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The Role of Opioid Analgesics in the Treatment of Pain in Cancer Patients

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1. Introduction

Cancer pain treatment is based on the analgesic ladder, established in 1986 by the World Health Organization (WHO; see Fig. 1) (WHO, 1996). Cancer pain management guidelines in Europe are based on EAPC (European Association for Palliative Care) recommendations. Oral morphine is recommended by the Expert Working Group of the EAPC at the third step of the WHO analgesic ladder, which comprises additional opioids (i.e. oxycodone, fentanyl, buprenorphine, methadone, and hydromorphone) for the treatment of moderate-to-severe pain intensity (Hanks et al., 2001). The use of an analgesic ladder should be individualized with an appropriate application of supportive drugs (laxatives and antiemetics) for the prevention and treatment of opioid adverse effects (Leppert, 2009a) and nonpharmacological measures, such as radiotherapy and invasive procedures (nerve blockades and neurolytic blocks) (Eidelman et al., 2007).

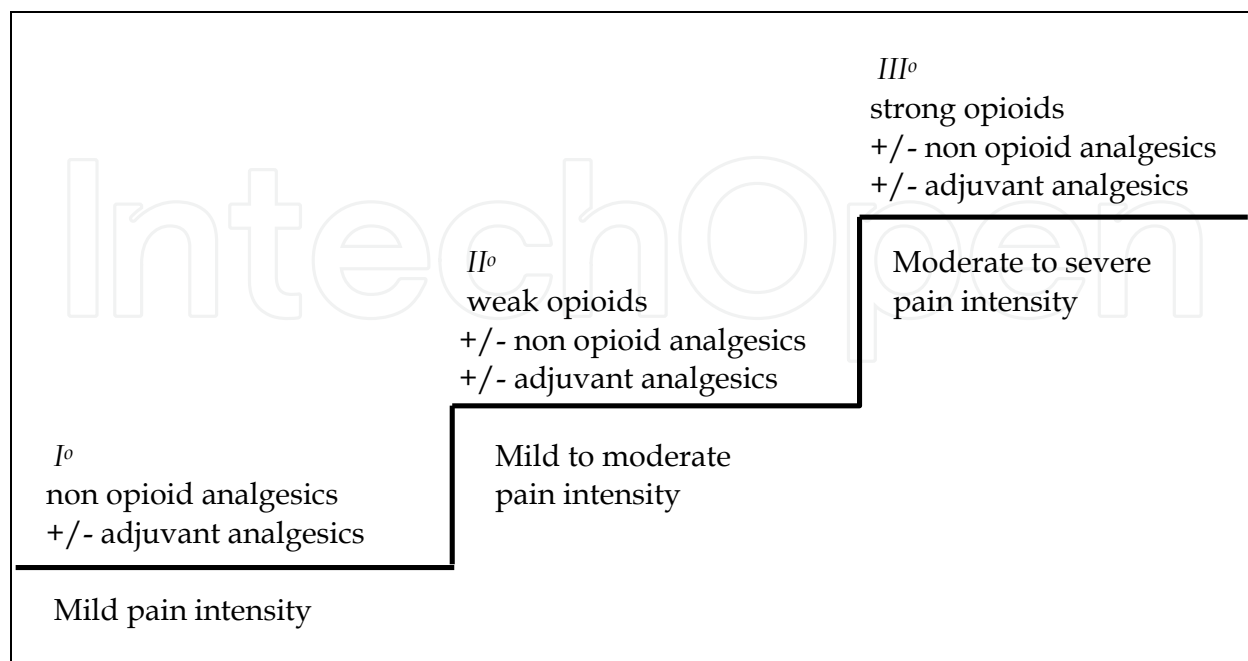


Fig. 1. World Health Organization three-step analgesic ladder

Each step of the WHO analgesic ladder: nonopioids (analgesics for mild pain, step 1 analgesics), weak opioids (analgesics for mild to moderate pain, step 2 opioid analgesics), and strong opioids (opioids for moderate-to-severe pain intensity, step 3 opioid analgesics) may be accompanied with adjuvant analgesics (coanalgesics), which can enhance opioid analgesia. In patients with bone pain, opioids may be combined with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and bisphosphonates along with local or systemic radiotherapy (Lussier et al., 2004). In patients with very severe neuropathic pain, a combination of opioids and NMDA (*N*-methyl *D*-aspartate)-receptor antagonists (e.g. ketamine) are recommended (Leppert, 2010a). Patients with neuropathic pain along with opioids may also receive anticonvulsants, and antidepressants (Bennett, 2011). Other drug groups used in patients with neuropathic pain component comprise local anesthetics and antiarrhythmics (Freynhagen & Bennett, 2009). Opioid analgesics should be supplemented with spasmolytics in patients with visceral colicky pain, especially in the course of bowel obstruction (Ripamonti et al., 2008).

2. Opioids for mild to moderate pain (weak opioids, step 2 opioid analgesics)

2.1 Tramadol

Tramadol displays opioid properties and acts on neurotransmission of noradrenalin and serotonin. Both enantiomers act synergistically and improve analgesia without increasing adverse effects. Tramadol is metabolized in the liver and excreted by the kidneys. The main metabolite is *O*-desmethyltramadol (M1), which displays analgesic activity with a higher affinity to μ -opioid receptors than the parent compound; (+)-M1 has 300 to 400 times greater affinity to μ -opioid receptors than tramadol and (-)-M1 mainly inhibits noradrenalin reuptake. Apart from *O,N*-didesmethyltramadol (M5, which has weak analgesic activity) and M1, other metabolites are inactive (Leppert and Mikolajczak, 2011). The elimination half-life of tramadol is 5 to 6 hours and that of M1 is 8 hours. During oral administration, 90% of tramadol is excreted by the kidneys and 10% in feces. Patients with renal impairment show a decreased excretion of tramadol and M1. In patients with advanced cirrhosis, there is a decrease in tramadol metabolism with decrease of hepatic clearance and increase in blood serum levels. In these patients, elimination half-life is increased 2.5-fold. The starting dose of immediate-release (IR) tramadol is 25 to 50 mg every 4 to 6 hours and that of controlled-release (CR) tablets or capsules is 50 to 100 mg twice daily; the daily dose should not exceed 400 mg (Dickman, 2007).

