical picture and non-surgical cause of guarded abdomen, we were almost certain of the diagnosis of tetanus. The patient was mechanically ventilated in the intensive care unit (ICU) postoperatively.

On admission to the ICU, he was started on an infusion of midazolam and morphine for sedation and analgesia. Upon spontaneous reversal of muscle relaxation, patient had severe, frequent generalised spasms, opisthotonus and high airway pressure (>40 cmH<sub>2</sub>O) even without any stimulation. This was as frequent as every 2 minutes. EEG done excluded status epilepticus and showed normal sleep pattern at 5 mg/h of midazolam and 2 mg/h of morphine. Muscle paralysis was recommenced with atracurium infusion and train-of-four monitoring to facilitate mechanical ventilation. In view of the need for prolonged paralysis, it was replaced by pancuronium infusion. Patient also received a bolus of intramuscular tetanus toxoid (40 units) and human tetanus immunoglobulin (500 IU), and metronidazole for 10 days.

Initially there was relative cardiovascular stability with midazolam infusion at 5 to 8 mg/h. His heart rate

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(HR) stayed around 100 / min while mean arterial blood pressure (MAP) remained about 93 mmHg with minimal variation. Train-of-four count of 2 was maintained with pancuronium infusion at 2 mg/h. On stimulation, there was no muscle spasm, only mild cardiovascular response.

Thirty-six hours after admission to the ICU, however, patient started to develop haemodynamic instability. Periods of tachycardia (130 to 150 per min) and hypertension (systolic blood pressure: 160 to 190 mmHg and diastolic blood pressure: 100 to 130 mmHg) lasted longer with minimal stimulation, despite midazolam infusion at 8 mg/h. There were also spontaneous episodes not related to stimulation. Midazolam infusion was increased to 10 mg/h and boluses of labetalol were required to control the sympathetic overactivity. Muscle rigidity was still present when pancuronium infusion was ceased.

By day 3 of his ICU admission BP became increasingly labile. Baseline of MAP increased to 113 mmHg and there was marked variation. We started magnesium sulphate infusion. The initial dose was 70 mg/kg, followed by continuous infusion of 1 to 3 g/h. Serum magnesium (Mg) was monitored 4 hourly to achieve a therapeutic level of 2.5 to 4 mmol/l (Fig. 1).

With the loading dose of magnesium sulphate, there was an immediate fall in baseline HR from 135/min to 100/min and decrease in pulse variation. Effect on BP was not immediate, but there were less episodes of prolonged rise in BP when serum Mg level reached 2 to 2.5 mmol/l. However, MAP remained high. After achieving serum Mg level of 2.74 mmol/l neuromuscular blockade was discontinued every morning to assess severity of spasm. Withdrawal resulted in unacceptable rigidity and neuromuscular blockade had to be resumed.

On day 5, despite maintaining the serum Mg level between 2.59 to 2.82 mmol/l, there was increasing tachycardia and hypertension. Attempts to alleviate this by gradual increase of midazolam infusion to 28 mg/h was unsuccessful. Being concerned with such a high dose of midazolam, an ASPECT Medical Systems A-1000 EEG monitor was used to measure Bispectral index which showed a range of 80 to 90. Magnesium sulphate infusion was then increased to achieve a serum Mg level of 3 to 4 mmol/l. Consequently both MAP and HR fell to a lower range with less variation. There was therefore no further adjustment of midazolam infusion rate.

Patient's stay in ICU was further complicated by the development of paralytic ileus (from days 3 to 15) requiring total parenteral nutrition. He also developed pneumonia requiring amikacin and was tracheostomised on day 6. Before aminoglycoside therapy was started, magnesium sulphate infusion was infused at a rate of 2 to 3 g/h with serum Mg reaching a level of 3.18 to 4 mmol/l. However 2 days after amikacin was started,

