

Clinical pharmacology: other adjuvants

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KEY LEARNING POINTS

- Nitrous oxide is a useful short-acting adjunct, which provides some analgesia in labor and is effective for procedural analgesia in adults and children in a wide variety of settings. Its adverse effects on vitamin B12, in particular with repeat exposure, require consideration and supplementation to avoid rare, but serious toxicity leading to bone marrow suppression and neuropathy.
- Continuous infusions of low doses of the *N*-methyl-*D*-aspartate (NMDA) receptor antagonist ketamine have opioid-sparing effects and reduce adverse effects of opioids in the acute pain setting. This approach also has a preventive analgesic effect, provides analgesia in pain poorly responsive to opioids, and may be particularly useful in settings of hyperalgesia, allodynia, and opioid tolerance.
- The alpha-2 adrenoreceptor agonists clonidine and dexmedetomidine have an opioid-sparing effect in the acute pain setting; however, they can lead to sedation and hypotension.
- Anticonvulsants, in particular the gabapentinoids gabapentin and pregabalin, are not only effective in acute neuropathic pain states, but also in reducing postoperative pain and opioid requirements. They may become an important component of multimodal analgesia.
- Antidepressants play no role as adjuvants in the treatment of acute pain, but have shown a preventive effect on the development of subsequent chronic pain states.
- Corticosteroids, in particular dexamethasone, are not only a very effective prophylaxis for postoperative nausea and vomiting, but also reduce pain and swelling in certain postoperative settings.
- Calcitonin is an effective treatment for the pain of vertebral crush fractures and for postamputation phantom limb pain.
- Systemic administration of lidocaine is an effective treatment of acute neuropathic pain of peripheral and central origin; due to its anti-inflammatory effect it might also be a useful adjuvant for perioperative pain treatment with benefits for analgesia and outcome.

INTRODUCTION

The pharmacological options for the treatment of acute pain are greater than ever, due in part to our better understanding of nociceptive pathways and their spinal

and cerebral processing and driven by the ever-increasing demand to treat pain more effectively. Nonsteroidal anti-inflammatory drugs and opioids continue to be the mainstay analgesics for acute pain, but the role of other so-called adjuvant drugs is expanding rapidly, many with

very clear indications for their use supported by scientific evidence from trials and meta-analyses. Mostly, these drugs are co-administered with standard analgesics as part of a multimodal regime, but in some instances, the literature suggests a more primary role for effective acute pain management. This chapter will discuss the current status of adjuvant drugs in the acute pain context, together with their clinical pharmacology.

NITROUS OXIDE

Introduction

The analgesic properties of nitrous oxide (N₂O) were recognized over 200 years ago,¹ and the use of this inorganic gas in anesthesia practice continues to date, although with the advent of newer, superior anesthetic and analgesic drugs with less potential for toxicity its popularity and routine use seems to be waning.² Nevertheless, its current role as a short-acting analgesic for a variety of indications persists, with sufficient evidence supporting its ongoing use. Its physical and chemical properties are briefly summarized in **Box 6.1** below.

Pharmacokinetics

In many countries, commercial preparations of N₂O for analgesic use are presented as gas mixtures containing 50 percent oxygen and 50 percent N₂O, contained in cylinders compressed to a pressure of 13,700 kPa. Delivery of this mixture to the patient is via a mask and pressure demand regulator that allows gas flow during inspiration.⁵ The inhaled N₂O reaches the alveoli and here concentrations rapidly approach the inspired concentration because of its

low solubility. The rate of uptake is increased by increased alveolar ventilation and decreased cardiac output. Subsequent distribution favors organs with relatively high blood flow particularly the brain and spinal cord, which are the predominant sites of action. N₂O is eliminated mostly via the lungs without undergoing any significant metabolism in humans, although minimal amounts are lost through the skin.⁶

Mechanism of action and clinical effects

Until recently, surprisingly little was known regarding the precise pharmacological mechanism of action of N₂O and its analgesic and anesthetic effects.⁶ Animal studies and some human studies have begun to unravel these rather complex neurochemical mechanisms, and it seems likely that N₂O mediates antinociceptive effects in the central nervous system by first releasing opioid peptides in the peri-aqueductal gray area of the midbrain and in the noradrenergic nuclei of the pons. This then leads to activation of descending inhibitory neurons that release noradrenaline on alpha-2 adrenoreceptors in the dorsal horn of the spinal cord.⁷ In essence, the net result is modulation of ascending pain transmission at the level of the spinal cord, i.e. “antinociception.”

Side effects and toxicity of nitrous oxide

Euphoric and dysphoric experiences are relatively common with analgesic concentrations of N₂O,⁸[II] although these are unlikely to depress consciousness unless other central nervous system depressants are used concomitantly. Cerebral blood flow, cerebral metabolic rate, and intracranial pressure are increased by nitrous oxide, and these effects can be significant.^{9, 10}[III] Mean arterial pressure is unchanged or slightly elevated, most likely due to its mild sympathomimetic effect increasing systemic vascular resistance. This effect offsets the mild, direct myocardial depressant actions, but also causes pulmonary vasoconstriction.³ Respiration is well maintained with subanesthetic concentrations of N₂O, but ventilatory responses to hypoxia and hypercarbia are attenuated.² N₂O does not produce skeletal muscle or uterine relaxation, and is not a trigger for malignant hyperpyrexia, but is a significant cause of nausea and vomiting.¹¹[II]

N₂O is much more soluble than nitrogen in blood and will enter air-filled spaces in the body more rapidly than nitrogen can escape, leading to an increase in either volume or pressure in that space. This precludes its use in a number of clinical situations including pneumothorax, bowel obstruction, pneumoencephalon, pneumopericardium, and recent middle ear and eye surgery.^{12, 13} One must also note that when N₂O is discontinued, this same physical phenomenon can also lead to its rapid movement into the alveoli lowering oxygen concentrations and can

