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Opioid Analgesics

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1. Introduction

Intensive research on the neurobiology of pain over the past two decades has revealed many receptors, ion channels and enzymes with potential as novel targets for development of a new generation of analgesic agents. However, despite large investment in preclinical and clinical development of small molecules and biologics as potential novel pain therapeutics, very few have reached the clinic. Hence, drugs used in the clinical setting for the pharmacological management of pain continue to be those that were first recommended in 1986 by the World Health Organisation (WHO) for the management of chronic cancer pain (WHO, 1986). Twenty-five years on, the WHO 3-step Analgesic Ladder (Figure 1) is still used widely to guide the pharmacological management of pain and opioid analgesics are the mainstay for alleviation of moderate to severe nociceptive pain.

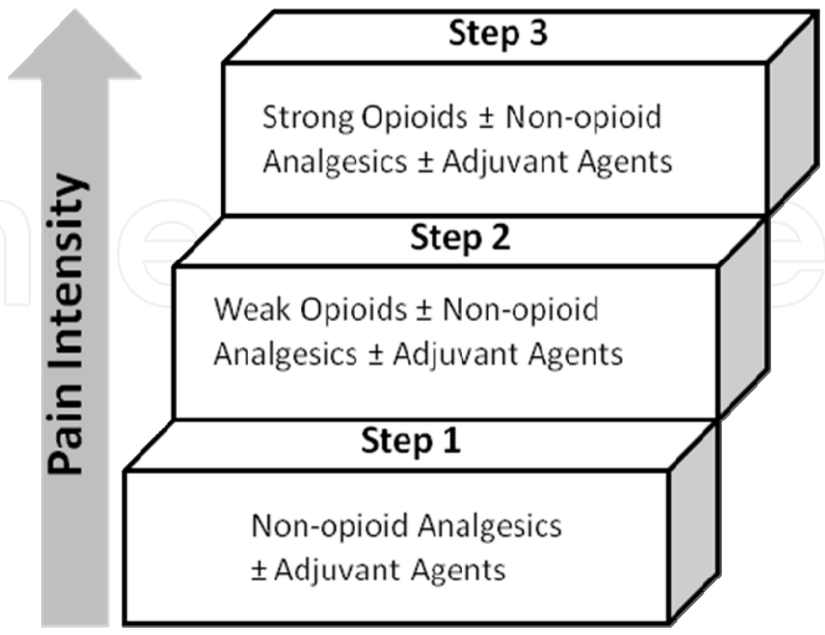


Fig. 1. World Health Organisation 3-Step Analgesic Ladder (WHO, 1986)

2. WHO Analgesic Ladder

The WHO Analgesic Ladder provides a succinct encapsulation of the guidelines for the management of chronic pain according to intensity (WHO, 1986). Specifically, for mild pain, non-opioid analgesics on Step 1 of the Analgesic Ladder including acetaminophen, aspirin and nonsteroidal anti-inflammatory drugs such as ibuprofen, are recommended. When the pain has a neuropathic component, addition of an adjuvant agent such as a tricyclic antidepressant, anticonvulsant or anti-arrhythmic agent, is recommended. Weak opioid analgesics such as codeine, tramadol and dextropropoxyphene are added to non-opioid analgesics when mild pain progresses to moderate pain (Step 2); adjuvants are again co-administered when the pain has a neuropathic component. Strong opioid analgesics are recommended for the management of moderate to severe nociceptive pain (Step 3) with morphine the strong opioid analgesic of choice due to its ready availability world-wide at low cost. Strong opioid analgesics are often co-administered with non-opioids, and adjuvants are added when pain has a neuropathic component (WHO, 1986).

According to the WHO guidelines, each patient should receive a period of individualized dose titration on a 'round the clock' rather than an 'as required' basis as this facilitates dosage optimization for the selected analgesic and/or adjuvant (WHO, 1986). Although many opioid analgesics have relatively short elimination half-lives (Table 1), most are available as sustained-release formulations that are administered once or twice-daily to optimize patient compliance as well as pain relief. For patients who experience break-through pain during ambulation or activities of daily living, additional bolus doses of immediate-release formulations are given on an "as required" basis. For most patients, the oral dosing route is preferred except where impaired gastrointestinal transit makes this impractical as in the immediate post-operative period or during labor.

3. Opioid analgesics

Opioid analgesics commonly used for the control of clinical pain include morphine, codeine, oxycodone, hydromorphone, buprenorphine, tramadol, fentanyl, remifentanil, pethidine and methadone. The potencies of these opioid analgesics differ markedly. Equi-analgesic doses and usual starting doses for the oral route derived from the acute pain setting are shown in Tables 2 and 3 respectively.

