

The use of atypical analgesics by intravenous infusion for acute pain: evidence base for lidocaine, ketamine and magnesium

David Hutchins

Mark Rockett

Abstract

Atypical analgesics include antiepileptics and other membrane stabilizers (lidocaine and mexilitine), antidepressants, alpha-2-noradrenergic agonists, N-methyl-D-aspartate (NMDA) antagonists, corticosteroids and cannabinoids. This review will focus on three drugs commonly infused as intravenous co-analgesics. We will review the theoretical mechanisms of action, efficacy and clinical effectiveness of lidocaine, ketamine and magnesium. The evidence base supporting their use has expanded in recent years and is discussed below.

Keywords Acute pain; atypical analgesic; infusion; ketamine; lidocaine; magnesium

Royal College of Anaesthetists CPD Matrix: 1A02, 1D02, 1H02, 2E01, 2E02.

Lidocaine

Lidocaine (2-(diethylamino)-N-(2,6-dimethyl phenyl)-acetamide) was developed in 1948 as the first amide-type local anaesthetic. In 1958, Clive-Lowe et al. published the first paper on the analgesic effects of lidocaine when given intravenously (IV).¹ More recently research has demonstrated that lidocaine is not only able to decrease pain scores, analgesic consumption and opioid side-effects, but also importantly promotes outcomes important for enhanced recovery after surgery (ERAS). These effects include early ambulation, early feeding (and reduced ileus), reduced time to fitness for discharge, and patient satisfaction.² In clinical studies of acute pain, IV lidocaine demonstrates analgesic, anti-hyperalgesic, and anti-inflammatory properties. However, the exact mechanism by which IV lidocaine produces systemic analgesia remains unclear.

David Hutchins *BMBS FRCA is an ST7 Anaesthesia Trainee and Former Advanced Pain Fellow at University Hospitals, Plymouth, UK. Conflicts of interest: none declared.*

Mark Rockett *MRCP FRCA PhD FFPANZCA FFPMRCA is a Consultant in Anaesthesia and Pain Medicine at Derriford Hospital and an Honorary Associate Professor at Plymouth University Department of Medicine and Dentistry, UK. Conflicts of interest: none declared.*

Learning objectives

After reading this article, you should be able to:

- describe the potential mechanism of action of lidocaine, ketamine and magnesium
- explain how these mechanisms may lead to analgesic effects
- recognize adverse effects of these drugs and how to safely manage toxicity

Mechanism of action (Table 1)

When lidocaine is used as a local anaesthetic to prevent nociceptive transmission, it is delivered close to nervous tissue, resulting in high local concentrations and competitive blockade of voltage-gated sodium channels (VGSC). However, when given IV, plasma levels are relatively low and there may be a preferential block of damaged or sensitized nerve fibres. It is suggested that systemic lidocaine may reduce and/or prevent the neoproliferation of active sodium channels and block their spontaneous firing, especially in damaged tissue and dorsal root ganglion.^{3,4}

Potential clinical benefits

In view of the multiple mechanisms of action of lidocaine, it is not surprising that it may have effects on several aspects of pain and recovery after surgery. Its analgesic effects may involve anti-inflammatory mechanisms or the prevention of central sensitization. Much of the evidence for the efficacy of IV lidocaine as an analgesic drug in the postoperative period has been summarized in a 2015 Cochrane review of 1200 participants undergoing all types of surgery under general anaesthesia.⁵ This meta-analysis revealed that pain scores in the immediate postoperative period (0–4 hours) were significantly lower in the lidocaine groups, with a significant effect up to 24 hours. However, the mean effect size was small -0.84 points on an 11-point scale (95% CI -1.10 to -0.59) at 0–4 hours and -0.34 (95% CI -0.57 to -0.11) at 24 hours. There was no effect at 48 hours after surgery. Analgesic effects were most apparent after laparoscopic and open abdominal surgery. The quality of evidence for improved early acute pain after laparoscopic abdominal surgery was classified as low, with an effect size of -1.14 (95% CI -1.51 to -0.78 9 RCTs), and moderate for open abdominal surgery with an effect size of -0.72 (95% CI -0.96 to -0.47 6 RCTs).

