Subcutaneous and intravenous route of opioid administration in cancer pain treatment

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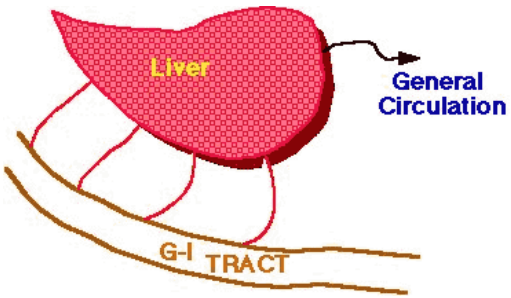
The contraindications and factors that limit *oral route* of drugs administration:

- 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**



Walsh D. : Palliative medicine, Saunders-Elsevier, 2008

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.

Walsh D. : Palliative medicine, Saunders-Elsevier, 2008

Most opioids can be administered subcutaneously

the class includes:

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

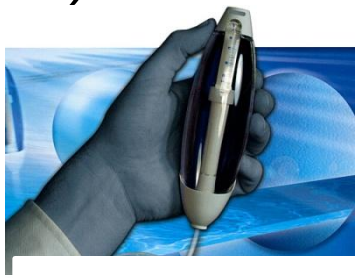
Advantages

- 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

Walsh D. Palliative medicine, Saunders-Elsevier, 2008.

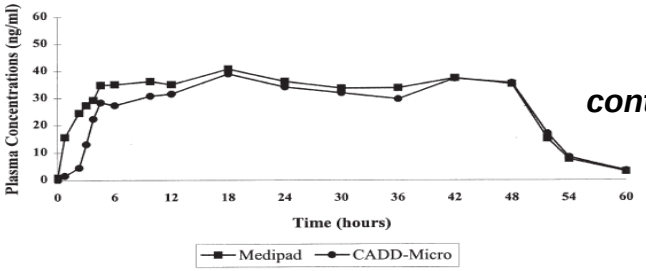
Trescot A.M. Opioid pharmacology. Pain Physician 2008

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

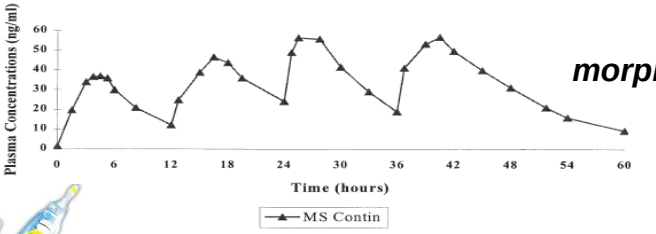


- significantly reduced incidence of infections

- stable concentration of opioids in blood serum (*in comparison to orall administration)*



continuous subcutaneous infusion



morphine SR – orally

Walsh D. Palliative medicine, Saunders-Elsevier, 2008.

Trescot A.M. Opioid pharmacology. Pain Physician 2008,

Pia Mikkelsen i wsp.: J. Pain and Symptom Management, 2002.

	CSCI	ISCI
Mean pain VAS (95% CI)	26.7 (15.9, 37.4)	27.2 (17.4, 36.9)
Mean pain CRS (95% CI)	1.3 (0.9, 1.7)	1.2 (0.8, 1.5)
Mean drowsiness VAS (95% CI)	28.7 (17.4, 40.0)	26.6 (14.5, 38.6)
Mean nausea VAS (95% CI)	21.0 (9.3, 32.7)	24.8 (9.7, 40.0)
Mean no. of BTA/day (95% CI)	1.6 (0.8, 2.4)	1.0 (0.5, 1.5)
Mean overall effectiveness (95% CI)	2.5 (2.1, 2.9)	2.9 (2.5, 3.3)

CSCI, continuous subcutaneous infusion; ISCI, intermittent subcutaneous injection;

	CSCI	ISCI
Dry mouth	10	10
Fatigue	9	11
Drowsiness	10	9
Poor sleep	8	6
Nausea	7	7
Constipation	6	5
Vomiting	5	4
Difficulty concentrating	3	4
Dizziness	3	3
Agitation	2	3

WATANABE S i wsp.: A Randomized Double-Blind Crossover Comparison of Continuous and Intermittent Subcutaneous Administration of Opioid for Cancer Pain. JOURNAL OF PALLIATIVE MEDICINE, 2008

Drawbacks / Disadvantages

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

This causes problems in changing the dosage or compsition of medicines. In order to modify the infusion volume in a given time unit, it is necessary prepare drug mix in the pump again.

