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Compounding for analgesia

By Dr Alison Haywood and Professor Beverley Glass

Rationale for compounding in analgesia

Pain, a unique symptom that may vary from patient to patient, can be divided into two categories: acute and chronic pain. Today, many healthcare practitioners realise that chronic pain is a very complex problem, and adequate treatment takes effort, thought, and in-depth problem solving skills, particularly in areas such as palliative care.

When considering dosage forms available for pain management (Figure 1), oral solid dosage forms are often the first choice, due to ease of administration. If a patient is unable to swallow oral solids, a commercially available oral liquid (e.g. hydromorphone, morphine, methadone, oxycodone, tramadol, naproxen, diclofenac, ibuprofen)[1] or alternative oral dosage form that does not need to be swallowed (e.g. fentanyl lozenges, bupenorphine sublingual tablets)[1] should be considered.

Alternative routes may also be investigated. Bupenorphine and fentanyl are available as transdermal preparations,[1] and paracetamol, oxycodone, diclofenac, ketoprofen and indomethacin are available as suppositories[1] (although some are low-dose formulations only suitable for children). Many drugs are available parenterally, however this requires specialist administration, is expensive, not always suitable for use at home, and in some patients there may be a lack of venous access or cachexia (i.e. there is little subcutaneous fat for hypodermoclysis).

Learning objectives

After reading this article you should be able to:

- Describe when compounding of medicines for analgesia might be necessary
- Describe suppositories as a compounded dosage form for meeting specific patient needs in analgesia
- Counsel patients on the appropriate use of compounded suppositories.

Competencies addressed:

4.2.2, 5.1.2, 5.1.4, 5.1.5, 5.2.7

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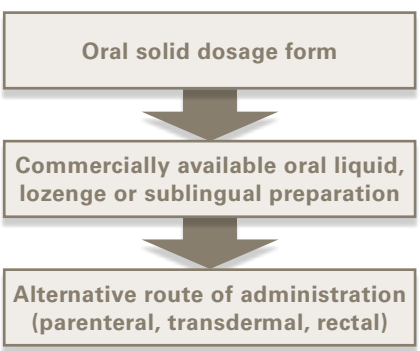
Why suppositories?

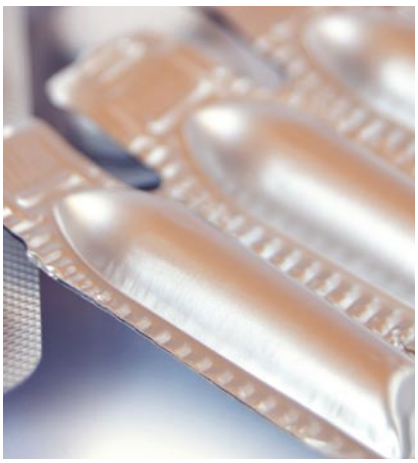
Suppositories have been used for centuries, dating back to Hippocrates, and have been administered by the rectal, vaginal and urethral routes. This article focuses on suppositories as an alternative:

a) to the oral route in patients with nausea and vomiting, dysphagia, delirium, or gastrointestinal absorptive impairment or obstruction
b) to repeated parenteral injections in patients with limited venous access, immunological deficiencies and bleeding disorders, or
c) when infusion pumps may not be available.[2–5] Further, parenteral administration may not be feasible at home owing to caregiver limitations, availability of technological support and cost.[2]

From a compounding point of view, suppositories are easily prepared and, together with appropriate patient and carer counselling, may provide an effective pain management alternative for those patient who have limited options. Further, compounding suppositories may also allow multiple drugs to be delivered in a single suppository thereby limiting the number of daily insertions.[2]

Figure 1. Management of analgesia in practice





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Patient acceptance and contraindications

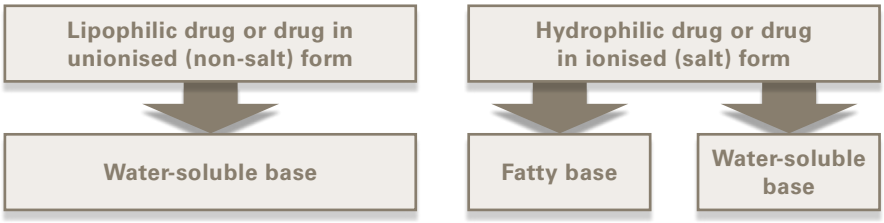
Caregiver willingness and patient compliance are limiting factors to the use of suppositories. Patient-related barriers include physical disabilities such as arthritis, which limits manual dexterity and suppository insertion. There may also be cultural and ethnic differences in acceptance of this dosage form. A lack of education regarding administration may limit dosing. This does however provide an opportunity for the pharmacist to become involved in counselling patients and caregivers on the use of suppositories.