Patients devoid of CYP2D6 activity (poor metabolizers) need a tramadol dose higher by 30% than those with normal CYP2D6 activity (extensive metabolizers) (Stamer et al., 2003). Tramadol analgesia depends on CYP2D6 genotype, with less analgesia in poor metabolizers being associated with lack of (+)-M1 formation (Stamer et al., 2007). Genotyping is helpful in patients with duplication of CYP2D6 gene (ultrarapid metabolizers [UM]) who are at greater risk to develop tramadol adverse effects. Tramadol metabolism through CYP2D6 may cause interactions with drugs inhibiting this enzyme (eg, cimetidine and ranitidine).

Serotonin syndrome has been reported in patients taking selective serotonin reuptake inhibitors (SSRIs) in conjunction with tramadol or opioids (Gnanadesigan et al., 2005). SSRIs (eg, fluoxetine, paroxetine, and, to less extent, sertraline) used in conjunction with tramadol may cause serotonin syndrome because SSRIs inhibit tramadol metabolism and increase serotonin level; generally, they should not be coadministered with tramadol. Serotonin

syndrome may appear with monoamine oxidase (MAO) inhibitors, olanzapine, risperidone, venlafaxine and mirtazapine (Davies and Glare, 2009).

The inhibition of tramadol metabolism to (+)M1 may attenuate tramadol analgesia. For example, coadministration of ondansetron (selective 5-HT₃ [hydroxytryptamine] receptor antagonist) blocks spinal 5-HT₃ receptors and competitively inhibits CYP2D6 although recent studies did not confirm such interaction (Rauers et al., 2010). Tramadol analgesia also may be impaired by coadministration of carbamazepine, which accelerates tramadol and M1 metabolism. Concomitant administration of tricyclic antidepressants increases the risk of seizures. Tramadol should be avoided in patients with history of epilepsy. In rats and mice, concomitant administration of tramadol and β -blocker and the 5-HT_{1A/1B} antagonist pindolol enhances analgesia (Leppert, 2009b).

Respiratory depression is rare in the chronic use of tramadol. When it does occur, respiratory depression is connected with the opioid mode of tramadol action, so naloxone should be administered. For example, respiratory depression was reported in a cancer patient with renal impairment (creatinine clearance 30 mL/min) and with UM genotype after renal carcinoma resection. As respiratory symptoms appeared more than 10 hours after the first tramadol dose, the accumulation of M1 was the cause. The patient recovered after intravenous (IV) naloxone bolus administration (0.4 mg). This case highlights that tramadol should not be prescribed in patients with UM genotype and renal impairment (Stamer et al., 2008).

2.2 Codeine

Codeine is a methylated morphine derivative that is found naturally, along with morphine, in the poppy seed. Codeine displays analgesic and antitussive activity. Codeine is available as IR and CR formulations but also in the form of paracetamol combined preparations. IR codeine is administered every 4-6 h in chronic pain with a starting single dose of about 30 mg. The daily doses of dihydrocodeine and codeine usually do not exceed 240 mg and 300 mg, respectively; when these analgesics are ineffective, opioids for moderate-to-severe pain (strong opioids) are introduced.

Codeine is metabolized in the liver and its bioavailability is 30% to 40% after oral administration. After oral administration of codeine, maximal plasma concentration is attained within 1 to 2 hours with plasma half-life of 2.5 to 3.5 hours and analgesia maintained for 4 to 6 hours (IR formulations). Codeine is partially metabolized to morphine and its metabolites and to codeine metabolites norcodeine (NORC) and codeine-6-glucuronide (C-6-G) (Lötsch et al., 2006). The analgesic effect of codeine is about equal to 1/10th of morphine analgesia. Polymorphism of CYP2D6 is responsible for the formation of morphine, and its metabolites may affect codeine analgesia. Other codeine metabolites, C-6-G predominantly, also display analgesic activity and contribute to codeine analgesia (Vree et al., 2000). In healthy volunteers, codeine is metabolized to C-6-G (81.0% \pm 9.3%), NORC (2.16% \pm 1.44%), morphine (0.50% \pm 0.39%), morphine-3-glucuronide (M-3-G; 2.10% \pm 1.24%), morphine-6-glucuronide (M-6-G; 0.80% \pm 0.63%), and normorphine (NORM; 2.44% \pm 2.42%). The half-life of codeine is 1.47 hours \pm 0.32 hours, and that of C-6-G is 2.75 hours \pm 0.79 hours. The plasma AUC of C-6-G is about tenfold higher than that of codeine. Protein binding of codeine and C-6-G in vivo is 56.1% \pm 2.5% and 34.0% \pm 3.6%, respectively (Vree & Verwey-van Wissen, 1992).

Lötsch et al. explored the contributions from codeine and its metabolites to central nervous analgesic effects independent from O-demethylation of codeine to morphine. A

pharmacokinetic/pharmacodynamic fit of the miotic effects by use of morphine as the only active compound was most significantly ($P < 0.0001$) improved when C-6-G as a second active moiety was added. CYP2D6-dependent formation of morphine does not explain exclusively the central nervous effects of codeine, and C-6-G is the most likely additional active moiety with possible contribution of NORC and the parent compound (Lötsch et al., 2006).

