Subcutaneous and intravenous route of opioid administration in cancer pain treatment

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The contraindications and factors that limit *oral route* of drugs administration:

- serious fatigue, which makes it impossible for patients to receive medication orally
- the need for continuous pain control in unconscious patients
- persistent nausea and vomiting
- obstruction of the gastrointestinal tract
- dysphagia or swallowing difficulties
- impaired laryngeal reflex
- gastrointestinal absorption disorders involving medicines
- the need for fast treatment of severe pain
- on request of the patient who would otherwise have to swallow a lot of pills
The oral route may also prove less than optimal in the context of impaired bioavailability after such administration

- metabolic inactivation by the mucous membrane and the intestinal flora
- metabolic inactivation by the liver

Alternative routes of administration of medicines, especially in palliative medicine:

- multiple injections
- continuous infusions,

both subcutaneous or intravenous.
The history of subcutaneous administration of morphine dates back to the American Civil War, with the first s.c. injections to injured soldiers having been made in 1863.

After over a hundred years, since 1979 s.c. infusions of morphine have been used in the treatment of cancer pain.
Most opioids can be administered subcutaneously. The class includes:

- morphine,
- diamorphine (in small doses),
- oxycodon,
- fentanyl,
- tramadol
Advantages

• the possibility to administer small volumes for a long time

• efficient absorption (*however in cachectic patients and those with disturbed peripheral circulation, the process of absorption can be significantly reduced*)

• lesser discomfort caused by tissue stretching – considerably smaller than the pain accompanying intramuscular injections.

• the possibility to administer anti-emetic medicines, analgesics, cholinolytics and sedatives – simultaneous treatment/control of a number of symptoms („drug combinations“)

• high surface/volume coefficient

• simple preparation of medicine mix and convenient operation of the syringe/pump (available pumps are usually lightweight, or small portable)

• significantly reduced incidence of infections

• stable concentration of opioids in blood serum (in comparison to oral administration)

Trescot A.M. Opioid pharmacology. Pain Physician 2008,
<table>
<thead>
<tr>
<th></th>
<th>CSCI</th>
<th>ISCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pain VAS (95% CI)</td>
<td>26.7 (15.9, 37.4)</td>
<td>27.2 (17.4, 36.9)</td>
</tr>
<tr>
<td>Mean pain CRS (95% CI)</td>
<td>1.3 (0.9, 1.7)</td>
<td>1.2 (0.8, 1.5)</td>
</tr>
<tr>
<td>Mean drowsiness VAS (95% CI)</td>
<td>28.7 (17.4, 40.0)</td>
<td>26.6 (14.5, 38.6)</td>
</tr>
<tr>
<td>Mean nausea VAS (95% CI)</td>
<td>21.0 (9.3, 32.7)</td>
<td>24.8 (9.7, 40.0)</td>
</tr>
<tr>
<td>Mean no. of BTA/day (95% CI)</td>
<td>1.6 (0.8, 2.4)</td>
<td>1.0 (0.5, 1.5)</td>
</tr>
<tr>
<td>Mean overall effectiveness (95% CI)</td>
<td>2.5 (2.1, 2.9)</td>
<td>2.9 (2.5, 3.3)</td>
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CSCI, continuous subcutaneous infusion; ISCI, intermittent subcutaneous injection;
Drawbacks / Disadvantages

The necessity to prepare the infusion drug mix for every 24 hours.

This causes problems in changing the dosage or composition of medicines.

In order to modify the infusion volume in a given time unit, it is necessary to prepare drug mix in the pump again.

The type of needle/cannula

the choice includes:

• short metal butterfly
• needles or teflon-coated cannulae.

Teflon-coated cannulae last twice as long as metal needles, therefore they should be used for subcutaneous infusions in terminally ill patients.

The duration of needle placement

the pH and osmolality of medicine/medicine mix.

Only isotonic solutions reduce the risk of skin irritations.

Such medicines as e.g. diazepam, prochlorperazine, cause considerable skin irritation and sterile skin abscesses.

Adding 1 mg of dexamethasone or 100 mg hydrocortisone to the solution/24 hours significantly increases the “survival time” of indwelling cannulae.