Box 6.1 Physical–chemical properties of nitrous oxide

- Colorless inorganic gas
- Sweet smelling
- Nonflammable, but supports combustion
- Specific gravity, 1.53
- Boiling point, –88°C
- Critical temperature, 36.5°C
- Critical pressure, 71.7 atmospheres
- Minimum alveolar concentration, 105
- Oil:water solubility coefficient, 3.2
- Blood:gas solubility coefficient, 0.47
- Presented as a 50/50 mixture of oxygen and nitrous oxide for analgesic use

Modified from multiple sources, including Refs 3, 4.

cause “diffusion hypoxia” unless supplemental oxygen is administered.³

Severe neurological and hematological complications can rarely occur with N₂O caused by its inhibition of vitamin B12, an essential coenzyme for methionine synthase. Methionine synthase itself is crucial in the formation of both methionine (involved in myelin formation) and tetrahydrofolate (involved in DNA synthesis).^{14, 15} Risk factors for these complications include the length of exposure to N₂O (and this includes repeated short-term use), critically ill patients, the elderly, and underlying vitamin B12 and folate deficiency. Clinical manifestations include progressive but reversible bone marrow suppression, and progressive neuropathy and myelopathy that may be irreversible.¹⁶

Therefore, N₂O should not be used in patients with known vitamin B12 deficiency and only after screening for such in patients at risk. Prophylactic administration of vitamin B12, methionine, and folinic or folic acid, as well as monitoring for neuropathy, is recommended if repeated use of N₂O is contemplated.^{14, 15}[V] There are limited human data on this to guide best practice, nevertheless this practice is currently endorsed by clinical guidelines.¹³[V]

N₂O has been shown to be teratogenic in animal studies, but similar effects in limited human studies have not been established.^{17, 18}

Clinical use of N₂O in acute pain management

N₂O for short-term analgesia can potentially be utilized in a range of clinical situations and across different age groups. Its use for labor pain, for example, is well-described worldwide, with established safety (both maternal and newborn), provided that it is supervised by physicians, nurses, or midwives, and evidence for some analgesic efficacy.¹⁹[I] It is typically used intermittently during the first stage of labor, but it can also be used at any time including late in the active second stage.¹⁹

In the pediatric population, effective procedural analgesia is essential to prevent undue distress (in children and parents) and longer-term emotional trauma. The current evidence supports the use of N₂O here, as it is efficacious and safe for a variety of emergencies, minor procedures, and other painful situations.²⁰[I] The most common emergency settings are suturing minor lacerations and the closed reduction of limb fractures,²¹[IV] but N₂O can also be used to facilitate insertion of peripheral intravenous cannulas as an effective alternative to topical local anesthetics.^{22, 23}[II] Other pediatric procedures where N₂O has been evaluated for analgesia include lumbar punctures,²¹[IV] dental treatments,²⁴[II] fiberoptic bronchoscopy,²⁵[II] and intra-articular injections.²⁶[IV]

Similarly, N₂O is also useful in adult acute pain management especially for short procedures, but also in the emergency setting, and even in the prehospital period

by lay responders.²⁷ Among other settings, it provides effective analgesia for sigmoidoscopy,²⁸[II] bronchoscopy,²⁹[I] venous access port insertion,³⁰[II] as well as reducing the discomfort associated with elective cardiac defibrillation.³¹[III]

Pain management in burn patients is notoriously difficult and the acute pain is usually due to the burn injury itself, but may also be associated with the multiple therapeutic procedures inevitably performed as part of its management.^{32, 33} There may be a role for N₂O as an adjuvant for painful procedures, such as dressing changes and debridements.³⁴

NMDA RECEPTOR ANTAGONISTS

Introduction

Drugs in this class include ketamine, dextromethorphan, memantine, and amantadine, although ketamine is by far the more widely studied and used drug of this group in both anesthesia and pain management. Indeed, substantial evidence from recent meta-analyses of randomized controlled trials (RCT) supports the emerging clinical use of ketamine as an adjuvant analgesic in acute pain management, in addition to its role in chronic pain and cancer pain settings.³⁵

Physical and chemical properties

Ketamine hydrochloride is a phencyclidine derivative, usually prepared as a racemic mixture and formulated as an acid solution with an added preservative. This preservative component precludes neuraxial administration due to concerns regarding neurotoxicity, although preservative-free preparations are available. In some countries the more potent S(+)-ketamine enantiomer is used. Oral, sublingual (transmucosal), and transdermal preparations are used only experimentally.

Pharmacokinetics

These are briefly summarized in **Table 6.1**.

Mechanism of action and clinical effects

The nervous system is the primary pharmacological target for ketamine, via central and possibly even peripheral mechanisms involving various receptors (of which the NMDA receptor is considered pivotal) and where it interacts principally as a noncompetitive antagonist.^{36, 37}

The NMDA receptor itself is a complex, ion channel-coupled receptor that is activated *in vivo* by glutamate, the predominant excitatory neurotransmitter of the central

Table 6.1 Ketamine pharmacokinetics.

Ketamine	
Absorption	Rapidly absorbed following sublingual, oral, and intramuscular administration Oral bioavailability approximately 20%
Distribution	Volume of distribution between 1–3 L/kg Distribution half-life 7–11 minutes 20–50% plasma protein bound
Metabolism	Extensive hepatic metabolism occurs including dealkylation, hydroxylation, and conjugation reactions Norketamine, the major metabolite, is active as an NMDA antagonist
Excretion	Renal clearance 15 mL/min/kg 90% excretion in the urine, mostly as metabolites, with about 2–4% unchanged 5% excreted in feces

NMDA, *N*-methyl-D-aspartate.

