Use of atypical analgesics by intravenous infusion (IV) for acute pain: evidence base for lidocaine, ketamine and magnesium

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Abstract

Atypical analgesics include antiepileptics and other membrane stabilizers (lidocaine and mexiletine), antidepressants, α-2-noradrenergic agonists, N-methyl-ᴅ-aspartate (NMDA) antagonists, corticosteroids and cannabinoids. This review will focus on three drugs commonly infused as 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

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.

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Learning objectives

After reading this article, you should be able to:
- describe the 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 low and there may be a preferential block of damaged and dysfunctional nerves. It is suggested that systemic lidocaine may reduce and/or prevent the neo-proliferation of active sodium channels and block their spontaneous firing, especially in damaged tissue.[3]

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 sensitisation.

Much of the evidence for the efficacy of IV lidocaine as an analgesic drug in the postoperative period has been summarized in a Cochrane review of 1200 participants undergoing all types of surgery under general anaesthesia.[4] 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 nine randomized controlled trials (RCTs)), and moderate for open abdominal surgery with an effect size of −0.72 (95% CI −0.96 to −0.47 six RCTs).

There was a dosing effect of lidocaine infusions, with only high-dose regimes given intraoperatively reducing pain in the immediate postoperative period (>2 mg/kg/hour). However, the greatest effect on pain at 24 hours was found using a low-dose regime (<2 mg/kg/hour) 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 three 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 the post-anaesthesia care unit (PACU) (−4.17, 95% CI −6.40 to −1.94) and later time points

Potential mechanisms of action of lidocaine

Anti-inflammatory effects	Lidocaine inhibits production and migration of pro-inflammatory cytokines, 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	Monoethylglycinexylidide, 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

(-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).

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.[5]

Adverse effects

Systemic lidocaine has a narrow therapeutic window. Therapeutic plasma level occurs 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.[3]

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.[3] Cardiovascular toxicity occurs when plasma levels exceed 10 µg/ml, for example flushing, arrhythmias, conduction abnormalities, oedema, and ultimately cardiovascular collapse. However, a recent Cochrane review found that there was no evidence that IV lidocaine was associated with an increased risk of adverse effects.[4] Allergic reactions and methaemoglobinaemia can 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 monoethylglycinexylidide (MEGX) (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.[8]

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, ketamine affects a wide range of intracellular neuronal processes.

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 interleukin-6 (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.[5—9]

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.[5]

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 postoperative

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