The Interaction between Magnesium and Other Neuromuscular Blocking Agents

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Two cases in which the interaction between magnesium and neuromuscular blocking agents proved hazardous are reported. The nature of the interaction was investigated in the rat phrenic nerve, phrenic nerve preparation. Magnesium potentiated the neuromuscular blocks produced by d-tubocurarine, decamethonium and succinylcholine. Proposed mechanisms of interaction as well as clinical implications are discussed. (Key words: Magnesium; Neuromuscular Blockers; d-tubocurarine; Succinylcholine; Decamethonium; Anesthesia.)

Magnesium sulfate (MgSO₄) is used in the treatment of pre-eclampsia and eclamptic toxemias in many parts of the world.¹,² The long-held belief that the magnesium ion has a central anesthetic action³,⁴ now seems in doubt,⁵ but its neuromuscular blocking action has been firmly established.⁶,⁷ Nevertheless, there is a paucity of clinical reports documenting difficulties which may occur owing to the administration of neuromuscular blockers to patients receiving magnesium therapy.

We recently observed two cases in which the interaction between magnesium and neuromuscular blockers proved hazardous to patients.

Case Reports

Case 1. A 19-year-old primigravida with a diagnosis of intrapartum pre-eclampsia was given phenobarbital (Luminal), 130 mg, and MsO₄, 10 g (20 ml of 50 per cent solution), intramuscularly. Approximately three hours later it was decided to perform a low-segment cesarean section. Atropine, 0.4 mg, was given intramuscularly; anesthesia was started using N₂O:O₂, followed by d-tubocurarine, 24 mg, intravenously.

After delivery, oxytocin (Pitocin), 4 units, was administered intravenously and another 16 units, added to 850 ml of molar lactate Ringer’s solution, infused slowly. The operation was finished 95 minutes after the injection of d-tubocurarine, at which time first atropine, 0.8 mg, and then neostigmine, 1 mg, were given. A peripheral nerve stimulator applied at the wrist was used to assess the reversal of the d-tubocurarine blockade, also confirmed by the ability of the patient to raise her head from the table on command and to keep it raised for five seconds.

An hour postoperatively, because of a rise in blood pressure to 170/110 mm Hg, restlessness, and hyperreflexia, MsO₄, 10 g, was given intramuscularly. Ten minutes later, the patient started to complain of difficulty in breathing and swallowing. Her breathing was observed to be shallow and slow, and the tendon reflexes disappeared. Therefore, magnesium toxicity was suspected, and 10 ml of 10 per cent solution of calcium gluconate were given slowly intravenously, together with artificial ventilation. Stimulation of the ulnar nerve at the wrist by a stimulator showed fatigue of the thenar muscles, with posttetanic facilitation. Neostigmine, 3 mg, and atropine, 0.8 mg, were given in divided doses. After the third mg of neostigmine, there was no apparent fatigue and the patient was more alert and responsive. She was kept under observation until the following morning. A serum sample withdrawn about an hour after administration of MsO₄, and 30–45 minutes after the calcium gluconate showed Mg⁺⁺ 8.4 mg/100 ml (normal 1.2–2.9 mg/100 ml) and Ca⁺⁺ 9.5 mg/100 ml (normal 9–11 mg/100 ml).

Case 2. A 24-year-old primigravida with pre-eclampsia was given phenobarbital, 150 mg, intramuscularly with MrO₄, 10 g, at 4:30 AM. The magnesium was repeated at 5:15, 6:40, and 9:35 AM, and at 1:15 and 6:30 PM. At 4:05 PM, phenobarbital, 60 mg was given, intramuscularly together with a 10-unit oxytocin intravenous drip. At 9:30 PM a hydralazine (Apresoline) drip was started (50 g in 1 liter of 5 per cent dextrose in water) and at 10:00 PM meperidine, 50 mg, and promethazine (Phenergan), 25 mg, were given intramuscularly. It was decided that because of cephalopelvic disproportion, cesarean section was needed. Sodium thiopental, 2.5 per cent solution intravenously in a dose of 150 mg, was given, followed by 50 mg of succinylcholine. Breathing was controlled using a mixture of N₂O and O₂.

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until respiratory activity started to return, at which time \( \alpha \)-tubocurarine, 30 mg, was injected.

Operation was finished 45 minutes later when atropine, 0.8 mg, was given, followed by 0.5-mg increments of neostigmine to a total of 3 mg. The myoneural blockade remained unaltered as judged by a nerve stimulator, and the anesthesiologist had to continue ventilating the patient manually. About 30 minutes later, another dose of atropine and neostigmine, 0.4 mg of the former and 0.5 mg of the latter, produced no apparent improvement of the paralytic state. Calcium gluconate, 10 ml of a 10 per cent solution, was then injected. This caused some improvement in that the patient could now open her eyes, but respiratory efforts were still inadequate, so that she had to be artificially ventilated until the next morning.