Modified from multiple sources, including Ref. 3.

nervous system.³⁸ The importance of this receptor in the context of acute and chronic pain cannot be overstated. Following injury to peripheral tissues or nerves, nociception invariably results in NMDA receptor activation, especially in the dorsal horn of the spinal cord. It is particularly noteworthy that these dorsal horn NMDA receptors are also implicated in opioid tolerance,³⁹ opioid-induced hyperalgesia (a paradoxical phenomenon whereby opioid-treated patients develop greater sensitivity to pain),⁴⁰ and are fundamental to the processes of “wind up” and “long-term potentiation” which occur in the development of persistent and neuropathic pain states.⁴¹

Therefore, NMDA receptor antagonist drugs could play an important role as adjuvant analgesics in the acute pain setting, particularly so in patients who have developed or are at risk of developing opioid tolerance, hyperalgesia, or neuropathic pain. Of the currently registered drugs in this class, ketamine seems to possess the ideal potency and selectivity for NMDA receptors,⁴¹ and appears, on balance, to be the most efficacious.^{42, 43, 44, 45}[I]

General anesthetic doses of ketamine characteristically induce a state of dissociative anesthesia, meaning that it causes a dissociation between the thalamocortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli.⁴⁶ For the purposes of pain management (acute and chronic) however, much smaller subanesthetic amounts are used (see below under Perioperative pain management), and this applies to both bolus doses and continuous infusions. Additional clinical effects may be observed with ketamine, such as mild cardiovascular stimulation, bronchodilation, and excessive salivation although these are far less prominent with subanesthetic doses. Respiration and upper airway reflexes are relatively well maintained with ketamine, as is uterine and skeletal muscle tone.⁴⁶

Side effects and toxicity

The widespread medical use of ketamine and other NMDA receptor antagonists has always been limited by

fears of undesirable side effects and concerns regarding abuse potential, as well as the uncertainty of possible long-term sequelae with chronic use.⁴⁷ By limiting the duration and using very low doses of ketamine for analgesic purposes, the overall incidence of many of these side effects is significantly attenuated.

Minor side effects include nausea and vomiting, as well as excessive salivation, and are rarely encountered and can be effectively managed with antiemetics and antisialagogues as necessary. On this point, it is interesting to note that ketamine used concurrently with opioid-based post-operative analgesia actually reduces the incidence of nausea and vomiting, probably via its opioid sparing effects.⁴²[I]

Central nervous system side effects can include dizziness, dreams, diplopia, nystagmus, dysphoria, hallucinations, and sedation. With low-dose ketamine, the overall incidence is low in the range of less than 10 percent and can be further minimized with coadministration of benzodiazepines or following general anesthesia.^{43, 44}

Ketamine is a well-known substance of abuse, with reports of nonmedical use for its psychoactive effects dating back almost 40 years.^{47, 48} For these reasons, it is a controlled drug in many countries including Australia and the United States. Long-term abuse may result in behavioral disturbances and altered memory function,⁴⁹ although this seems highly unlikely to be relevant in the current context of short-term, low-dose ketamine use in acute pain management.

Clinical use in acute pain management

Based on the current understanding of the mechanism of action of ketamine on the NMDA receptor in particular, and supported by extensive clinical data from randomized controlled trials and meta-analyses, the use of ketamine (in subanesthetic doses) is indicated in a number of clinical settings, as summarized in **Table 6.2**. The doses suggested are a guide only and reflect the significant heterogeneity amongst published data.

Table 6.2 The role of ketamine in acute pain management.

Acute procedural pain	Perioperative pain management	Acute neuropathic pain
In the emergency department, e.g. fracture reductions	As an opioid-sparing drug, e.g. in combination with opioid-based analgesia when treating severe postoperative pain in recovery rooms, on postoperative wards and in intensive care units	Medical conditions, e.g. acute zoster, poststroke, multiple sclerosis
In the burn unit, e.g. burn dressings	As a recovery room rescue co-analgesic postoperatively for severe pain	Surgical conditions or trauma, e.g. spinal cord injury, burns, postamputation
In oncology wards, e.g. lumbar puncture, bone marrow biopsy	For opioid-tolerant patients, e.g. chronic opioid use or abuse	
In radiology suites, e.g. contrast enemas	For opioid-resistant pain, e.g. opioid-induced hyperalgesia or allodynia in neuropathic pain as "preventive" analgesia	

Adapted from multiple sources, including Refs 35, 42, 43, 44, 45.

ACUTE PROCEDURAL PAIN

A wide range of painful procedures and interventions commonly encountered in emergency departments, burn units, and oncology wards can be managed effectively with ketamine, much in the same manner as described under Nitrous oxide above, and while there is greater clinical experience in pediatric patients its use can be extended to all age groups.²⁰[I], ⁵⁰[V], ⁵¹[II]

Typically, intravenous doses less than 1 mg/kg are described in the literature, although higher doses can be used when sedation is also desirable, but this must be done with caution and only by practitioners who are appropriately trained in managing such patients in the correct environment.

PERIOPERATIVE PAIN MANAGEMENT

There is keen interest in the use of low-dose ketamine as an adjuvant to opioid-based analgesia in the perioperative period, and this potential role has been examined in three recent meta-analyses, demonstrating efficacy for at least 24 hours post operation, highlighted by improved pain scores, reduced opioid consumption, and decreased nausea and vomiting.^{42, 43, 44}[I] These meta-analyses also confirmed that in this context, adverse effects due to ketamine itself are either mild or absent, most likely a reflection of the small doses used.