Gasche et al. depicted a patient who received oral codeine in a daily dose of 75 mg (25 mg three times a day) and who, after 4 days of treatment, experienced respiratory depression. The patient recovered after IV administration of naloxone (0.4 mg). The cause of the symptoms was CYP2D6 UM phenotype. The patient was concomitantly treated with clarithromycin and voriconazole, both known inhibitors of CYP3A4. This together with CYP2D6 gene duplication led to increased morphine formation. Blood concentrations of M-3-G and M-6-G were substantially elevated, also due to renal failure (Gasche et al., 2004). Recent reports (Kircheiner et al., 2007; Voronov et al., 2007) indicate that there is a significant risk of respiratory depression in infants whose mothers with CYP2D6 UM and UGT2B7•2/•2 genotypes taking codeine during breastfeeding (Madadi et al., 2009b). Guidelines for maternal codeine use during breastfeeding were issued in Canada (Madadi et al., 2009a) but it seems safer not to use codeine and substitute it with other analgesics in this patient group. Apart from morphine glucuronides, codeine and its metabolites (C-6-G and NORC) also contribute to codeine analgesic effects (Lötsch et al., 2006).

2.3 Dihydrocodeine

Dihydrocodeine (DHC) is a semi synthetic analogue of codeine. Apart from analgesic and antitussive activity, DHC also is used in the treatment of opioid addiction. After subcutaneous (sc) administration of DHC, 30 mg, analgesia is similar to that induced by 10 mg of morphine. After parenteral administration, DHC is twice as potent as codeine. Bioavailability of DHC after oral administration is 20%, which indicates that its analgesia after oral administration is slightly stronger than that of codeine (bioavailability after oral administration equals 30%–40%). After oral administration of DHC, the maximal serum concentration appears after 1.7 hours, plasma half-life varies 3.5 to 5.5 hours, and analgesia lasts 4-6 hours. DHC pharmacokinetics was assessed in 12 extensive metabolizers of CYP2D6 (Ammon et al., 1999). They received a single oral DHC dose of 60 mg, then after 60 hours, they were treated for 3 days with 60 mg dosed twice daily; for the next 3 days with 90 mg twice daily; and for 3 subsequent days 120 mg twice daily. In the 60 to 120 mg DHC dose range, pharmacokinetics of DHC and dihydromorphine (DHM) displayed linear characteristics: area under the curve (AUC), c_{max} (maximum serum concentration), and c_{ssmin} (minimum serum concentration at steady state) for both compounds increased depending on the drug dose (Rowell et al., 1983). Even though DHM displays higher affinity (about 100-fold) to the μ -opioid receptors and exhibits higher analgesic activity in comparison to the parent compound, the role of DHM and its glucuronides in DHC analgesia has not been unequivocally established. The starting dose of IR DHC is usually 30 mg every 4 to 6 hours, and that of CR tablets is 60 mg twice daily (Leppert, 2010b).

Renal clearance and the clearance to DHC metabolites, glucuronidation, and O-demethylation to dihydrocodeine-6-glucuronide (DHC-6-G) and DHM, respectively, are not dose dependent, which indicates that metabolism and excretion of DHC and its metabolites are also not dose dependent. Moreover, the ratio of DHC to DHM for AUC does not change

depending on the dose, which suggests a lack of saturation effect of the O-demethylation process of DHC to DHM depending on CYP2D6 in patients normally metabolizing the substrates of this enzyme. Pharmacokinetic parameters were similar after single and multiple doses of 60 mg of DHC (Ammon et al., 1999). Single-dose and multiple-dose pharmacokinetics of IR and CR DHC formulations provide support for a twice-daily dosage schedule of CR DHC. DHC is metabolized in the liver to main metabolites: DHM, DHC-6-G, and nordihydrocodeine (NORDHC). NORDHC is further glucuronidated to NORDHC-6-glucuronide and O-demethylated to nordihydromorphine (NDHM). DHM undergoes glucuronidation to dihydromorphine-3-glucuronide (DHM-3-G) and dihydromorphine-6-glucuronide (DHM-6-G) and N-demethylation to NDHM. It may be concluded that DHC undergoes the first pass effect after oral administration, which is connected with the formation of significantly higher amount of metabolites after oral than after parenteral administration (Rowell et al., 1983). Studies performed to date (Schmidt et al., 2003; Webb et al., 2001) indicate that DHC analgesia is independent of CYP2D6 activity (Leppert and Majkowicz, 2010).

3. Opioids for moderate to severe pain (strong opioids, step 3 opioid analgesics)

3.1 Morphine

Morphine is the standard drug for the treatment of moderate to severe cancer pain and is a comparator for other strong opioids (Caraceni et al., 2011). This is predominantly due to large clinical experience and different routes of morphine administration (eg, oral, SC, IV, intrathecal, topical). Morphine is a hydrophilic opioid and a pure opioid agonist that acts predominantly through the activation of μ -opioid receptors (Flemming, 2010). Plasma half-life of IR formulations equals 2 to 3 hours and the bioavailability after oral morphine administration equals about 30% to 40%. Morphine undergoes glucuronidation; thus, there is little risk of pharmacokinetic interactions with other drugs.

The active metabolite responsible for analgesia is morphine-6-glucuronide (M-6-G). The accumulation of morphine and M-6-G may cause nausea and vomiting, sedation, and finally, respiratory depression. Morphine-3-glucuronide (M-3-G) is devoid of analgesic properties but may be responsible for neurotoxic effects and opioid hyperalgesia (paradoxical pain) (Gretton & Riley, 2008). The main drawback of morphine is the fact that M-3-G and M-6-G may accumulate especially in patients with renal impairment and renal failure, leading to possible intense adverse effects associated with accumulation of metabolites. In severe pain syndromes a change from oral to parenteral or intrathecal route of morphine administration may be beneficial. In case of renal problems, a switch from morphine to other opioids, such as fentanyl, methadone, or buprenorphine, is recommended. Similar to other opioids, morphine often causes constipation; therefore, the use of laxative prophylaxis is recommended. Common morphine adverse effects and possible management possibilities are showed in Table 1.

