

ALTERNATIVE APPROACHES TO THE APPLICATION OF OPIOIDS

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Summary

Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. The oral application of opioids is preferred as the easiest and most economic use, but there are potential side effects as nausea, dysphagia, malabsorption, confusion and cognitive disorders, as well as unsatisfactory abatement of pain in spite of high dosage. When oral administration is not applicable, alternative routes are recommended. 53–70% of patients with carcinoma require an alternative route of opioid administration. 50% of carcinoma patients need to alternate between the administration routes more than once during the last four weeks of their lives. Alternative routes of opioid administration include: transmucosal and sublingual, intranasal, transdermal, subcutaneous and intravenous, intramuscular, rectal, tube for feeding and intrathecal and epidural route. The onset of the effect of oral transmucosal and sublingual opioids is 15 to 30 minutes, intranasal opioids 2-3 minutes, intravenous opioids 15-30 seconds, and inhalation opioids 6-12 seconds. The ideal drug for pervasive carcinoma pain should be efficient, with a quick onset, short acting, only few side effects and uncomplicated application.

KEYWORDS: *administration of opioids, pain management, fentanyl*

ALTERNATIVNI PUTEVI U PRIMJENI OPIOIDA

Sažetak

Liječenje boli opijatima smatra se uspješno ako je analgezija zadovoljavajuća, a nisu prisutne neprihvatljive nuspojave. Oralna primjena opioida smatra se najjednostavnijom i najekonomičnijom primjenom, ali uz oralnu primjenu mogu se pojaviti nuspojave kao mučnina, disfagija, malapsorbicija, smušenost i kognitivne smetnje, kao i nezadovoljavajuće smanjenje boli unatoč visokim dozama. U slučajevima kad oralna primjena nije primjenjiva, preporučuju se alternativni načini primjene opioida. 53–70 % bolesnika s karcinomom trebaju alternativni put unosa opioida. 50% bolesnika s karcinomom imaju potrebu promjene puta unosa lijeka više od dva puta u zadnja četiri tjedna života. U alternativne načine primjene opioida spada primjena opioida transmukozno, sublingvalno, intranazalno, transdermalno, subkutano, intravenski, intramuskularno, rektalna primjena opioida, primjena putem sonde za hranjenje te intartekalna i epiduralna primjena opioida. Početak djelovanja oralnih transmukoznih i sublingvalnih opioida je 15 do 30 minuta, intranazalnih opioida 2-3 minute, intravenjskih opioidi 15-30 sekunda, a inhalacijskih opioida 6-12 sekunda. Idealan lijek za probadajuću karcinomsku bol treba biti efikasan s brzim početkom, kratkim djelovanjem i s malo nuspojava te jednostavnom primjenom.

KLJUČNE RIJEČI: *primjena opioida, liječenje boli, fentaniil*

INTRODUCTION

Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria, a

substantial minority of patients treated with oral morphine (10% to 30%) do not have a successful outcome because of (1) excessive adverse effects, (2) inadequate analgesia, or (3) a combination of both excessive adverse effects along with inade-

quate analgesia. In general, four different approaches to the management of opioid adverse effects have been described (dose reduction of systemic opioid symptomatic management of the adverse effect opioid rotation, switching route of systemic administration) (4). It is vital to perform an assessment of the patient before introducing opioids into therapy, as a way of ascertaining whether the patient is a candidate for opioid analgesia. With the assessment, the patient's realistic perception of the diagnosis and cause of pain are stated, and also whether all other paths of pain treatment are exhausted. The patient's history is of particular importance as to ascertain the mental health of the patient, as well as the occurrence of any history of misuse of drugs or alcohol in the past. Naturally, a physical examination of the patient is required, and also an assessment of the patient's physical status as well as evaluation of the expected improvement in the functional status and its measuring. With the history and physical examination it is also important to assess the patient's psychological and psycho-social status, as well as the individual's ability to evaluate the intensity of pain and to understand and accept the aims of the treatment. If the patient fulfils the conditions for the use of opioids new questions arise: „Which opioids, and which path of application?“ There are numerous factors to consider when answering this question. The oral application of opioids is preferred as the easiest and most economic use, but there are potential side effects as nausea, dysphagia, malabsorption, confusion and cognitive disorders, as well as unsatisfactory abatement of pain in spite of high dosage. When oral administration is not applicable, alternative routes are recommended. 53–70% of patients with carcinoma require an alternative route of opioid administration (5). 50% of carcinoma patients need to alternate between the administration routes more than once during the last four weeks of their lives (6). The alternative routes of opioid application include:

- Transmucosal and sublingual
- Intranasal
- Transdermal
- Subcutaneous and intravenous
- Intramuscular
- Rectal
- Tube for feeding
- Intrathecal and epidural

Alternative routes to the use of opioids in pervasive carcinoma pain are oral transmucosal, sublingual, intranasal and inhalation paths of distribution. The onset of the effect of oral transmucosal and sublingual opioids is 15 to 30 minutes, intranasal opioids 2-3 minutes, intravenous opioids 15-30 seconds, and inhalation opioids 6-12 seconds. The ideal drug for pervasive carcinoma pain should be efficient, with a quick onset, short acting, only few side effects and uncomplicated application

1. TRANSMUCOSAL AND SUBLINGUAL USE OF OPIOIDS

Fentanyl is also available for patients suffering from pervasive carcinoma pain, in the form of oral transmucosal fentanyl citrate tablet, buccal fentanyl tablet, sublingual fentanyl tablet. Breakthrough cancer pain is a common problem in patients with cancer. Fentanyl buccal tablet is used for the treatment of breakthrough cancer pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain. Fentanyl buccal tablet treatment should be individually titrated to an effective dose that provides adequate analgesia and minimizes undesirable effects. To reach the safest effective dose for the individual patient as soon as possible, the dose titration process is critical. Buccal fentanyl tablet have an agency start in 15 to 30 minutes, and with a duration of two hours. The absorption of the drug is unchanged with mucositis. Sublingual tablets should be administered directly under the tongue at the deepest part. Sublingual tablets should not be swallowed, but allowed to completely dissolve in the sublingual cavity without chewing or sucking. Patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved. The fentanyl lollipop is an opioid medication that combines both fentanyl and citrate to provide potent pain relief via the mucous membranes of the mouth for the treatment of breakthrough cancer pain. The pharmacological profile is adapted to pervasive carcinoma pain as a result of faster analgesia compared to orally administered morphine.

2. INTRANASAL OPIOIDS

The intranasal use of opioids is an alternative route of application in cases when oral adminis-

tration is not possible. Transmucosal administration allows fast absorption and has a quick start-up effect, and so is appropriate for decrease pervasive carcinoma pain. The nasal epithelium is well vascularized and also has a large surface for absorption (15-20 ml volume, surface 150 – 180 cm²). The absorbed drugs avoid a first-pass metabolism and thus augment the bio-disposability of the drug. This way of application has produced a high rate of acceptance by the patients. Fentanyl nasal spray is safe for usage, has a fast onset of the effect, only small volumes are necessary and by that overdosage is avoided, and also a nasal application is tolerated by patients with swallow difficulties or nausea and vomiting (7, 8).

3. TRANSDERMAL USE OF OPIOIDS

Transdermal usage (fentanyl, buprenorphin) of opioids bypasses absorption into the digestion tract. The drug-level in the plasma is in a slow rise during 12-18 hours (the peak of agency occurring ≈ 18-24 hours after application) and in a slow descent during 20-24 hours after removing the patch. As a result, transdermal patches are not suitable for a fast titration. Patients that need a high dose of transdermal patches should take an equally potent dose of oral or parenteral opioids. They should be used with opioid non-naive patients experiencing a relatively stable pain. As with momentary, controlled releasing of opioids, patients require an additional analgesic for pervasive pain. The agency of the patch is 3, 4 or even up to 7 days. Indications for the use of transdermal fentanyl and buprenorphin patches are high intensity pain, difficulty swallowing, damaged gastrointestinal functions and kidney damage.

