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**Editorial I****Magnesium: an emerging drug in anaesthesia**

The role of magnesium in medicine has advanced considerably over the last 10 yr as exemplified by the two papers on the subject in the current issue of the *British Journal of Anaesthesia*.<sup>1 2</sup> It is now generally accepted that magnesium is a critical nutrient and that magnesium deficiency has adverse effects on a variety of physiological processes. Magnesium deficiency should be avoided in the perioperative period and in critical care, particularly in diabetics. For the anaesthetist, pharmacological use of i.v. administered magnesium salts represents far more interesting possibilities. For more than 100 yr, magnesium salts have been used i.v. to achieve a variety of endpoints from the production of general anaesthesia to the treatment of myocardial infarctions. For most of the twentieth century, however, magnesium infusions were used primarily for the purpose of treating eclamptic convulsions, and even this usage was controversial since the evidence was largely empirical with little scientific basis. From an anaesthesia perspective, the only real awareness of magnesium was as an agent that could potentiate non-depolarizing neuromuscular blocking agents.

In the latter part of the last century, good scientific studies began to elucidate a proper pharmacological basis for the use of this ion. Impressive obstetric research established beyond doubt that magnesium was the best drug for the prevention and treatment of eclamptic convulsions,<sup>3</sup> although the mechanism remains unclear. A variety of possibilities have been invoked to explain this remarkable degree of efficacy, including cerebral vasodilatation, blood–brain barrier protection, and various anticonvulsant actions.<sup>4</sup> The fact remains that magnesium is highly effective and has a low rate of complications in the management of pre-eclampsia and is more effective than standard anticonvulsants and vasodilators for the prevention of convulsions.

The establishment of the role of magnesium as a calcium channel competitor formed the basis for numerous

scientific studies describing an array of cardiovascular effects that could be of potential benefit in a number of areas, particularly in anaesthesia and critical care. These studies demonstrated that magnesium is a highly effective arteriolar vasodilator but with minimal dilatory effects on the venous circulation, resulting in maintained cardiac filling and enhanced cardiac output.<sup>5</sup> In the presence of excess catecholamines, magnesium maintains beta-agonist effects while demonstrating excellent alpha-adrenergic antagonist actions in animals and humans.<sup>6 7</sup> In addition, it reverses diastolic dysfunction<sup>8</sup> in the presence of catecholamines and is highly effective against catecholamine-induced arrhythmias.<sup>9</sup> The only other arrhythmia for which magnesium therapy appears to be consistently effective is torsade de pointes, although magnesium deficiency appears to contribute to the incidence and severity of many other forms of arrhythmia, particularly after cardiac surgery.

From a cardiovascular perspective, magnesium appears to be a very safe drug. Early reports of cardiac toxicity in animal work failed to take account of the neuromuscular weakness induced by high plasma concentrations of magnesium. Intact animal studies where ventilation is maintained suggest a therapeutic ratio of at least 10:1 with plasma concentrations of 6 mmol litre<sup>-1</sup> being described as 'haemodynamically safe'<sup>8</sup> and up to 9 mmol litre<sup>-1</sup> resulting in only moderate hypotension.<sup>6</sup> Reports of cardiac toxicity in obstetric overdose have emphasized the importance of the respiratory component<sup>10</sup> and rapid and complete recovery from massive overdose has been described, provided ventilatory support is instituted rapidly.<sup>11</sup> Certainly, magnesium appears to be substantially safer than any other comparably effective cardiovascular agent, provided ventilatory impairment is avoided.

The well-known potentiation of neuromuscular block seen with elevated plasma magnesium concentrations is

the result of competition by magnesium for calcium channels in the pre-synaptic nerve terminal inhibiting acetylcholine release at the motor endplate. Similar inhibition of calcium-mediated neuroendocrine secretion by magnesium has been demonstrated, particularly of the release of catecholamines, with clinically useful effects.<sup>12</sup>

These observations encouraged the use of magnesium infusions in the management of a variety of conditions of catecholamine excess, including severe tetanus,<sup>13 14</sup> the anaesthetic management of phaeochromocytoma<sup>15</sup> and in autonomic storms in intensive care.<sup>16</sup> None of these conditions is readily amenable to large, randomized controlled trials, but excellent results have been reported in case studies and patient series in all of these conditions. The use of magnesium in the most challenging of these conditions, phaeochromocytoma, has now been widely reported as being both safe and effective.<sup>17</sup> It is of particular interest that magnesium has been effective in controlling the potentially catastrophic haemodynamic disturbances of phaeochromocytoma crisis where more traditional agents have failed.<sup>18 19</sup> The intriguing possibility that combinations of magnesium and nicardipine may be particularly beneficial in phaeochromocytoma is currently being explored (A.L. Rosas and A.M. Roche, personal communications). Magnesium has also been shown to be effective in controlling the response to intubation, limiting catecholamine release, and minimizing changes in arterial pressure and heart rate.<sup>20</sup> This is a particularly attractive option in pre-eclamptic patients requiring general anaesthesia for Caesarean section.<sup>21</sup>