Numerous oral CR formulations of morphine, designed for 12-hour and 24-hour administration, were developed (Ridgway et al., 2010). Local administration of morphine prevents systemic adverse effects. The starting daily dose of oral morphine is usually 20 to 30 mg (for opioid-naïve patients) or 40 to 60 mg (for patients unsuccessfully treated with weak opioids) (Ripamonti et al., 2009). The dose of parenteral (SC or IV) morphine is one third of the morphine oral dose (Donnelly et al., 2002).

Adverse effect	Symptomatology	Treatment	Comments
Gastric stasis	Epigastric fullness, nausea	Metoclopramide 10 mg t.i.d.	If the symptom persists a switch to alternative opioid may be useful
Nausea/vomiting induced by vestibular stimulation	Symptoms appear on movement	Promethazine or cyclizine 25 mg t.i.d.	If intractable consider levomepromazine
Constipation	Flatulence, abdominal pain painful bowel movements,	Stool softener (macrogol or lactulose) plus stimulant (senna or bisacodyl). If no effect rectal measures or methylnaltrexone	If no effect consider switch to transdermal fentanyl or transdermal buprenorphine
Sedation	Drowsiness	Reduce dose of morphine, consider methylphenidate 5-10 mg o.d.-b.d.	May be caused by co-administered medications e.g. neuroleptics, benzodiazepines, antidepressants and co morbidities (hepatic/renal failure). Consider opioid switch
Neurotoxicity/cognitive failure	Hyperalgesia, allodynia, myoclonic jerks/agitation, hallucinations	Reduce dose of morphine, haloperidol - 1 - 2 mg b.d. or risperidone 1 - 2 mg o.d.-b.d.	If no improvement consider opioid switch

Table 1. Common adverse effects of morphine and management possibilities

3.2 Oxycodone

Oral oxycodone is along with oral morphine recommended as a first choice opioid analgesic for the treatment of moderate to severe cancer-related pain (King et al., 2011). It is a semi synthetic thebaine derivative, a strong opioid that displays a significant affinity to κ -opioid receptors along with agonistic effect mediated by μ -opioid receptors. Limited cross-tolerance is observed between oxycodone and morphine in rats and in clinical studies (Maddocks et al, 1996). In comparison to morphine, oxycodone possesses lower affinity to μ -opioid receptors and similar lipid solubility. Oxycodone permeates the blood-brain barrier very quickly, which may explain its stronger analgesic effect in comparison to other opioids. Oxycodone does not display immunosuppressive effects in experimental studies. It has high oral bioavailability (60%-87%); the plasma half-life is 2 to 3 hours after IV administration, 3 hours after treatment with IR oral solution, and 8 hours after CR tablets. The bioavailability of rectal administration is similar to oral route (61%), but it displays greater variability.

Oxycodone is metabolized in the liver primarily to noroxycodone through CYP3A4 and, to a much less extent, to oxymorphone via CYP2D6. Noroxycodone is metabolized to

noroxymorphone through CYP2D6, and oxymorphone is metabolized to noroxymorphone by CYP3A4. However, analgesia observed after oxycodone administration relies primarily on the parent compound. Noroxycodone has 17% of the potency of oxycodone. Oxymorphone, in spite of high affinity for μ -opioid receptors, is produced in very small amounts. Noroxymorphone is produced in a significant amount and displays significant affinity for opioid receptors. However, the blood-brain barrier is extremely impermeable to noroxymorphone; thus, its role in analgesia is negligible. Low blood-brain barrier permeability is also characteristic of noroxycodone and oxymorphone (Leppert, 2010c).

In patients with liver cirrhosis and hepatic diseases, the oxycodone dose should be reduced by half. Oxycodone is excreted through the kidneys. In patients with renal insufficiency, the oxycodone dose also should be reduced. In patients with renal failure, the oxycodone half-life is prolonged and ranges from 1.8 to 26 hours. The elimination of noroxycodone and oxymorphone also is impaired in patients with renal failure. CYP2D6 polymorphism probably does not influence oxycodone analgesia and adverse effects. Sertraline minimally inhibits CYP2D6 and intensifies adverse effects of oxycodone (eg, hallucinations, tremors), whereas fluoxetine and quinidine (significant CYP2D6 inhibitors) do not intensify oxycodone adverse effects. Oxycodone reduces oral bioavailability of cyclosporine by half. In healthy patients, rifampin, a CYP3A4 inducer, greatly decreased oral and IV oxycodone AUC by 86% and 53%, respectively ($P < 0.001$), and modestly reduced analgesia and increased plasma metabolite-to-parent compound ratios for noroxycodone and noroxymorphone ($P < 0.001$) (Nieminen et al., 2009). A pharmacodynamic interaction of oxycodone with other drugs acting on the central nervous system, such as benzodiazepines, neuroleptics, and antidepressants, may intensify oxycodone adverse effects, especially sedation, and respiratory depression may be intensified in the case of patients who are more sensitive to opioids.

3.3 Hydromorphone

Oral hydromorphone is an alternative to oral morphine and oral oxycodone as a first choice opioid analgesic for the treatment of moderate to severe cancer pain (Pigni et al, 2011). Hydromorphone has about 5 to 10 times more potent analgesic effect than morphine and similar pharmacodynamic properties. Hydromorphone analgesia is mainly due to μ -opioid-receptor agonist effects; it also features some affinity for δ - but not for κ -opioid receptors (Murray & Hagen, 1995). After hydromorphone administration, analgesia lasts for about 4 to 6 hours and the plasma half-life is about 2.5 hours; sustained-release oral preparations provide analgesia for 12-24 hours (Gardner-Nix & Mercadante, 2010).