Contraindications to the use of rectal medicines are relative rather than absolute. Medical contraindications include neuropathy (<500 neutrophils per microlitre), thrombocytopenia (<20,000 platelets per microlitre), diarrhoea, anorectal disease such as perianal abscess and fistulas, and prior abdominoperineal resection.[2]

New developments

Davis, et al.[2] have reviewed medicines administered rectally in cancer patients, including the suppository bases used and bioavailability for each active ingredient. In recent years, there have been many unique suppositories investigated including hollow-type suppositories, hydrogel suppositories, layered-double or triple suppositories, reversed-micellar-solution suppositories, sustained release suppositories (cellulose derivatives, carboxyvinyl polymers, or alginic acid), thermo-reversible-liquid suppositories and effervescent suppositories.[6] A study by Moolenaar, et al.[7] reported the clinical efficacy, safety and pharmacokinetics of a controlled release morphine sulphate suppository. The sustained-release suppository can be used to avoid the four-hourly rectal dosing schedule, usually required due to the fast rectal absorption and elimination of morphine. Each suppository contained 30.0 mg morphine sulphate, 108 mg aerosil R972, 300 mg hydroxypropyl methylcellulose (HPMC) 4,000 and 2,390 mg Witepsol W25.

Figure 2. How to choose a suppository base



Compounding suppositories

Active ingredient

Options available include sourcing the active ingredient as a pure drug powder or alternatively tablet or capsule contents can be used. The use of capsules is preferred over tablets due to the ease of use and that they generally contain fewer excipients (this can be evaluated by comparing the CMIs of the solid oral dosage forms available).

Excipients/suppository bases

Suppository bases

Four classifications of suppository bases are usually described. The most common are (i) the fatty or oleaginous (oil type) bases which melt at body temperature to release the medication, and (ii) the water-soluble or water-miscible polymer bases where the drug is released as a consequence of the progressive dissolution of the base into the intrarectal aqueous phase. Glycerin-gelatin bases (iii) are seldom used except as laxatives. The fourth group of bases (iv) contain various ingredients including disintegrating agents, natural gums, effervescent agents, collagen, and fibrin.[6]

Fatty or oleaginous bases: the most frequently employed suppository bases, principally because cocoa butter (theobroma oil) is a fatty base. Ingredients used in these bases include hydrogenated fatty acids of vegetable oils such as palm kernel oil and cottonseed oil, glyceryl monostearate, and glyceryl monopalmitate. Commercially available fatty bases are often prepared with the fatty materials emulsified or with an emulsifying agent, which emulsifies when the suppository makes contact with the aqueous body fluids.[6]

Water-soluble and water-miscible polymer bases: consist mainly of polyethylene glycols (PEGs) and poloxomers. PEGs are polymers of ethylene oxide and water, prepared to various chain lengths, molecular weights and physical states. The numerical designations of PEGs refer to the average molecular weights of each of the polymers, with the hardness increasing with an increase in the molecular weight, e.g. 300, 400 and 600 are clear, colourless liquids, and 1,000 and above are wax-like, white solids. Various combinations of PEGs may be combined by fusion to achieve a base of the desired consistency and characteristics. Commercially available bases contain combinations of the various PEGs in appropriate proportions.[6]

How to choose a suppository base

The lipid-water partition coefficient of a drug is an important consideration in the selection of the base and in anticipating drug release from that base. A lipophilic drug that is distributed in a fatty base in low concentration has less of a tendency to escape to the surrounding aqueous rectal fluids than a hydrophilic drug. However, water soluble bases which dissolve in the anorectal fluids will release both water-soluble and oil-soluble drugs for absorption.

