Magnesium and Pain

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KEY POINTS

- Magnesium is believed to produce analgesia through N-methyl-D-aspartate receptor antagonism.
- Based on available data, the incidence of significant side effects arising from intravenous magnesium administration appears to be low.
- Current research suggests that intravenous magnesium can reduce perioperative opioid use and has a modest effect on postoperative pain scores.
- Optimal dosing regimens are yet to be clarified and this remains a subject for further research.
- The role of magnesium in the treatment of chronic pain is not yet well established.

INTRODUCTION

Over recent decades there has been increasing interest in the analgesic potential of magnesium.[1–3] There is a growing body of evidence that intravenous magnesium administered perioperatively can reduce opioid consumption and postoperative pain scores.[1,2] Given enhanced international focus on opioid stewardship and opioid sparing anaesthetic techniques, interest in magnesium for this purpose is only likely to increase. This tutorial will discuss the proposed mechanism via which magnesium might produce analgesia, the evidence for its use perioperatively and in chronic pain, its side effect profile, as well as other applications relevant to pain and analgesia.

MAGNESIUM IN THE BODY

Magnesium is the second most common intracellular cation in the human body.[2] It has numerous physiological functions, including cell signaling, maintenance of electrical potential across cell membranes, and as a cofactor for a large number of enzymes.[4,5] As a drug, magnesium has a variety of clinical uses, including analgesia (Table). For a more detailed explanation of the role of magnesium in the body, and its uses pertinent to anaesthesia outside of analgesia, please refer to ATOTW 90.[4]

MAGNESIUM, THE N-METHYL-D-ASPARTATE RECEPTOR, AND PAIN

Magnesium has been described as an N-methyl-D-aspartate (NMDA) receptor antagonist.[2] NMDA receptors are ligand-gated ion channels that play a key role in pain pathways.

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TAKE ONLINE TEST

Therapeutic	Analgesic
Pre-eclampsia and eclampsia	Perioperative pain
Severe asthma	Chronic pain
Arrhythmia	Local anaesthetic adjunct
Phaeochromocytoma surgery: inhibition of catecholamine release	

Table. Pharmacological uses of magnesium

The process via which a noxious stimulus produces the experience of pain involves the relay of action potentials by a peripheral, primary afferent neurone (C or A delta fibre) to the dorsal horn of the spinal cord.[6] Here it synapses with a second order neurone, which ascends within the spinothalamic tract, and in turn synapses with a third order neurone in the thalamus.[6]

One of the substances released by primary afferent neurones in response to stimulation is glutamate.[6] Glutamate is an excitatory neurotransmitter throughout the nervous system, which acts on NMDA receptors. When glutamate is released from primary afferent neurones in response to a noxious stimulus, it binds to NMDA receptors on the postsynaptic membrane. However, under normal physiological conditions the central pore of the NMDA receptor is blocked by magnesium, preventing the passage of ions.[6] Only if there is sustained depolarisation resulting from high frequency stimulation of C-fibres is the magnesium 'plug' removed, permitting activation of the NMDA receptor and calcium influx - a phenomenon known as wind up[6] (Figure). Intense and ongoing stimulation results in a further increase in excitability of neurones in the dorsal horn, leading to central sensitization.[6,7] This produces pain hypersensitivity, meaning that pain can be experienced even with a reduction in intensity or cessation of painful stimuli.[7] Thus it is proposed that magnesium has no direct analgesic effect, but produces an antinociceptive effect through binding to NMDA receptors, restoring the magnesium 'plug' and inhibiting the entry of calcium ions into the cell, preventing activation and reducing excitability.[7,8] This additionally serves to attenuate central sensitization.[7,8]

USE OF MAGNESIUM PERIOPERATIVELY

With regards to pain and analgesia, the majority of research concerning magnesium has investigated the effects of its use perioperatively. Most significantly, two large meta-analyses published in 2012 and 2013 demonstrated a reduction in opioid requirements and postoperative pain scores associated with administration of intravenous magnesium.[1,2] They both reported a significant reduction in cumulative 24-hour opioid consumption: a 24.4% reduction—equating to a mean reduction of 7.6 mg intravenous morphine equivalent;[1] and a mean reduction of 10.5 mg intravenous morphine equivalent.[2] In addition to decreased opioid consumption there was a small but statistically significant reduction in pain score both at rest (VAS < 1) and on movement (<1).[1]

