Review paper

Jolanta Życzkowska, Jerzy Wordliczek
Departament of Pain Treatment and Palliative Care, the Jagiellonian University Medical College, Krakow, Poland

Subcutaneous and intravenous administration of analgesics in palliative medicine

Abstract

Pain is one of the most frequent complaints reported by cancer patients. In their terminal periods, the proportion of patients suffering from pain reaches 75%. Even, the most convenient route of administration of medicines is the oral route, not every clinical situation permits the oral therapy. Alternative routes of administration of medicines, especially in palliative medicine, involve multiple injections or continuous infusions, both subcutaneous and intravenous. Most opioids (morphine, diamorphine in small doses, oxycodon, pethidine, fentanyl, tramadol) can be administered subcutaneously. There are no significant differences between the subcutaneous and intravenous (*i.v.*) application of medicines in terms of their absorption, efficacy and the frequency of side effects. 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. The role of intravenous administration of medicines increase especially at the terminal stages of cancer patients' life. An appropriate choice of administration route 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.

Key words: subcutaneous administration of medicines, intravenous administration of medicines, opioids, analgesics, palliative medicine

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Introduction

Pain is one of the most frequent complaints reported by cancer patients. The number of cancer patients constantly increases [1]. Each year, about 9 million new cases are reported, and it is expected that in the year 2030 the number will exceed 15 million [2]. The incidence and intensity of pain is associated with the type of the underlying disease and its stage. In their terminal periods, in patients receiving palliative care, the proportion of patients suffering from pain reaches 75% [3].

At present, the strategy of treatment of cancer pain is primarily based on the three-step analgesic ladder formulated in 1986 [4]. Thanks to its practical application, it is possible to control pain in 85–90% patients. The most important element of WHO guidelines and a major reason for the effectiveness of treatment is the use of opioid medicines to control moderate to severe pain. Despite the existence of a number of new strong synthetic opioids, morphine is still the most popular medicine from the third step of the analgesic ladder and still constitutes the golden standard of pain treatment.

The most convenient route of administration of medicines is the oral route. It is the most natural manner of administration, which does not cause additional discomfort or pain to patients.

Address for correspondence: Jerzy Wordliczek
Department of Pain Treatment and Palliative Care CMUJ
Tel: (+ 48 12) 424 88 84, fax: (+48 12) 424 88 83
e-mail: mswordli@cyf-kr.edu.pl

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However, not every clinical situation permits the oral therapy. There are certain contraindications and factors that limit this route of administration, including the following [5]:

— 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, such as:

— for some medicines, limited transport through the intestinal mucous membrane;
— interaction of foods with medicines;
— metabolic inactivation by the mucous membrane and the intestinal flora;
— metabolic inactivation by the liver (the so-called first-pass effect) [5].

Alternative routes of administration of medicines, especially in palliative medicine, involve multiple injections or continuous infusions, both subcutaneous and intravenous.

Subcutaneous administration of medicines

The history of subcutaneous administration of morphine dates back to the American Civil War, with the first subcutaneous (*s.c.*) injections to injected 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. At present, this is one of the most often used administration routes for medicines in palliative medicine.

Most opioids can be administered subcutaneously. The class includes: morphine, diamorphine (in small doses), oxycodon, pethidine, fentanyl, tramadol [6–8]. Subcutaneous administration of methadone is usually avoided owing to strong cutaneous response at injection sites. However, there are reports suggesting that with the application of the hypodermoclysis line, local cutaneous side effects are considerably smaller [9].

Subcutaneous administration of medicines, both as injections repeated every 4 hours and as continuous infusion, has a number of significant advantages. They involve:

— the possibility to administer small volumes for a long time;
— efficient absorption;
— lesser discomfort caused by tissue stretching — considerably smaller than the pain accompanying intramuscular or intravenous 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/hypodermatoclysis pump (available pumps are usually lightweight, portable, small or elastomeric);
— significantly reduced incidence of infections;
— stable concentration of medicines in blood serum [5, 10].