Ketamine is similarly useful when coadministered with morphine as a bolus in the recovery room when treating severe pain that is initially recalcitrant to opioids alone.⁵²[II]

The most commonly utilized method of administration, however, is via a separate continuous intravenous infusion of ketamine (approximately 100–200 µg/kg per hour), administered concurrently with the opioid-based analgesic (via continuous infusion or patient-controlled analgesic (PCA) device); a fixed combination of ketamine

and morphine via an intravenous PCA device has not been shown to be effective as a postoperative analgesic technique in five randomized controlled trials.^{53, 54, 55, 56, 57}[II]

The issues of opioid tolerance and opioid-induced hyperalgesia are extremely relevant to the current and future practice of acute pain management, the underlying key theme being lack of opioid potency leading to inadequately treated acute pain, especially in perioperative patients. Strategies which utilize multimodal analgesia, including adjuvants such as ketamine, are recommended in these patients.^{58, 59, 60, 61}[IV] Those considered at risk include all patients treated with long-term opioids (especially in high doses) regardless of indication, as well as those who chronically abuse illicit opioids.⁴⁰ It is of note that even opioid-naïve patients can be at risk of these phenomena acutely and then benefit from ketamine, such as when high-dose remifentanyl is used intraoperatively.⁶²[II]

A further useful property of ketamine in the perioperative period lies in its so-called preventive analgesic properties, whereby the reduction in postoperative pain intensity or analgesic consumption (or both), continues past the expected clinical duration of action of the drug.⁶³[I], ⁶⁴ The implications of this phenomenon go beyond the superior analgesia and opioid-sparing effects observed in the acute phase and signify the ability of this drug to reduce peripheral and central sensitization that arises from noxious perioperative stimuli.⁶⁵ In a practical sense, wound hyperalgesia and residual pain is reduced, even after 12 months.⁶⁶[II] It remains to be seen if this application can be extended to the prevention of persistent postsurgical pain.⁶⁷

ACUTE NEUROPATHIC PAIN

Neuropathic pain may be an early presenting feature in a wide range of conditions, in both surgical and

nonsurgical settings. The true prevalence of acute neuropathic pain is unclear, although one Australian study suggested an incidence of 1–3 percent in an acute pain service.⁶⁸ Typically, this type of pain is not completely responsive to opioids at usual doses,^{69,70} and adjuvants are more likely to be needed. Ketamine might be such an adjuvant, although admittedly much of the data on this are either from experimental studies,⁷¹ or are extrapolated from chronic pain studies.⁷² There is currently only moderate evidence for the use of ketamine in neuropathic pain, but it might still be a reasonable option if other alternatives have been unsuccessful. This might be particularly true for acute neuropathic pain states, such as spinal cord injury pain,⁷³ [II] central poststroke pain,⁷⁴ [V] and ischemic pain.⁷⁵ [II]

ALPHA-2 ADRENORECEPTOR AGONISTS

Introduction

Drugs such as clonidine and dexmedetomidine are included in this group of alpha-2 adrenoreceptor agonists that are useful adjuvants in acute pain management. Other newer drugs in this class that have even greater selectivity and fewer side effects have been developed, but as yet have not reached mainstream clinical use. Within the context of acute pain management and based on supportive evidence from clinical trials and reviews, it seems the main areas of clinical utility for these drugs lies in the perioperative period and in intensive care units. Furthermore, the role of these drugs in the management of selected chronic pain states, and in cancer pain management continues to evolve.

Physical and chemical properties

Clonidine and dexmedetomidine are both imidazole ring compounds. Clonidine is prepared for oral and parenteral administration (as well as for use in regional analgesia),

whereas dexmedetomidine is currently available for intravenous use only, typically prepared as an infusion in intensive care units. The relative selectivity of these two drugs for alpha-2 receptors compared to alpha-1 receptors differs, with clonidine being less selective (approximately 220:1) compared to dexmedetomidine (approximately 1620:1).⁷⁶

Pharmacokinetics

These are briefly summarized in the **Table 6.3**.

Mechanism of action and clinical effects

Adrenoreceptors are ubiquitous in humans and mediate a vast range of complex homeostatic functions within the central nervous system, as well as peripheral organs. For example, in the central nervous system (i.e. brain and spinal cord) alpha-2 adrenoreceptors are involved in nociception, alertness, regulation of blood pressure, and sympathetic nerve function, whereas in the periphery these receptors control vascular and smooth muscle contraction, a range of gastrointestinal and metabolic functions, as well as endothelial and urogenital function.⁷⁸

Pharmacological agonists at these receptors, such as clonidine and dexmedetomidine, exert their various effects by initially binding to this receptor and then activating inhibitory G-proteins.⁷⁸ Subsequent intracellular events and cascades include activation of second messengers, and actions directly on neuronal ion channel function, all of which ultimately lead to a targeted cellular response. Typically, the observed clinical effects of these drugs are analgesia, sedation, and sympatholysis, affecting the cardiovascular system in particular.⁷⁹

With regards to analgesic mechanisms, the primary site of action is in the spinal cord, but it is recognized that supraspinal and even peripheral sites of action coexist,⁸⁰ although their relative importance is still to be

Table 6.3 Pharmacokinetics of selected alpha-2 adrenoreceptor agonists.

	Clonidine	Dexmedetomidine
Absorption	Rapidly and well absorbed following oral and intramuscular administration; oral bioavailability 100%	N/A; prepared only for intravenous administration
Distribution	Volume of distribution between 1.7–2.5 L/kg; 20% plasma protein bound	Volume of distribution 1.33 L/kg; 94% plasma protein bound
Metabolism	Less than half the administered dose undergoes hepatic metabolism; five inactive metabolites identified	Quite extensive hepatic metabolism
Excretion	Approximately two-thirds of the administered dose excreted in urine (half of this unchanged) and the rest is excreted in the feces; clearance 1.9–4.3 mL/min/kg	95% excretion of metabolites in the urine with a small remainder excreted in the feces; clearance approximately 39 L/hour

Modified from multiple sources including Refs 4, 77.

determined.⁷⁷ The potential mechanisms of alpha-2 adrenoceptor-mediated analgesia are multifactorial, but ultimately these effects are mediated by changes in neuronal ion channel function leading to modulation of nociception.⁷⁷ It is also of great interest that spinal alpha-2 receptors have been implicated in the development of neuropathic pain in experimental animal models, and that the administration of alpha-2 agonists results in antihyperalgesic effects.^{80, 81, 82}

The sedative (and anxiolytic) actions are due to alpha-2 agonist actions in the locus ceruleus of the brain stem and are dose dependent in nature. When used intraoperatively they have significant anesthetic-sparing effects in the order of 30–40 percent.⁸³ In contrast to opioids, respiratory depression does not occur however, nor do these compounds potentiate opioid-induced respiratory depression.⁸⁴

