Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig†

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Summary

In spite of its well known propensity to cause accidental paralysis by a specific mechanism of action, Mg\(^{2+}\)-induced neuromuscular block has not been examined systematically for its characteristics of muscle response to nerve stimulation. We examined in seven anaesthetized domestic pigs the mechanomyographic (MMG) and neurally evoked compound electromyographic (ncEMG, EMG) responses of the tibialis anterior muscle to stimulation of its motor nerve, at baseline and during three levels of neuromuscular block induced by infusion of MgSO\(_4\) (at approximately 25 %, 50 % and 75 % depression of the 0.1-Hz EMG). We observed that: at 0.1 Hz, the MMG tended to be more depressed than the EMG; the train-of-four (2 Hz) was essentially non-fading; the tetanic force (50 Hz) showed tetanic ascent instead of tetanic fade and reached its baseline control value at 5 s in spite of depression of the twitch; the EMG counterpart of the tetanus showed escalation of the train of ncEMG, so that the fourth ncEMG was much greater than the first; and the post-tetanic twitch was also relatively spared from Mg\(^{2+}\)-induced neuromuscular block. Sparing of the tetanus and post-tetanic twitch resulted in large gains in the tetanus : twitch ratio and the post- : pre-tetanic twitch resulted in large gains in the tetanus: tietanic twitch ratio and the post- : pre-tetanic twitch ratio, which increased at the 75 % level of depression from 2.8 (so 0.7) to 11.5 (4.0), and from 1.5 (0.3) to 4.6 (1.4) (P < 0.01), respectively. These characteristics of neuromuscular block by Mg\(^{2+}\) reflect its prejunctional mechanism of action by depression of transmitter release. (Br. J. Anaesth. 1996; 76: 278–283)

Key words


The non-depolarizing neuromuscular block produced by blockers of the curare-type (“curariform”) is recognized by train-of-four (TOF) fade, tetanic fade and post-tetanic enhancement of twitch response (‘post-tetanic potentiation’). In comparison, depolarizing neuromuscular block does not manifest fade or post-tetanic potentiation, but the changing nature of its block from phase I to phase II is recognized by these signs [1, 2]. Between the non-depolarizing and depolarizing blocks, mechanomyographic (MMG) and electromyographic (EMG) responses to motor nerve stimulation differ in relative sensitivity [1]. Fade observed during curariform neuromuscular block in vivo is generally attributed to diminution of successive end-plate potentials (EPP) observed in vitro, which in turn is attributed to depression of acetylcholine mobilization prejunctionally [3]. TOF fade [4] has yielded the “TOF count” [5], a method which is now used as a routine to estimate curariform neuromuscular block clinically. The diminishing TOF ratio during continuous administration of suxamethonium is also useful in defining phase II vs phase I neuromuscular block [2, 6]. At the end of surgery, these monitoring techniques also guide dosing and reversal of neuromuscular block in anaesthetic practice.

In contrast with the extensive literature on curariform and depolarizing neuromuscular blocks, there is a remarkable paucity of literature on the features of magnesium-induced neuromuscular block in vivo. Many reports have documented accidental paralysis as a side effect of magnesium sulphate (MgSO\(_4\)) therapy [7]. Magnesium (Mg\(^{2+}\)) blocks prejunctionally, with a different mechanism of action from the curariform and depolarizing blockers.

As indications for MgSO\(_4\) therapy have increased rapidly [8, 9], we feel that Mg\(^{2+}\) deserves an independent study of its neuromuscular blocking characteristics. We have recently quantified the dose–response relationship of Mg\(^{2+}\)-induced neuromuscular block in an animal model while studying the effect of Mg\(^{2+}\) on the refractoriness of neuromuscular transmission [10]. The present study describes in qualitative and quantitative terms the MMG and EMG responses to motor nerve stimulation during three levels of Mg\(^{2+}\)-induced neuromuscular block.

Materials and methods

With institutional approval, seven male Duroc brown pigs, 9–12 kg, were anaesthetized with pento-barbitone 50 mg kg\(^{-1}\) i.p., supplemented with
2–5 mg kg\(^{-1}\) i.v. as required during the study. A cuffed tracheal tube of 6-mm internal diameter was inserted and ventilation of the lungs was controlled with a Harvard respirator pump at a rate of 15 times per minute. Tidal volume of air was adjusted to maintain an end-expiratory carbon dioxide concentration of 4–4.5 %. A cannula was inserted into a carotid artery for continuous monitoring of arterial pressure. A peripheral venous cannula was inserted for hydration and infusion of MgSO\(_4\). Each pig received approximately 120–180 ml of 5 % glucose in normal saline during the entire experiment. The oesophageal temperature was maintained at 36–38 °C by a heating lamp. A pair of fine Grass EEC platinum solid needle electrodes (type E2) were inserted s.c., slightly posterior and distal to the proximal head of the fibula. Several attempts were made to position these electrodes close together (1–2 mm at the tips) and as close to the common peroneal nerve as possible, so that the electrical stimulus required for supramaximal stimulation and the stimulus artefact were as small as possible.