In Poland, most often used are single injections repeated every 4 hours. In some developed countries, portable, convenient to use, battery-powered or elastomeric pumps for continuous *s.c.* infusions constitute standard procedure in situations that demand subcutaneous administration of medicines [11], but in Poland, they are unfortunately still rarely used owing to their cost. One of the minor drawbacks related to the use of these simple devices is the need to prepare the infusion drug mix for every 24 hours. This causes problems in changing the dosage of medicines. In order to modify the infusion volume in a given time unit, it is necessary prepare drug mix in the pump again [5, 12].

Watanabe et al. [13] in a randomised double-blind trial did not demonstrate statistically significant differences in opioid efficacy and the occurrence of side-effects after subcutaneous continuous infusion of opioids *vs*. divided-dose injections in patients with stable cancer pain.

Subcutaneous administration of medicines requires that attention should be paid to the type of needle/cannula. The choice includes short metal butterfly needles or teflon-coated cannulae. The latter, on average, last twice as long as metal needles, therefore they should be used for subcutaneous infusions in terminally ill patients.

Below, follows an overview of fundamental principles governing the location and exchange of *s.c.* canulae:

— the needle/cannula 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;
— transfusion sets ought to be changed every 24 hours;
— the location of the cannula should be changed in the event of oedema or the haematoma at needle insertion site, the presences of blood in the drain or leakage at needle insertion site;
— the needle insertion site should be routinely changed every 5–7 days [5].

The duration of needle placement, apart from the above-mentioned type of cannula, is influenced by the type of needle/cannula on 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 [5].

Next, the stability and compatibility of the infusion mix are influenced by such factors as its volume, pH, the temperature in which the mix is prepared, stored and administered, the order of adding individual medicines to the mix and the presence of preservatives [5].

Although, as already mentioned above, one of 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. [5].

O'Doherty et al. [14], in their article published in 2001 mention six most frequently administered medicines in subcutaneous infusions using an automatic syringe: diamorphine, haloperidol, levomepromazine, cyclizine, midazolam and metoclopramid. Data comes from 165 palliative medicine centres, from the UK and from Ireland. Most frequent *s.c.* drug mixes include:
— 2 medicines: diamorphine + midazolam; diamorphine + levomepromazine; diamorphine + haloperidol;
— 3 medicines: diamorphine + cyclizine + haloperidol; diamorphine + cyclizine + midazolam; diamorphine + haloperidol + midazolam.

Palliative medicine specialists surveyed most often use mixtures of three (52% centres surveyed) or four different medicines (36% centres surveyed).

Five years later, Wilcock et al. [15] analysed the medicine mixes administered subcutaneously in 328 automatic syringes during a prospective study of 15 palliative medicine centres. 44% reported a mixture of two medicines, whereas 30% reported three different compounds. Comparing the data with the earlier survey, one can see a significant trend to reduce the number of medicines combined.

When analysing the literature concerning subcutaneous analgesic administration, one can find publications that focus on its drawbacks and limitations. Fonzo-Christe et al. [16] evaluated the use of subcutaneous medicines in the elderly in geriatric wards. They demonstrated a frequent occurrence of such adverse events as: pain (88%), inflammatory infiltration (75%) and oedema (51%). Among the medicines that in over 50% of the centres surveyed were administered subcutaneously (e.g. morphine, hydromorphone, haloperidol, levomepromasine, furosemide, glucopyrronium, dexamethasone), only morphine and dexamethason were licensed for subcutaneous use in Switzerland. However, some pain medicines (fentanyl, ketorolac), antimuscarinic and anti-emetic (glycopyrronium, ondansetron, metoclopramid), antipsychotic (haloperidol) and benzodiazepines (clonazepam, midazolam), even though they are not licensed for subcutaneous use, they are recommended for *s.c.* use in palliative medicine by reference manuals.

Few publications offer data concerning the assessment of stability of medicine mixes and safety of their use. These are, however, research results based on small groups. Positive results were obtained with the following combinations of medicines: morphine + midazolam + haloperidol + hyoscine [17–19], tramadol + hyoscine [20] and tramadol + dexametazon [21]. Great care must be taken, however, in prescribing these medicines, as there is a distinct gap in research evaluating the efficacy and safety of a considerable number of preparations using the route discussed.

