

Revisiting old friends: update on opioid pharmacology

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SUMMARY

Opioids are commonly prescribed for pain due to malignant and non-malignant diseases. They are effective, but have potentially fatal toxicities.

Opioid analgesics act as agonists at the mu opioid receptor. Some products combine a mu agonist and antagonist, but there are limitations to their use.

Genetic variations may explain why people respond differently to opioids. Some patients have an inadequate response to codeine because they poorly metabolise it to morphine.

Switching from one opioid to another is sometimes necessary, but must be done carefully. Use conversion tables as a reference, but be aware of their limitations.

Introduction

Opioid drugs are prescribed for acute and chronic pain of moderate or severe intensity arising from both malignant and non-malignant diseases (see Table).^{1,2} They benefit many patients, but there are increasing numbers of unintentional fatal overdoses.³ A clinician weighing up the potential benefits and harms of opioids is also confronted with an array of newly available drugs and formulations. Understanding the pharmacology of opioids can assist decision making.

Pharmacodynamics

Morphine and codeine, the main analgesic alkaloids produced from the opium poppy, were isolated in the 19th century, but it was not until the 1970s that their receptors were discovered. Since then, three opioid receptors – mu, kappa and delta – have been described and their genes cloned. A fourth receptor, the nociceptin-orphanin FQ receptor, is considered ‘opioid-like’ because of important structural and pharmacological differences.⁴ The endogenous peptides which interact with these receptors are endorphin, dynorphin, enkephalin and nociceptin.

Opioid receptors are widespread. They are found not only within the nervous system but also in other tissues, including the gastrointestinal tract and the cardiovascular and immune systems.

Mu opioid receptor

Activation of the mu opioid receptor (mu is named for morphine) results in:

- inhibition of adenylyl cyclase
- closure of voltage-gated calcium channels
- opening of potassium channels and membrane hyperpolarisation.

These cellular events can inhibit neuronal firing and neurotransmitter release.

All of the opioid analgesics act as agonists at the mu receptor. Mu activation inhibits the ascending pain pathway, which includes neurons passing through the dorsal horn of the spinal cord, brainstem, thalamus and cortex. Mu agonists also activate the inhibitory descending pain pathway, which involves sites in the brainstem. Peripheral mu receptors located at the site of tissue injury and inflammation may also mediate analgesia.⁵

Mu receptor agonism is responsible for the euphoria associated with opioids. This effect is distinct from the pain pathways and depends on the mesolimbic dopaminergic system. Other prominent mu effects include sedation, pupillary constriction, respiratory depression and constipation.

Delta and kappa opioid receptors

Delta and kappa receptors are also present in the pain pathways and they may play a role in analgesia and adverse effects associated with some commonly used opioids. For example at least some of the analgesic properties of oxycodone appear to be related to kappa receptor agonism.⁶

Non-opioid receptors

Some of the opioid analgesics also act at non-opioid receptors. These actions may be either therapeutic or unwanted.

Tramadol inhibits both serotonin and noradrenaline reuptake. Its active metabolite, desmethyltramadol, only inhibits noradrenaline reuptake. These monoaminergic effects contribute to analgesia, however serotonin toxicity is associated with the use of tramadol