Walsh D. : Palliative medicine, Saunders-Elsevier, 2008
Penson J, Fisher RA.: Palliative care for people with cancer, Arnold, 2005.

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.

Walsh D. Palliative medicine, Saunders-Elsevier, 2008.

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. diazepame, 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

Walsh D. : Palliative medicine, Saunders-Elsevier, 2008

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 ≤ 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.

Walsh D. : Palliative medicine, Saunders-Elsevier, 2008

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).

No. of drugs	% of units
1	1
2	7
3	52
4	36
5	2
6	1
>6	1

….however five years later,

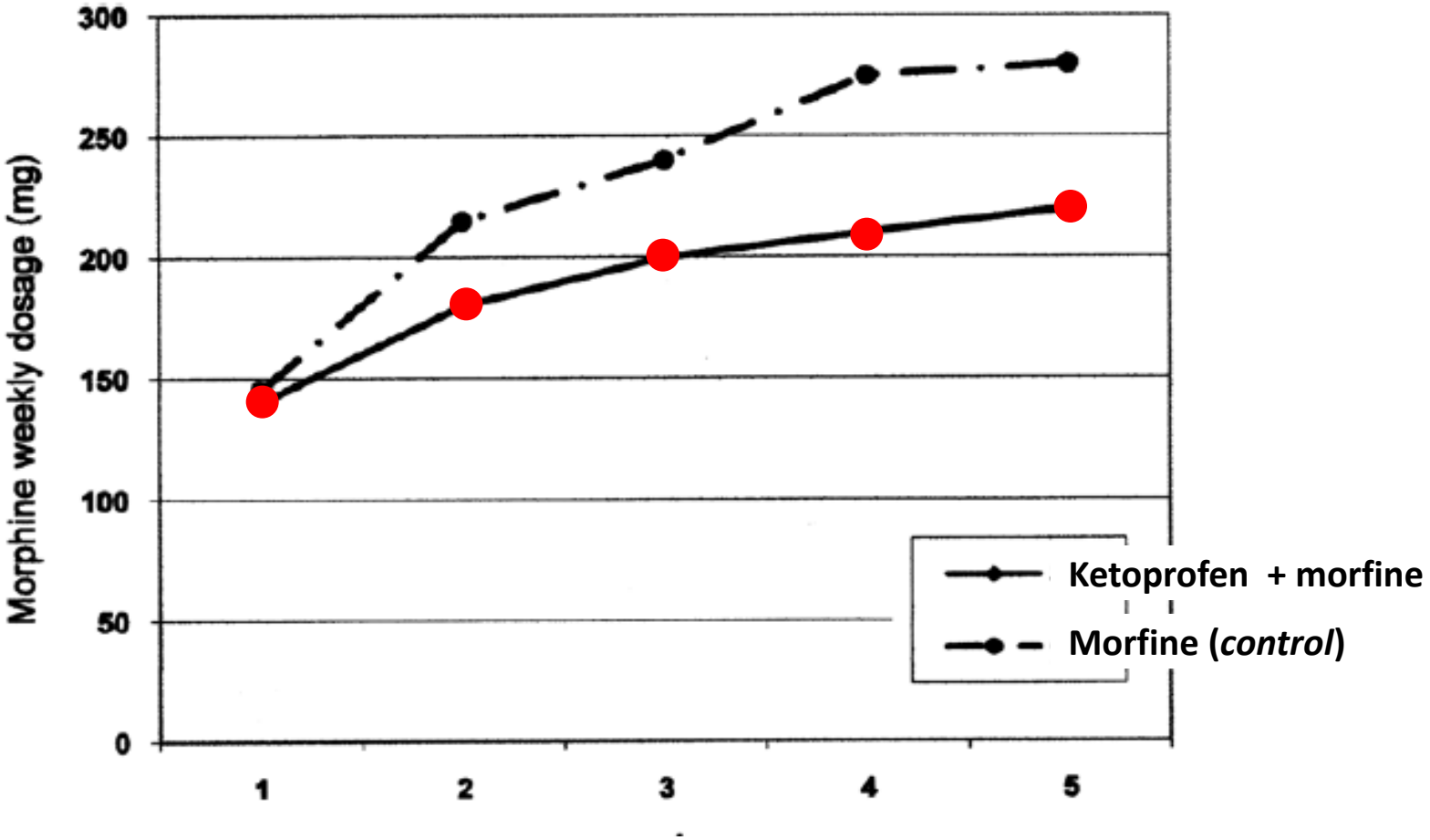
Wilcock analysed the medicine mixes administered subcutaneously in 328 automatic syringes during a prospective study *of 15 palliative medicine centres* observed that:

44% reported a mixture of two medicines,

30% reported three different compounds.