The usefulness of subcutaneous administration of third-stage analgesic ladder medicines has been induced in *European guidelines Morphine and alternative opioids in cancer pain: the EAPC recommendations* of 2001 [22]:

8. If patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful. (C)

The advantages of subcutaneous injection are as follows:

— *a smaller needle is required, the chance of damage to nerves is less so that the site of injection is not crucial, and the possibility of inadvertent intravenous injection is less because veins can be seen more easily.*

— *multiple or continuous subcutaneous administration of a medicine is comfortable and painless thanks to butterfly needle insertion, usually in the vicinity of the subclavicular region; this method is less painful for the patient and is considerably cheaper.*

— *absorption is similar and peak plasma concentrations are achieved within 15–30 minutes, with a more rapid onset of drug action than after oral morphine administration.*

10. *In patients requiring continuous parenteral morphine, the preferred method is by subcutaneous infusion. (C)*

Portable battery-operated syringe drivers are now widely used to administer drugs by continuous slow infusion to patients with advanced cancer who are unable to take oral medication.

Subcutaneously administered medicines are absorbed primarily by capillary diffusion, which makes it possible to avoid the so-called first-pass effect. There are no significant differences between the subcutaneous and intravenous application of medicines in terms of their absorption, efficacy and the frequency of side effects [23]. However, in cachectic patients and those with disturbed peripheral circulation, the process of absorption can be significantly reduced. Patients tolerate well the subcutaneous infusion rate of ≤ 5 ml/hr. Greater volumes are used for subcutaneous supplementing of liquids in dehydrated patients. Subcutaneous infusions should not located at sites of lymphoedema both because of limited absorption and increased risk of infection at the injection site [5].

The subcutaneous route of administration of medicines can also be used for the so-called Patient-Controlled *s.c*. Analgesia (PCA) combined with continuous *s.c*. infusion of an analgesic. This method is usually used in the case of incidental pains with large daily differences in pain intensity, in patients who wish to maintain control over the therapy used (high internal locus of control) and in patients with an "extreme" sense of anxiety of adverse events (AE). Contraindications to PCA are as follows: alcoholism, substance addiction, cognitive disorders and the lack of knowledge and experience of the pain-treatment team [11].

It is necessary, however, to bear in mind that there exist situations in subcutaneous administration of medicines is inadvisable or in which continuous infusion may be necessary. European guidelines *Morphine and alternative opioids in cancer pain: the EAPC recommendations* of 2001 suggest that [22]:

11. *Intravenous infusion of morphine may be preferred in patients:*
    a. who already have an indwelling intravenous line,
    b. with generalized oedema,
    c. who develop erythema, soreness or sterile abscesses with subcutaneous administration,
    d. with coagulation disorders,
    e. with poor peripheral circulation.

In recent years, in palliative medicine wards, the number of cancer patients has increased with subcutaneous ports or central vein catheters, which greatly modifies the therapeutic options and their efficacy [24].

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. Intravenous opioids ensure their complete absorption and rapid pain relief (10–15 minutes after *i.v*. morphine administration, 2–5 minutes after *i.v*. methadone administration). Harris et al. [25] compared the time necessary to achieve satisfactory degree of severe cancer pain control from the onset of *i.v. vs*. oral morphine administration. The target was reached in 100% of patients studied after 3 hours from the beginning of *i.v.* treatment, and after 11 hours in the oral administration group.

In the latest, 2009 edition of the *Palliative Medicine* manual edited by Bruera E., results of a number of trials determining the time necessary to obtain relief during morphine titration. In *i.v*. administration, the time of titration was 9.7 to 100 minutes, while oral titration the time was longer — from 1 to 2.3 days [11].