Excipients

Suppositories may include suspending agents (e.g. micronised silica gel) to suspend the active ingredient, ensure content uniformity of the final product and thus accurate dosing.

Method

1. In the absence of compendial or other formulae, calculate the required quantity of each ingredient for the total amount required and determine the appropriate suppository base to be used (see Figure 3).
2. The active ingredient should be ground into a fine powder in a mortar and pestle. A small particle size is desirable for drugs present

Figure 3. Calculation of the amount of active ingredient and choice of base – an example

Step 1: Is the drug in a salt form? How many waters are attached or is it anhydrous?

- Morphine (Mw 285.3): $C_{17}H_{19}NO_3$
- Morphine sulphate (Mw 758.8): $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$
  Note: *there are 2 morphine molecules and 5 waters in this salt.*
- Morphine HCl (Mw 375.8): $C_{17}H_{19}NO_3,HCl,3H_2O$
  Note: *there is 1 morphine molecule and 3 waters in this salt.*

Conversion calculations:

- How much morphine is in 25 mg of morphine sulphate?
  Answer: 285.3 x 2/758.8 x 25 = 18.79 mg of morphine.
  Tip: *To determine how much morphine is in morphine sulphate multiply the sulphate by 0.75.*
- How do I convert an amount of morphine sulphate to morphine hydrochloride (HCl)?
  Answer: 285.3/375.8 x 25 = 18.98 mg of morphine in morphine HCl
  Tip: *To determine how much morphine HCl is equivalent to the sulphate multiply the amount of morphine sulphate by 0.99 (i.e. 24.75 mg of the HCl ~ 25 mg of the sulphate).*

Step 2: Choose a suitable suppository base.

- Morphine – unionised (non-salt), therefore use a water-soluble base.
- Morphine sulphate or HCl – water-soluble (ionised salt), therefore either base.

in the undissolved state, since this will facilitate dissolution, absorption and result in good bioavailability. This is of particular importance for those drugs with limited water solubility.

3. Excipients such as suspending agents should be incorporated using the principal of geometric dilution.
4. The suppository base should be melted using low heat, since many bases are sensitive to high temperatures.
5. The powdered ingredients should then be incorporated by slow sprinkling on the surface of the melt, with constant stirring.
6. The base should be allowed to cool slightly before pouring into a suitable mould. To ensure content uniformity of each suppository, the base should be poured immediately after stirring.
7. The suppositories should be appropriately labelled and packaged.

Calibration of suppository moulds and displacement values

When an amount as a dose (as distinct from a percentage) of medicament is prescribed, it is necessary to make an allowance for the volume occupied by the medicament in each suppository (i.e. displacement value). *APF21*[8] provides displacement values for a limited number of drugs. It is also important to calibrate the suppository mould with the suppository base to be used. Suppliers of suppository moulds will usually provide this information with their equipment.

Packaging

Suppositories may be individually wrapped in foil and placed in a sealed container (e.g. 50 g ointment jar), or supplied in a disposable mould. Contact your local supplier for equipment and packaging options.

Labelling

Compounded products are to be labelled according to regulatory requirements[9] and should include the approved pharmacopoeial name (where applicable) and the name and strength of any preservatives used. The label must also be in accordance with the relevant state law.[8] A complete list of ingredients and their amounts/proportions should be included when non-pharmacopoeial products are prepared. Ancillary labels should be used to indicate specific storage conditions, provide an expiry date and indicate specific usage conditions. Suitable labels to indicate internal or external use, such as Label L *CAUTION NOT TO BE TAKEN* should be included.

Storage

In the absence of any published stability data, the APF recommends an expiry date 28 days from that of manufacture.[8] Suppositories should be stored in a cool (<25°C), dry place, protected from light. Ideally, polyethylene glycol and Witepsol bases should not be stored in the refrigerator due to problems with cracking, however in certain regions of Australia, where there are extremes of temperature and humidity; refrigeration (2–8°C) may be the only option.

