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Opioids for pain after oral surgery

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Abstract

Aim: To describe the role of opioids in the management of pain after oral surgery.
Materials and methods: A review of the literature describing the pharmacokinetics, benefits and harms of opioids in terms of systematic review evidence, interactions, use in children, pregnancy and breastfeeding.
Results: A 10-mg intramuscular dose of morphine is recognised as a very effective analgesic for post-operative pain with a number needed to treat (NNT) of 2.9. Codeine 60 mg has an NNT of 16.7 suggesting poor analgesic effectiveness, but in combination with 1 g paracetamol is an effective analgesic for the management of post-operative pain with an NNT of 2.2.
Conclusions: Morphine is effective for severe pain experienced by inpatients undergoing oral surgery, ideally administered intravenously or alternatively by intramuscular injection. Codeine is very effective when combined with paracetamol and is suitable for day-case and outpatient oral surgery experiencing moderate to severe pain.

Clinical relevance

Scientific rationale

This article provides an update for Oral Surgeons on the use of opioids for post-operative pain control.

Principal findings

Opioids are effective for moderate to severe pain after oral surgery but are associated with adverse effects such as nausea, vomiting and constipation. Opioids should be avoided in pregnant patients or those who are breastfeeding.

Practical implications

Patients with moderate to severe pain benefit from the use of opioids. Adverse effects can be appropriately managed through careful dosing, patient counselling and symptomatic treatment so concern about side effects of opioids should not deter surgeons from using them.

Introduction

This fourth article in the series discusses the use of opioids in the management of pain in patients undergoing oral surgery procedures in primary and secondary care. Other articles in this series describe pain pathways and the use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) in the management of pain following oral surgery[1–4].

Pain ladder

The term 'pain ladder' was coined by the World Health Organisation (WHO) to describe their guidelines for the use of drugs in the management of pain. The WHO pain ladder[5] was originally applied to the management of cancer pain, but is now accepted for the management of all types of pain. It is based on the concept of starting pain therapy with 'first step' drugs and then to climb the ladder if pain is still present. The WHO guidelines recommend prompt oral administration of drugs when pain occurs, starting, if the patient is not in severe pain, with non-opioid drugs such as paracetamol (acetaminophen), NSAIDs or cyclooxygenase-2 inhibitors.

If complete pain relief is not achieved, further treatment, such as a mild opioid (codeine phosphate dihydrocodeine or Tramadol), is added to the existing non-opioid regime. If this is still insufficient, the mild opioid is replaced by a stronger opioid, such as morphine, while continuing the non-opioid therapy, escalating opioid dose until the patient is pain-free or at the maximum possible relief without intolerable side effects. If the initial presentation is severe pain, this stepping process should be skipped, and a strong opioid should be started immediately in combination with a non-opioid analgesic[6].

Patients may experience mild, moderate or even severe pain after undergoing oral surgery procedures. These patients will require effective analgesics that are safe and simple to use (see Table 1).

Moderate to severe pain may not be managed by NSAIDS or paracetamol alone or in combination. For these patients, there is the requirement to prescribe further analgesia. This fourth article in this series discusses the use of opioid analgesics for the management of pain in patients undergoing oral surgery in both primary and secondary care.

Background

An *opioid* is a compound that has pharmacological activity at an opioid receptor. It may be endogenous or administered, naturally occurring or synthetic. This differs from the term *opiate*, which is now reserved to describe alkaloids derived naturally from the opium poppy (*Papaver somniferum*)[7]. The term *narcotic* in the UK implies an addictive drug affecting mood or behaviour while *narcotic* in the USA can refer to opioids for medicinal use as well as illegally used opium derivatives.

Opium is an extract of the juice of the poppy, which has been used for social and medicinal purposes for thousands of years as an agent to produce analgesia, euphoria and sleep. It was introduced in Britain at the end of the 17th century. Morphine is the most abundant opiate found in opium. The structure of morphine was determined in 1902, and since then, many semi-synthetic and synthetic compounds have been produced by chemical modification of morphine (codeine, diamorphine, pethidine)[8].