Prompted by these two cases, we tried to define the nature of the interaction between Mg\(^{2+}\) and some of the clinically-used neuromuscular blockers in an isolated neuromuscular preparation.

Method

Male rats of Sprague-Dawley strain, ranging in weight from 220 to 240 g, were guillotined, with no anesthesia. Phrenic nerve-diaphragm preparations were dissected according to the method described by Bulbring (1946).\(^8\) From each rat a fanlike piece of the left hemidiaphragm was incised with the corresponding phrenic nerve attached. The costal attachment was fixed to a pair of curved hooks at the bottom of an organ bath while the tendinous end was attached to a strain gauge by a thread. Another thread attached to the end of the nerve was then passed through two platinum electrodes embedded in perspex. The nerve was drawn gently through, with no undue tension. The preparation was kept in Tyrode solution containing double dextrose, well aerated with oxygen (95 per cent) and carbon dioxide (5 per cent). The bath was filled with 100 ml of the solution and temperature kept constant at 37 C. Supramaximal rectangular pulses of 0.1-msec duration at a frequency of 6/min were used to stimulate the preparation indirectly via the phrenic nerve. Force of contraction was determined after calibrating the strain gauge with weights. Twitch tensions developed by the preparations before addition of the drugs varied between 4 and 7 g. The contractions were recorded using a Beckman dynograph.

Preparations remained in the organ bath for an hour before commencement of the bioassay; preliminary experiments had showed complete stabilization at this time. In the experiments with succinylcholine, the preparations were washed before the start, and four more times, with Tyrode solution. The drugs were injected into the organ bath quickly and dispersed almost instantaneously by the bubbling gases. Each preparation received only one antagonist. Three doses separated by 20-min intervals were added to the bath to give the following concentrations: \( \alpha \)-tubocurarine chloride 0.4 \( \mu \)g/ml, then 0.6 \( \mu \)g/ml, then 0.8 \( \mu \)g/ml; decamethonium bromide (C10) 30 \( \mu \)g/ml, then 50 \( \mu \)g/ml, then 60 \( \mu \)g/ml; succinylcholine chloride 3 \( \mu \)g/ml, then 5 \( \mu \)g/ml, then 7 \( \mu \)g/ml. Thus, a dose-response curve was constructed for each antagonist. A subliminal dose of MgSO\(_4\), i.e., a dose that does not cause neuromuscular blockade, was determined. This dose of MgSO\(_4\) was added to a fraction of the dosage of each neuromuscular blocking agent in the same way and a second dose-response curve constructed for each. By doing a six-point bioassay analysis\(^9\) in a partial hierarchical design,\(^10\) the degree of potentiation of each drug by magnesium could be determined.

Results

Neuromuscular blockade is expressed as percentage of control twitch height. Preliminary experiments demonstrated the stability of the preparations over the two-hour period. All drugs tested had similar time courses. A dose of 0.1 mg/ml of magnesium sulfate (8 \( \times \) \( 10^{-3} \) M) caused no decrease in twitch tension in five preparations. The dose was chosen after an assay of the Mg\(^{2+}\)-containing solutions for three magnitudes of blockade: a 0.4 mg/ml solution produced 19 per cent blockade, a 0.5 mg/ml solution caused 53 per cent blockade, and a 0.6 mg/ml solution caused 87 per cent blockade. In the experiments with succinylcholine, repeated washing of the preparation before the start resulted in better conformity of responses. This was probably the result of removal of plasma and, therefore, removal of pseudocholinesterase, which governs the rate of hydrolysis of succinylcholine.\(^11\) The dose-response curves for \( \alpha \)-tubocurarine,
C10, and succinylcholine, with and without the subliminal Mg** dose, are shown in figure 1, showing the degrees of potentiation obtained as visible in the parallel shifts of the curves to the left. The degree of potentiation with d-tubocurarine was 4.1 (3.9-4.2); C10, 3.7 (3.5-4.3); succinylcholine, 1.9 (1.7-2.0). Figure 2 shows reduction of dosages when subliminal doses of magnesium were added to produce comparable degrees of blockade.

