Techniques of opioid administration

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Abstract

Opiates remain the mainstay of the management of severe pain in acute, chronic and palliative settings across all population ages. Pharmacological advancement allows alternative routes of drug delivery best suited to individual patients and their conditions, with improved efficacy and safety. The different approaches to administration vary in their convenience, both to staff and patients, which can translate to differences in prescription compliance. Furthermore, the choice of technique can reduce the amount of drug administered, thereby improving the side effect profile. All opiates, regardless of the technique employed, require meticulous and careful titration based upon sound understanding. Training of staff and education of patients regarding the logistics of the chosen route is important to ensure optimal opiate delivery and detection of undesirable adverse events. Abuse and diversion of opiates warrants judicious administration and prescription considerations.

Keywords Administration; analgesia; delivery; opiate; opioid; pain; palliative; route; site; technique

Royal College of Anaesthetists CPD Matrix: 1A02, 1D02

Learning objectives

After reading this article, you should be able to:

- describe the different routes of opiate administration
- describe the advantages and disadvantages of different routes
- recognise how opiate pharmacology can dictate the route of administration
- relate dose equivalents between different opiate routes of administration
- evaluate the options of opioid delivery in order to provide tailored administration according to individual patient requirements

Methods to provide analgesia remain relatively limited, revolving principally around primary or secondary (antineuropathic) analgesics, local anaesthetic techniques and neuromodulation. Opiates are a group of primary analgesics which are in established practice and have long been an important method for providing analgesia across all settings, and form the main pharmacological treatment for acute perioperative pain control. The reliance on their use has led to advances in drug delivery and pharmacology, which has improved the overall management of pain, patient satisfaction and safety.

Variations in the routes of opiate administration seek to overcome three basic problems. The first is simply the ease and tolerability of administration. The second is targeting specific sites of opiate receptors for localized or generalized effects, whilst the last is the reduction in non-analgesic opiate effects, though rarely these effects can be used to an advantage (e.g. antitussive). The varying options to administer opiates all have advantages and disadvantages with respect to these three domains, and no single method is 100% effective in all three.

Methods of administration utilise both the pharmacokinetic property of the specific drug in question and the delivery system, whether a pharmaceutical preparation or medical equipment, such that one route of delivery may be effective for one drug and be inappropriate for another.

The physician is therefore required to select the appropriate drug and route of administration to suit the individual patient under their care. Each opiate has a defined therapeutic index and once the proposed drug and method of administration has been established, the aim is then to titrate to clinical effectiveness, whilst minimising adverse effects. Titration dose and timing depends upon the opiate, dose, and route used.

Classification of techniques

Methods of administration can be divided into simple or advanced. Simple methods are, by their nature, relatively safe owing to the fact that plasma and effector-site concentrations take time to be achieved, and so too do any adverse effects, allowing time for help or assistance. Examples include the oral, rectal, intramuscular and subcutaneous methods. Advanced methods rely on a greater understanding of the drug or equipment, and have the potential to result in the rapid onset of adverse effects, to which the administrator needs to be aware of and to be able to manage.

Comparison and equivalency

Regardless of the drug or route used, the standard by which the clinical effectiveness is benchmarked is that of immediate-release (IR) oral morphine, that is, 10 mg morphine per oral. Understanding the relative potencies of different opiates through different routes is essential in converting between opiates. This occurs frequently when specific routes become inaccessible, or side-effects develop to a particular drug. Rotational opiate conversions are also necessary when tolerance develops. Listed conversions, however, are not exact as they do not take into account incomplete cross-tolerance and are derived mainly from single-dose studies in opiate-naive patients. Actual conversions depend upon many factors individual to the patient which should be born in mind when calculating the new opiate and route. A safety factor of 25% dose reduction, and up to 50% for higher

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doses, on that calculated is therefore advisable when converting to alternative drugs/routes before upward titration again to achieve therapeutic effectiveness, whilst monitoring the patient for signs of toxicity or withdrawal[1] (Table 1).

Caution is especially important if converting between two non-oral opiates as it is common practice to convert back to an oral morphine equivalent (OME) before converting on to the desired opiate and route, regardless of the initial opiate used. This established practice can potentially increase the statistical error within the conversion process. One example where the route of opiate delivery is commonly changed is in 'step-down' analgesia, when a patient-controlled intravenous administration is changed to oral administration. In the case of morphine, understanding that the bioavailability of morphine is 30% allows the calculation that 10 mg intravenous morphine would be equivalent to requiring 30 mg of oral morphine.