Worldwide, opioids are the mainstay of managing moderate to severe acute pain in hospital practice. Many opioids are available for medical use, but the pharmacological action of all of them is very similar. They only differ in respect of their relative efficacy, their pharmacokinetics and their other actions. Their activity is reversed by an opioid antagonist such as naloxone[9].

Traditionally, opioids have been classified as weak, intermediate or strong according to their analgesic activity and propensity to addiction. Codeine is described as a weak opioid although at high dose can cause respiratory depression so this classification is not about safety[10].

Pharmokinetics

Opioid analgesics bind to the various physiological receptors recognised by endogenous opioid peptides, such as enkephalins and endorphins. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa and delta); other receptor types exist but have not been as well characterised. All three opioid receptors are widely, but differentially, distributed throughout the central and peripheral nervous system as well as in endocrine and immune cells. The pharmacodynamic response to an opioid depends upon the receptor to which it binds and its affinity for that receptor[11].

Opioids produce the majority of their therapeutic and adverse effects by acting as agonists at μ opioid receptors. Interestingly, endogenous opioids do not cause any side effects. Unlike the non-opioids, which exhibit a ceiling effect, the analgesic response to opioids acting at μ-receptors continues to improve as their dose is increased. Although their analgesic efficacy is unlimited, side effects often preclude the use of doses adequate to completely relieve severe pain[12,13].

Table 1 Recommendations of analgesic regime for oral surgery

Mild pain	Forceps extraction	Paracetamol 1 g every 6 h regularly (maximum 4g/24 h)
Moderate pain	Surgical removal of tooth	Ibuprofen 400 mg every 6 h regularly (maximum of 2.4 g/24 h) and Paracetamol 1 g every 6 h as necessary (maximum of 4 g/24 h)
Severe pain	Surgical removal of tooth involving bone removal	Ibuprofen 400 mg every 6 h regularly (maximum of 2.4 g/24 h) and Paracetamol 1 g/codeine 60 mg combination every 6 h regularly (maximum of 4 g paracetamol/24 h)

When non-steroidal anti-inflammatory drugs contraindicated: Paracetamol 1 g/codeine 60 mg combination every 6 h regularly (maximum of 4 g paracetamol/24 h). Moderate pain for inpatients. More difficult surgical removal of teeth or major surgery: Morphine by intravenous titration or intermittent intramuscular injection. These adult protocols are based on evidence from post-operative pain systematic reviews. The *British National Formulary* and other sources contain more extensive lists of analgesics.

Opioids bind to plasma proteins with varying degrees of affinity, the compounds rapidly leave the blood and localise in highest concentrations in tissues that are highly perfused, such as the lungs, liver, kidneys and spleen. The opioids are converted to their metabolites, which are then readily excreted by the kidneys.

Unlike non-opioid analgesics, which are primarily given orally, opioid analgesics are administered using a variety of routes. The availability of more concentrated dosage forms, controlled release oral opioid preparations and transdermal opioid preparations are among the most important recent innovations in opioid analgesia treatment[4].

Giving an opioid analgesic orally is the most common route of administration. Liquid preparations of opioids are absorbed more rapidly than solid tablets. Although absorption from the gastrointestinal tract may be rapid, the bioavailability of some compounds taken by this route may be considerably reduced because of significant first-pass metabolism by glucuronidation in the liver. Therefore, the oral dose required to elicit a therapeutic effect may be much higher than that required when parenteral administration is used[14].

Rectal administration may be used for patients who cannot swallow or when intravenous sites are not available. There are many suppository formulations available[15].

Opioids can also be given intramuscularly whereby the drug is injected into a muscle, most often the deltoid or vastus lateralis muscles. Giving analgesics by the intramuscular route is not ideal as intramuscular injections may be painful or unacceptable to some patients and drug absorption is variable and unpredictable. While it is preferable to administer opioids by the intravenous route, there may be issues with nurse training. Intravenous drug administration should always be done slowly to minimise adverse effects. A patient with severe acute pain should receive an opioid such as morphine by intravenous titration against their verbal reported pain score until this is reduced to an acceptable level. This is common practice in the acute recovery area of operating suites. This may be followed by a maintenance infusion although more commonly the patient is transferred to the ward area where they receive intermittent intramuscular morphine injections. Intravenous opioid administration requires skilled nursing and pharmacy support and an infusion pump is required for continuous or patient-controlled administration[16].