The fundamental principles governing the location and exchange of s.c. cannulae:

- The needle/cannulae can be placed on the chest, the abdominal wall or the thigh.

- In agitated patients, it is better to insert the needle into the patient's back close to the scapula in order to avoid accidental removal of cannulae.

- Patients tolerate well the subcutaneous infusion rate of $\leq 5$ ml/hr. Greater volumes are used for subcutaneous supplementing of liquids in dehydrated patients.

- Transfusion sets ought to be changed every 24 hours, and the needle insertion site should be routinely changed every 5–7 days.

- The location of the cannula should be changed in the event of oedema or the haematoma at needle insertion site.

*Walsh D. Palliative medicine, Saunders-Elsevier, 2008.*
The main advantages of subcutaneous infusions is the opportunity to simultaneously use several preparations, Experience shows that under optimal conditions the infusion should contain as few components (i.e. different medicines) as possible and in lowest possible concentrations.

In 2001 O'Doherty C et al. demonstrated that palliative medicine specialists (*in 165 centers of palliative medicine*) surveyed most often use mixtures of:

- three different medicines (52% centres surveyed)
- or four different medicines (36% centres surveyed).

....however five years later,

Wilcock analysed the medicine mixes administered subcutaneously in 328 automatic syringes during a prospective study *of 15 palliative medicine centres* observed that:

- 44% reported a mixture of two medicines,
- 30% reported three different compounds.

ketoprofen administered with morphine significantly reduces weekly requirement for morphine
Adverse effect

sedation

hallucination

constipation

nausea

vomiting

dizziness
intravenous infusion of opioids may be preferable in patients:

- with a central vein catheter placed for other reasons,
- with generalized oedema,
- who develop erythema, soreness or sterile abscesses with s.c administration,
- with coagulation disorders,
- with poor peripheral circulation.

...in recent years, in palliative medicine wards, the number of cancer patients has increased with i.v. ports or central vein catheters, which greatly modifies the therapeutic options and their efficacy...
The intravenous route is also preferable if medicines need to be administered frequently for the purpose of “fact and effective control” of pain and other symptoms.

Cumulative percentage of patients who had satisfactory pain relief at successive time points.
The time necessary to obtain pain relief during morphine titration.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Response time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagen et al.</td>
<td>9</td>
<td>89 minutes</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>491</td>
<td>&lt;100 minutes</td>
</tr>
<tr>
<td>Harris et al.</td>
<td>62</td>
<td>&lt;1 hour</td>
</tr>
<tr>
<td>Mercadante et al.</td>
<td>49</td>
<td>9.7 minutes</td>
</tr>
<tr>
<td>Soares et al.</td>
<td>18</td>
<td>11 minutes</td>
</tr>
</tbody>
</table>

Table 89.6  
Oral opioid titration for acute crescendo cancer pain

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Time to response</th>
<th></th>
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<tbody>
<tr>
<td>Klepstad et al.</td>
<td>120</td>
<td>2.1 days (SR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7 days (IR)</td>
<td></td>
</tr>
<tr>
<td>Klepstad et al.</td>
<td>40</td>
<td>2.3 days</td>
<td></td>
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<tr>
<td>Lichter</td>
<td>50</td>
<td>1 day (every 4 hours)</td>
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half-elimination time

...is an important parameter as it will indicate when a steady state is reached with the drug. As five half-lives are needed for steady state, it can be calculated that for morphine it will take from 10 to 20 hours to reach a steady state, whereas for methadone it may take between 20 and 650 hours! ...
I. Assessment of effective dose of analgesic

Intravenously 1–2 mg of MF every 5–10 minutes, until perceptible pain control is achieved

II. Continuation of treatment:

if the effective dose obtained via titration was 6 mg, (the half-elimination time of morphine is 3–4 the hours, which means that in this instance, 3 mg of morphine will biodegrade and must be supplemented in order to maintain the MEAC in blood serum) therefore the patients will need to have 3 mg of morphine supplemented within 3 hours,

continuous i.v. or s.c. infusion of 1 mg morphine per 1 hour;

After patient titration and determining the effective dose of opioid, one can:

• continue continuous i.v. infusion;

• change the route of administration to continuous s.c. infusion or apply single s.c. boluses every 4 hours (in an identical daily dose as during i.v. infusion);

• change in the route of administration to oral using the dosage conversion rate of 1:2 or 1:3, e.g. aqueous solution of morphine every 4 hours or controlled release tablets administered every 12 hours.