Three other identical electrodes were used for detection of the neurally evoked compound electromyogram (ncEMG), as described previously [11]. Guided by palpation of the twitch, the sensing electrode was inserted s.c. along the frontal aspect of the tibialis anterior muscle, crosswise to the muscle at its belly. A reference electrode was inserted s.c. near the insertion of this muscle, away from all muscles. A reference electrode was inserted s.c. between the stimulating and sensing pairs of electrodes. The EMG sensing electrode was repositioned several times to assure an optimal waveform, without double peaking or excessive stimulus artefact. Each preparation must produce a stable unipolar waveform typical of the ncEMG, as described previously [11], before the experiment can begin. The electric stimuli were generated by a Grass S88 stimulator and passed through a Grass SIU5 stimulus isolation unit. The supramaximal stimulus was determined, and 20–50 % of the voltage added. The stimulus was rectangular and of 0.1 ms duration. The ncEMG response was digitized, processed and reconverted to analogue waveforms for immediate online recording, as described previously [12]. Side by side with the ncEMG, the MMG response of the same tibialis anterior muscle was recorded simultaneously. The tendon was detached from its insertion with a chip of bone, freed from constraints and connected to a Grass force displacement transducer (FT10C). The motor nerve was stimulated at 0.1 Hz. Periodically (see below) the 0.1-Hz stimulation was interrupted for TOF (2 Hz) and tetanic (50 Hz, 5 s) stimulations. The first post-tetanic 0.1-Hz stimulation was delivered 5 s after the tetanus. Of the 250 ncEMG responses corresponding to a 50-Hz, 5-s tetanus, the first four could be processed and recorded in time before the first post-tetanic twitch was evoked. These four were recorded online for analysis.

After the preparation had stabilized for 30–45 min,

![Figure 1](image1.png) **Figure 1** Differential depression by Mg\(^{2+}\) of the neurally evoked 0.1-Hz MMG (□) and EMG (▲) responses from their respective baselines at approximately 25 % (level I), 50 % (level II) and 75 % (level III) depression of the ncEMG.

![Figure 2](image2.png) **Figure 2** Neurally evoked MMG twitch (0.1 Hz), TOF (2 Hz), tetanus (50 Hz, 5 s) and post-tetanic twitches at baseline (upper panel) and during Mg\(^{2+}\)-induced neuromuscular block (lower panel). Note the increasing tetanus ("tetanic ascent") during neuromuscular block. In this experiment, the 0.1-Hz twitch was depressed by 45 %. TOF responses neither clearly faded nor escalated at baseline or during block. The tetanus was sustained at baseline. It was depressed by 32 % during block, but increased steadily so that at 5 s it was depressed by only 11 % from baseline. The post-tetanic twitch was potentiated at baseline. The potentiation was augmented during block, so that the post-tetanic twitch was depressed by only 16 % from baseline.
Baseline values of a series of EMG and MMG responses were obtained. The series consisted of 0.1 Hz ("twitch"), TOF, tetanic and post-tetanic responses. MgSO₄ was then infused to establish three levels of neuromuscular block in succession, at approximately 25 %, 50 % and 75 % depression of the 0.1-Hz EMG. Each level, when established, was maintained 5–10 min at the end of which a series of twitch, TOF, tetanic and post-tetanic responses were again obtained. Because various EMG and MMG variables of response were expected to differ, the three levels of neuromuscular block were established according to the amplitude of the 0.1-Hz EMG, irrespective of other variables. Levels I, II and III therefore refer to approximately 25 %, 50 % and 75 % depression of the amplitude of the 0.1-Hz nCEMG, respectively. Data are expressed as mean (SD), and paired data sets were compared with repeat measures ANOVA or Student’s paired t test (two-tailed). P < 0.05 was considered statistically significant.