When the transdermal route is used, the opioid is absorbed through the surface of the skin. Fentanyl is available in a transdermal drug delivery system that provides continuous opioid administration without pumps or needles. Transdermal opioids are contraindicated for use in acute post-operative pain as they are slow release and there is high incidence of side effects[17].

Benefits

The effectiveness of opioids in the management of acute pain has been reported in a number of randomised controlled trial and systematic reviews[18–21]. The NNT is commonly used to measure the efficacy of an analgesic. NNT represents the number of patients that achieve at least a 50% pain relief as compared with placebo. The smaller the number, the more effective the analgesic.

Morphine is considered the gold standard for acute pain management. A 10 mg intramuscular dose of morphine is recognised as a very effective analgesic for post-operative pain with an NNT of 2.9 (2.6–3.6.)[12].

Patients may control post-operative pain by self-administration of intravenous opioids, such as morphine, using devices designed for this purpose. This is known as patient-controlled analgesia or PCA. Post-operative pain management with PCA involves self-administration of small doses of opioids intravenously by means of a programmable pump designed for this purpose. Previous studies have shown that often patients prefer PCA to traditional methods of pain management, such as a nurse administering an analgesic upon a patient's request[22].

A Cochrane systematic review by Hudcova *et al*. demonstrated that PCA provided slightly better pain control and increased patient satisfaction when compared with conventional methods. Patients tended to use higher doses of medication with PCA and suffered a higher occurrence of itching, but otherwise adverse effects were similar between groups. PCA is however rarely required following oral surgery procedures[23].

A single oral dose of 30 mg dihydrocodeine has an NNT of 8.1(4.1 to 540) and so does not provide very effective analgesia for acute post-operative pain. Dihydrocodeine 30 mg dose has been shown to be also significantly less effective than 400 mg ibuprofen with an NNT of 2.5 (2.4–2.7). This data is however based on a Cochrane systematic review involving only three trials[24].

A Cochrane review by Derry *et al*. assessed evidence from 2411 adults with moderate to severe post-operative pain in studies comparing single doses of codeine 60 mg with placebo. The number of individuals achieving a clinically useful amount of pain relief (at least 50%) with codeine compared with placebo was low. In all types of surgery combined, 12

participants would need to be treated with codeine 60 mg for one to experience this amount of pain relief who would not have done so with placebo. The authors separated trials utilising a dental pain model. Following dental surgery, the NNT was 21 (12 to 96) (15 studies, 1146 participants). The authors concluded that single dose codeine 60 mg provides good analgesia to few individuals, but does not compare favourably with commonly used alternatives such as paracetamol, NSAIDs and their combinations with codeine, especially after dental surgery[25].

Codeine in combination with paracetamol is an effective analgesic for the management of post-operative pain with an NNT for a single dose of 1000 mg paracetamol with 60g codeine of 2.2 (1.8–2.9) based on data from 197 patients[26].

Tramadol has been shown to be an effective analgesic in post-operative pain control. A single 100 mg oral dose of tramadol is equivalent to 1000 mg paracetamol. A 100 mg dose was found to have an NNT of 4.6 (3.6–6.4). In dental extraction trials, however, there seemed to be an increase in reporting of adverse effects such as vomiting, nausea and dizziness[27].

Harms

The fear of healthcare staff and patients about opioid addiction and or side effects continues to be responsible for reluctance to administer or use appropriate opioid doses. As with any other medication, opioids do have side effects. It is important however to realise that these adverse effects can be appropriately managed through careful dosing, patient counselling and symptomatic treatment. Fear of side effects of opioids should not negate adequate pain management.

Nausea and vomiting is a predictable and significant side effect in many patients, especially those suffering acute pain. The mechanism is thought to be stimulation of opioid receptors within the chemoreceptor trigger zone in the area postrema of the medulla[11]. However, prophylactic anti-emetics can be prescribed to counter this side effect.