3.1 Opioid-related adverse effects

Apart from their desired analgesic action, clinically prescribed opioids also produce many undesired effects including respiratory depression, sedation, nausea, vomiting, constipation, pruritus, tolerance and dependence, to name but a few (Zollner & Stein, 2007). Although studies using μ-opioid (MOP) receptor knockout mice suggest that the analgesic and adverse effects of opioid analgesics are all produced by activation of the MOP receptor, clinical experience shows that there are marked between-opioid differences with respect to analgesic and tolerability profiles within the same patient (Smith, 2008). However, the precise mechanistic basis underpinning these observations is not well understood.

Opioid Analgesic	Elimination Half-life (h)	Duration of Action (h)
Codeine	3	4-6
Meperidine	3.5	4-6
Fentanyl	3.7	0.5-1 (IV); 72 (TD); 2-4 (TM)
Hydromorphone	2-3	4-5
Methadone	24#	4-6
Morphine	2.5	3-4
Oxycodone	3	8-12 (CR), 3-4 (IR)
Tramadol	5-7	4-6 (IR), 24 (ER)
Buprenorphine	3	6

#large inter-individual variability in range 12-150 h
IV = intravenous; TD = transdermal; TM = transmucosal
IR = immediate release; ER = extended release; CR = controlled release

Table 1. Typical Mean Elimination Half-lives and Durations of Action for Commonly Prescribed Opioid Analgesics (adapted from Mather & Smith 1998; Trescot et al., 2008; Argoff & Silvershein, 2009)

Opioid Analgesic	Dose × Conversion Factor
Codeine	x 0.16
Meperidine (IV)	× 0.4
Methadone	× 1.5
Oxycodone	× 1.5
Buprenorphine	× 50
Morphine (IV)	× 3
Morphine (oral)	× 1

IV = intravenous

Table 2. Opioid Analgesic Dose Conversion Table to Oral Morphine (adapted from Nissen et al., 2011)

Opioid Analgesic	Oral Administration	
	Dose	Inter-dosing Interval (h)
Codeine	15-60 mg	3-6
Fentanyl	100-200 µg (IV)	6[a]
Hydromorphone	2-4 mg	3-4
Methadone	5-10 mg	24
Morphine	15-30 mg (IR)	4 (IR)
Oxycodone	10 mg (CR), 5-10 mg (IR)	12 (CR), 4-6 (IR)
Tramadol	50-100 mg (IR), 100 mg (ER)	4-6 (IR), 24 (ER)

CR = controlled-release; ER = extended-release; IR = immediate-release; IV = intravenous;
[a]Not more than 4 doses per day.

Table 3. Common Starting Doses for Selected Opioid Analgesics (adapted from Mather & Smith; Argoff & Silvershein, 2009)

3.1.1 Respiratory depression

Opioid-related deaths continue to be reported in the acute pain setting underpinned by opioid-induced ventilatory impairment that often develops due to a combination of factors including opioid-induced central respiratory depression, sedation and/or upper airway obstruction (Macintyre et al., 2011). It is recommended that all patients be monitored for opioid-induced ventilatory impairment using sedation scores as a '6th vital sign' so that it can be detected early and appropriate intervention initiated (Macintyre et al., 2011).

3.2 Strategies for minimizing opioid-related adverse effects

It is essential to assess patients to ensure that adverse effects are genuinely opioid-related rather than being due to another medical problem. Strategies recommended (Swegle & Logemann, 2006) for minimizing opioid-related adverse effects are as follows:

1. Titrating opioid doses slowly
2. Dose reduction to assess if satisfactory analgesia can be obtained with tolerable side-effects
3. Symptom management including pro-active preventative treatment of nausea and constipation
4. Addition of, or increasing non-opioid or adjuvant analgesic doses for an opioid sparing effect
5. Opioid rotation
6. Changing the route of administration
7. Frequent re-assessment

3.3 Strategies for managing intolerable opioid-related adverse effects

For patients experiencing poor pain relief together with intolerable opioid-related side-effects such as severe vomiting, severe dysphagia or bowel obstruction, changing from the oral to the parenteral (e.g. intravenous, subcutaneous, intramuscular), rectal, buccal, sublingual, transdermal or spinal (epidural, intrathecal) route of administration, may reduce adverse effects to a tolerable level and restore satisfactory analgesia (Walsh, 2005). Another strategy for restoring satisfactory analgesia with tolerable side-effects in such patients is 'opioid rotation' that involves switching from one strong opioid analgesic to another (Smith, 2008; Knotkova et al., 2009; Vissers et al., 2010). Additional clinical strategies for restoring analgesia in patients experiencing inadequate pain relief and intolerable opioid-related side-effects include use of neurolytic blocks as an adjunct or alternative to pharmacotherapy (Eisenberg et al., 2005) or progression to use of anaesthetic intervention if 'opioid rotation' fails (Riley et al., 2007).