No. of drugs	Frequency
1	66 (20%) one
2	143 (44%) one
3	100 (30%)
4	18 (5%)
5	1 (<1%)

O'Doherty C et al.: Drugs and syringe drivers: a survey of adult specialist palliative care practice in the United Kingdom and Eire. Palliat Med 2001;.
Wilcock A i wsp.: Drugs given by a syringe driver: a prospective multicentre survey of palliative care services in the UK. Palliative Medicine 2006,



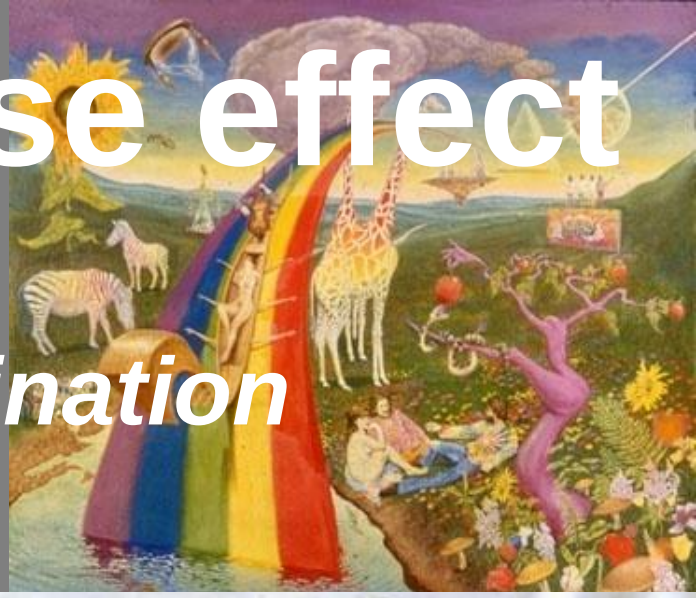
ketoprofen administered with morfine significantly reduces weekly requirement for morfine

Moselli NM et al.: Long-term continuous subcutaneous infusion of ketoprofen combined with morphine: a safe and effective approach to cancer pain. Clin J Pain. 2010.

Adverse effect

sedation

hallucination



nausea
vomiting

dizziness

constipation

i.v. opioids

intravenous infusion of opioids

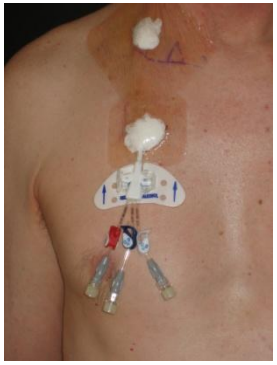
may be preferable in patients:

- *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.*

Bruera E i wsp.: Textbook of palliative medicine, Hodder-Arnold, 2009.
Morphine and alternative opioids in cancer pain: the EAPC recommendations. British Journal of Cancer, 2001, 84, 587–593