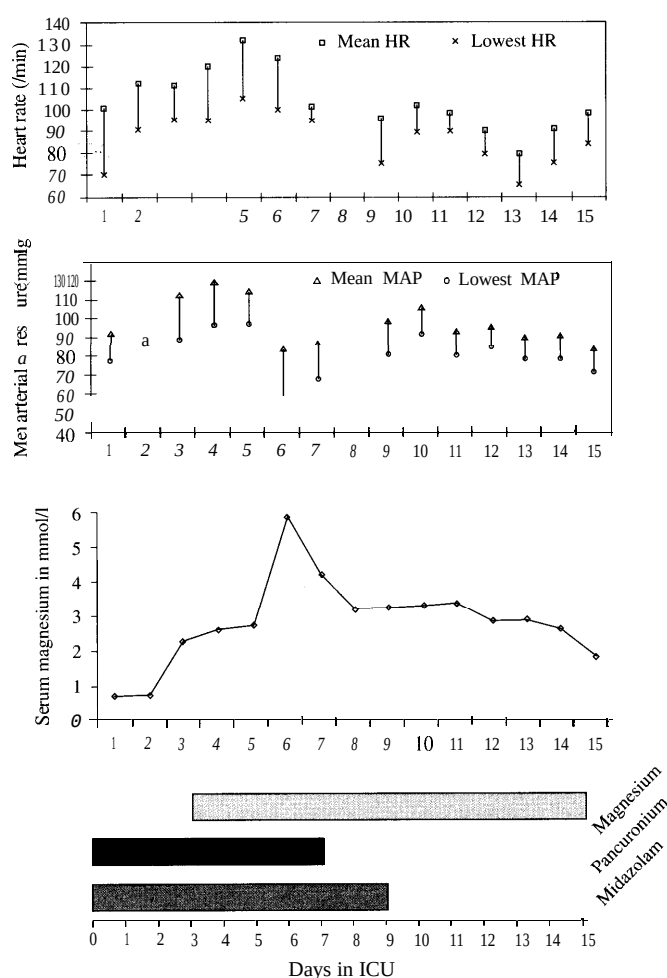


Fig. 1. Haemodynamic parameters versus serum magnesium level. The relationship between the haemodynamic parameters and the serum magnesium level is profiled here. The haemodynamic profile is represented by the lowest heart rate and mean arterial pressure for each day. As sympathetic overactivity is the abnormality in tetanus, the daily lowest HR and MAP is taken as the baseline. The index of variation above the baseline (due to sympathetic overactivity) is represented by the mean HR and mean MAP over each 24 hour period. Data on day 8 were lost and hence not presented in the figure.

magnesium sulphate infusion rate had to be increased to 4 g/h to maintain serum Mg level of 3.1 to 3.2 mmol/l. There was no change in the renal function clinically. Fraxiparine was started as prophylaxis against deep vein thrombosis.

On day 7, with a serum Mg level of above 3 mmol/l, neuromuscular blockade was successfully weaned off with no evidence of spasm. Two days later, autonomic instability appeared to settle. Sedation was steadily reduced and by day 11, he was weaned off the ventilator. Magnesium sulphate infusion was discontinued on day 15. He was discharged to the general ward following which he made a full recovery.

## Discussion

Tetanus is a toxin-mediated infection due to *Clostridium tetani* (a gram-positive bacillus). It is rare in Singa-

pore. There were only a few reported cases locally.<sup>1,2</sup> Most sporadic cases were generalised tetanus in adults, mainly foreigners. It presents as a diagnostic dilemma when tetanus mimics acute abdomen. As this is the first report of the use of magnesium sulphate locally, we would like to discuss in detail our experience, especially its efficacy, dosage and duration required for our patient.

### Diagnosis

The diagnosis of tetanus is made exclusively upon clinical findings obtained from patient's history and physical examination, as demonstrated in our patient. However, tetanus mimicking acute abdomen is difficult to differentiate and diagnosis of one does not exclude the other. The decision not to operate and subsequent paralysis of patient would mask abdominal signs if there were intra-abdominal pathology. On the other hand, the patient may undergo a laparotomy unnecessarily.<sup>2</sup> In this case appendectomy was done because a careful surgeon elicited tenderness at the right iliac fossa, despite generalised guarding. Early acute appendicitis based on histology was found, despite a grossly normal appendix at laparotomy. One common finding between our case and that reported by Chan et al<sup>2</sup> was the presence of dilated bowel. This might be an early sign of sympathetic overactivity causing paralytic ileus in tetanus.

### Ventilatory Support

Ventilatory support was continued postoperatively for the following reasons. Firstly, there was respiratory embarrassment preoperatively due to a reduction in vital capacity secondary to chest wall rigidity." Secondly, the effects of anaesthesia and surgical pain would have further aggravated this in the postoperative period.

### Control of Autonomic Dysfunction

The cardiovascular instability in tetanus is due to the effect of tetanospasmin on the autonomic nervous system, characterised by markedly elevated catecholamine concentrations. This leads to periods of hypertension and tachycardia. In Figure 1, we showed the changes in heart rate and mean arterial pressure with serum magnesium level. Tachycardia and hypertension were initially treated with boluses of labetalol, an alpha- and beta-adrenergic blocker but this was stopped after 1 day. Several reports on fatal cardiac arrest and pulmonary oedema in patients treated with beta-adrenergic blockers were made from the late 1970s.<sup>4</sup> This was thought to be due to continuing myocardial depression with sudden, precipitous decrease in sympathetic activity. Wesley et al<sup>5</sup> in 1983 observed cardiac arrest in 5 out of 15 patients treated with labetalol. Hence, despite successful reports

on therapy with beta-blocker, we chose other alternatives.

Magnesium sulphate has been used as an adjunct to the conventional therapy of neuromuscular blockade and mechanical ventilation. The aims are to control sympathetic overactivity, reduce muscle spasms and shortened the period of mechanical ventilation. Magnesium is thought to work by: a) reducing the release of catecholamine at adrenal glands and peripheral terminals, b) protecting myocardium from the adverse biochemical effects of excess adrenergic drive, c) potentiating neuromuscular blockade to reduce muscle spasm.