There are a number of dose-dependent cardiovascular effects that are due to central decreases in sympathetic tone, as well as peripheral actions on vasculature. Heart rate and blood pressure both decrease at clinically relevant doses of alpha-2 agonists, the effect more prominent in patients with higher resting sympathetic tone, and less prominent in healthy and physiologically unstressed individuals. Baroreceptor reflexes are not impaired and the responses to vasopressors are maintained.⁸⁴

Other clinical effects include a dry mouth due to a decrease in salivation, an ability to decrease post-operative shivering, and a decrease in intraocular pressure by about 30 percent.⁸⁴

Side effects and toxicity

The sedative effects are dose dependent and can result in an unrouseable patient if inappropriate doses are used; therefore titration of the drug is essential to achieve the desired clinical effects (see below under Clinical use in acute pain management). These drugs should be avoided in patients who are hypovolemic or hemodynamically unstable, in patients with underlying bradyarrhythmias, and where controlled hypotension is to be employed as part of the anaesthetic.⁸⁵ Other side effects include constipation and impairment of sexual function.

Clinical use in acute pain management

On the basis of evidence from clinical trials and recent reviews,^{76, 83, 86, 87, 88} the use of clonidine (and to a lesser extent dexmedetomidine) is indicated in the following clinical settings.

PERIOPERATIVE SYSTEMIC USE

Clonidine administered either as a premedication or intraoperatively, in doses ranging from 2 to 5 µg/kg, has

been extensively trialled in a wide range of pediatric and adult surgical populations with success achieving appropriate levels of anxiolysis and sedation, as well as reducing anesthetic requirements. In addition to this, intra- and postoperative opioid analgesic requirements were significantly reduced in the order of 30–50 percent, with an attendant decrease in opioid-related side effects such as nausea, vomiting, and pruritis.^{89, 90, 91, 92, 93}[II] Sedation and bradycardia are the most common side effects but rarely of clinical consequence, even in neonates when the drugs are administered to the mother prior to cesarean section.⁸⁹[II] In some situations, the sedative effects may actually be beneficial in preventing agitation in the recovery room, such as shown in pediatric patients following sevoflurane anesthesia.⁹⁴[II] In addition, by continuing the clonidine for four days postoperatively in high-risk patients undergoing noncardiac surgery, cardiac morbidity and mortality has been found to be reduced, even at two years.⁹⁵[II]

The addition of clonidine to an opioid-based PCA device does not achieve sustained analgesic benefits and does not reduce morphine consumption, a situation that bears similarity to ketamine as discussed above under NMDA receptor antagonists.⁹⁶[II]

As far as intraoperative dexmedetomidine is concerned, the limited data thus far do suggest similar benefits to clonidine with regards to postoperative analgesia and opioid-sparing effects,^{97, 98}[II] but further clinical studies are required.

USE IN THE INTENSIVE CARE UNIT

The importance of appropriate sedation and analgesia in intensive care patients cannot be overstated.⁹⁹ A number of different agents have been used over the years for this purpose including opioids, benzodiazepines, and propofol, but none of them are ideal and each has their own undesirable effects in critically ill patients. Dexmedetomidine is easily titratable as an intravenous infusion and possesses a number of desirable properties such as sedation and analgesia, but does not impair respiratory function, which is highly important to prevent prolonged mechanical ventilation.¹⁰⁰[II] In cardiac surgery patients, for example, postoperative analgesic requirements in the intensive care unit are reduced by about 50 percent.¹⁰¹[II]

ACUTE NEUROPATHIC PAIN

Despite abundant animal data implicating adrenergic mechanisms in neuropathic pain models and the efficacy of alpha-2 agonists in these experiments, there is currently a notable lack of human data to support the use of these drugs for this indication. Even in chronic neuropathic pain states, the evidence for these drugs, either systemically or more commonly via neuraxial routes, is weak at best.¹⁰² Further work is required in this field if the

promising experimental results are to be extrapolated and realized in humans.

ANTICONVULSANTS

Introduction

The use of anticonvulsant drugs in chronic and neuropathic pain conditions is common and well supported by clinical evidence.^{103, 104, 105} While the use of these drugs in acute pain management may seem quite novel, there is mounting experimental and clinical evidence supporting their inclusion in the multimodal analgesic mix.¹⁰⁶ In addition, some of these drugs may have a niche role as primary analgesics for specific indications. Of the numerous anticonvulsants currently available, only a few appear to have potential clinical utility in acute pain management and these include gabapentin, pregabalin, and valproate.

Physical and chemical properties

Anticonvulsants are chemically diverse and while gabapentin and pregabalin are structurally similar to the endogenous neurotransmitter gamma-aminobutyric acid (GABA), valproate (a carboxylic acid compound) does not share any such structural similarities. These drugs are all prepared for oral administration, although parenteral forms of valproate are available as well.

Pharmacokinetics

These are briefly summarized in **Table 6.4**.

Table 6.4 Pharmacokinetics of selected anticonvulsants.

	Gabapentin	Pregabalin	Valproate
Absorption	Variable bioavailability dependent on dose; e.g. daily doses/ bioavailability: 1200 mg/47%; 2400 mg/34%; 3600 mg/33%; 4800 mg/27%	Good oral absorption; oral bioavailability > 90% independent of dose	Rapid and almost complete oral absorption
Distribution	Volume of distribution 58 L; less than 3% bound to plasma proteins	Volume of distribution 0.56 L/kg; not bound to plasma proteins	Nonlinear kinetics; concentration-dependent plasma protein binding (90%)
Metabolism	No significant metabolism in humans	No significant metabolism in humans	Complex metabolism, including glucuronidation and oxidation
Excretion	Eliminated via renal excretion, mostly as unchanged drug; elimination half life 5–7 hours	Eliminated via renal excretion, mostly as unchanged drug; elimination half-life 6.3 hours	Significant metabolism prior to excretion; half-life range 3.8–15.7 hours

Modified from multiple sources.