Table Opioids commonly used for acute and chronic pain ^{1,2}

Drug	Formulations available	Oral bioavailability	Half-life (immediate-release formulation) *	Clearance mechanism	Comments
morphine	immediate release (oral, parenteral) sustained release 12 hourly or 24 hourly (oral)	30%	3 hours	liver metabolism (mainly glucuronidation) important active metabolites (M3G, M6G) renally cleared	active metabolites are problematic in renal failure
oxycodone	immediate release (oral, parenteral) sustained release 12 hourly (oral)	70%	2.5 hours	liver metabolism (mainly CYP) some active metabolites with small contribution to effect approximately 20% of dose renally cleared	also available combined with naloxone (sustained release only) for management of opioid bowel dysfunction
hydromorphone	immediate release (oral, parenteral) sustained release 24 hourly (oral)	30%	2.5 hours	liver metabolism (mainly glucuronidation) active metabolite H3G is both implicated in toxicity and renally cleared	significantly more potent than morphine and oxycodone
fentanyl	immediate release (buccal/oral, parenteral) sustained release (transdermal)	50% (lozenge)	3 hours (following an intravenous dose)	liver metabolism (mainly CYP3A4) no active metabolites	lowest dose patch (12 microgram/hour) is not suitable for opioid-naïve patients as it can cause serious toxicity suitable choice in renal failure
methadone	immediate release (oral, parenteral)	40-90%	15-60 hours	liver metabolism (mainly CYP) no active metabolites	due to complex pharmacokinetics should be commenced under specialist supervision
buprenorphine	immediate release (sublingual, used for opioid maintenance treatment) sustained release (transdermal)	30% (sublingual route)	35 hours (following sublingual administration)	liver metabolism (mainly CYP) active metabolites	a partial mu agonist that may induce withdrawal in an opioid-tolerant patient
codeine	immediate release (oral, parenteral)	60%	3 hours	liver metabolism (mainly glucuronidation) variable proportion of dose converted to morphine	not suitable for chronic pain significant variability in analgesic response between patients
tramadol	immediate release (oral, parenteral) sustained release (oral)	70%	6 hours	liver metabolism active metabolite is important for therapeutic effect	risk of serotonin toxicity in overdose or in combination with other serotonergic drugs

* half-lives are approximate as published values vary depending on the study and the exact formulation used

M3G morphine-3-glucuronide

M6G morphine-6-glucuronide

CYP cytochrome P450

H3G hydromorphone-3-glucuronide

in combination with other serotonergic drugs, such as selective serotonin reuptake inhibitors, or in overdose. A newly available analgesic, tapentadol, is structurally and pharmacologically similar to desmethyltramadol. It is both a mu agonist and noradrenaline reuptake inhibitor.

Methadone is another opioid with clinically important actions at non-opioid receptors. The d-isomer of methadone is an N-methyl D-aspartate receptor

antagonist which contributes to analgesia and has a role in treating opioid-induced hyperalgesia. Methadone also inhibits the hERG potassium channel, prolonging the QT interval in some patients and increasing the risk of cardiac arrhythmia.⁷

Tolerance and withdrawal

Opioids can cause tolerance and this can lead to an unpleasant withdrawal syndrome if ceased suddenly after chronic use. Tolerance and withdrawal may be

anticipated in all patients using a strong mu agonist, and withdrawal can be managed, for example by using a weaning regimen when stopping treatment.

The cellular events involved with tolerance are complex and begin even after a single dose of a mu agonist.⁸ However, a period of days to weeks of consistent use is generally required for clinically significant problems to arise.

Addiction

Opioid addiction, while related to the phenomena of tolerance and withdrawal, implies behaviours that result in adverse social and health outcomes for the patient. Addiction is a potentially catastrophic outcome of opioid treatment and may not be as rare as previously thought. One study of patients using opioids for chronic non-cancer pain suggested a 34.9% prevalence of DSM-5 diagnosable opioid-use disorder.⁹ This figure is substantially higher than that found in earlier studies.¹⁰ The potential for addiction should be considered before and during chronic opioid therapy. Tools such as the Opioid Risk Tool¹¹ may be used to facilitate assessment.

Pharmacokinetics

Differences in the pharmacokinetics of opioid drugs influence the routes of administration and the problems that arise in disease states such as renal failure.

Bioavailability

Knowing the oral bioavailability of opioids is useful when estimating the dose to prescribe when switching from the parenteral to oral routes and vice versa. The oral bioavailability of opioids ranges from low (for example buprenorphine 10%) to moderate (for example morphine 30%) and to relatively high (for example oxycodone 70%). The low oral bioavailability of buprenorphine is due to high first-pass metabolism and explains why it is given via the sublingual or transdermal routes.

As there are interindividual differences in the extent of absorption and first-pass metabolism for each drug, oral bioavailability tends to vary between patients. Generally, drugs with a higher oral bioavailability show less variability between patients.

Distribution

All effective analgesic opioids are distributed to the central nervous system. There is evidence that efflux transport proteins such as P-glycoprotein influence the distribution of opioids to the central nervous system, but the clinical implications are unclear. The ability of P-glycoprotein to pump some opioid drugs out of the central nervous system is exploited in the case of loperamide. This is an effective peripheral mu agonist, but as it has low central nervous system concentrations at usual doses, it can be used to treat diarrhoea.