Neurophysiological studies have demonstrated that magnesium is a physiological and pharmacological blocker of *N*-methyl-D-aspartate (NMDA) receptors in neuronal tissue. This observation raised a variety of possibilities for the use of magnesium as a neuroprotective agent in a number of forms of neurological injury,<sup>22</sup> and for neuronal protection of the premature fetus.<sup>23</sup> As the role of the NMDA receptor in pain perception has become apparent, there has been increasing use of magnesium for the management of both acute<sup>24</sup> and chronic pain.<sup>25</sup> There have been several recent reports of improved postoperative pain control from the addition of magnesium to epidural or spinal infusions during surgery. However, the evidence supporting the use of magnesium for both neuronal protection and pain management is inconsistent and currently far less convincing than that regarding its cardiovascular effectiveness. Magnesium has no primary analgesic activity but may have value as a secondary analgesic, enhancing the actions of more established pain medication. Several recent reports have described the efficacy of magnesium infusions in moderate dosage both during surgery and in the postoperative period for decreasing postoperative morphine requirements.<sup>26 27</sup>

A number of these issues are addressed in the reports of magnesium use presented in the current issue of the

*British Journal of Anaesthesia*. Jee and colleagues<sup>1</sup> describe a placebo-controlled, randomized study of the effect of a single bolus dose of magnesium sulphate (50 mg kg<sup>-1</sup>) on the haemodynamic and catecholamine responses to the production of pneumoperitoneum for laparoscopic cholecystectomy. In this study, magnesium limited the haemodynamic response to capnoperitoneum, prevented the increase in catecholamines seen in the control group, and attenuated increases in vasopressin release. Given the relatively short duration of a single bolus dose of magnesium and the modest plasma magnesium concentrations achieved, a continuous infusion during the surgical intervention may have been even more effective. This study is particularly relevant to phaeochromocytoma management as laparoscopic resection of these tumours is becoming increasingly popular and haemodynamic control during the establishment of a capnoperitoneum has been described as being problematic. In the other study, Ryu and colleagues<sup>2</sup> report on a randomized, controlled trial comparing infusions of remifentanyl with infusions of magnesium sulphate for the maintenance of hypotension during middle ear surgery. Similar, satisfactory, levels of intraoperative hypotension were achieved in both groups, but magnesium provided better control of arterial pressure in the immediate post-extubation period. Of particular interest in this study was the fact that magnesium was associated with a substantially decreased incidence of nausea and vomiting and a lower requirement for rescue antiemetics in a procedure in which nausea and vomiting is a common complication. In addition, postoperative pain scores were lower in the magnesium group up to 30 min after operation, the requirement for rescue analgesia was also decreased, and the incidence of postoperative shivering was lower in the magnesium group. It is also interesting that the sevoflurane end-tidal partial pressure required to maintain a BIS value between 40 and 60 was significantly lower in the magnesium group, confirming previous observations that magnesium may decrease anaesthetic requirements to a modest degree. Magnesium has previously been favourably compared with sodium nitroprusside for the maintenance of hypotensive anaesthesia<sup>28</sup> in choroidal surgery. In none of these reports did magnesium pose difficulty in terms of reversal of neuromuscular block, but the doses used were relatively small and the use of relaxants was limited.

A variety of other effects attributed to magnesium, including myocardial protection, improved control of severe asthma, tocolysis, and many antiarrhythmic actions have not been substantiated, so magnesium use in these areas is, at best, supportive of more standard therapy. However, as a vasodilator and  $\alpha$ -adrenergic antagonist, magnesium is at least as effective as other, potentially more hazardous agents with some potential benefits, as illustrated in the studies published in this issue. Given the large safety margin of this readily

available, inexpensive agent, there is a strong argument to be made for magnesium to be regarded as the first-line agent for the management of intraoperative hypertensive events. A single bolus dose of up to 60 mg kg<sup>-1</sup>, repeated within 5–10 min if necessary, will provide rapid control of hypertensive events related to catecholamine excess and is far safer than the use of  $\beta$ -adrenergic antagonists in situations of potential  $\alpha$ -adrenergic crisis. In this era of recreational pharmacology, magnesium may be extremely valuable in managing the cardiovascular problems associated with cocaine, methamphetamine, and 3,4-methylenedioxy-methamphetamine ('Ecstasy').

Magnesium is a calcium competitor with many of the actions of the dihydropyridines, but with a broader spectrum of action that includes inhibition of transmitter release and NMDA receptor antagonism. A role for magnesium infusions for cardiovascular control in anaesthesia and critical care is gradually becoming established. Novel applications and established indications make it one of the more interesting emerging agents in the anaesthetic pharmacopoeia.

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