i.v. opioids

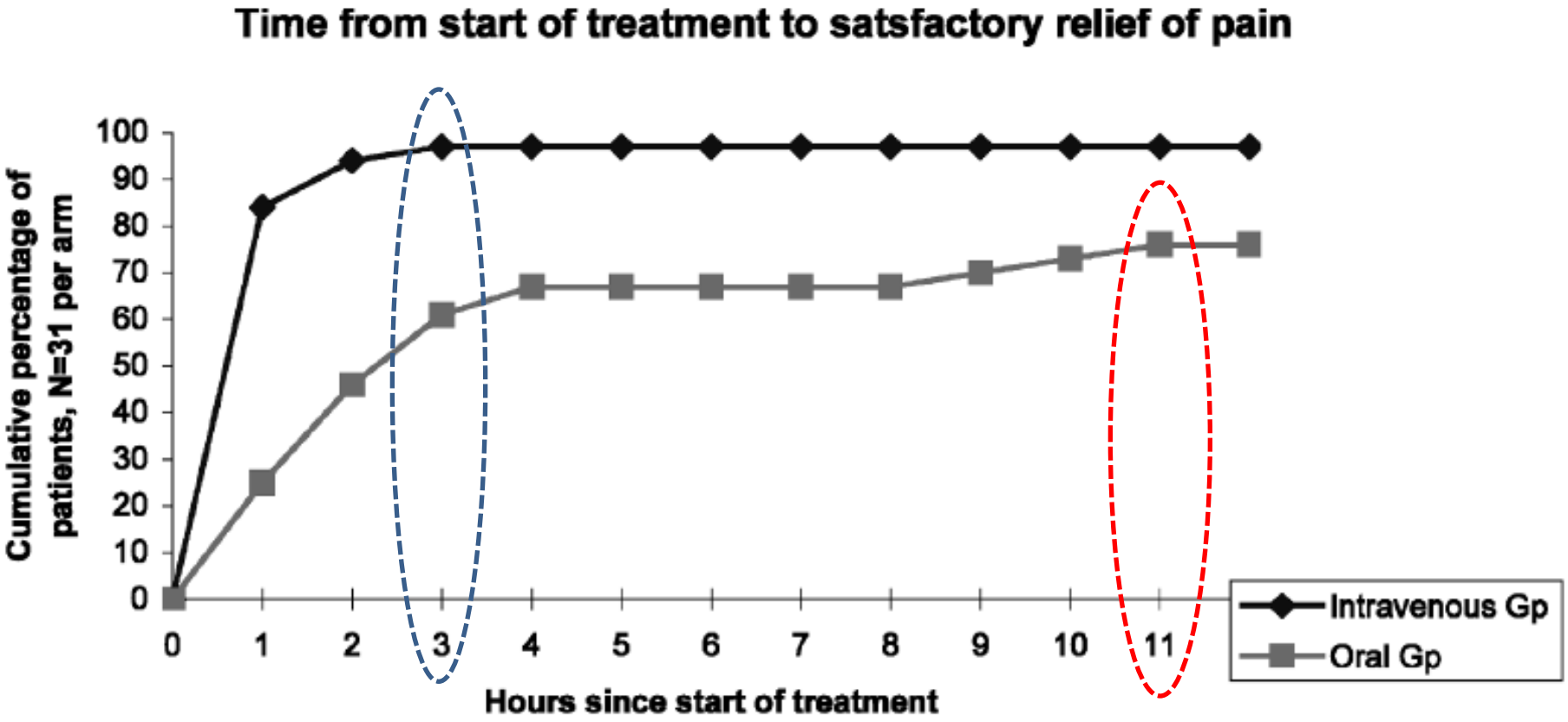
…in recent years, in palliative medicine wards, the number of cancer patients has increased with i.v. ports or central vein catheters, which greatly modifies the therapeutic options and their efficacy…



Mercadante S et al.: Frequency, Indications, Outcomes, and Predictive Factors of Opioid Switching in an Acute Palliative Care Unit. Journal of Pain and Symptom Management, 2009

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.

Bruera E i wsp.: Textbook of palliative medicine, Hodder-Arnold, 2009.



Cumulative percentage of patients who had satisfactory pain relief at successive time points.

Harris J.T., Suresh Kumar K., Rajagopal M.R. Intravenous morphine for rapid control of severe cancer pain. Palliat. Med. 2003.

The time necessary to obtain pain relief during morphine titration.

Study	No. of patients	Response time
Hagen *et al.*[51]	9	89 minutes
Kumar *et al.*[53]	491	<100 minutes
Harris *et al.*[52]	62	<1 hour
Mercadante *et al.*[40]	49	9.7 minutes
Soares *et al.*[49]	18	11 minutes

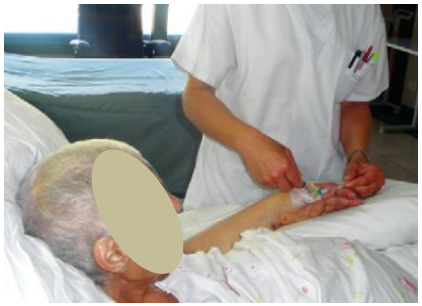


Table 89.6 *Oral opioid titration for acute crescendo cancer pain*

Study	No. of patients	Time to response
Klepstad *et al.*[68]	120	2.1 days (SR) 1.7 days (IR)
Klepstad *et al.*[69]	40	2.3 days
Lichter[41]	50	1 day (every 4 hours)

