Clinical Use of Opioids

Rokhsareh Aghili1, Amir Farshchi2*, Mahdi Shiri3

1 Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
2 Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
3 Department of Toxicology, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT
For the treatment of pain, opioids are the main analgesic approaches. Opioid therapy involves the use of either weak or strong opiates, and both are often prescribed in conjunction to adequately control acute pain. Strong opiates often have additional routes beyond oral administration. Poor understanding of opioids and concerns about governmental retaliation for prescribing opioids can lead to treatment failure. Desired goal in handling of patients with chronic pain is achieving and sustaining an acceptable quality-of-life. In this narrative review, we discuss classifying and clinical use of opioids.

Keywords: Opioid, pain, analgesia

1. Introduction
The term opioid is used to describe substances that have morphine-like actions [1,2]. For the treatment of pain and relieve suffering, opioids are the main analgesic approaches. In clinic, opioids can be classified according to their receptor interactions (agonist, partial agonist, agonist-antagonist, and antagonist), the pain intensity for which they are conventionally used (moderate or severe), and their half-life (short or long). The opiates merely treat the symptoms while the underlying disease remains. Opioid therapy involves the use of either weak or strong opiates, and both are often prescribed in conjunction to adequately control acute pain. Weak opiates typically come in oral preparations and are combined with varying formulations of acetaminophen, aspirin, or ibuprofen. All of these drugs have ceiling doses related to the non-opioid ingredients. Ceiling dose is defined as a dose beyond which additional drug provides no further analgesia [2]. Strong opiates that are proper choice for severe pain are not mixed with other medications. The clinical use of opioids is for three goals: (1) analgesic, (2) antitussive, and (3) antidiarrheal. Opioids such as codeine can suppress the cough reflex by a direct effect on the cough center in the medulla of the brain [1]. In patients with exhausting diarrhea, dysenteries or after ileostomy or colostomy, opioids can be used because of their constipating effects. The dose of opioid as antitussive and an antidiarrheal drug is much lower than the analgesic dose [3]. Immediate release and sustained release preparations are now available. Strong opiates often have additional routes beyond oral administration including transdermal, parenteral, and neuraxial [4]. Opioid doses should be titrated based on response. Prior experience with opiates and other adjuvant agents can seriously influence treatment pattern. Practices have shown patients who have had previous opiate treatment or have opioid abuse require more therapy. These challenging patients are present in all countries. Hence, many communities have pain specialists to help manage them. Tachycardia and hypertension are the main clinical signs indicating that a patient is in acute pain. Poor understanding of opioids and concern about governmental retaliation for prescribing opioids can lead to treatment failure [5]. Relief of suffering without the adverse events such as decreased respiratory ventilation, reduced bowel motility, and urinary retention are the main goals of opioid therapy. In addition, Tollison has reported that under treatment of acute pain can lead to the development of chronic pain states. Desired goal in handling of patients with chronic pain is achieving and sustaining an acceptable quality of life.

2. Limitations of Opioid Therapy
Despite being the standard of analgesia therapy, opiates have adverse clinical effects, which can limit their use. It is important to know that there is a huge attempt in the pharmaceutical industry to develop mu1 selective agonist agents with all of the positive aspects of opiates but without side-effects. One of the most important side-effects is respiratory complication. Use of opiates during obstetrical analgesia must be considered, because the fetus is more susceptible to the respiratory depressant of the opioids than the mother [1]. Some evidence indicates prolonged exposure to opioids leads to immunosuppression more than short-term exposures [6]. The prevalence of drug abuse, physical and psychological dependence, or addiction in patients with chronic pain has been increased. However, misunderstanding of the nature and risk of addiction is a barrier to successful use of opioids in pain treatment.

3. Opioid Receptors
There are three main classical opioid receptor types mentioned in literatures, namely, mu, delta, and kappa (m, d, and k). Highly, selective ligands allowed for type-specific labeling of the three classical opioid receptors (e.g., DAMGO for m, DPDPDE for d, and U-50,488 and U-69,593 for k) made possible definition of ligand-binding characteristics of each of the receptor types. Each receptor has a specific anatomical distribution in brain, spinal cord, and the periphery. To establish the receptor types, in vivo administration of selective antagonists and agonists have been used [1]. In table 1, some opioid agonists and antagonists have been shown.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mu-receptor</th>
<th>Delta-receptor</th>
<th>Kappa-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Potent agonist</td>
<td>-</td>
<td>Agonist</td>
</tr>
<tr>
<td>Methadone</td>
<td>Potent agonist</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Potent agonist</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Potent agonist</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Antagonist</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial agonist</td>
<td>-</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Partial agonist</td>
<td>-</td>
<td>Potent agonist</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Partial agonist</td>
<td>-</td>
<td>Agonist</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Potent antagonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Potent antagonist</td>
<td>Antagonist</td>
<td>Potent antagonist</td>
</tr>
</tbody>
</table>

*Corresponding author. Tel.: +98 2164122318, Fax: +98 2166482606, E-mail: farshchi_a@razi.tums.ac.ir, Amir Farshchi
4. Opioid Agonist Analgesics

Various opioids have been administered by the different routes used in the management of pain are discussed in the following section.