In 1997, by maintaining a serum level of 2 to 3.3 mmol/l, Attygalle and Rodrigo<sup>3</sup> successfully used magnesium sulphate as a sole agent to control spasms and maintain cardiovascular stability. In our patient, however, we were unable to control spasms without neuromuscular blockade at this serum level. In addition, a second surge of sympathetic overactivity occurred despite initial cardiovascular response to magnesium sulphate. Sedation had to be deepened and magnesium sulphate increased to achieve serum level of 3 to 4 mmol/l before autonomic dysfunction was controlled. We were unable to ascertain if this difference in findings in magnesium requirement was due to either a) earlier commencement of magnesium therapy by Attygalle, before the sympathetic overactivity occurred or b) an individual variation.

Peetermans and Schepens,<sup>6</sup> in a retrospective study of 27 tetanus patients treated with diazepam and supportive measures, reported a mean duration of 25.7 days (range 4 to 55) of ICU stay. Sixteen out of 27 patients required 27.5 mean days (range 4 to 38) of muscle paralysis and artificial ventilation. Attygalle and Rodrigo,<sup>3</sup> using magnesium sulphate as a sole agent in 8 patients, needed a mean period of 21 days (18 to 31) of ICU stay and 8.4 days (range 2 to 20) of ventilatory support in 5 patients. Using magnesium sulphate as an adjunct therapy, our patient required only 7 days of muscle paralysis, 11 days of mechanical ventilation and 15 days of ICU stay.

When James and Manson<sup>7</sup> studied the use of magnesium sulphate for tetanus therapy, infusion rate was kept at 1 to 3 g/h to maintain a steady level of serum Mg of between 2.5 to 4 mmol/l. However, because of wide individual variation, they recommended that frequent estimation of serum Mg should be done. For our patient, infusion rate of 1 to 3 g/h was initially sufficient to maintain the serum Mg level at therapeutic range. However, after amikacin was started, we observed a need to increase magnesium sulphate infusion rate to 4 g/h in order to maintain a serum Mg at 3.1 to 3.2 mmol/l. When magnesium sulphate infusion was ceased, serum Mg continued to fall below the normal range.

Hypomagnesemia associated with the use of aminoglycoside has been reported. Primary drug-induced magnesuria has been suggested, probably secondary to a reduction in tubular absorption of electrolytes. Others postulated that abnormal electrolyte losses are due to hyperaldosteronism or inappropriately low inorganic parathyroid hormone (iPTH)—the causes for high aldosterone or low iPTH remains unclear. In most cases, this phenomenon occurred after several weeks of aminoglycoside therapy but those occurring within a few days of therapy has been reported.<sup>8</sup> Aminoglycoside-induced magnesium depletion is especially significant in this patient since our therapeutic aim was to maintain a steady level of 3 to 4 mmol/l. Hence, should aminoglycoside be used together with magnesium sulphate, frequent estimation of serum Mg remains the safest way to ensure a steady therapeutic level of serum Mg.

Our use of the ASPECT monitor yielded some interesting points. We were surprised that despite such a high dose of midazolam infusion, Bispectral index reading remained high. This raised the possibility that sedation was inadequate and the patient might have been aware. We were unable to ascertain if this was due to: i) hyper-metabolism present in sympathetic overactivity ii) tolerance to midazolam or iii) technical fault of monitor. Nevertheless, the patient subsequently confirmed that he had no recollection of events during his ICU stay. This amnesic effect of midazolam further enhances its suitability for sedation in tetanus. Moreover the parenteral form of diazepam and lorazepam contain propylene glycol as a solvent which may increase the risk of lactic acidosis in extended courses of therapy. Midazolam, being a water-soluble agent, does not pose that problem.<sup>9</sup>

## Conclusion

Treatment of tetanus consists of a few components: a) sedation, b) controlling muscle rigidity, c) controlling cardiovascular instability, d) general supportive measures including adequate nutrition, prophylaxis against stress ulcer and deep vein thrombosis, good general

nursing care and physiotherapy to prevent long-term mobility problems. Conventional therapy with penicillin is currently replaced with metronidazole as the former may adversely affect outcome by acting synergistically with tetanospasmin in producing muscle spasm.<sup>9</sup> The traditional "stepwise management" of high dose sedation to control muscle rigidity and cardiovascular instability, failing which addition of neuromuscular blockade and mechanical ventilation may not be appropriate anymore given the good data on magnesium sulphate. A magnesium serum level of 3 to 4 mmol/l, in addition to sedation and muscle paralysis, was effective in reducing muscle spasms and control of sympathetic overactivity in our patient, thus finally reducing ventilation period and ICU stay. Concurrent use of aminoglycoside in tetanus can significantly lower the serum Mg level, necessitating frequent serum assays.

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