The drug is metabolized mainly to hydromorphone-3-glucuronide that is devoid of analgesic activity and may accumulate in patients with renal failure; it may induce neurotoxic adverse effects to larger extent than the respective morphine metabolite (morphine-3-glucuronide) (Wright et al., 2001). Hydromorphone in small amount is also metabolized to 6-hydroxy-hydromorphone, but its role is unknown. Due to glucuronidation, the risk of hydromorphone pharmacokinetic interactions with other drugs seems to be low (Sarhill et al., 2001). Adverse effects are similar to those of morphine; however, hydromorphone less frequently induces nausea and vomiting, constipation, itching, and probably more slowly develops tolerance to analgesia (Wirz et al., 2008). In comparative studies conducted in cancer patients with pain hydromorphone displays similar analgesic efficacy to morphine (Miller et al., 1999) and oxycodone (Hagen and Babul, 1997).

Hydromorphone is especially useful for patients requiring high opioid doses via parenteral route due to strong analgesic effects and increased solubility that enables the possibility administering small volumes of the drug in SC injections.

3.4 Fentanyl

Fentanyl is a lipophilic opioid, μ -opioid-receptor agonist, with analgesic effect about 100 times more potent than that of morphine. In chronic pain treatment, transdermal fentanyl (TF) patches are applied, usually on the upper trunk. There are five types of patches that release 12, 25, 50, 75, and 100 $\mu\text{g}/\text{h}$ equal to approximately 0.3, 0.6, 1.2, 1.8, and 2.4 mg fentanyl dose per day, respectively. Patches are changed every 72 hours. Patients need access to short-acting opioid preparations (i.e. oral or parenteral morphine, buccal fentanyl tablets, oral transmucosal fentanyl citrate [OTFC] or fentanyl spray) during TF therapy to effectively manage breakthrough pain episodes. Fentanyl is metabolized mainly to inactive norfentanyl; thus, it may be used in patients with renal impairment. Because the fentanyl metabolic pathway is through CYP3A4, the drugs inhibiting or inducing this enzyme should be avoided. Caution is recommended when using drugs metabolized via CYP3A4. In comparison to morphine, the advantages of TF include milder constipation, nausea, and drowsiness (Ahmedzai & Brooks, 1997).

When starting TF in opioid-naïve or strong opioid-naïve patients, one patch at a dose of 12 and 25 $\mu\text{g}/\text{h}$ is recommended, respectively. TF also may be used in opioid switch, especially in patients treated with morphine who suffer from intractable constipation. In an open-label study of 16 patients with cancer pain unable to take oral opioids, TF was effective and well tolerated (Leppert et al., 2000). A good analgesic effect was achieved in 11 patients, with a partial effect in an additional 2 patients. TF was effective and well-tolerated in patients formerly treated with weak opioids that did not provide satisfactory analgesia (Vielvoye-Kerkmeer et al., 2000). The indications for TF include patients' preferences, intense constipation during morphine treatment, morphine intolerance, nausea, and vomiting. TF should not be used in patients with unstable pain syndromes, especially with neuropathic pain component due to the long plasma half-life (20 h) of the drug, which hinders quick and effective dose titration. Fentanyl may be successfully used by other routes (e.g. SC, IV, intranasal inhaled, buccal) in the treatment of breakthrough pain (Slatkin et al., 2008).

3.5 Buprenorphine

Buprenorphine is a partial μ -opioid-receptor agonist and κ -receptor antagonist. A ceiling analgesic effect may be obtained at high doses (ie, 15 mg); however, such high doses are not used in clinical practice. The analgesic potency of buprenorphine is about 100 times greater than oral morphine (Likar et al., 2008). Buprenorphine may be administered sublingually due to low oral bioavailability at doses 0.2 to 0.8 mg, usually 3 times daily. It also may be administered by parenteral route (SC or IV).

Buprenorphine is metabolized to the active metabolite norbuprenorphine via CYP3A4. The parent compound and norbuprenorphine undergo glucuronidation; thus, the risk of pharmacokinetic interactions with other drugs is low. Compared with morphine, buprenorphine less frequently induces constipation, nausea, and vomiting, which is probably associated with higher lipophilicity. Buprenorphine is mainly excreted with feces (2/3) and 1/3 of the drug is excreted with urine therefore, it may be used in patients with

renal failure. Respiratory depression is rare; however, when the symptom appears, naloxone injection should be administered at a dose of 2 mg, followed by continuous infusion (4 mg/h). Buprenorphine displays antihyperalgesic activity and may be successfully used in the treatment of neuropathic pain (Mercadante et al., 2007).

Buprenorphine is administered in transdermal patches (TB) releasing 35, 52.5, and 70 $\mu\text{g}/\text{h}$, which corresponds to 0.8, 1.2, and 1.6 mg/d, respectively. The patches are changed every 84 to 96 hours. In some countries, patches releasing 5 and 10 $\mu\text{g}/\text{h}$, changed weekly, are available. The starting dose for strong opioid-naïve patients is usually one patch of 35 $\mu\text{g}/\text{h}$. However, opioid-naïve patients and those with renal or hepatic impairment may start with a dose of 17.5 $\mu\text{g}/\text{h}$. The treatment is usually well-tolerated. At doses up to 140 $\mu\text{g}/\text{h}$, TB does not display ceiling analgesia (Kress, 2009). Breakthrough pain may be treated with sublingual buprenorphine tablets or with IR morphine administered by oral or parenteral route (Mercadante et al., 2006).