**Results**

The three levels of neuromuscular block actually established were 25 (3)%, 51 (3)% and 74 (2)% depression of the nCEMG, respectively (fig. 1). The MMG twitch response tended to be more depressed than the EMG counterpart. Figure 2 illustrates the MMG twitch, TOF, tetanic and post-tetanic twitch responses at baseline and during Mg²⁺-induced neuromuscular block. Figure 3 illustrates the EMG counterparts. The TOF ratio at control was 1 with every experiment. The TOF responses remained non-fading in character during all levels of Mg²⁺-induced neuromuscular block, although the EMG and MMG TOF ratios were both slightly but consistently diminished from 1 (P < 0.05) to approximately 0.9.

Mg²⁺-induced neuromuscular block did not cause tetanic fade. Instead, it caused a tetanic increase so that the tetanic contractile force was greater at 5 s (fig. 2, T₅₀) than at the beginning of tetanus (fig. 2.

![Figure 3](image)

**Figure 3** Neurally evoked compound EMG responses at baseline (upper panel) and during Mg²⁺-induced neuromuscular block (lower panel). The TOF responses (2 Hz) did not fade at baseline but faded slightly during block. The next four nCEMG responses, marked "50 Hz, 5 s", represent the first 80 ms of the 5-s tetanus. They showed marked escalation during neuromuscular block. This escalation is the EMG counterpart of the increasing tetanic force. As is in the case of the MMG, the 5-s post-tetanic twitch was less depressed than the pre-tetanic twitch. The 50 Hz and 2 Hz EMG were displaced with the same spacing for clarity [11, 12].

![Figure 4](image)

**Figure 4** Tetanic ascent observed during Mg²⁺-induced neuromuscular block. The thick line = the 5-s tetanus; the vertical error bars = SD. T₅₀a and T₅₀b = tetanic force at the beginning and end of the 5-s, 50-Hz tetanus, respectively. The thin numbered horizontal or slanting lines = individual pigs. Level tetanus at baseline (pigs 1, 2) ascended with any neuromuscular block, while fading tetanus at baseline (pigs 5, 6, 7) reversed at deeper levels of block to show an ascent.
As a result of tetanic and post-tetanic sparing, the tetanus:twitch ratio and the post-:pre-tetanic twitch ratio increase markedly. This set of characteristics clearly distinguish Mg\textsuperscript{2+}-induced neuromuscular block from curariform, phase I (depolarizing), phase II (post-depolarizing, desensitization) and post-junctional irreversible non-depolarizing (α-bungarotoxin) types of neuromuscular block [27] (table 2).

TOF fade is explained by diminution in successive EPP, which result from depressed mobilization of the transmitter, which in turn is caused by occupation of the prejunctional "mobilization receptors", according to Bowman [3]. This theory requires that neuromuscular block achieved by occupation of postjunctural receptors alone, such as by α-bungarotoxin, does not manifest tetanic or TOF fade. This, indeed, is the case [27]. In the case of Mg\textsuperscript{2+}, our observations are explicable by the generally accepted main mechanism of neuromuscular action of Mg\textsuperscript{2+}, which is depression of pre-junctional release of acetylcholine. As successive motor impulses lead to accumulation of Ca\textsuperscript{2+} in the motor nerve terminal, successive EPP become less depressed by Mg\textsuperscript{2+}. This escalation of the train of EPP results in "tetanic escalation" of the ncEMG responses. It also causes the increasing tetanic force ("tetanic ascent") which spares the tetanus from depression. The enhanced post-tetanic potentiation can similarly be explained by accumulation of Ca\textsuperscript{2+} during tetanic stimulation. The MMG twitch tends to be more depressed than its corresponding EMG because Mg\textsuperscript{2+} is also thought to directly depress the contractility of the muscle [13]. The reason for the slight TOF fade is unclear. Ramanathan and colleagues [28] reported TOF escalation in pre-eclamptic patients. Toxaemia of pregnancy may account for the difference. In any case, the TOF ratio did not change by more than 10% from baseline.

From the above, it becomes obvious that the word "non-depolarizing" is generic and fails to distinguish prejunctional (mobilization, release) and post-junctional (competitive, non-competitive) non-depolarizing neuromuscular blocks from curariform (mobilization and competitive) block (table 2). Because of this, we prefer to call neuromuscular block of the curare type "curariform" block, to facilitate its distinction from other types of non-depolarizing neuromuscular block, including the "release block" by Mg\textsuperscript{2+}.