Oral opiates

Advantages of the oral route are that it is simple, easy and well tolerated in most patients. Furthermore, no additional equipment is required, relying instead on the differing pharmacological and pharmaceutical properties of the opioid to achieve differing effects.

Unfortunately, the oral route is not always available or desirable. For example, physical restriction of oral access with limited mouth opening after head-and-neck surgery. A reduced consciousness level renders this route equally impractical unless an oro- or naso-gastric tube is utilised. Finally, gastroparesis and ileus can prevent drug transit. Opiates can act directly on μ opioid receptors in the gut wall further exacerbating this state.

Another disadvantage of this route is that of first pass metabolism. This renders fentanyl unsuitable due its extensive hepatic metabolism. Finally, orally administered medications, once through the liver, enter the hepatic vein, joining the systemic circulation. The resultant widespread distribution, means that relatively small amounts reach the main opiate receptor concentrations in the brain and spinal cord. A fraction of drug will also stimulate receptors in the chemoreceptor trigger zone resulting in nausea, which can further compromise the gastrointestinal function in some individuals and their ability to receive subsequent dosing.

Different pharmaceutical preparations exist in an attempt to modify the delivery of certain opiates. Preparations such as liquid, capsule, and encapsulation exist. These are broadly divided into either IR or slow-release (SR) preparations (also called extended-release, prolonged-release or controlled-release).

IR preparations typically have an onset of action 20–30 minutes, with analgesia obtained in 45–60 minutes, and a duration of action extending to around 3–4 hours. They are usually simple preparations of the active drug and some can be supplied in liquid form, such as oral morphine and oxycodone liquid/syrup. Differences in pharmacokinetics are mainly related to the different pharmacologic properties of each drug.

SR preparations, by contrast, utilise pharmaceutical techniques to alter the release of the active molecules, delaying their delivery. This allows a higher initial dose to be given and a sustained plasma level with a duration of action of 12–24 hours, avoiding the peaks and troughs typically associated with multiple IR dosing. The disadvantage, however, is that the onset is slow, typically taking 3–4 hours for peak effect. The use of SR preparations is not usually practical as a sole preparation in acute or cancer pain management (i.e. outside of non-cancer chronic pain), and tends to follow, or complement, the use of IR preparations. This is best achieved by calculating the total daily IR dose required and halving it for a twice-daily SR regime, with 10% of the total daily dose continued *pro re nata* as IR for incident or breakthrough analgesia. Over reliance on IR preparations in the chronic pain setting should alert the prescriber to look for abnormal pain behaviour.

Morphine comes in IR and SR forms and has a bioavailability of 30%. Most of the metabolites of morphine-3-glucuronide provide no analgesia, while morphine-6-glucuronide is more potent than morphine. Both are renally excreted.

Codeine is a prodrug and requires hepatic first pass metabolism with the enzyme CYP2D6 for conversion to morphine, with about 10% of the dose being converted to morphine. About 8–10% of Caucasians lack this enzyme, however, and therefore would achieve no benefit, whereas fast acetylators have a reduced duration of affect.

Oxycodone is another orally available opioid for the treatment of moderate-to-severe pain. Oxycodone's bioavailability is significantly higher than morphine's (up to 87%), and it has an analgesic onset of action of about 15 minutes, peaking at about 1 hour, with a slightly longer half-life. The SR preparation is indicated where treatment is expected to be prolonged, and has a biphasic release pattern, unlike other SR opiate preparations, resulting in an initial rapid release followed by a more sustained release. A tamper-resistant preparation which produces a lower oxycodone concentration when crushed is available but still requires judicious prescribing to prevent abuse and diversion. A

Approximate equi-analgesic potencies of opioids for oral administration

	Potency ratio with oral morphine	Equiv. dose (mg) to 10 mg oral morphine
Codeine phosphate	0.1	100
Dihydrocodeine	0.1	100
Hydromorphone	7.5	1.3
Methadone	[a]	[a]
Morphine	1	10
Oxycodone	2	5
Tapentadol	0.4	25
Tramadol	0.15	67

[a] The relative potency of methadone depends on the starting dose and the duration of administration. Conversions to and from methadone should always be undertaken with specialist advice.

Source: British Pain Society: Dose Equivalent and Changing Opioids. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids

Table 1