Mechanism of action and clinical effects

Anticonvulsant drugs exert multiple pharmacological actions on the nervous system, with remarkable similarities between the antiseizure and analgesic mechanisms.¹⁰⁷ With regards to their specific analgesic mechanisms, it appears that gabapentin, pregabalin, and valproate all interact with voltage-gated calcium channels and suppress activity at NMDA and AMPA receptors as well.¹⁰⁶ Other anticonvulsants have significant voltage-gated sodium blocking effects, thought to be important in neuropathic pain mechanisms.

Experimental studies in animals have shown the ability of some (but not all) anticonvulsants to attenuate nociceptive processes in both inflammatory and neuropathic pain models.^{107, 108} Furthermore, human studies with gabapentin and pregabalin, for example, show their ability to suppress experimentally induced skin hyperalgesia in otherwise healthy volunteers,¹⁰⁹ while also enhancing the analgesic effects of opioids.¹¹⁰ These findings have forged the way towards a number of clinical trials in the perioperative setting.

Side effects and toxicity

Side effects are relatively common with all anticonvulsant drugs currently in use, some of which are dose dependent and others idiosyncratic.¹⁰⁷ Gabapentin and pregabalin both have similar side-effect profiles, with sedation, dizziness, ataxia, diplopia, nausea, and peripheral edema among some of the more common side effects.

Valproate causes similar central nervous system side effects, but in addition may result in blood dyscrasias, elevated liver function tests, and rare skin reactions. The teratogenic potential of these drugs in rats is established,

with some suggestions of potential adverse effects in pregnant women. In the context of acute pain management, particularly in the perioperative setting, it would be sensible to avoid these drugs in early pregnancy.

Clinical use in acute pain management

Specific anticonvulsants certainly have a potential role in acute pain management but thus far only for particular indications such as in the perioperative period, in acute neuropathic pain states, and in acute migraine.

PERIOPERATIVE USE: GABAPENTINOIDS

Anticonvulsants for perioperative pain management are currently only in the initial stages of clinical use. Pre-clinical data discussed above have suggested a role as an adjunct to opioids in particular, especially the perioperative setting, and this has now led to a significant number of very recent clinical trials evaluating the effect of gabapentin.

In these double-blinded randomized controlled trials, gabapentin was administered preoperatively in single doses ranging from 300 to 1200 mg, and in some cases continued into the early postoperative period. The types of surgery varied significantly, including gynecological surgery, orthopedic and spinal surgery, as well as oncological surgery, and even transplant surgery. There were even suggestions of improved postoperative pulmonary function following hysterectomy,¹¹¹[II] and enhanced functional recovery following knee surgery.¹¹²[II]

Similar results were found in the few studies performed with pregabalin in the setting of dental pain¹¹³[II] and after spinal fusion.¹¹⁴[II]

A number of meta-analyses of these trials have been performed in 2006 and 2007.^{115, 116, 117, 118, 119}[I] Overall, they confirm the analgesic (at rest and with movement) and opioid-sparing effects of even single doses of gabapentin preoperatively, while leading to minor adverse effects, in particular increasing the incidence of sedation.^{115, 116, 117, 118, 119}[I] In parallel, the use of gabapentinoids perioperatively led to a decrease in nausea (number needed to treat (NNT) 25), vomiting (NNT 6), and urinary retention (NNT 7).¹¹⁹[I] These effects were not dose-dependent in the dose range of 300–1200 mg investigated in the studies analyzed.¹¹⁹[I]

It would seem from these data that gabapentinoids are establishing themselves in the paradigm of multimodal analgesia in the perioperative period; their role as “protective premedication” has been previously discussed in the literature.¹²⁰ However, the studies included in the above meta-analyses used a wide range of gabapentin and pregabalin doses and regimens of dosing. This means that any particular dosing regimen cannot be recommended currently; it is also unclear of which duration the perioperative intake of these compounds should be and if

there are any long-term benefits such as reduced chronic pain from the perioperative use.

PERIOPERATIVE USE: OTHER ANTICONVULSANTS

In comparison to the gabapentinoids, other anticonvulsant drugs have received much less attention, with very few clinical studies examining their role in the perioperative period and no relevant findings. One study found no benefit in intravenous valproate administered postoperatively.¹²¹[II]

Furthermore, a recent meta-analysis of carbamazepine in both acute and chronic pain concluded there was currently no role for this drug in acute pain management.¹²²[I]

ACUTE NEUROPATHIC PAIN

As outlined for ketamine and clonidine (see above under NMDA receptor antagonists and Alpha-2 adrenoreceptor agonists, respectively), neuropathic pain may be a significant presenting feature in various surgical and non-surgical conditions, and the use of adjuvant drugs is more likely to result in effective analgesia. There are compelling data on the use of anticonvulsant drugs in a range of chronic neuropathic pain conditions.^{103, 104, 105} By extrapolation, they could also be used in acute situations as well.¹³ Specific acute neuropathic pain conditions where anticonvulsants have been used successfully include spinal cord injury (gabapentin),¹²³[II] Guillain–Barré syndrome (carbamazepine and gabapentin),^{124, 125}[II] and post-amputation phantom limb pain (gabapentin).¹²⁶[II]

ACUTE MIGRAINE HEADACHES – ABORTIVE THERAPY USING VALPROATE

Migraine refers to a common group of primary headache disorders, affecting nearly 20 percent of women and about 6 percent of men, but also affecting up to 3 percent of children.¹²⁷ Vast numbers of trials and reviews concerning pharmacological treatment and prevention of migraines have resulted in evidence-based guidelines.^{13, 127, 128}

Valproate is not only considered beneficial in migraine prophylaxis,¹²⁹ but there are studies that also suggest intravenous valproate is beneficial in aborting acute episodes of migraine,¹³⁰[III], ¹³¹[II], ¹³²[III], ¹³³[II] although it is generally agreed that simple analgesics and triptans should be tried initially.^{13, 134}[I] Patients with acute migraine who have not responded to these initial measures commonly present to emergency departments,¹³⁵ and this is where additional treatments such as intravenous valproate may have a crucial role, particularly if nausea and vomiting (which is common in migraine) precludes administration of standard oral treatments. The effective doses used ranged from 300 mg to a maximum

of 1200 mg in these studies, resulting in rapid improvements in pain and other migraine symptoms. To date, no trials have compared the relative efficacy of different valproate doses so it would seem reasonable to try to administer the minimum effective dose in clinical practice, until further studies clarifying this issue are published.