**Discussion**

There is a clear distinction between prejunctional and postjunctional sites of action and between mobilization and release mechanisms of the prejunctional actions of neuromuscular blocking agents. For decades, Mg\textsuperscript{2+} has been recognized as the prototype of the latter mechanism of prejunctional neuromuscular block in vitro [13]. It causes accidental paralysis by itself or in interaction with other neuromuscular blockers in vivo. In addition to obstetric use, Mg\textsuperscript{2+} is being used increasingly by paediatricians [14], endocrinologists [15], cardiologists [16–19], cardiac surgeons [20] and emergency [21, 22] and other specialists [8, 23]. Examples of new indications for MgSO\textsubscript{4} which are of interest to anaesthetists are phaeochromocytoma [24–26], refractory cardiac arrhythmia [16] and resuscitation [21, 22]. A method of diagnosis of Mg\textsuperscript{2+}-induced neuromuscular block by nerve stimulation therefore deserves exploration.

According to our results, Mg\textsuperscript{2+}-induced neuromuscular block may be characterized as follows: the MMG response tends to be more depressed than the EMG response; TOF responses do not fade; tetanus does not fade, instead its contractile force increases; the train of successive EMG responses during tetanic stimulation escalate; the peak tetanic force does not diminish although the tetanus starts at a lower point; and the physiological potentiation of the post-tetanic twitch is augmented so that the post-tetanic twitch is relatively spared. As a result of tetanic and post-tetanic sparing, the tetanus:twitch ratio and the post-:pre-tetanic twitch ratio increase markedly.

Slide 3: The first (•) and fourth (○) of the train of ncEMG of a tetanus (50 Hz) evoked at baseline and at three levels of Mg\textsuperscript{2+}-induced neuromuscular block. At each level, the first ncEMG corresponds to the singly evoked ncEMG (0.1 Hz) and shows the degree of neuromuscular block. The fourth ncEMG was relatively spared from the block. The fourth : first ratio did not change by more than 10 % from baseline. Note that the tetanic force measured at 5 s did not diminish from baseline (P > 0.5, all three levels) in spite of depression of the twitch (□). The post-tetanic twitch was slightly depressed from baseline (P < 0.05), but less so than the twitch at any level (P < 0.01).
The clinical implications of our observations can only be speculative at present, and only a few obvious possibilities are examined below. First, neuromuscular block by the same mechanism of action should exhibit similar or the same patterns of response to nerve stimulation. Aminoglycoside antibiotic-induced neuromuscular block should exhibit similar or the same patterns of neuromuscular block by the same mechanism of obvious possibilities are examined below. First, only be speculative at present, and only a few motions such as headlift or breathing may be less seconds to reach maximum may imply that sustained depressions, all of which are tetanic in nature, may be well tetanic sparing should imply that in spite of tetanic sparing repre- sents a margin of safety of physiological functions. On the other hand, however, this pattern of paresis may lead to failure to observe Mg²⁺-induced neuromuscular block clinically, which is a danger. Finally, in a patient who has previously received both MgSO₄ and a curariform blocker, detection of TOF and tetanic fades should reveal the continuous presence of the curariform block while demonstration of a tetanic ascent should imply dominance of Mg²⁺-induced neuromuscular block. A level tetanus may imply absence of any neuromuscular block or a balance of tetanic fade and tetanic ascent.

### Table 1
Tetanus and Post-tetanic twitch, as multiples of the pre-tetanic twitch, during 25% (level I), 50% (level II) and 75% (level III) Mg²⁺-induced depression of the 0.1-Hz ncEMG. *P < 0.05: level I, II or III vs baseline values, both rows

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<tr>
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<th>Baseline</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
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<td>Tetanus twitch ratio*</td>
<td>2.7 (0.7)</td>
<td>4.6 (1.7)</td>
<td>6.7 (2.7)</td>
<td>11.5 (4.3)</td>
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<tr>
<td>Post- twitch ratio*</td>
<td>1.5 (0.3)</td>
<td>2.2 (0.6)</td>
<td>3.0 (0.9)</td>
<td>4.6 (1.4)</td>
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### Table 2
Patterns of mechanomyographic neuromuscular responses to nerve stimulation distinguishing various mechanisms of neuromuscular block in vivo

<table>
<thead>
<tr>
<th></th>
<th>MMG vs EMG</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Curariform</th>
<th>α-Bungarotoxin</th>
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<td>Tetanus sparing</td>
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<td>Decrease</td>
<td>?</td>
<td>More sensitive</td>
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<td>Post-tetanic twitch</td>
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<td>Minimal</td>
<td>Clear</td>
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**References**


12. Lee C, Katz RL, Lee ASJ, Glaser B. A new instrument for...