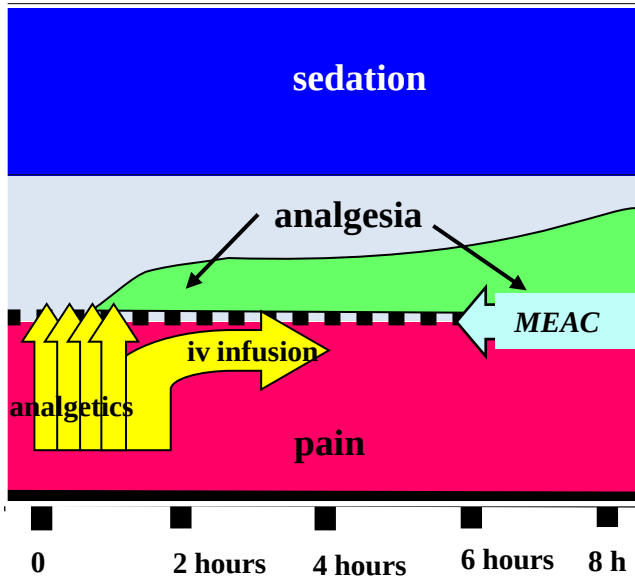
Ripamonti C Alternative routes for systemic opioid delivery - Textbook of palliative medicine, 2009, 415–430.

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! . . .

Kalso E.: Clinical pharmacology of opioids in the pain treatment. Pain 2008-An Updated Review. IASP Press

continuous i.v. opioid infusion



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;

Mercadante S.: Opoioid titration in cancer pain. A critical review. EJP, 2007.

Mercadante S i wsp.: Frequency, Indications, Outcomes, and Predictive Factors of Opioid Switching in an Acute Palliative Care Unit. J. Pain and Symptom Management , 2009.

Dobrogowski J, Krajnik M, Wordliczek J.: Consensus statement with focus on cancer pain management. Oncology in Clinical Practice, 2009

i.v. opioids

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.

Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br. J. Cancer 2001; 84: 587–593.

Takahashi M.,. The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. Palliat. Med. 2003; 17: 673–678.

Mercadante S i wsp.: Frequency, Indications, Outcomes, and Predictive Factors of Opioid Switching in an Acute Palliative Care Unit. J. Pain and Symptom Management , 2009.

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.

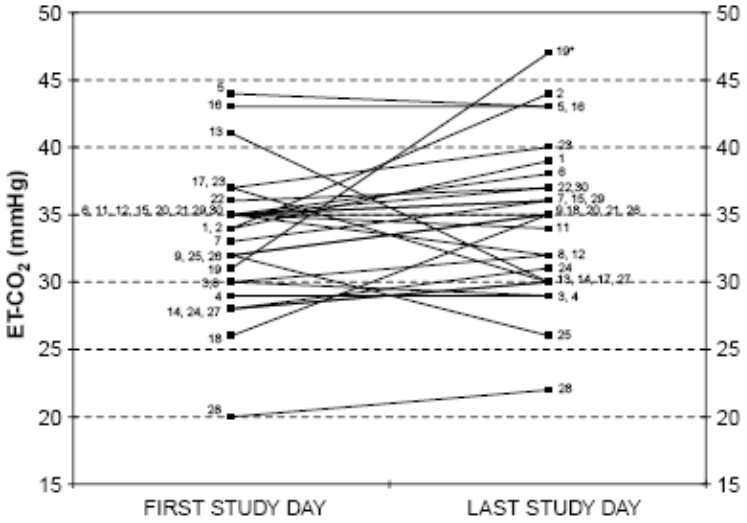


Figure 1 ET-CO_2 changes in individual patients. Numbers represent individual study subjects ($n = 29$).

Bassam Estfan et al. Respiratory function during parenteral opioid titration for cancer pain. Palliative Medicine 2007;