ANTIDEPRESSANTS

Introduction

While antidepressants, in particular the tricyclic compounds, are the most effective treatment of chronic neuropathic pain¹³⁶ and other chronic pain states, they play only a minor role as adjuncts for the treatment of acute pain.

Clinical use in acute pain management

Neither in experimental¹³⁷ nor in clinical acute pain after othopedic¹³⁸[II] and breast surgery¹³⁹[II] did tricyclic antidepressants show any analgesic effect.

However, antidepressants had a preventive effect on the development of neuropathic pain in a number of acute settings. Perioperative use of venlafaxine in breast surgery reduced the incidence of chronic pain assessed six months after the operation.¹³⁹[II] Similarly, amitriptyline given to patients with acute herpes zoster halved the incidence of postherpetic neuralgia at six months.¹⁴⁰

In analogy to the effectiveness of tricyclic antidepressants in chronic neuropathic pain, there might also be a role for them in the treatment of acute neuropathic pain states.¹³

CORTICOSTEROIDS

Introduction

Synthetic corticosteroids have anti-inflammatory, analgesic, and antiemetic properties that are all potentially useful in acute pain management, notably in the perioperative setting.

Physical and chemical properties

The adrenal cortex produces steroid hormones that are involved in a vast number of physiological functions but, from a more simplistic pharmacological point of view, they can be considered either glucocorticoids or mineralocorticoids. The former are more relevant to the current discussion as they have important effects on inflammation. A range of synthetic drugs are available

clinically and they all share similarities in basic steroid composition; dexamethasone is most commonly studied in acute pain settings. Multiple formulations exist, but only the oral and parenteral forms are relevant to this discussion.

Pharmacokinetics

These are briefly summarized for dexamethasone in **Table 6.5**.

Mechanism of action and clinical effects

At a cellular level, all steroids bind to intracellular receptors and gain entry into the nucleus, subsequently altering gene expression and leading to tissue-specific effects. Glucocorticoids result in metabolic and immunosuppressive effects, as well as dramatic anti-inflammatory effects, the latter due to inhibition of phospholipase enzyme causing decreased production of prostaglandins and other eicosanoids. These fatty acid derivatives are normally induced following tissue injury (including surgery) and are pronociceptive. The more selective inhibition of these substances forms the basis for treatment with nonsteroidal anti-inflammatory drugs, and steroids therefore can be expected to result in similar responses.

Despite considerable advances in the understanding of mechanisms leading to nausea and vomiting, the mechanism of action of the antiemetic effects of corticosteroids remain unknown.¹⁴¹

Side effects and toxicity

Single dose and even short-term use of steroids in the acute pain management context is virtually devoid of significant adverse effects based on clinical experience in anesthesia and chemotherapy settings.

Table 6.5 Pharmacokinetics of dexamethasone.

Dexamethasone	
Absorption	Oral bioavailability 50–70% Rapidly absorbed following intramuscular injection
Distribution	Small amounts plasma protein bound
Metabolism	Predominantly hepatically metabolized
Excretion	Inactive metabolites excreted in the urine, mostly glucuronides and sulfates

Compiled from multiple sources.

Clinical use in acute pain management

The best described use of steroids in acute pain management is in the perioperative period, particularly in dental surgery,^{142, 143} but also in laparoscopic cholecystectomy,¹⁴⁴ and to a lesser extent in orthopedic, ambulatory, and pediatric ear, nose, and throat (ENT) surgery.^{76, 86, 145, 146} Steroids, such as betamethasone in doses 9–12 mg and dexamethasone in doses 8–10 mg, given either as a premedication or intraoperatively, resulted in reductions in pain and postoperative nausea and vomiting^{142, 143, 145, 146}[II],¹⁴⁷[I] and in the case of dental surgery, the incidence of severe postoperative swelling was less.^{142, 143}[II] Theoretical concerns regarding increased wound infections due to potential immune suppression have not eventuated. The use of steroids perioperatively as a prophylaxis against postoperative nausea and vomiting is widespread,¹⁴⁸ and their analgesic benefits are a welcome secondary effect.

CALCITONIN

Introduction

Calcitonin has analgesic effects that were realized over 30 years ago in both animal models and in humans, paving the way towards novel applications in pain management.¹⁴⁹ It has potential use in a number of acute and chronic pain conditions, but only some of these have been subjected to sufficiently rigorous trials and meta-analyses, thus limiting the present use of this useful drug.

Physical and chemical properties

Calcitonin is a 32 amino acid polypeptide hormone secreted by parafollicular cells in the thyroid gland. Salmon calcitonin (molecular weight, 3431) is synthesized for medical use, as it is considered significantly more potent than the human type. It is presented in various forms for administration via intranasal, rectal, subcutaneous, intramuscular, and intravenous routes.¹⁴⁹

Table 6.6 Pharmacokinetics of (salmon) calcitonin.

Calcitonin	
Absorption	Not administered orally as it is a protein, and would be inactivated in the gut; bioavailability after subcutaneous (s.c.) or intramuscular (i.m.) injection is about 70%; onset is immediate following intravenous administration, and 15 minutes following s.c. or i.m.; peak plasma levels within one hour
Distribution	Volume of distribution 0.15–0.30 L/kg
Metabolism	Rapidly metabolized to unidentified and inactive metabolites, mainly in the kidneys, blood, and peripheral tissues
Excretion	95% excreted by the kidney; elimination half life 60–90 minutes

Modified from multiple sources, including Ref. 149.