Metabolism

The metabolism of opioids occurs mainly in the liver via the cytochrome P450 (CYP) system and conjugating enzymes. Metabolism can result in both inactive compounds (usually excreted by the kidneys) and active metabolites with their own pharmacological properties.

Fentanyl and methadone are metabolised to pharmacologically inactive metabolites, therefore metabolism is their clearance mechanism. Factors affecting metabolism such as hepatic dysfunction, metabolising enzyme polymorphisms and drug-drug interactions determine the steady-state concentrations of these drugs during chronic therapy.

Codeine is a prodrug which is converted by CYP2D6 to its active metabolite, morphine. Both morphine and tramadol also form active metabolites. Tramadol becomes desmethyltramadol which is a more potent mu agonist than the parent drug and is also a noradrenaline reuptake inhibitor.

Morphine is conjugated to form morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is a mu agonist and in chronic dosing is responsible for some of the analgesic effects and toxicity of morphine. As it is excreted unchanged by the kidneys, morphine-6-glucuronide exposure increases significantly in renal failure and can lead to toxicity. Although morphine itself is not cleared by the kidney, it is problematic in renal failure because of its renally excreted active metabolites.

By contrast, fentanyl is entirely metabolised to inactive compounds. It is therefore often preferred in moderate to severe renal failure.

Half-life

The half-life is important when determining dosing intervals. Commonly prescribed oral opioids, such as morphine and oxycodone, have relatively short half-lives of around 2–4 hours. In chronic therapy, sustained-release formulations prolong their apparent half-life by extending the absorption phase. Depending on the product, these formulations allow once-daily or twice-daily dosing. They also reduce undesirable fluctuations in the plasma concentration.

Fentanyl, when formulated in a skin patch, is absorbed slowly, prolonging the apparent half-life and allowing patch changes every three days. It should be noted that fentanyl patches are not suitable for opioid-naïve patients – even the lowest strength patch available delivers a potentially toxic dose.

By contrast, methadone itself has a long half-life and can often be given twice daily as an analgesic for chronic pain. When used for opioid maintenance therapy it can be given once daily. However, the half-

life is variable (15–60 hours) so patients require careful titration of the dose under specialist supervision.

Combination products

Opioids may be formulated with other drugs with the aim of increasing efficacy or reducing adverse effects.

Codeine combinations

Products combining codeine with a non-opioid analgesic (for example, ibuprofen or paracetamol) and sometimes additional drugs (for example doxylamine) are available over the counter. While a combination is convenient, problems include the inability to alter the dose of the individual drugs and a scarcity of good quality evidence for their effectiveness.¹² The non-opioid component can also have serious toxicity, especially if taken in excessive amounts.

Opioids combined with naloxone

Naloxone is an antagonist at opioid receptors. In Australia, naloxone is available in combination with buprenorphine or oxycodone.

The naloxone with buprenorphine combination is used for maintenance therapy in opioid addiction and is intended to deter patients from injecting the drug. Naloxone has minimal effects when administered sublingually, but can precipitate withdrawal symptoms if used parenterally.

The naloxone with oxycodone combination is marketed for chronic severe pain and treatment of the bowel dysfunction caused by opioids. Oral naloxone has a low systemic bioavailability and in its controlled-release formulation it antagonises opioid effects on the gastrointestinal tract with minimal effects on the central nervous system. There is evidence that the combination can reduce constipation without compromising analgesia or precipitating withdrawal.¹³

There are potential limitations with the oxycodone and naloxone combination. The product information advises against exceeding a total daily dose of 80 mg oxycodone/40 mg naloxone because of evidence that higher naloxone doses may reduce analgesia and precipitate withdrawal. Use of the combination is therefore limited to patients with low to moderate oxycodone requirements. Other situations that result in increased systemic exposure to naloxone, such as hepatic dysfunction, also present problems for this combination. Finally, opioids are usually only one of a number of factors causing bowel dysfunction and the naloxone/oxycodone combination should be prescribed in conjunction with other strategies, including laxatives.