4.1. Morphine

Morphine remains the most widely used opioid for the management of pain. Morphine produces analgesia, mood changes, drowsiness, and mental clouding. Its analgesic effect is selective, without loss of consciousness, touch, and vibration sensation. Irregular and severe (with high doses) pain is controlled by morphine [2]. Morphine analgesia (like other opioids) is limited by adverse effects of the medications (e.g., respiratory depression). Morphine and most of the opioids can provide further analgesia with additional doses; while non-steroidal anti-inflammatory drugs with higher doses do not provide any additional pain relief. Morphine with a dose of 10 mg intramuscular (IM) is the standard compare against other opioids (Table 2). In pharmacological pain model, morphine is also a gold standard [7,8]. A single oral dose of 60 mg (3 times larger than parenteral dose) has the same analgesic effect of 10 mg, IM. It can be justified with the first-pass metabolism in the liver in oral route [1,9]. The bioavailability of oral morphine is 25% [1]. For postoperative pain, cardiac pain, pulmonary edema and minor surgical procedures, morphine can be a good choice intravenously (2.5-10 mg) [1,2]. Morphine can also be administrated epidurally and intrathecally for postoperative analgesia [1]. It must be administrated every 4 h because its half-life is 2-4 h [10]. To switch to sustained highly doses, at first we must produce analgesia with a short-acting dose [1]. Morphine causes histamine release which can lead to pruritus. Furthermore, liver is the main organ for opioids metabolism. Thus, in patients with hepatic disease, opioid administration needs more caution. Morphine is metabolized to two main metabolites. Morphine-6-glucuronide (M6G) and M3G, by morphine glucuronidation. M6G - a mu opioid receptor agonist - crosses the blood-brain barrier more slowly than morphine. Also, it has been shown that M6G is more potent than morphine in various pain models [10-12]. M3G is not analgesic metabolite, and animal studies have shown that it may be responsible for the neurotoxic symptoms, occasionally occurred with high doses of morphine [10-12].

Morphine and other opioids can cause a number of adverse effects such as:

1. Respiratory depression: In healthy volunteers, morphine 0.15 mg/kg and M6G 0.2 mg/kg cause reductions in ventilator response to CO₂ [13].
2. Nausea and vomiting: Many studies have shown that the rate of nausea and vomiting with M6G may be less than morphine [14].
3. Urinary retention: The kidney has a critical role in M6G and M3G excretion [15]. The main predictors of higher morphine metabolites concentrations are: impaired renal function, first pass metabolism in oral route and increased patient age [16,17].
4. Others: Dizziness, mental clouding, dysphoria, hypotension, increased biliary tract pressure, and constipation [2].

4.2. Hydromorphone

Hydromorphone is a morphine derivative that affects seven times more than morphine intramuscularly [1,2]. The onset of hydromorphone action is rapidly, and similar to morphine. It has short half-life of 2-3 h and in hepatic or renal deficient patients and in the elderly there is less drug accumulation [2]. Hydromorphone-3-glucuronide (H3G) is the main metabolite of hydromorphone, a structural analogue of morphine-3-glucuronide (M3G). Both M3G and H3G do not have any analgesic action. It has been shown that M3G and H3G are excreted by the kidney. Some articles have reported dose dependent neurotoxic effects of the metabolite [18-20].

4.3. Codeine

Codeine can be administrated orally (codeine sulfate) or parent rally (codeine phosphate). Codeine has been classified as a weak opioid. However, P450 is an enzyme has a critical role in analgesic action of codeine [21]. This action depends on the metabolism of about 10% of the dose given to morphine, through the CYP2D6 cytochrome [10]. The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent drug and is excreted by the kidney. People who are carriers of the CYP2D6 gene duplication (ultra rapid metabolites) have significantly higher levels of morphine and its metabolites taking the similar dose of codeine [22]. Codeine has no advantages in comparison with morphine if injection rout is used. When codeine is combined with aspirin or acetaminophen, the synergic analgesia should be considered. Codeine has limited utility in high dose administration because of adverse effects such as nausea, vomiting, dizziness, and constipation [3].