There was a dosing effect of lidocaine infusions, with only high dose regimes given intra-operatively reducing pain in the immediate postoperative period (>2 mg/kg/hr). However, the greatest effect on pain at 24 hours was found using a low dose regime (<2 mg/kg/h) for more than 24 hours.

This review also considered the evidence for other potential beneficial effects of lidocaine. Ileus was reduced in the lidocaine groups, with a relative risk of 0.38 (95% CI 0.15 to 0.99 3 RCTs). Length of hospital stay was reduced by a mean of -0.31 days in the lidocaine groups (95% CI -0.56 to -0.07). Lidocaine infusion also reduced opioid use (mg morphine equivalents) in the intraoperative period (-3.30 , 95% CI -6.59 to -0.02), immediate postoperative period in PACU (-4.17 , 95% CI -6.40 to -1.94) and later time points (-5.36 , 95% CI -7.12 to -3.59). Perhaps

due to a reduction in opioid intake, nausea and vomiting were also reduced in the lidocaine group during PACU stay (RR 0.72, 95% CI 0.53 to 0.99) and at later time points (RR 0.82, 95% CI 0.70 to 0.97).

A more recent literature review highlighted the significant reduction in pain scores and postoperative opioid consumption in specific abdominal and urological surgery, neuropathic pain, critical limb ischaemia and opioid-refractory malignant pain. For radical prostatectomy surgery for example, a 1.5 mg/kg bolus before induction of anaesthesia followed with an infusion of 3 mg/min for patients >70 kg (and 2 mg/min for patients <70 kg) continued for 60 minutes postoperatively, reduced post-operative pain scores at 24 hours ($p = 0.001$), significant reduction in morphine use in the postoperative care area and a 50% reduction in overall morphine consumption.³ A meta-analysis of lidocaine in patients undergoing cholecystectomy found significantly reduced postoperative pain scores, opioid use, and adverse effects.⁶ Further research in spinal fusion surgery also illustrates a significant reduction in chronic back pain intensity.⁷

Aside from acute postoperative pain, there is also evidence of a reduction in chronic post-surgical pain at 3–6 months following breast surgery.⁸

Lidocaine has demonstrated analgesic efficacy in the non-surgical setting; including procedural pain related to burns and in renal colic.

The effect of lidocaine on neuroplastic processes such as central sensitization, is suggested by its preventive analgesic effect (analgesia extending beyond 5.5 half-lives after cessation of administration) in a wide range of clinical scenarios.⁹

However, the argument for perioperative lidocaine may be more complex. The Cochrane re-review in 2018 of 4525 participants in 68 trials reported ‘very low evidence’ of benefit from IV lidocaine on pain score at rest (early time points), postoperative ileus, time to first bowel movement, postoperative nausea and overall postoperative opioid consumption. The authors do report low subjective confidence in the estimated mean effects, and that ‘true effects maybe substantially different’ due to inconsistency, imprecision and study quality. Eighteen studies still await classification. There was however ‘moderate quality evidence’ reported for reduced pain scores at rest 24 hours and 48 hours following surgery.¹⁰

Adverse effects

Systemic lidocaine has a narrow therapeutic window. Therapeutic plasma level occur at 2.5–3.5 µg/ml and toxicity may become apparent at 5 µg/ml. In addition to dose, other factors that will influence the plasma concentration of free lidocaine include acid–base status, hypercapnia and hypoxia, low plasma protein levels, and diminished hepatic or renal function.⁴

Adverse effects are usually dose related and sequential if carefully monitored. The central nervous system is first affected with plasma levels of 5–10 µg/ml. Symptoms include numbness of the tongue, metallic taste, light-headedness and tinnitus. If undetected this will continue to visual disturbances, muscle twitching, unconsciousness and seizures. In clinical practice, the more common complaints are sleepiness, light-headedness and euphoria. Cardiovascular toxicity occurs when plasma levels

exceed 10 mcg/ml, e.g. flushing, arrhythmias, conduction abnormalities, oedema and, ultimately, cardiovascular collapse. However, a 2015 Cochrane review found that there was no evidence that IV lidocaine was associated with an increased risk of adverse effects.⁵ Allergic reactions and methaemoglobinaemia may occur, but this is more commonly seen with ester-type local anaesthetics.