Discussion

In reviewing the literature, we found only a suggestion that the effect of magnesium may be additive to that of curare-like drugs. However, the cases we observed suggested potentiation. In the first case, the second dose of magnesium was the same as a previous dose which did not affect the deep tendon reflexes, the respiratory mechanism or production of clinical evidence of paralysis. Nevertheless, when magnesium was combined with a subliminal blood level of d-tubocurarine, a blood level at which the neuromuscular junction tested by a peripheral nerve stimulator was normal, severe paralysis ensued. The second case was also suggestive. d-Tubocurarine was injected about five hours after the last dose of magnesium, from which the patient did not recover in spite of 3.5 mg neostigmine and 1 g calcium gluconate. Apart from Mg**, there was no other obvious cause, such as myasthenia gravis, circulatory impairment, other electrolytic abnormalities, acid-base imbalance or use of intraperitoneal antibiotics, to account for the failure of reversal. The dosages of magnesium given were within the accepted range and the patients had adequate urinary flow, so that the possibility that excessive hypermagnesemia was a contributing factor may be excluded. Of all the drugs given to the two patients, none except d-tubocurarine and magnesium act at the myoneural junction.

The conjecture was supported by the fol-
Fig. 2. Effects of magnesium on degrees of neuromuscular blockade produced by d-tubocurarine, decamethonium, and succinylcholine. When a subliminal dose of magnesium, 0.1 mg/ml, is added, the reduction in dosage of the other drugs required to produce a comparable degree of blockade is apparent.

In the following laboratory work, Del Castillo and Engbaek17 (1954) have shown that Mg++ blockade at the neuromuscular junction is the result of: 1) decrease in the amount of acetylcholine liberated from the motor nerve terminals; 2) diminution in the depolarizing action of acetylcholine at the endplate; 3) depression of the excitability of the muscle fiber membrane. The first site is the most important, since transmission of impulses across the myoneural junction could be restored by administering calcium, in spite of reduced endplate sensitivity and an increased threshold of the muscle membrane. It appears that calcium ions are needed for the release of acetylcholine and that magnesium interferes with this release. Assuming that d-tubocurarine acts through competition with acetylcholine at the postjunctional membrane, then decreasing the release of acetylcholine from the motor nerve terminal, will free more receptors at the postjunctional membrane for occupation by d-tubocurarine. The same explanation would hold true for the “depolarizing blockers” when desensitization of the postsynaptic membrane would be expected to be enhanced. Several investigators have suggested a presynaptic site of action for both depolarizing and nondepolarizing blockers.18-19 Freeman (1968) suggested that succinylcholine may act by competing with calcium in the presynaptic membrane, leading to a decrease in the release of acetylcholine.11 Since magnesium is supposed to act through the same mechanism, it is difficult to imagine more than an additive effect if the drugs are combined. Thus, with the potentiation obtained in this study, different receptors have to be postulated for the two. Succinylcholine (as well as C10 and d-tubocurarine) may act at a different area in the process of release of acetylcholine from the calcium-coupling part.

One final point is the lower degree of potentiation of succinylcholine compared with C10 and d-tubocurarine. We believe this is not the result of a fundamental difference in the modes of action, but rather occurs for two reasons. The first is the potentiation of pseudocholinesterase by magnesium; this has been confirmed before by more than one investigator,16-17 and would lead to more destruction of succinylcholine in the magnesium-containing bath. The second is that reducing the concentration of succinylcholine in the bath, as we did when demonstrating potentiation, made available relatively more of the succinylcholine to interact with the enzyme, hence more became hydrolyzed. Thus, it may be the increased hydrolysis of succinylcholine which accounts for the difference in degree of potentiation.

From the clinical point of view, a nitrous oxide-neuromuscular blocking technique has been recommended for patients with pre-eclampsia. The lack of toxicity, the satisfactory skeletal muscle relaxation without affecting uterine tone, and the minimal fetal depression are obvious advantages. However, we feel that in patients on magnesium sulfate therapy such advantages are outweighed by the haz-
ard of interaction between Mg** and the neuromuscular blockers. A safer alternative may involve the use of regional techniques or inhalational agents such as cyclopropane. The latter, unlike diethyl ether, does not block the neuromuscular junction in the usual anesthetic concentrations and is not liable to potentiate magnesium.

Conclusions

Magnesium potentiates neuromuscular blockade produced by d-tubocurarine, decamethonium or succinylcholine, as demonstrated in the rat phrenic nerve-diaphragm preparation. This confirms speculation following observation of two clinical cases, and should serve as a warning of the possible hazard of mixing these drugs.

References


Drugs

MEPERIDINE Meperidine (1 mg/kg) injected intravenously increased blood flow significantly in the forearms and legs of healthy patients. These effects of meperidine were not obliterated by antihistaminics or intravenous administration of atropine. (Nadasit, M., and Zsoter, T. T.: The Effect of Meperidine on the Peripheral Circulation, Clin. Pharmacol. Ther. 10: 239 (March) 1969.)