In order to maintain analgesia, it is necessary to administer frequent (every 4 hours) boluses or continuous pump infusion. The latter option is practised considerably more frequently, especially in hospitalised patients to maintain a stable concentration of medicine in blood and convenience for the nursing staff as well as avoidance of repeated painful injections. Continuous intravenous opioid infusion can be a safe and effective method of pain control in patients earlier unsuccessfully treated with maximal tolerated doses of opioid administered by

a different route. Most often used are short-acting opioids such as: morphine, hydromorphone and fentanyl [26, 27]. Owing to their short half-life, the risk of toxic symptoms caused by the accumulation and increased serum levels is much smaller than in the case of methadone or levorfanol, which are characterized by considerably longer half life.

Dobrogowski et al. [28] in a recently published *Position on pain treatment in cancer patients* propose the following manner of titration, i.e. a determination of an effective and safe dose of a strong opioid omitting the 2nd step of the analgesic ladder:

— intravenously: 1–2 mg every 5–10 minutes, until perceptible pain control is achieved (or the emergence of adverse events, such as sedation);
— continuation of treatment: e.g. if the effective dose obtained via titration was 6 mg, depending on the clinical condition of the patient, the following should be applied:
— continuous *i.v.* or *s.c*. infusion of 1 mg morphine per hour (the half-life 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 therapeutic concentration in blood serum; therefore the patients will need to have 3 mg of morphine supplemented within 3 hours, hence the continuous infusion rate amounts to 1 mg/hr) [24].

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

— continue continuous *i.v*. infusion;
— change the route of administration to subcutaneous 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 [29, 22], e.g. aqueous solution of morphine every 4 hours or controlled release tablets administered every 12 hours. The total daily dosage of oral preparations is the same (e.g. the patient who requires 60 mg of morphine per twenty-four hours can receive 10 mg of aqueous solution every 4 hours or 2 doses of 30 mg as controlled release tablets).

European guidelines *Morphine and alternative opioids in cancer pain: the EAPC recommendations* recommend the following conversion mode of morphine dosage depending on the administration route [22]:

12. *The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3.*

When changing from the oral to intravenous preparation, the dose of the oral preparation should be divided by 3.

The potency and clinical effects of *i.v*. and *s.c*. morphine is the same [22, 23], although according to some authors, bioavailability of morphine and its active metabolites — M6G and M3G — is significantly higher after *i.v*. [30] administration.

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 [31].

Parenteral administration of opioids may have additional important advantages, such as:

— no constipation in patients receiving *i.v*. morphine, which the authors of the study attributed to the reduced capacity of medicine binding with opioid receptors in the gastrointestinal tract compared with patients receiving oral opioids [32];
— less frequent nausea and vomiting when using *s.c*. or *i.v*. opioids compared to the oral route [33–35];
— significant improvement in pain management quality (using continuous subcutaneous or intravenous infusion opioids).

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 [36].

Intravenous morphine boluses are an irreplaceable method of relieving piercing pain, especially in hospital wards. The effectiveness of this method is described not only in patients receiving morphine as basic pain relief medicine (20% of the daily dose of morphine converted to oral dosage) [37, 38], but also in patients treated with other opioids, e.g. by transcutaneous buprenorphine [39].

In Intensive Care Units, where sometimes patients with very severe, difficult to control cancer pain are referred, *i.v*. fentanyl is preferentially used. The time necessary to obtain the therapeutic effect is c.a. 11 minutes [27]. After determining the optimal dose of medicine, the intravenous route of administration can be switched to transdermal fentanyl using the conversion rate of 1:1 [40].

Patient Controlled Analgesia (PCA) is most often used during intravenous administration of medicines. Both in adults and in children, intravenous morphine or fentanyl are given [11, 41, 42]. As previously mentioned, morphine is the most popular opioid in palliative medicine. Its usefulness increases especially in terminal patients, given the quickly

progressing changes in the clinical condition of the patient. The different possibilities of administration (oral, per rectum, intravenous, intramuscular, subcutaneous, epidural, intrathecal, to brain chambers and 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) and, in smaller quantities, to morphine-6-glucuronate (M6G) and normorphine. All 3 metabolites are active. It is thought that M6G in a way contributes to the analgesic effect of morphine, while M3G and normorphine have neurostimulant properties, causing convulsions and opioid hyperalgesia (paradoxical pain after opioid administration). M3G has little or no affinity to mi receptors and the absence of internal activity. There is also evidence that M3G antagonises analgesic activity of morphine and M6G, as well as plays an essential part in the development of the tolerance and hyperalgesia [43].