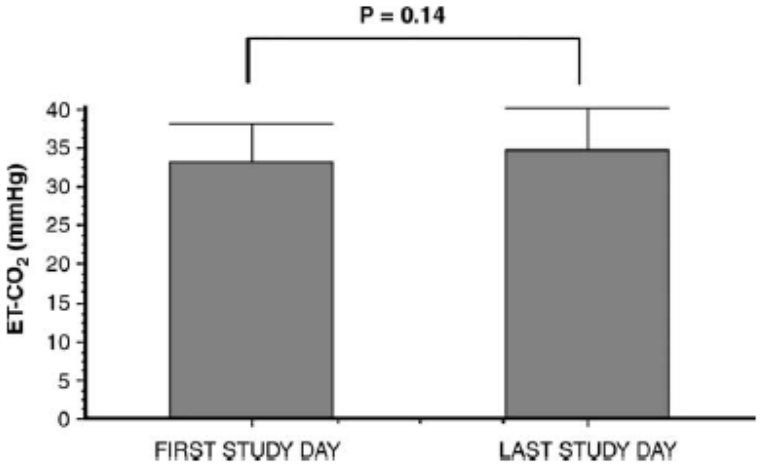


Figure 2 Mean and standard deviation of ET-CO_2 on the first and last study days ($n = 29$).

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

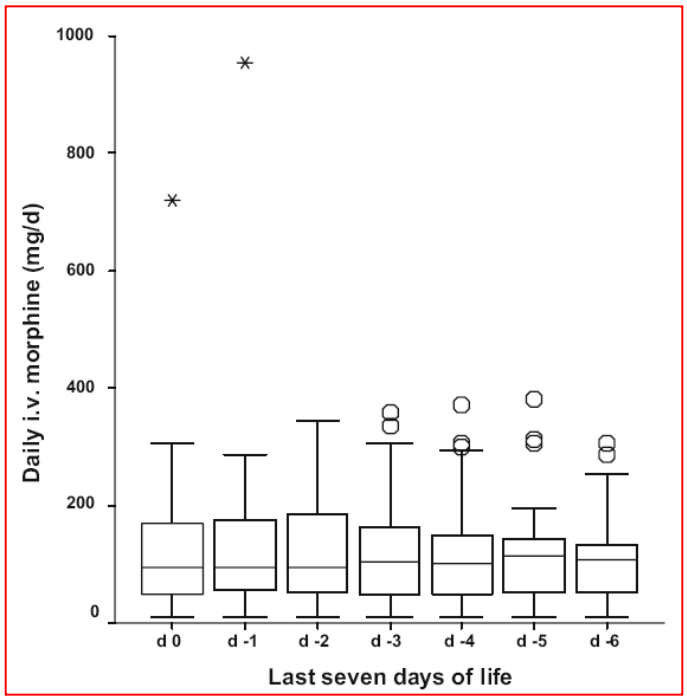
- ***a stable concentration of medicine in blood***
- ***convenience for the nursing staff***
- ***avoidance of repeated painful injections.***
- ***Continuous intravenous opioid infusion can be a safe and effective method of pain control***

Mercadante S., Rapid Titration with Intravenous Morphine for Severe Cancer Pain and Immediate Oral Conversion. Cancer 2002;.
Guilherme L., Intravenous Fentanyl for Cancer Pain: A "Fast Titration" Protocol for the Emergency Room. J. Pain Symptom Manage. 2003;

Intravenous PCA (*Patient-Controlled Analgesia*)

i.v. opioids

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



Schiessl C.: Intravenous morphine consumption in outpatients with cancer during their last week of life—an analysis based on patient-controlled analgesia data. Support Care Cancer (2008) 16:917–923

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.

Jon Raphael et al.: Part 1: Pathophysiology; Oncological, Pharmacological, and Psychological Treatments: A Perspective from the British Pain Society Endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. Pain Medicine, 2010.

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: M3G : M6G — 1 : 24.3 : 3.1;**
- ***i.v.*** **morphine : M3G : M6G — 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

Takahashi M., The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. Palliat. Med. 2003.

significant improvement in pain management quality !!!

Enting et al. demonstrated :

…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 RH : A prospective study evaluating the response of patients with unrelieved cancer pain to parenteral opioids. Cancer 2002 ,

Parenteral administration of opioids may have additional important advantages:

i.v. opioids

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.**

Mazumdar A., Intravenous morphine can avoid distressing constipation associated with oral morphine: a retrospective analysis of our experience in 11 patients in t he palliative care in-patient unit. Am. J. Hosp. Palliat. Care 2008;

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

Stuart-Harris R. Regular subcutaneous bolus morphine via an indwelling cannula for pain from advanced cancer. Palliat. Med. 1991.

Pia Mikkelsen i wsp.: A Pharmacokinetic and Tolerability Evaluation of Two Continuous SubcutaneousInfusion Systems Compared to an Oral Controlled-Release Morphine. Journal of Pain and Symptom Management, 2002.

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)

Mercadante S.: Intravenous morphine for management of cancer pain. Lancet Oncol . 2010.