3.6 Methadone

Methadone is a synthetic opioid and a racemate of dextrorotatory (S-methadone) and levorotatory (D-methadone) isomers. Methadone activates μ , κ , and Δ receptors (D-methadone); it displays moderate antagonistic effect to NMDA receptors (both enantiomers) and strongly inhibits the reuptake of serotonin and noradrenalin in the central nervous system (S-methadone). In high doses, methadone blocks potassium channels required for rapid cardiac muscle repolarization, which may explain the risk of developing ventricular arrhythmia.

Methadone is administered mostly to patients with cancer pain who undergo opioid switch; usually methadone is given every 8 hours. In comparison to morphine, 10 times less demand for laxatives and 2 times less nausea and vomiting were observed. Methadone may be administered as the first strong opioid to patients who have been treated with opioids for moderate pain or to opioid-naïve patients (the starting dose is usually 3–5 mg every 8 h) (Ripamonti et al., 1998) although EAPC recommends methadone as the second or the third-line opioid. Methadone can be administered to patients with renal impairment. It has weak immunosuppressive effect and does not suppress the functioning of natural killer cells. Methadone is tenfold less expensive than the CR morphine and 25-fold cheaper than TF.

Methadone is a highly lipophilic and basic drug with a high distribution volume (4.1 ± 0.65 L/kg) and a high affinity to tissues, where it cumulates after multiple administrations (in brain, lung, liver, gut, kidney, and muscles). The high affinity to tissues together with a gradual, retarded release to plasma is the cause of a prolonged half-life. The bioavailability of the drug after oral administration oscillates between 70% and 90%. The half-life is about 24 hours, but it occurs in the range of 8 to 120 hours. Analgesia lasts for 6 to 12 hours. A stable level is reached within 2 to 4 days. Methadone is metabolized mostly via liver enzymes, but also in the intestine wall via N-demethylation to inactive metabolites. The main enzyme responsible for methadone N-demethylation is CYP3A4 with a lesser CYP1A2 and CYP2D6 involvement and a significant CYP2B6 role. The drug is excreted mainly via the alimentary tract, but also through kidneys (depending on the urine pH). In chronic renal disease, methadone does not accumulate; in severe renal failure, a dose reduction may be considered. Methadone is not eliminated in the process of hemodialysis. Methadone is more difficult to use than other opioids due to complicated pharmacokinetics, numerous drug interactions, and possible QT prolongation; therefore, it should be used by physicians experienced in chronic pain management (Leppert, 2009c).

3.7 Tapentadol

Tapentadol chloride ([-]-[1R,2R]-3-[3-Dimethylamino-1-ethyl-2-methyl-propyl]-phenol hydrochloride) is an opioid with two analgesic mechanisms: agonist of μ -opioid receptors with 50 times less affinity than morphine, and inhibition of norepinephrine reuptake (Tzschentke et al., 2007). Bioavailability after oral administration is over 30%, the drug is metabolized to inactive metabolites through glucuronidation and excreted via kidneys (Kneip et al., 2008). In experimental studies tapentadol is effective in the treatment of neuropathic pain and in inflammatory pain. In clinical studies conducted in patients with low back pain, those with postoperative pain, and those with osteoarthritis, IR tapentadol at doses 50, 75, and 100 mg had more favorable adverse-effects profiles with less intense gastrointestinal adverse effects (ie, nausea, vomiting, constipation) in comparison to IR oxycodone at doses 10 and 15 mg. Clinical studies on tapentadol use in patients with cancer pain are ongoing.

4. Conclusions

Opioids are usually effective when administered alone or with adjuvant analgesics. The traditional WHO step-by-step approach should be used individually, based on the clinical assessment of pain type and intensity. Patients with severe pain intensity should use strong opioids (opioids for moderate-to-severe pain) without climbing up the analgesic ladder. Opioids may be combined with nonopioid analgesics and adjuvant analgesics appropriate for a given pain type. Understanding important attributes of commonly used opioids can help assist selection.

In case of lack of efficacy of orally or transdermally administered opioids, it may be beneficial to change the route of administration to parenteral or intrathecal (Enting et al., 2002). Another possibility is opioid switch that may improve analgesia and reduce adverse effects (Mercadante & Bruera, 2006). A good example may be patients suffering from severe constipation who may benefit when switching from morphine to TF (Ahmedzai & Brooks, 1997) and from codeine or DHC to tramadol (Leppert & Majkowicz, 2010). A newer approach is the concomitant use of two opioids, although little evidence supports such procedure (Fallon & Laird, 2011). Future studies may address genetic disposition responsible for individual patients' response to opioid analgesics (Lötsch et al., 2009).

5. References

- Ahmedzai S, Brooks D. Transdermal Fentanyl versus Sustained-Release Oral Morphine in Cancer Pain: Preference, Efficacy and Quality of Life. *J Pain Symptom Manage* 1997; 13: 254 – 261.
- Ammon S, Hofmann U, Griese EU, Gugeler N, Mikus G. Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple oral dosing. *Br J Clin Pharmacol* 1999; 48: 317-322.
- Benett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: a systematic review. *Palliat Med* 2011; 25: 553-559.
- Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliat Med* 2011; 25: 402-409.