When lidocaine is given as a prolonged infusion there is hepatic competition for its metabolism by MEGX (mono-ethylglycinexylidide – an active metabolite). It is therefore recommended to reduce the infusion rate by 20% if given for more than 24 hours. In addition, there are some early signals that subcutaneous lidocaine can result in stable therapeutic plasma lidocaine concentrations and therefore may be safer than IV.

In the event of local anaesthetic systemic toxicity, consensus guidelines suggest that lipid emulsion should be considered in patients with refractory hypotension, bradycardia, or tachycardia; and given in addition to advanced life support in patients with circulatory collapse.

Ketamine

Ketamine is a phencyclidine derivative first synthesized in 1963. It is known commonly as a ‘dissociative anaesthetic’ agent widely used in anaesthesia and pain management. It continues to be one of the main anaesthetic agents in remote areas due to its cardiorespiratory stability and preservation of airway reflexes. The isomeric formulation S (+) ketamine has twice the analgesic potency, is shorter acting and has slightly less adverse cognitive effects in adults.¹¹

Proposed mechanism of action

Despite over 50 years of clinical use, the mechanism of action of ketamine remains partly unclear. In addition to NMDA blockade and some opioid receptor activity, ketamine impacts on a wide range of intracellular neuronal processes.¹²

The analgesic effects of ketamine appear to involve both short term and long term disturbance of cellular function. The supraspinal blockade of the NR2B NMDA sub-unit is generally thought to be the most important anti-nociceptive effect. However, immediate analgesic effects are most likely mediated by a combination of opioid system sensitization and aminergic anti-nociception (via serotonergic and noradrenergic activation and inhibition of their re-uptake). Anti-neuropathic effects may also rely on a combination of immediate receptor mediated action (NMDA and hyperpolarization-activated cyclic nucleotide channels [HCN1]) and initiation of longer lasting cell signalling cascades including NMDA receptor expression, glial cell activation and changes in synaptic structure and function.

Ketamine may also have anti-inflammatory effects, by inhibiting inflammatory cell recruitment, cytokine production and down-regulating inflammatory mediators. Intraoperative administration of ketamine has been shown to have an inhibitory effect on the early postoperative IL-6 inflammatory response.

Evidence for efficacy of perioperative ketamine

Ketamine’s main role is as an adjuvant in the treatment of pain associated with central sensitization, such as in severe acute

pain, neuropathic pain and opioid-resistant pain.^{13,14} Ketamine prevents opioid tolerance and opioid-induced hypersensitivity.¹²

The addition of ketamine to a morphine patient-controlled analgesia was found to be opioid-sparing, improve analgesia, improve respiratory outcomes and increase patient satisfaction following thoracotomy. Combining morphine with ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting. Ketamine may also be effective in postoperative pain where central sensitization plays a role. These clinical situations may include pain in opioid tolerant patients, persistent post-operative pain and pain relief beyond the expected duration of effect (preventative analgesia).⁹

Adverse effects

Ketamine induces visual hallucinations and out of body experiences which has led to its recreational abuse. These effects are proportional to plasma levels of ketamine. Therefore, 0.25–0.5 mg/kg bolus doses post induction of anaesthesia, and low dose infusions limited to 0.1–0.2 mg/kg/h in awake patients carry low risks of adverse effects.

Case reports of chronic ketamine abusers have demonstrated multiple neuropsychiatric complications including cognitive impairment and increased social avoidance and schizotypal symptoms. About 20–30% of chronic abusers report 'ketamine cystitis'. This is described as urinary tract symptoms due to ketamine-induced vesicopathy ± hydroureter.¹⁴ The exact mechanism of this is unclear but cystoscopic features include inflammatory changes with haemorrhagic or ulcerative cystitis. Hepatotoxicity ± cholangiopathy and corneal oedema has also been reported. In general, these complications are reversible and cessation of abuse is the best treatment.¹⁴

Magnesium

Magnesium was first isolated in 1808 by the English chemist, Sir Humphrey Davy. It is the fourth most common cation in the body, and the second most common intracellular ion. It is an essential constituent of over 300 enzyme systems, involved in energy generation, nucleic acid synthesis, receptor-binding and ion flux. Given its diverse actions within the body magnesium salts have been used to treat a variety of clinical conditions for over a 100 years. The first randomized controlled trial exploring its analgesic properties was published in 1996.