These findings are supported by subsequent systematic reviews. Firstly from 2015, which reported both a reduction in postoperative pain scores and analgesic consumption,[9] and from 2020, which reported reduced postoperative opioid consumption (mean of 5.6 mg IV morphine equivalent), though without any significant difference in post-operative pain scores.[10] Another systematic review found evidence of benefit, though of variable magnitude, in orthopaedic surgery.[3] The latter reported reduced analgesic consumption, without reduction in pain intensity, though the findings varied significantly by trial. Across six trials it was reported, for example, that doses of postoperative 24-hour consumption of analgesia was reduced by 16% to 57%.[3]

The above constitutes a body of evidence demonstrating that magnesium has the potential to reduce perioperative opioid consumption, and to some extent pain scores. Despite this, some practitioners may question whether these reductions are sufficient to warrant the inclusion of magnesium as part of an analgesic strategy. While a cost-benefit analysis is beyond the scope of this article, and will vary based on local pricing, this sentiment may be felt particularly in settings where opioids are much more readily or cheaply available than magnesium. In response to such perspectives, firstly it should be noted that the role of any agent employed within a multi-modal strategy is to contribute to the cumulative effect, and for this magnesium appears to have clear potential. Secondly, although its effects on pain scores may be modest, the opioid-sparing effects of magnesium can be clinically significant. Perioperative opioid use can cause both early adverse effects, such as postoperative nausea and vomiting and respiratory depression, and longer term problems such as abuse, addiction, and other harms.[11] While opioids have an important role in perioperative pain management when used appropriately, magnesium could facilitate reduced cumulative doses, and serve as an additional element within an opioid-sparing multimodal analgesic strategy.[11] Therefore although there is a lack of evidence for a profound effect on pain scores, it appears that magnesium may have a role in perioperative pain management, and in view of the available evidence anaesthetic practitioners should consider whether magnesium might have a place in their practice.

Dosing

An area warranting further research is optimal dosing. In a perioperative context, an initial bolus of 30–50 mg/kg has been suggested,[5,7] and this was the dose used in the majority of trials included in the aforementioned meta-analyses.[1,2] In many cases,

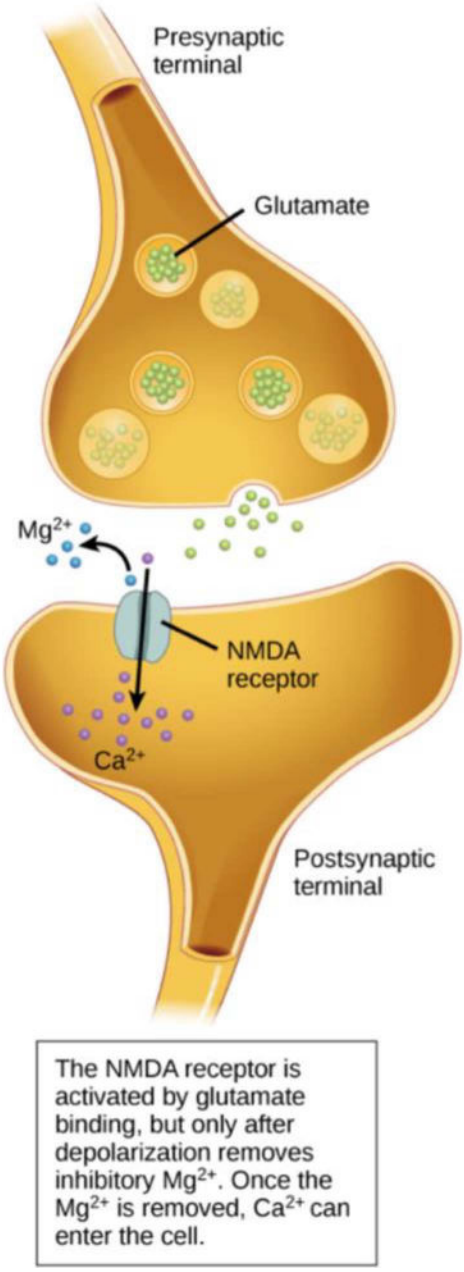

Figure. Calcium (Ca^{2+}) entry through postsynaptic N-methyl-D-aspartate (NMDA) receptors is modulated by magnesium (Mg^{2+}). (Source: openstax, available at: https://openstax.org/books/biology/pages/1-introduction [accessed 08/07/2024]. Distributed under Creative Commons Attribution 4.0 International License. CC License: https://creativecommons.org/licenses/by/4.0/. This image was edited by the author to exclude less relevant elements).

though not all, this was followed by an infusion. While a dose range of 6–20 mg/kg/hour has been cited,[5,7] there has been significant variation in the infusion regimens used in studies, making it difficult to recommend a particular dose range where an infusion is used.