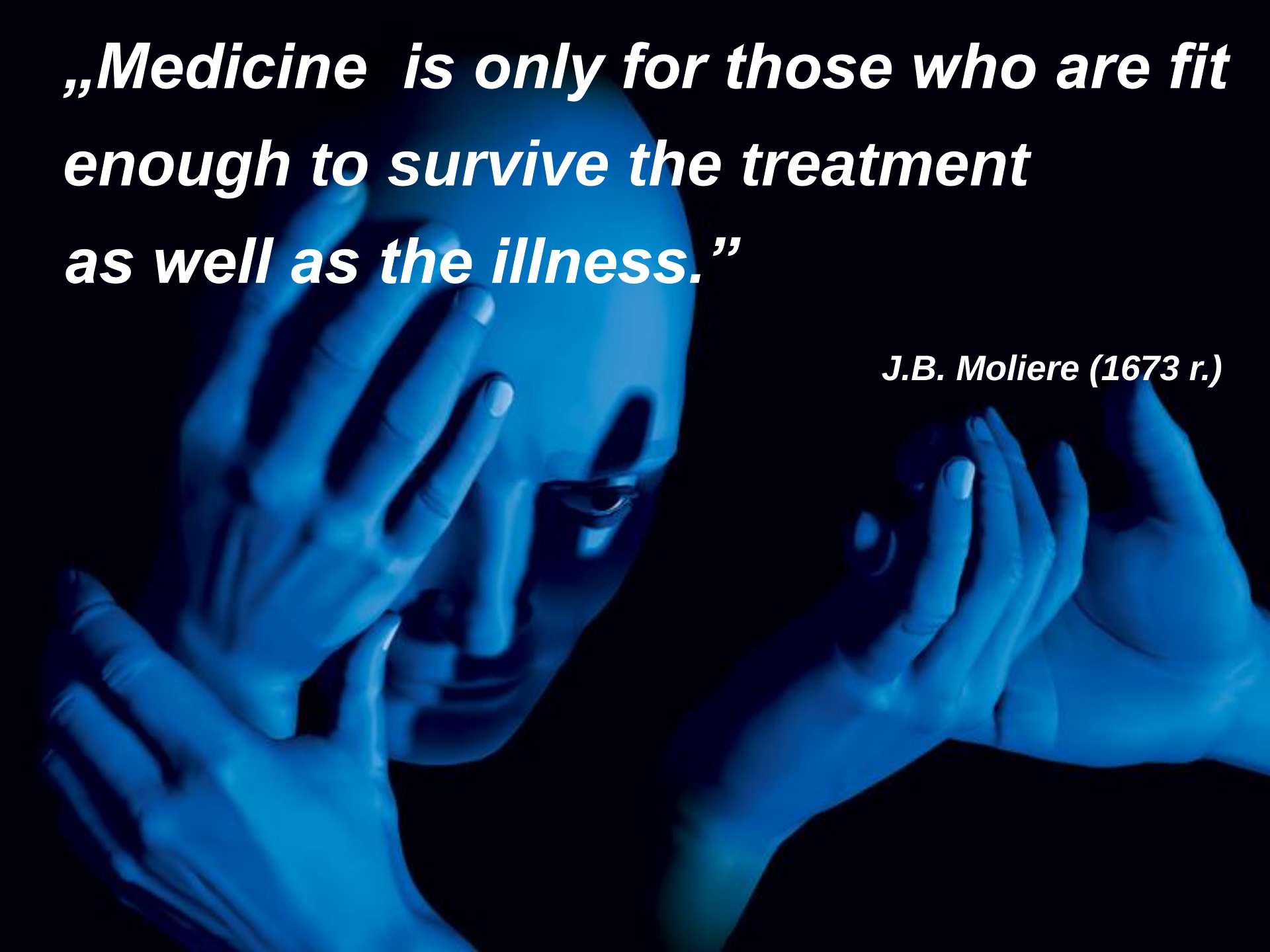
The need for education,

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.

Jon Raphael et al.: Part 1: Pathophysiology; Oncological, Pharmacological, and Psychological Treatments: A Perspective from the British Pain Society Endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. Pain Medicine, 2010.


„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.*

Mercadante S i wsp.: Frequency, Indications, Outcomes, and Predictive Factors of Opioid Switching in an Acute Palliative Care Unit. *Journal of Pain and Symptom Management, 2009*