Proposed mechanism of action

Although the mechanism of action is not yet fully understood, magnesium is regarded as a non-competitive NMDA-receptor antagonist at the spinal cord. It also has anti-inflammatory effects; reducing IL-6 and TNF-alpha plasma levels in the post-operative setting, and there is evidence from animal studies of an anti-neuropathic effects. Additionally, magnesium has alpha adrenergic antagonistic effects and inhibits calcium-mediated neuroendocrine secretion.¹⁵ Both of these effects may impact on nociceptive processing. Hypomagnesemia can activate inflammatory neuroendocrine pathways, and some anti-inflammatory effects may be due to the treatment of subclinical hypomagnesemia, which can be prevalent in patients following colorectal surgery.

Clinical evidence of IV magnesium in acute pain

IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect with improved pain scores at rest and on movement at 4 and 24 hours.¹⁶ IV magnesium has prolonged the duration of sensory block from spinal anaesthesia for abdominal hysterectomy and reduced postoperative pain scores in the first 4 hours after surgery. For umbilical hernia repair and hip arthroplasty under spinal anaesthetic, IV magnesium prolonged the time to first rescue analgesia and was opioid-sparing in the first 24 and 48 hours, respectively, after surgery. IV magnesium bolus of 50 mg/kg followed by 15 mg/kg infusion significantly reduces pain following primary total knee arthroplasty, and minimized the difference between primary and secondary arthroplasty pain (second joint replacement pain experienced is often greater than first joint pain secondary to hyperalgesia).¹⁷ After mastectomy patients receiving IV magnesium had better recovery scores at 24 hours and reduced opioid requirements after discharge. IV magnesium sulphate (4 g) reduces remifentanyl-induced acute opioid tolerance and hyperalgesia. Most trials have employed a bolus dose ranging between 30 and 50 mg/kg and total perioperative doses range from 1.03 g to 23.5 g. To date, we are not aware of any dose-finding studies or clinical data to support any particular regime.¹⁶

Potential risks

Clinically significant hypermagnesaemia more commonly occurs in renal failure or after prolonged and excessive IV infusion. Minor side effects include flushing, nausea, headache and

Potential mechanisms of action of lidocaine

Anti-inflammatory effects	Lidocaine inhibits production of pro-inflammatory cytokines, migration of granulocytes and the release of lysosomal enzymes
Anti-hyperalgesic effects	Lidocaine modulates NMDA receptors via a glycine-like effect and reduces the calcium-mediated increase in excitability of central nociceptive neurons
Inhibition of nociceptive transmission	Mono-ethylglycinexylidide (MEGX), an active metabolite of lidocaine, inhibits glycine transporter 1, leading to increased extracellular glycine concentrations. Glycine is an inhibitory neurotransmitter and may reduce nociceptive transmission
Stimulation of inhibitory descending pathways	Lidocaine may increase acetylcholine in the cerebrospinal fluid via muscarinic (M3) and nicotinic receptors. This effect may increase descending inhibitory pathway activity

Table 1

Magnesium toxicity

Magnesium concentration	Features
0.75–0.95 mmol/L (1.7–2.2 mg/dL)	Normal range
2–3.5 mmol/L (5–8 mg/dL)	Flushing, ECG changes
4–5 mmol/L (9–12 mg/dL)	Drowsiness, slurred speech, absent deep tendon reflexes
More than 6 mmol/L (more than 15 mg/dL)	Muscle paralysis, respiratory depression
More than 8 mmol/L (more than 20 mg/dL)	Cardiac arrest

Table 2

dizziness. Dose-related side effects include somnolence, areflexia, muscle weakness, cardiac conduction abnormalities and cardiac arrest. There are case studies of parenteral magnesium overdose in patients undergoing treatment for pre-eclampsia/eclampsia. Although there have been fatalities, the majority of cases have been successfully resuscitated from cardiac arrest with good outcomes. Toxic levels are unlikely if standard regimens are used with continuous hourly monitoring of deep tendon reflexes, respiratory rate, oxygen saturations and urine output. Toxic effects not reversed by stopping the infusion can be reliably treated with calcium or dialysis in renal failure. The features of magnesium toxicity and serum magnesium concentrations are shown in Table 2. ◆

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