4.4. Oxycodone

Oxycodone has the same potency as morphine. It affects about 10 times more than codeine. This opioid agonist derived from the opium alkaloid, thebaine. Oxycodone is available in tablets and solution forms. It can also be combined with aspirin or acetaminophen [1,2]. It is metabolized by the liver primarily to noroxycodone and oxymorphone. These metabolites have clinically very small analgesic effects [23,24]. Oxymorphone is the production that is metabolized by CYP2D6. It has more potent than oxycodone. Noroxycodone is the major metabolite that is produced by CYP3A4. It is a weakly active [23,25,26]. Physical dependence on oxycodone is common in chronic patients because its potency is like morphine [3]. Pharmacological studies in animals have discussed that oxycodone is actively pass into the brain resulting in a brain concentration is six times higher than those of plasma levels [27]. An experimental pain model has suggested that oxycodone could be better than morphine for visceral pain [28].

4.5. Pethidine

Pethidine (meperidine) is a synthetic widely used opioid. The onset of action is 10 min in IM injection and 15 min in oral rout [29]. It is highly potential for addiction. It seems that it is the most effective opioid in the treatment of renal colic, but many studies have shown it does not have more effect than morphine or hydromorphone [30,31]. Duration of analgesia is about 1-3 h [2]. Oral administration of pethidine is not suitable for long term therapy. Due to the high dose is needed, and the adverse effects may be bolded. It is often chosen for patients with biliary colic or pancreatitis [29]. Also, there was no any evidence that shows pethidine is better than morphine in the treatment of biliary colic [32]. Nausea and vomiting in pethidine administration are more than morphine [33,34]. Generalized seizures can be occurred in overdose cases. Pethidine is metabolized to norpethidine (normeperidine). Accumulation of norpethidine is associated with central nervous system excitation, myoclonus, tremulousness and seizures [35].

Table 2. Principles of opioid equianalgesics

<table>
<thead>
<tr>
<th>Opioid</th>
<th>P.O. Dose (mg)</th>
<th>I.M. Dose (mg)</th>
<th>I.V. Dose (mg)</th>
<th>Duration of effect (hours)</th>
<th>Trade Name</th>
<th>Intrinsic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
<td>5</td>
<td>4-5</td>
<td>Dilaudid</td>
<td>High</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td>1.5</td>
<td>4-5</td>
<td>Percodan</td>
<td>Low</td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>130</td>
<td>60</td>
<td>4-6</td>
<td>Demerol</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>300</td>
<td>2</td>
<td>50</td>
<td>3-3</td>
<td>Dolophine</td>
<td>High</td>
</tr>
<tr>
<td>Pethidine</td>
<td>300</td>
<td>75</td>
<td>50</td>
<td>4-5</td>
<td>Buprenex</td>
<td>High</td>
</tr>
<tr>
<td>Methadone</td>
<td>20</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3 (sol.)</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nalorphine toxicity is considered in patients with poor renal function because of half-life enhancement. It is important to know that naloxone may increase the problems related to nalorphine toxicity [29]. Pethidine can cause serotonergic syndrome when it is taken with monoamine oxidizer inhibitors. The main clinical signs are hyperthermia, excitation, delusions, and seizures [36].

### 4.6. Methadone

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with addiction to opioid and in patients with chronic pain [29]. It has mu-opioid receptor mediated analgesic effects [37,38]. Effective analgesic efficacy, availability by the oral route and suppressing withdrawal symptoms in addicts are the main advantages of this drug [2]. The long half-life and oral formulation make methadone a good choice in chronic pain like cancer. So, it has limited use for acute pain treatment. Methadone is metabolized primarily by the cytochrome P450 group of enzymes such as CYP2B6, CYP3A4, and CYP2D6 [39].

### 4.7. Fentanyl

Fentanyl is a synthetic, highly potent phenylpiperidine derivative, structurally related to pethidine [29]. It is 80 times more potent than morphine [2]. Fentanyl is commonly used in the treatment of acute pain [41]. Pain relief can be affected by mu-opioid receptors after fentanyl administration. Respiratory depression with fentanyl is shorter than pethidine. Thus, it is proper for anesthesia and postoperative analgesia. For anesthesia, fentanyl is commonly combined with the neuroleptic agent [29]. Intravenous, intrathecal, epidural and transdermal routes are available for fentanyl [1,2]. In the management of chronic pain like cancer, frequently transdermal rout is used [29]. Fentanyl transdermal is available in doses ranging 25-100 µg/h [29]. Rapid infusion of large doses of fentanyl can cause increased muscle tone of the thorax leading to the chest wall rigidity and the development of rigid chest syndrome [6]. In addition, the Food and Drug Administration has recently issued warnings due to deaths in patients using fentanyl patches. It is metabolized almost in the liver to minimally active metabolites. About 10% of un-metabolized fentanyl is excreted by renal system [29].