Pharmacokinetics

These are briefly summarized in **Table 6.6**.

Mechanism of action and clinical effects

Calcitonin binds to a transmembrane G-protein coupled receptor, resulting in actions by intracellular second messengers such as c-AMP and calcium. The primary physiological role of calcitonin appears to be calcium homeostasis, although this function is predominantly served by vitamin D and parathyroid hormone.¹⁴⁹

The analgesic mechanisms are atypical, having been studied at length in animals and humans.¹⁴⁹ Calcitonin receptors are widespread in tissues and importantly they are found on central serotonergic neurons associated with pain pathways. The current hypothesis is that calcitonin produces antinociceptive effects via neuromodulation of central serotonergic pain pathways.

Side effects and toxicity

The more common side effects include nausea and vomiting, facial flushing, and dizziness. Antiemetics may significantly attenuate the nausea and vomiting, and are commonly co-administered. Less commonly, flu-like symptoms may occur (i.e. fevers, chills, arthralgias) and rashes may sometimes develop. Localized or generalized hypersensitivity reactions may occur in very rare cases.¹⁴⁹

Long-term administration (up to five years) is considered safe and does not seem to cause any serious side effects.¹⁵⁰

Clinical use in acute pain management

Calcitonin has found clinical utility in acute, chronic, and cancer pain management.¹⁴⁹ In the field of acute pain management, it is a useful adjuvant in vertebral fractures and in phantom limb pain.

ACUTE OSTEOPOROTIC VERTEBRAL CRUSH FRACTURES

Pain caused by acute osteoporotic vertebral fractures is intense and debilitating, typically lasting several weeks, and commonly persisting long term. A recent review examined 14 trials that have been undertaken to date, analyzing the effects of daily calcitonin (administered in various forms) in such patients.¹⁵⁰ The patients reported better analgesia at rest and with movement, used less additional analgesics, and perhaps most importantly, had significantly improved mobility and functional capacity.¹⁵⁰[I]

The doses used ranged from 50 to 200 IU depending on the route of administration and the duration of treatment was at least two weeks, and even up to one year in one study. Evidence-based clinical guidelines recommend the use of calcitonin as a first-line agent in the management of acute osteoporotic vertebral fractures.¹⁵¹

ACUTE PHANTOM LIMB PAIN

Phantom limb pain following amputations is very common with some suggestions as high as 60–70 percent in the first year.¹⁵² Various treatments are reported in the literature for both acute and chronic phantom limb pain, yet consensus guidelines founded on a clear evidence base are notably lacking at this time. Nevertheless, treatment of acute phantom limb pain with calcitonin is a viable option, based on case series results^{153, 154, 155}[III] and one double-blinded randomized controlled trial,¹⁵⁶[II] patients experienced rapid and sustained pain relief, even after two years.

As noted with treatment of vertebral crush fractures, the optimal dose and route of administration for phantom pain is not known.

LIDOCAINE (SYSTEMIC ADMINISTRATION)

Introduction

Since the early 1950s, reports have appeared in the literature on the systemic, commonly intravenous, use of local anesthetics, specifically lidocaine (lignocaine) to provide pain relief.¹⁵⁷ In an elegant experiment, Boas *et al.*¹⁵⁸ could show very early that there was selectivity of the analgesic effect for neuropathic over nociceptive pain. The assumed mechanism of action is inhibition of ectopic discharge of damaged neurons,¹⁵⁹ mediated by blockade of sodium channels, which are overexpressed in these pathological states.¹⁶⁰ Clinically, this effect, which occurs at plasma concentration far below those to induce conduction blockade, has been utilized in a wide range of clinical settings.¹⁶¹

As physical and chemical properties, pharmacokinetics, mechanism of action, side effects, and toxicity of the local anesthetics for neural blockade are covered in

Chapter 7, Clinical pharmacology: local anesthetics, only the clinical systemic use will be discussed here.

Clinical use in acute pain management

The effects of systemic lidocaine on neuropathic pain have been analyzed in detail in a recent meta-analysis of 13 RCTs.^{161, 162} Overall, lidocaine, commonly administered in a single slow bolus dose of 5 mg/kg or as an infusion at a rate of 1–2 mg per minute, resulted in relief of neuropathic pain superior to placebo and equivalent to other compounds commonly used in this setting. Lidocaine was effective in neuropathic pain of central and peripheral origin.¹⁶²[I] Adverse effects were minor and included nausea, vomiting, drowsiness, and fatigue; the incidence of such adverse effects was again similar to other compounds used to treat neuropathic pain.¹⁶²[I] However, in an RCT, ketamine was superior to lidocaine in treating pain after spinal cord injury.⁷³[II] Systemic lidocaine has also been used in pain conditions other than neuropathic pain.

In the postoperative setting, parenteral lidocaine has been used as an adjunct to systemic analgesia under the hypothesis, that its anti-inflammatory effects might positively modulate the surgery-induced stress response. After major abdominal surgery, intravenous lidocaine as a bolus followed by infusion resulted in attenuated stress response leading to improved pain control and reduced opioid requirements, as well as faster bowel recovery and reduced hospital stay in a number of RCTs.^{163, 164, 165}[II]

For the treatment of burns pain, a Cochrane review found no published RCTs and use in this indication can only be based on case series or case reports.¹⁶⁶[V]

Subcutaneous administration of lidocaine can be an option in intractable terminal cancer pain.¹⁶⁷[IV]

In view of its parenteral route of administration and rapid onset of effect, parenteral lidocaine might be a useful compound in the treatment of acute neuropathic pain. It might also play a future role as an adjunct to other systemic analgesics in the perioperative setting.

CONCLUSIONS

Adjuvant analgesics comprise a large and pharmacologically diverse group of drugs that may be used to complement the standard multimodal analgesic regime in the treatment of acute pain. Their specific roles in acute pain management are rapidly expanding and there is sufficient evidence at present to guide their use in a variety of indications.

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