The opioid effect on the gastrointestinal system in delaying gastric emptying and altering intestinal tone and motility may also add to the nausea and vomiting effect. Intestinal tone is increased and propulsive contractions are reduced, resulting in constipation[5]. For short-term opioid therapy, patients should be counselled to increase water and fibre intake; a laxative can also be prescribed. It is generally believed that morphine should not be used for patients having day-case surgery because of the potential for nausea and vomiting[28].

Itching tends not to be a severe problem when opioids are used for acute pain relief, but if required, then antihistamines are useful to counteract this. Non-sedating antihistamines are preferable so as to avoid increasing any opioid induced drowsiness[29].

Some patients may complain of drowsiness when commencing opioid treatment, although individual responses vary markedly. Certain opioids, such as morphine, can be more sedating than others. Drowsiness may affect performance of skilled tasks such as driving with effects of alcohol enhanced.

Euphoria is often reported although dysphoria may also occur. Morphine and most μ and κ agonists cause pupil constriction by the excitatory action on the parasympathetic nerve innervations[30].

Opioids cause an inhibition of the brain stem respiratory centres resulting in a reduction in both respiratory rate and tidal volume. The respiratory depression can be profound with the respiratory centre becoming less responsive to carbon dioxide. Therapeutic doses of opioids have little effect on blood pressure, heart rate or rhythm in reasonably fit supine patients, but hypotension may arise on standing up. Over dosage of opioids can be managed by giving naloxone intravenously. Naloxone is a μ -opioid receptor competitive antagonist; its rapid blockade of those receptors produces rapid reversal of symptoms[4].

Interactions

Opioid analgesics do have interactions with other prescribed and non-prescribed medication, including alcohol. Clinicians are advised to consult the British National Formulary or other international equivalent to determine the importance and nature of potential drug interactions for their patient[31].

Therapeutics

The choice of opioid is largely influenced by the traditional prescribing practices prevailing in each country. Diamorphine, for example, is never used medically in the USA and many European countries but is used in the UK. However, more commonly used opioids in the UK like other parts of world are codeine, dihydrocodeine, tramadol and morphine.

Codeine

Codeine (3-methylmorphine) is useful in controlling mild to moderate pain. The drug is well absorbed orally when compared with morphine but has a low affinity for opioid receptors. Approximately, 10% of the drug is

demethylated in the liver to morphine, which is responsible for the analgesic effects. Codeine is marketed as both a single preparation and in combination preparations with paracetamol, as *co-codamol*, ibuprofen as *Neurofen-Plus*. These combinations provide greater pain relief than either agent alone. The analgesic effect does not increase appreciably at higher doses. Unlike morphine, codeine it causes little or no euphoria and is rarely addictive. Codeine has an oral bioavailability of approximately 50%, significantly higher than morphine at 25% but not as high as tramadol at 75%. Some medications have the ability to block the conversion of codeine to morphine in the liver; these include selective serotonin reuptake inhibitors and some antihistamines (diphenhydramine)[5].

In the UK, codeine and higher strength codeine combinations, such as 30/500 co-codamol (30 mg codeine phosphate is combined with 500 mg paracetamol) are prescription-only medicines. Lower strength combinations, such as 8/500 or 12.8/500 are available as pharmacy medicines over the counter. Codeine is also used as an antitussive and less commonly as an antidiarrhoeal agent[11].

Respiratory depression is not clinically significant at normal doses; however, codeine is associated with constipation. The elimination half-life of codeine is 2.9 h.

The adult dose for codeine is 30–60 mg every 4 h orally to a maximum of 240 mg daily. Codeine can also be administered by intramuscular injection at a dose of 30–60 mg every 4 h[4].

Dihydrocodeine

Dihydrocodeine is pharmacologically very similar to codeine having no substantial advantages or disadvantages over codeine. The half-life of the drug is 4 h[32].

Dose: Oral 30 mg every 4–6 h. Child over 4 years 0.5–1 mg/kg every 4–6 h.

Subcutaneous/intramuscular (SC/IM): Adult 50 mg every 4–6 h. Child over 4 years 0.5–1 mg/kg every 4–6 h.