### 4.8. Buprenorphine

Buprenorphine is a semi-synthetic derivative of thebaine, opium alkaloid that binds strongly to the mu receptors. Its potency is 25-50 times than morphine. Buprenorphine onset of action is similar to morphine (15-60 min). This drug is unique among other opioids because it can be administered sublingually. A 0.4 mg sublingual dose is equipotent to 10 mg morphine intramuscularly [42]. In oral rout of administration, buprenorphine is eliminated pre-systemically, and it has not enough potency [42]. Twenty-four hours after, sublingual administration and 2-3 h after parenteral injection, one-third of buprenorphine is metabolized in the liver and gut through glucuronidation to buprenorphine-3-glucuronide metabolite that is inactive, and through CYP3A4 to norbuprenorphine. The latter metabolite has 40 times less analgesic effect than buprenorphine [43]. Buprenorphine has minimal effects on the cardiovascular system [29]. The risk of respiratory depression is low compared with morphine, methadone, hydromorphone and fentanyl, even in the doses used for the treatment of opioid addiction [43]. The respiratory depression is only partially reversible with naloxone [44]. Studies of animal pain models and also case reports in the clinic have shown that buprenorphine is a good choice for neuropathic pain [43,45]. Abstinence syndromes may be seen in patients dependent on opioids [29]. Withdrawal symptoms are milder than other opioids [43]. Usual side-effects associated with buprenorphine are sedation, diaphoresis, nausea, constipation, and respiratory depression [2].

### 4.9. Diamorphine

Diamorphine (diacetylmorphine, heroin) is a potent and fast-acting opioid. Diamorphine is hydrolyzed to monoacetylmorphine (MAM) and morphine. The analgesic effects of diamorphine have been mediated by MAM and morphine [46]. Use of this drug is prohibited in many countries like USA and Canada. In recent years, there has been considerable agitation to revive its use. However, double-blind studies have not supported the claim that heroin is more effective than morphine in relieving severe chronic pain, at least when is given by the IM route [47].

### 4.10. Dihydrocodeine

Dihydrocodeine is a semi-synthetic derivative of codeine and has similar mu-opioid agonist activity [29]. Dihydromorphine is less efficacious than morphine (it is a partial agonist). Also, it has adverse effects that limit the maximum tolerated dose when one attempts to achieve analgesia comparable to that of morphine. This compound is rarely used alone, but is combined in formulations containing aspirin or acetaminophen and other drugs [47].

### 4.11. Tramadol

Tramadol is a central-acting analgesic and is commonly referred to as an atypical acting analgesic because of its various effects as an opioid agonist, a serotonin and noradrenaline reuptake inhibitor [10], since it is only partially antagonized by naloxone. The recommended dosage is 50-100 mg orally four times daily [47], but it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain in these doses [48]. Tramadol is an effective treatment in patients with neuropathic pain or after surgery [49,50]. Tramadol is metabolized by CYP2D6 to O-desmethyltramadol (or M1), which is a more potent mu-opioid receptor agonist in comparison to tramadol [10,51]. Stamer showed in patients who are poor metabolizers, tramadol may cause less analgesic effect [52]. SHT3 receptor inhibition (e.g., ondansetron) decreased the analgesic effect of tramadol [53,54]. The adverse effects of tramadol are different from other opioids. This opioid caused lower respiratory depression significantly at equianalgesic doses [55-57]. Respiratory depression was only seen in patients with severe renal failure, due to accumulation of the metabolite M1 [58]. In addition, toxicity includes association with seizures. Also, the drug is relatively contraindicated in patients with a history of epilepsy and for use with other drugs that have lower seizure threshold. Moreover, studies have indicated that tramadol given within recommended dose limits does not increase the incidence of seizures in comparison with other analgesic agents [59,60]. Gastrointestinal motor function can be less affected by tramadol in comparison with morphine [61-63]. The most common adverse effects are nausea and vomiting that occur with the similar rates have compared with other opioids. But, these symptoms typically abate following several days of therapy [47,64]. Any clinically relevant effects on the cardiovascular system have not far been reported. The findings have indicated that the analgesic action of tramadol is largely independent on receptor action. This agent may be useful in atypical pain such as chronic neuropathic pain.

### 5. Conclusion

The effective clinical use of opioids requires skill of drug selection, knowledge on administration routes, dosage guidelines and probable adverse effects. Clinical use of opioids is influenced by pain intensity, pharmacokinetic and formulary considerations, the presence of coexisting disease and previous adverse effects. Finally, acceptable quality of life should be considered in patients with chronic pain.
References