USE OF MAGNESIUM FOR CHRONIC PAIN

The use of magnesium has been explored for a number of chronic pain conditions, including migraine, postherpetic neuralgia, complex regional pain syndrome, and lower back pain.[5,8] Unfortunately, while some small studies found benefit in particular conditions, there is currently an absence of consistent, high-quality evidence of its effectiveness for chronic pain disorders generally.[8] However, most of the studies conducted concerning magnesium in chronic pain conditions have involved small sample sizes and have been of only short duration.[8] Amongst the nine randomised controlled trials included in a 2021 systematic

review, for example, the smallest trial had seven participants, and the largest only forty, with three trials following up over twelve weeks but another three having only three to four weeks of follow up.[8] Given not only the function of NMDA receptors in pain transmission but their postulated role in central sensitization, there remains the possibility that magnesium might be found to have utility in this area. Larger trials with longer follow up would be beneficial in exploring this.

OTHER USES

Additional potential applications of magnesium pertinent to pain management include its use to prolong the effect of local anaesthetics. A recent meta-analysis of studies in which magnesium was used as a local anaesthetic adjuvant, and administered perineurally, identified that the addition of magnesium produced significant prolongation of peripheral nerve blockade.[12] This encompassed randomized controlled trials involving upper and lower extremity blocks, and truncal blocks. Specifically, the addition of magnesium was reported to reduce postoperative pain scores in brachial plexus, sciatic, femoral nerve and transversus abdominis plane (TAP) blocks.[12] It has also been found to prolong sensory block achieved with spinal anaesthesia (7). In view of regional anaesthesia's role as part of a multimodal, opioid sparing analgesic strategy, this offers another potentially useful application for magnesium.

SIDE EFFECTS

Although its administration for analgesic purposes is less well established, intravenous magnesium is widely used in the treatment of pre-eclampsia. This is reassuring with regards to its safety profile, as in this context it has a low incidence of serious complications.[13] For example, in a study of more than 10,000 parturients receiving a total dose of 28 g of magnesium over 24 hours there was no difference in serious morbidity compared with placebo.[1]

A serious potential side effect that could result from intravenous magnesium administration is magnesium toxicity, which can lead to respiratory depression and cardiac arrest if severe. However, across 24 studies incorporated into an integrative review of side effects related to the use of magnesium for pre-eclampsia, only one death was deemed attributable to magnesium, and this was in a patient whose serum magnesium level was reported at 24 mEq/L (normal range 1.3-2.1 mEq/L).[14] It seems that, based on available data, magnesium toxicity is rare. It is nevertheless important that clinicians remain vigilant to developing signs and symptoms of toxicity, which include hypotension, vomiting, lethargy, absent reflexes, and arrhythmias.

Magnesium is recognised as causing potentiation of nondepolarising muscle-blocking drugs.[14] This is due to its action as a calcium channel blocker at presynaptic nerve terminals, leading to reduced release of acetylcholine from presynaptic vesicles.[7] Anaesthetic practitioners should be mindful of this when administering these drugs to patients who are also receiving perioperative magnesium.

Intravenous magnesium administration may be associated with an increased risk of bradycardia, though this was not a consistent finding between meta-analyses.[1,2] It carries a risk of hypotension through vascular smooth muscle relaxation, though evidence of hypotensive effect is lacking from the limited data on this available from trials evaluating magnesium in an analgesic context,[1] and it has been described as a very safe drug from a cardiovascular perspective.[13]

While incidence of serious side effects associated with magnesium appears rare, it is important to adhere to relevant national and local guidance with regards to dosing to minimise the likelihood of adverse effects, and monitor for them.

SUMMARY

Intravenous magnesium is a relatively inexpensive drug with a low reported incidence of serious side effects, which might be considered as part of a multi-modal perioperative analgesic strategy. Its potential analgesic effects are mediated through its action at the NMDA receptor. There is evidence that intravenous administration reduces perioperative opioid requirements and has a statistically significant effect on pain scores, though the latter is small. Given that the benefits of magnesium in an analgesic context are modest, individual practitioners must determine the usefulness of magnesium as applied to their own practice. However, in view of its reassuring safety profile, as well as international efforts to promote opioid sparing analgesia and engage with opioid stewardship, it may well have a role in contributing to a perioperative analgesic strategy. Future areas for research include use in chronic pain and clarifying optimal dosing.

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