The titration of *i.v. opioids* is not only an effective and rapid method of pain relief, but also is safe and unrelated to increased risk of respiratory centre depression.

**Figure 1** ET-CO₂ changes in individual patients. Numbers represent individual study subjects (*n* = 29).

**Figure 2** Mean and standard deviation of ET-CO₂ on the first and last study days (*n* = 29).

Continuous pump infusion is practised considerably more frequently, especially in hospitalised patients to maintain:

- a stable concentration of medicine in blood
- convenience for the nursing staff
- avoidance of repeated painful injections.
- Continuous intravenous opioid infusion can be a safe and effective method of pain control.
Intravenous PCA (Patient-Controlled Analgesia)

30 - 40% of terminal patients in their final days require increased doses of analgesics.

Morphine is the most popular opioid in palliative medicine.

The different possibilities of administration
oral,
per rectum,
intravenous,
intramuscular,
subcutaneous,
epidural,
intrathecal,
to brain ventricles
topical

The possibility to quickly modify the dose and the broadest experience in its practical application by many generations of doctors, makes morphine an irreplaceable means of pain control in patients at the terminal stages of their lives.

Morphine is metabolized (> 90%) mostly in the liver to:

- morphine-3-glucuronate (M3G)
- in smaller quantities, to morphine-6-glucuronate (M6G)
- normorphine

All 3 metabolites are active.

- M6G in a way contributes to the analgesic effect of morphine,
- M3G and normorphine have neurostimulant properties, causing convulsions, the development of the tolerance, and opioid hyperalgesia (paradoxical pain after opioid administration).
Concentration rates after **oral** vs. **intravenous** morphine administration

- **oral** morphine: \( \text{M3G} : \text{M6G} \rightarrow 1 : 24.3 : 3.1; \)
- **i.v.** morphine: \( \text{M3G} : \text{M6G} \rightarrow 1 : 8.5 : 1.1. \)

The risk of the development of tolerance and opioid hyperalgesia is significantly lower in the case of parenteral administration of morphine.


...significant improvement in pain control after continuous s.c. or i.v. infusion in 71% cancer pain patients studied, in whom previously used oral or transcutaneous analgesics were ineffective...

Enting et al. demonstrated: significant improvement in pain management quality!!!
Parenteral administration of opioids may have additional important advantages:

*less frequency of constipation* in patients receiving *i.v. morphine*, which is attributed to the reduced capacity of medicine binding with opioid receptors in the GI tract compared with patients receiving oral opioids.


*less frequent nausea and vomiting* when compared to the oral route


_Gordon J. Wood i wsp.: Management of Intractable Nausea and Vomiting in Patients at the End of Life. JAMA, 2007._
Panel: Intravenous morphine for management of cancer pain

Advantages
- Total drug availability and predictable effects
- Short onset for opioid titration and breakthrough pain
- Flexible modalities: boluses, continuous infusion, patient-controlled analgesia
- Less initial metabolite formation
- Unlimited volumes
- Best for patients with oral tract precluded or poor gastrointestinal absorption

Disadvantages
- Need to maintain the intravenous route
- Increased cost
- More complex management for caregivers
- Close supervision needed
- Availability of sites (unless permanent access)

The need for education, especially involving oncologists and all those who consult cancer patients in their own practice.

because

An appropriate choice of administration route of opioids or its exchange to an alternative one may in a number of cases improve the comfort and quality of life of patients receiving palliative care.

„Medicine is only for those who are fit enough to survive the treatment as well as the illness.‖

J.B. Moliere (1673 r.)
Equianalgesic doses of opioids (mg/d):

Morfina 100 mg *p.o.*

Morfina 33 mg *i.v.*

Fentanyl 1 mg *t.d.*

metadon 20 mg *p.o.*

metadon 16 mg *i.v.*

Oxycodone 70 mg *p.o.*

Buprenorfina 1.3 mg *t.d.*