Opioid rotation

Opioid rotation is defined as changing from one opioid to another, usually during chronic therapy, in an attempt to manage inadequate analgesia or

intolerable adverse effects. About 50% of patients may be expected to improve with opioid rotation.¹⁴

One strategy is to stop the current opioid and immediately replace it with a so-called equianalgesic dose of another opioid ('stop and go' approach). The dose of the new drug is chosen with the aid of published equianalgesic tables. This compares the various opioids back to a reference dose of morphine (such as 30 mg oral morphine). The dose is reduced (for example by 50%) to allow for incomplete cross-tolerance and intra-individual variability, and provision is made for breakthrough analgesia. Clinical monitoring during the changeover period is required.

This method of opioid rotation with the use of equianalgesic tables has been questioned. The tables could be contributing to the increase in opioid-related overdose and mortality by exposing patients to toxic drug concentrations.¹⁵ Switching to methadone is particularly problematic because of the long time required to reach steady state and the variability in how patients respond to the drug.

Equianalgesic tables are also limited because they are usually derived from data that do not represent patients with chronic pain (for example patients with postoperative pain or even healthy people). A titration strategy for opioid rotation has been suggested in an attempt to overcome these problems. Using this strategy the dose of the current opioid is gradually reduced as the new opioid is introduced and its dose is up-titrated.¹⁶

Pharmacogenetics

Genes affect the way in which the body processes and responds to drugs. Genetic differences explain some of the inter-individual variability in patients' responses to opioids. For example, the CYP2D6 genotype influences the response to codeine. Poor metabolisers (5–10% of Caucasians) do not convert codeine efficiently to morphine. They obtain little analgesia from codeine, whereas ultra-rapid metabolisers (1–2% of Caucasians) may experience toxicity. Reports of codeine-related deaths in children following tonsillectomy¹⁷ have been linked to ultra-rapid metabolism. Consequently the US Food and Drug Administration has issued a black box warning for codeine use in children after tonsillectomy. As CYP2D6 genotyping is not routine before prescribing codeine, the potential for metabolic variation to result in poor response or toxicity should be considered.

Recent research has examined whether variations in the gene coding for the main target of opioid analgesic drugs (that is, OPRM1 which codes for the mu opioid receptor) affect clinical parameters such as opioid dose and adverse effects. Preclinical studies have linked an OPRM1 gene polymorphism



SELF-TEST QUESTIONS

True or false?

- Codeine is a prodrug of morphine.
- Codeine may be ineffective in patients with ultrarapid CYP2D6 metabolism.

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(118A>G which has an adenine nucleobase replaced by guanine) to the need for higher drug doses and a poorer analgesic response. However, a recent meta-analysis¹⁸ found the genetic variation correlated poorly and inconsistently with parameters such as dose requirements. At present, genetic testing does not have a role in clinical decision making.

Conclusion

Opioids are an important part of treatment for moderate to severe pain. In the past, these drugs were mainly used to treat the pain of cancer and trauma,

but are increasingly used for a wider spectrum of pain syndromes. Acute toxicity can have a fatal outcome. Repeated use can result in problems such as tolerance and addiction. It is therefore important that knowledge of opioid pharmacology is used by clinicians to balance the beneficial and harmful effects of the drugs. ◀

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See also Medicines Safety Update: Codeine use in children after tonsillectomy and/or adenoidectomy

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Dental note

Opioids in dental practice

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Opioids are not generally regarded as a significant part of pain management protocols in general dental practice. Most dental pain can be managed with paracetamol, ibuprofen or a combination of these drugs.

An unsubstantiated emphasis is often placed on combination products containing codeine. The quantity of codeine in these combinations is insufficient for an effective analgesic effect and there is no greater benefit over paracetamol and ibuprofen alone.

Dental pain should always be addressed from a diagnostic approach. The pivotal step is identifying the cause of the pain. Once identified, managing the local cause such as an odontogenic infection will manage the pain. Analgesics then play a supportive but significantly less important role and paracetamol and ibuprofen are appropriate.

The main problems with opioids are patients who actively seek prescriptions. Contacting the patient's doctor is recommended.

Dental practitioners are responsible for the oral health care of patients on methadone programs. There are a number of very significant concerns with respect to the maintenance of oral health in an often adverse oral environment. When possible, patients should be under careful dental review with a stringent preventive program in place to intercept the irreversible damage that may be associated with methadone. The main concern is dry mouth. Salivary hypofunction is a major risk factor in the development of dental caries, but this can be overcome by careful education and support programs. Nausea and vomiting may also be problematic for some patients and should be discussed as a routine part of the dental consultation.

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