The rate of morphine absorption from the gastrointestinal tract is variable, with approx. 30–40% bioavailability. By changing the route of administration, different concentrations of morphine and its metabolites in blood serum can be obtained. Bioavailability of morphine after continuous *s.c.* infusion is lower than its bioavailability after *i.v*. infusion [30]. For example, after parenteral administration, normorphine is usually present in the serum only in small quantities, but oral administration generates large quantities of this neurotoxic metabolite [11].

Concentration rates after oral vs. i.v. morphine administration are as follows [29]:

— oral morphine: M3G : M6G — 1 : 24.3 : 3.1;
— *i.v*. morphine : M3G : M6G — 1 : 8,5 : 1,1.

The model of central opioid activity depends on opioid pharmacokinetics, phase of distribution determined chiefly by the transport across the blood-brain barrier, interaction with receptors and signal transduction.

In the case of morphine, the biophase of distribution is an important factor determining the onset of its activity, because the low lipophylicity of morphine causes slows down the passage of the medicine across the blood-brain barrier (84%), which manifests itself as the phenomenon of hysteresis concerning the relationship among the peak concentration of medicine in blood serum and "peak analgesia" [44, 45].

Hysteresis can be defined as "the delay or the lagging of the result behind its cause". Two major causes of the delay phase in case of morphine are: limited access to the place of medicine activity or slow kinetics of the receptor, with the delay lasting even up to 34 minutes [11].

In conclusion, it is worth mentioning the increasing role of intravenous administration of medicines at the terminal stages of cancer patients' life. In spite of the preference for oral administration when pain is relatively stable, quite often, especially in the last days of the life one observes the tendency to change opioid administration route to intravenous or subcutaneous [46]. Data concerning changes in opioid dosage at terminal stages of life are not unequivocal. Some researchers advocate an escalation of pain relief medicines [47], while others are in favour of stable dosage in last seven days of life [48]. These data conform to authors' own unpublic research presented at the last Congress on Palliative Medicine. MEDD in the last twenty-four hours of life and average MEDD of the last three and five days were comparable.

Maier et al. conducted a retrospective survey based on the Berlin Home Care programme including 18% cancer patients in Berlin in 2002. Analysed were, among others, the relationships between the route of administration of opioid medicines and the intensity and unpleasantness of pain in last 72 hours of the lives of patients at hospices and family homes. The intensity of pain was rated using a 4-grade scale. The greatest exacerbation of pain (over 50%) was most often noted with the transdermal opioid administration route, while with repeated subcutaneous injections they were somewhat rarer. Continuous intravenous infusion was associated with unsatisfactory pain control in approx. 35% cases, continuous subcutaneous infusion in approx. 13% cases, and oral administration with less than 10% patients treated via this route. Similar results were obtained when studying the relationship between the route of administration and the unpleasantness of pain. Most frequently, considerable unpleasantness accompanied the transdermal route, followed by repeated hypodermic injections and continuous intravenous infusions. The continuous subcutaneous infusion and the oral route were associated with the least frequently reported strongest unpleasantness of pain. The authors concluded that in the event of any problems with pain control via transdermal opioid administration, it is necessary to change the route of administration. In these cases, continuous subcutaneous infusion can

constitute the optimal method. It was also underscored that in a number of cases oral administration of medicines in the final days of patients' lives is possible and should not be changed, since it is not only convenient, but also very effective [49].

Mercandante et al. demonstrated that despite the rich literature and the ever broader knowledge in the area of pain treatment, many patients suffering from moderate or even severe cancer pain still do not receive an appropriate therapy [50]. Authors underscore the need for education, especially involving oncologists and all those who consult cancer patients in their own practice. It is important not only to know the arsenal of medicines that we have at our disposal, but also, as was demonstrated in this article, the possibility to change their administration routes depending on the clinical condition and context of the patient. An appropriate choice of administration route 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.

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