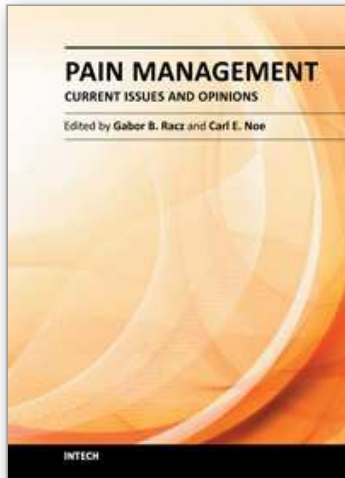
- Davies MP, Glare P. Tramadol. In: Opioids in cancer pain. Second Edition; Davies MP, Glare P, Quigley C, Hardy JR. Eds. Oxford, Oxford University Press 2009, pp. 99-118.
- Dickman A. Tramadol: a review of this atypical opioid. *Eur J Palliat Care* 2007; 14: 181-185.
- Donnelly S, Davis MP, Walsh D, Naughton M. Morphine in cancer pain management: a practical guide. *Support Care Cancer* 2002; 10: 13 - 25.
- Eidelman A, White T, Swarm RA: Interventional therapies for cancer pain management: important adjuvants to systemic analgesics. *J Natl Compr Canc Netw* 2007; 5: 753-760
- Enting RH, Oldenmenger WH, van der Rijt CCD, Wilms EB, Elfrink EJ, Elswijk I, Sillevius Smitt PAE. A Prospective Study Evaluating the Response of Patients with Unrelieved Cancer Pain to Parenteral Opioids. *Cancer* 2002; 94: 3049 - 3056.
- Fallon MT, Laird BJA. A systematic review of combination step III opioid therapy in cancer pain: An EPCRC opioid guideline project. *Palliat Med* 2011; 25: 597-603.
- Flemming K. The Use of Morphine to Treat Cancer-Related Pain: A Synthesis of Quantitative and Qualitative Research. *J Pain Symptom Manage* 2010; 39: 139 - 154.
- Freyenhagen RJ, Bennett MI. Diagnosis and management of neuropathic pain. *BMJ* 2009; 339: 391-395.
- Gardner-Nix J, Mercadante S. The Role of OROS® Hydromorphone in the Management of Cancer Pain. *Pain Pract* 2010; 10: 72-77.
- Gasche Y, Daali Y, Fathi M. et al. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. *N Engl J Med* 2004; 351: 2827-2831.
- Gnanadesigan N, Espinoza RT, Smith R, Israel M, Reuben DB. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? *J Am Med Dir Assoc* 2005; 6: 265-269
- Gretton S, Riley J. Morphine metabolites: a review of their clinical effects. *Eur J Palliat Care* 2008; 15: 110 - 114.
- Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer* 1997; 79: 1428-1437.
- Hanks GW, de Conno F, Cherny N, Hanna M, Kalso E, McQuay HJ, Mercadante S, et al. Expert Working Group of the Research Network of the European Association for Palliative Care: Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; 84: 587-593.
- King SJ, Reid C, Forbes K, Hanks G. A systematic review of oxycodone in the management of cancer pain. *Palliat Med* 2011; 25: 454-470.
- Kirchheiner J, Schmidt H, Tzetzkov M, Keulen J-T, Lötsch J, Roots I, Brockmüller J. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* 2007; 7: 257-265.
- Kneip C, Terlinden R, Beier H, Chen G. Investigations Into the Drug-Drug Interaction potential of tapentadol in Human Liver Microsomes and fresh Human Hepatocytes. *Drug Metabol Lett* 2008; 2: 67-75.
- Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* 2009; 13: 219 - 230.
- Leppert W, Luczak J, Gorzelinska L, Kozikowska J. Research from the Palliative Care Department in Poznan on treatment of neoplasm pain with Durogesic (transdermal fentanyl) (Polish). *Przegl Lek* 2000; 57: 59 - 64.

- Leppert W, Majkovicz M. The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain. *Int J Clin Pract* 2010; 64: 1681 – 1687.
- Leppert W, Mikolajczak P. Analgesic Effects and Assays of Controlled-Release Tramadol and O-desmethyltramadol in Cancer Patients with Pain. *Curr Pharmaceut Biotechnol* 2011; 12: 306 – 312.
- Leppert W. Dihydrocodeine as an analgesic for the treatment of moderate to severe chronic pain. *Curr Drug Metab* 2010; 11: 494-506.
- Leppert W. Progress in pharmacological pain treatment with opioid analgesics (Polish). *Wspolcz Onkol* 2009; 13: 66-73.
- Leppert W. Role of oxycodone and oxycodone/naloxone in cancer pain management. *Pharmacol Rep* 2010; 62: 578 – 591.
- Leppert W. The role of ketamine in the management of neuropathic cancer pain – a Polish experience. *Proceedings of the 3rd International Congress on Neuropathic pain, NeuPSIG, Athens (Greece), May 27 – 30, 2010, Ed. Christopher D. Wells. Medimond International Proceedings 2010, pp. 199 – 203.*
- Leppert W. The role of methadone in cancer pain treatment – a review. *Int J Clin Pract* 2009; 63: 1095 – 1109.
- Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. *Pharmacol Rep* 2009; 61: 978-992.
- Likar R, Krainer B, Sittl R. Challenging the equipotency calculation for transdermal buprenorphine: four case studies. *Int J Clin Pract* 2008; 62: 152 – 156.
- Lötsch J, Geisslinger G, Tegeder I. Genetic modulation of the pharmacological treatment of pain. *Pharmacol Ther* 2009; 124: 168-184.
- Lötsch J, Skarke C, Schmidt H, Rohrbacher M, Hofmann U, Schwab M, Geisslinger G. Evidence for morphine-independent central nervous opioid effects after administration of codeine: Contribution of other codeine metabolites. *Clin Pharmacol Ther* 2006; 79: 35-48.
- Lussier D, Huskey AG, Portenoy RK. Adjuvant Analgesics in Cancer Pain Management. *Oncologist* 2004; 9: 571-591.
- Madadi P, Moretti M, Djokanovic N, Bozzo P, Nulman I, Ito S, Koren G. Guidelines for maternal codeine use during breastfeeding. *Can Fam Phys* 2009; 55: 1077-1078.
- Madadi P, Ross CJD, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. Pharmacogenetics of Neonatal Opioid Toxicity Following Maternal Use of Codeine During Breastfeeding: A Case-Control Study. *Clin Pharmacol Ther* 2009; 85: 31-35.
- Maddocks I, Somogyi A, Abbott F, Hayball P, Parker D. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. *J Pain Symptom Manage* 1996; 12: 182-189.
- Mercadante S, Bruera E. Opioid switching: a systematic and critical review. *Cancer Treat Rev* 2006; 32: 304 – 315.
- Mercadante S, Ferrera P, Villari P. Is there a ceiling effect of transdermal buprenorphine? Preliminary data in cancer patients. *Support Care Cancer* 2007; 15: 441 – 444.
- Mercadante S, Villari P, Ferrera P. et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. *J Pain Symptom Manage* 2006; 32: 175 – 179.
- Miller MG, McCarthy N, O'Boyle CA et al. Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999; 18: 9 – 16.

- Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage* 1995; 29 (Suppl): S57 - S66.
- Nieminen TH, Hagelberg NM, Saari TI, Pertovaara A, Neuvonen M, Laine K, Neuvonen PJ, Olkkola KT. Rifampin Greatly Reduces the Plasma Concentrations of Intravenous and Oral Oxycodone. *Anesthesiology* 2009; 110: 1371-1378.
- Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. *Palliat Med* 2011; 25: 471-477.
- Rauers NI, Stuber F, Lee E.-H. et al. Antagonistic Effects of Ondansetron and Tramadol? A Randomized Placebo and Active Drug Controlled Study. *J Pain* 2010; 11: 1274-1281.
- Ridgway D, Sopata M, Burneckis A, Jespersen L, Andersen C. Clinical Efficacy and Safety of Once-Daily Dosing of a Novel, Prolonged-Release Oral Morphine Tablet Compared With Twice-Daily Dosing of a Standard Controlled-Release Morphine Tablet in Patients With Cancer Pain: A Randomized, Double-Blind, Exploratory Crossover Study. *J Pain Symptom Manage* 2010; 39: 712 - 720.
- Ripamonti C, Groff L, Brunelli C, Polastri D, Stavakis A, De Conno F. Switching From Morphine to Oral Methadone in treating Cancer Pain: What Is the Equianalgesic Dose Ratio? *J Clin Oncol* 1998; 16: 3216 - 3221.
- Ripamonti CI, Campa T, Fagnoni E, Brunelli C, Luzzani M, Maltoni M, De Conno F. on behalf of MERITO Study Group. Normal-release Oral Morphine Starting Dose in Cancer Patients With Pain. *Clin J Pain* 2009; 25: 386-390.
- Ripamonti CI, Easson AM, Gerdes H. Management of malignant bowel obstruction. *Eur J Cancer* 2008; 44: 1105 - 1115.
- Rowell FJ, Seymour RA, Rawlins MD. Pharmacokinetics of Intravenous and Oral Dihydrocodeine and its Acid Metabolites. *Eur J Clin Pharmacol* 1983; 25: 419-424.
- Sarhill N, Walsh D, Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. *Support Care Cancer* 2001; 9: 84 - 96.
- Schmidt H, Vormfelde SV, Walchner-Bonjean M. et al. The role of active metabolites in dihydrocodeine effects. *Int J Clin Pharmacol Ther* 2003; 41: 95-106.
- Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl Buccal Tablet for Relief of Breakthrough Pain in Opioid-Tolerant Patients With Cancer-Related Chronic Pain. *J Support Oncol* 2008; 5: 327 - 334.
- Stamer U, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of Tramadol and O-desmethyltramadol Enantiomers in Different CYP2D6 Genotypes. *Clin Pharmacol Ther* 2007; 82: 41-47.
- Stamer U, Stuber F, Muders T, Musshoff F. Respiratory Depression with Tramadol in a Patient with Renal Impairment and CYP2D6 Gene Duplication. *Anesth Analg* 2008; 107: 926-929.
- Stamer UM, Lehnen K, Höthker F, Bayerer B, Wolf S, Hoeft A, Stuber F. Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* 2003; 105: 231-238.
- Tzschentke TM, Christoph T, Kögel B. et al. (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol Hydrochloride (Tapentadol HCl): a Novel μ -Opioid Receptor Agonist/Norepinephrine Reuptake Inhibitor with Broad-Spectrum Analgesic Properties. *J Pharmacol Exp Ther* 2007; 323: 265 - 276.
- Vielvoye-Kerkmeer APE, Mattern C, Uitendaal MP. Transdermal Fentanyl in Opioid-Naive Cancer Pain Patients: An Open Trial Using Transdermal Fentanyl for the Treatment

- of Chronic Cancer Pain in Opioid-Naive Patients and a Group Using Codeine. *J Pain Symptom Manage* 2000; 19: 185 - 192.
- Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant – an ultra-rapid metabolizer. *Pediatric Anesthesia* 2007; 17: 684-687.
- Vree TB, van Dongen RTM, Koopman-Kimenai PM. Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract* 2000; 54: 395-398.
- Vree TB, Verwey-van Wissen CP. Pharmacokinetics and metabolism of codeine in humans. *Biopharm Drug Disp* 1992; 13: 445-460.
- Webb JA, Rostami-Hodjegan A, Abdul-Manap R, Hofmann U, Mikus G, Kamali F. Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; 52: 35-43.
- Wirz S, Wartenberg HC, Nadstawek J. Less nausea, emesis, and constipation comparing hydromorphone and morphine? A prospective open-labeled investigation on cancer pain. *Support Care Cancer* 2008; 16: 999 - 1009.
- World Health Organization: *Cancer Pain Relief and Palliative Care*. Geneva: World Health Organization, 1996.
- Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci* 2001; 69: 409-420

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