The advantages of transdermal patches are:

- Avoidance of the first access through the liver, higher bioavailability and efficiency
- Non-invasive usage
- Not affected by food and the capacity of gastrointestinal resorption of the individual
- No problem with application to patients with swallowing difficulties
- The agency of the drug is controlled, continuous, and the plasma concentration is kept constant during long time intervals
- Flexible dosage that is adapted to the patient needs

- The independence of the patient
- Easy use (9)

Ionsys is a transdermal fentanyl patch programmed ahead, completely non-invasive. Ionsys is only used in hospitals in treating acute post-operative pain, and the apparatus enables 6 doses in one hour during 24 hours of use or until 80 doses of fentanyl are delivered (each individual dose 40 µg). Ionsys is a time saver for the hospital staff in regard to intravenous PCA analgesia. It is safe and easy to use and intended for hospitalized patients. Ionsys is compact and independent, without the addition of equipment as in i.v. PCA pumps. The activation does not require the use of a needle, i.e, it is a non-invasive analgesic method with which the possibility of needle infection is removed. It is attached to the outer aorta of the upper arm or breast cage. After the patient presses the system button, an low intensity electric field activates for a fast transport of fentanyl through the skin into the blood system. The technically advanced process is called iontophoresis. The original design reduces the possibility of malusage. Ionsys will be automatically disconnected after the highest number of doses are administered after the 24-hour period is over.

4. SUBCUTANEUS AND INTRAVENOUS CONTINUED USE

Subcutaneous and intravenous continued infusion is applied to patients suffering from permanent nausea and vomiting, dysphagia, intestinal obstruction, malabsorption, when the analgesic demands are not orally practicable, as well as to patients that demand a fast titration of opioids and as a treatment for pervasive pain. All available opioids for parenteral intravenous use are also for subcutaneous administration. With a continuous infusion a stable drug level in the blood is achieved, and patient controlled analgesia (PCA) may be used in a combined continuous infusion with intermittent bolus doses, which allows a better pain control. The place of the subcutaneous infusion needs to be checked and if possible, rotated every 48 to 72 hours in neutrophenic patients as a means to minimize the risks of infection in said areas. When the renal function is orderly, a bolus can be administered every 3 hours, and the dosage needs to be adjusted every 12 to 24 hours. If the

parenteral route is to be used for a period of time, a continued infusion may result in a constant level of medicine in the plasma, curtail the risk of side effects, and lead to a better drug-tolerance, as well as fewer medical personnel interventions. Syringes of 25- or 27-gauge are used for boluses as well as for infusions. The syringes are set up for 7 days, and after that testing of local irritation or infection is made, and in cases of no local infection they may be left for longer. A family member may be educated for administering subcutaneous opioids. PCA analgesia has proven its efficiency and high patient tolerance.

The subcutaneous use of opioids is an alternative to its intravenous use in cases of carcinoma pain due to its easy and less painful administration, it is easier to use in a home environment, the patient has a greater freedom and control of the pain, the need for painful and frequent intravenous and intramuscular injections is eliminated, and a risk of infections is lower. Also, secondary problems of edema, ascites, pleural effusion and pulmonary congestion of continued intravenous infusion are evaded. Subcutaneous administration may be used with occasional or continued infusion, constant drug-level in the plasma, avoidance of the first-pass metabolism and a smaller possibility of hyperhydration.

Besides the advantages there are also some deficiencies of the subcutaneous administration of opioids. There is a clinical confinement because some drugs cannot be administered subcutaneously. Some relative contra-indications with the subcutaneous administration of opioids are a strong thrombocytopenia, as well as a strong edema. As a side-effect of subcutaneous administration infections in the area of the infusion are possible.

Subcutaneous administration to bed-ridden patients is made to the abdominal or the upper breast cage, and to day-patients in the abdomen, thigh or upper arm. In patients with cachexia a subcutaneous administration to the thoracic area should be avoided as to avoid the risk of pneumothorax. If a large volume of opioids is administered, the abdominal area is the best option due to its large surface. Opioid non-naive patients start off with a small primary dose and titrate the dosage gradually. The basic dosage is augmented every 10 to 15 minutes until efficient. Over time it may be augmented by 25-50%, depending on the

clinical situation and used dosage. With patients on an opioid therapy frequent assessments of sedation and comfort are necessary. The aggravation of pain requires more frequent pain-assessments and a quicker titration, and also necessary is to try and avoid sedation.