Quality control and self-inspection

The pharmacist is responsible for ensuring the quality of extemporaneously prepared products and should verify that products are prepared according to documented procedures and meet product specifications before releasing them for dispensing.[8] Self-inspections should also be conducted at regular intervals to identify areas for improvement and the resulting actions should be documented.[8]

Counselling/instructions for patients

Important counselling information would include the usefulness of suppositories as a dosage form and also establishing whether there are any patient or carer barriers to the use of this dosage form. Directions for use should include the following (adapted from *Proladone* (oxycodone pectinate) CMI[10]):

- If possible, go to the toilet and empty your bowels before using your suppository.
- Wash your hands thoroughly with soap and water.
- If the suppository is too soft to use, put it in the refrigerator for about 15 minutes. (The instruction to chill by holding it under cold water for a few minutes should only be

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used if the packaging protects the suppository from water.)

- Put on a disposable glove, if desired. (These may be supplied with the suppositories.)
- Remove the suppository from the packaging. (If suppositories are supplied in a disposable mould, detailed instructions should be given on how to remove it.)
- Moisten the suppository by dipping it briefly in cool water. (This will provide lubrication and is especially important for water soluble bases that can cause pain due to their hygroscopic nature.)
- Lie on your side and raise your knee to your chest. Push the suppository gently, pointed end first, into your rectum (back passage). (Some may argue that retention is superior when the base rather than the apex is delivered first, since the lower edge of the external sphincter contracts along the edge of the apex forcing the suppository upwards, which facilitates retention.)[2]
- Remain lying down for a few minutes, to allow the suppository to melt/dissolve.
- Throw away used materials and wash your hands thoroughly.
- Try not to go to the toilet for at least an hour after using the suppository.
- If you are not sure how to use a suppository, ask your pharmacist.

Pharmacist role

Suppositories provide a practical example for pharmacists across all areas of practice in community, hospital and aged care of how compounding can be used to enhance the safe and effective use of medicines to meet patients' specific needs. Pharmacists have an important role to play in educating patients and carers of the usefulness of this dosage form and overcoming psychological barriers to their use.

Key learning points

- Patients' unique needs for pain medication may be met by pharmacists compounding suppositories, where other routes of administration are not available.
- It is important to determine the amount of active ingredient for the suppository taking into account the type of salt (e.g. sulphate/HCl) and whether it is anhydrous or not.
- Choice of a suitable base is the next step in the process of compounding suppositories. For drugs which are in their ionised (salt) form (e.g. sulphate/HCl/sodium), both water-soluble and fatty bases can be used, although fatty bases are often preferred, because the water-soluble bases may cause evacuation in some patients. However, fatty bases are not suitable for the non-salt form of the drug.
- Labelling and packaging the suppositories appropriately is then undertaken with consideration given as to how they will be stored.
- Counselling of the patient on storage (<25°C), expiry (28 days) and use is the final responsibility of the pharmacist in this process.

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Questions

A score of 3 out of 4 attracts three quarters of a credit point.

1. There are several reasons why a patient may require administration of their oral opioids via the rectal route. Which **ONE** of the following reasons is **INCORRECT**?

a) Patients are unable or unwilling to swallow.
b) Patients are suffering from severe nausea and vomiting.
c) Patients require their medication to be delivered at home.
d) Patients have access to infusion pumps.
e) Patients with immunological deficiencies and bleeding disorders are unable to have repeated parenteral injections.

2. Which of the following drugs used in pain management is **not** suitable for compounding in a fatty suppository base?

a) Morphine sulphate.
b) Oxycodone HCl.
c) Indomethacin sodium.
d) Methadone HCl.
e) Hydromorphone.

3. Given the following formula (per suppository):

Morphine sulphate	30 mg
Aerosil R972	108 mg
HPMC 4000	300 mg
Witepsol W 25	2,390 mg

You have been supplied with morphine HCl. How much morphine HCl do you need per suppository to deliver the required dose of morphine?

a) 29.7 mg.
b) 30 mg.
c) 22.5 mg.
d) 33 mg.
e) 15 mg.

4. Packaging, labelling and storage of compounded suppositories are the responsibility of the pharmacist. Which of the following statements is **CORRECT**?

a) Suppositories should be individually wrapped in foil, but do not need to be placed in sealed container.
b) Labelling requires the inclusion of the pharmacological name of the drug ONLY.
c) *"CAUTION NOT TO BE TAKEN"* need not be included on the label.
d) An expiry date of 3 months from the date of manufacture is acceptable.
e) Although storage below 25°C is recommended, refrigeration may be required in certain climatic regions of Australia.