Tramadol

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used to treat moderate to severe pain. In Europe, the drug has been used since the 1970s for a range of pain conditions, and in the USA since the late 1980s.

It has selectivity for the μ-receptor and a weak inhibitor of the reuptake of noradrenaline and serotonin. This resembles the action of tricyclic antidepressants and tramadol potentiates descending inhibitory pathways. This action has proven efficacy in the management of chronic pain.

Tramadol does not have clinically significant respiratory depressant effect, and although generally well tolerated, it may cause nausea and vomiting, dizziness and drowsiness. In many countries, tramadol is not a controlled drug because it has a low potential for abuse and addiction. Tramadol has been used for pain after oral surgery. Tramadol undergoes hepatic metabolism, with metabolites being excreted by the kidneys. It has a half-life of 7 h[33].

Dose: Adult/Child over 12 years

- by mouth 50–100 mg not more often than every 4 h
- IM/intravenous (IV) 50–100 mg every 4–6 h
- For management of post-operative pain the British Notational Formulary recommends 100 mg initially then 50 mg every 10–20 min if necessary during the first h to total maximum of 250 mg (including initial dose) in first h, then 50–100 mg every 4–6 h; max 600 mg daily.

Morphine

Morphine is still the most commonly used opioid for acute pain. It derives its name from Morpheus, the Greek god of dreams. Morphine remains the gold standard with which other opioids are compared.

The absorption of morphine by mouth is variable; therefore, it is commonly given by intravenous or intramuscular injection. Most morphine like drugs undergo considerable first pass metabolism and are therefore markedly less potent when taken orally than when injected. The half-life of morphine is 2–3 h. Hepatic metabolism is the main mode of inactivation, while metabolites are excreted in urine.

PCA refers to the methods of pain relief that use electronic or disposable devices and allow patients to self-administer analgesic drugs. While PCA may be used for a variety of analgesic groups, they have been most commonly used for morphine. Opioid consumption may be higher when comparing PCA with conventional administration but the incidence of side effects is the same[14].

Dose

IM/SC – 10 mg initially every 4 h. (5 mg in elderly/frail)

Diamorphine

Diamorphine (heroin) is a semi-synthetic opioid with no activity at the μ-receptor. It is rapidly converted to

an active metabolite that is further metabolised to morphine. Diamorphine is not used medically in the USA or many European countries but is used in the UK. This difference is purely based on tradition[34].

Children

Codeine 1–12 years 3 mg/kg daily divided into doses.

Dihydrocodeine Oral Child over 4 years 0.5–1 mg/kg every 4–6 h.

SC/IM: Child over 4 years 0.5–1 mg/kg every 4–6 h

Tramadol is not recommended for children under 12 years old

Morphine 12–18 years – 2.5–10 mg every 4 h.

Pregnancy and lactation

Opioids should be avoided in pregnant patients or those who are breastfeeding.

Opioids should be used with caution in patients with impaired respiratory function and should be avoided in patients with COPD and patients presenting with head injury before full neurological investigation[11].

Opioids should be used with caution in patients with hypotension, urethral stenosis, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract and convulsive disorders. A reduced dose is recommended in elderly patients, in hypothyroidism and in adrenocortical insufficiency. Opioid dose should be reduced in patients with hepatic/renal impairments or avoided totally[35].

Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; however, this is rarely a problem with therapeutic use and not a problem with post-operative pain management. Caution may however advised if prescribing for patients with a history of drug dependence although this should never override proper pain relief.

Summary

Patients with moderate to severe pain are often undertreated in both developing and developed countries because opioids, which are the mainstay of pain relief in such cases, are mostly inaccessible. Opioids are categorised as controlled substances and therefore are subjected to stringent control. This poses a significant public health challenge.

The development of addiction in patients receiving opioids for acute pain is extremely rare, and their use should never be limited because of this concern. Patients may require reassurance about this.

Morphine is very appropriate for severe pain experienced by inpatients undergoing oral surgery, ideally administered intravenously or alternatively by intramuscular injection. Codeine is very effective when combined with paracetamol and suitable for day-case and outpatient oral surgery experiencing moderate to severe pain.

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