Five half-lives of the drug are necessary as to achieve a stable dosage in the plasma. For the grand part of opioids the time of half-life is three hours (15 hours are needed to achieve as stable plasma drug-dosage). The deficiency of an appropriate starting strong doze is the most frequent cause of bad analgesia. All opioids available for intravenous administration are also available for subcutaneous use.

5. INTRAMUSCULAR ADMINISTRATION OF OPIOIDS

Intramuscular injections are best avoided since they are painful and unpleasant, and with an unpredictable absorption. Thrombocytopenic patients face a greater risk of hematomas in the area of injection, and neutrophenic patients or individuals on a chronic steroid therapy face a greater risk of evolving infections in the injection areas as well as systemic infections. If this manner of injecting opioids is used, the active concentration of the opioid should be administered in as small a volume as possible. Intermittent subcutaneous administration of opioids should have priority since it is less painful, and equally efficient.

6. RECTAL ADMINISTRATION OF OPIOIDS

Rectal administration is an alternative when taking the drug by mouth is not possible because of nausea and vomiting, as well as obstructions in the digestion tract. The drug is absorbed through the lower and middle rectal veins and then bridging the portal circulation into vena cava (the first path through the liver being circumvented). The drug is also absorbed through the upper rectal veins, going through the liver by way of the portal blood circulation. The titration and individualisation of the dosage are necessary. The deficiencies of the rectal administration of opioids are the limited absorption due to the limited area of the rectum, the solubility of the suppository may be abated by the small amount of liquid in the rectum, the

absorption may be interrupted by defecation, constipation may block the drug's contact with mucosa which in turn complicates the absorption of the drug. Rectal administration is contra-indicated with pain of the rectum (fissures and hemorrhoids), diarrhea, and with patients psychologically unable to place a suppository. Most commonly used rectal opioids are morphine, hydromorphone and oxycodone.

7. OPIOID ADMINISTRATION BY FEEDING TUBE

The use of a feeding tube has been increasing with carcinoma patients during the last decade (over 15% patients). Tube feeding causes a significant distress with patients that need to be guarded against tearing the tube out. There are several different kinds of feeding tubes that may be used for analgesia including nasogastric tube, percutaneous percutaneous gastrostoma, open gastrostoma and jejunostoma. The indications for opioid analgesia by way of a probe are intubated patients and on a mechanical ventilation, patients with a mechanical obstruction in the oropharyngeal region or esophagus (a tumor or a consequence of radiation or chemo-therapy), as well as neurological illness with a consequent difficulty swallowing (10).

8. INTRATHECAL AND EPIDURAL ADMINISTRATION OF OPIOIDS

Intrathecal and epidural opioid administration are options when the highest dose of opioids with any other means of application are not efficient or if they manifest unacceptable side effects (i.e. nausea, vomiting, effusive sedation, confusion), and also if extremely high doses of opioids are needed to decrease the pain. Before the intrathecal or epidural administration less invasive methods of opioid application should be tried. Opioids may be applicable by placing a percutaneous or tunneled catheter in the epidural or intrathecal space. The application may be with bolus injections, intermittent or continued injections of bolus doses. The advantage of this way of opioid administration is its considerably smaller doses in comparison with a systemic application, and also an overall smaller dose results in lesser side effects. Also, the agency of the opioid is longer than

with other means of application. The correct selection of patients and time-projection for this manner of application is of significant importance for the selection of this application of opioids. If it is a matter of only days of life a percutaneous catheter placement is adequate (with a higher infection risk), but if a longer period of life is considered a tunneled catheter is used which can administer satisfactory analgesia for months. If the expected life period is longer than three months a programmed pump is recommended. The epidural and the intrathecal use are equally efficient. The intrathecal use is preferred in reference to the epidural with prolonged therapies, and is also more efficient with skeletal metastasis. The obstruction of the catheter and epidural fibrosis are the most common complications when using the epidural catheter. The doses of opioids that are used intravenously are higher than epidural and intrathecal doses, and epidural doses are also higher than intrathecal doses (100 mg morphine intravenously during 24 hours is as efficient as 10 mg epidural morphine or 1 mg intrathecal during 24 hours) (11).

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