3.4 Tolerance to the analgesic effects of opioids

In the absence of disease progression, tolerance to the analgesic effects of an opioid manifests in patients with clinical pain as the need for progressively higher opioid doses in order to maintain the same level of pain relief (South & Smith, 2001). In rodent studies, analgesic tolerance is demonstrated by a rightward shift in the analgesia dose-response curve for a particular opioid administered after a period of chronic dosing relative to the dose-response curve determined for the same opioid in opioid-naïve animals (South & Smith, 2001).

3.5 Tolerance to opioid-related side-effects

As already noted, opioid-related adverse effects that may occur after the initation of opioid analgesic treatment in opioid-naïve patients include respiratory depression, somnolence,

nausea, vomiting, miosis, pruritus, constipation, and euphoria/dysphoria. With chronic dosing, tolerance often develops to sedation, nausea and respiratory depression whereas tolerance to constipation and miosis is minimal (Chang et al., 2007).

3.6 Opioid analgesics and renal impairment

Several opioid analgesics including morphine, hydromorphone and meperidine are metabolized in the liver to pharmacologically active metabolites that may accumulate in patients with renal impairment. Hence, for patients with renal impairment, opioid analgesics including oxycodone and fentanyl that are devoid of active metabolites, are preferred (King et al., 2011).

4. Weak opioid analgesics

4.1 Codeine

Codeine (7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol) is an opioid alkaloid found in opium, the dried exudate of the unripe seed capsule of the opium poppy, *Papaver somniferum*, at 0.7 to 2.5% (Boerner, 1975). Due to its high consumption rates globally, codeine is generally synthesized by O-methylation of morphine, an abundant opium constituent at 10-15% (Lenz et al., 1986).

Codeine is a weak opioid analgesic that binds to the μ-opioid (MOP) receptor with low affinity (Ki = 0.7 μM) (Volpe et al., 2011). Its analgesic properties are generally thought to be derived from the fact that it is a prodrug for morphine as up to 10% of oral doses are O-demethylated to morphine by cytochrome P450 2D6 (CYP2D6), an enzyme subject to genetic polymorphism (Kadiev et al., 2008, Somogyi et al., 2007, Zollner & Stein, 2007). Supporting this notion, plasma morphine concentrations are virtually undetectable and codeine lacks efficacy in individuals with the poor metabolizer (PM) CYP2D6 phenotype (Poulsen et al., 1996). By contrast, codeine is extensively metabolized to morphine in those with the ultra-metabolizer (UM) phenotype who also have an increased risk of respiratory depression after regular doses of codeine (Kirchheiner et al., 2007).

Doses of codeine generally do not exceed 60 mg (Trescot et al., 2008). Codeine is available in a range of prescription and over-the-counter medicines, often in combination with paracetamol, aspirin or ibuprofen for pain relief (Moore et al., 1997; Moore et al., 2011). It is also the active ingredient in many cough suppressant mixtures and anti-diarrhoeal products (Schiller, 1995; Wee, 2008). Codeine is susceptible to metabolic drug-drug interactions with other commonly prescribed medications that are also metabolized by CYP2D6 including both CYP2D6 inhibitors (e.g. cimetidine) and CYP2D6 inducers (e.g. rifampicin) (Caraco et al., 1997; Zhou, 2009).

4.2 Meperidine (pethidine)

Meperidine (pethidine; ethyl-1-methyl-4-phenylpiperidine-4-carboxylate), is a synthetic MOP receptor agonist that binds with low affinity (Ki = 450 nM) at the MOP receptor (Volpe et al., 2011). Meperidine is a weak opioid analgesic with potency at ~10% that of morphine for the relief of acute post-operative pain (Latta et al., 2002). Meperidine is metabolized by hepatic esterases to pethidinic acid, an inactive metabolite, and by N-demethylation to a neurotoxic metabolite, normeperidine (Gilman et al., 1980, Armstrong et al., 2009). After multiple doses, normeperidine may accumulate in plasma and cerebrospinal fluid causing tremors, twitches, myoclonus and seizures as it has a longer plasma half-life than

meperidine itself (Plummer et al., 1995; Simopoulos et al., 2002). Meperidine is contra-indicated in patients with impaired renal function as they are at increased risk of normeperidine neurotoxicity due to its faster accumulation (Marinella, 1997; Reutens & Stewart-Wynne, 1989). Generally, meperidine use is discouraged in favour of more efficacious and less toxic opioid analgesics (Latta et al., 2002).

4.3 Tramadol

Tramadol ((1RS,2RS)-2-[(dimethylamino)methyl]- 1 -(3-methoxyphenyl)-cyclo-hexanol hydrochloride) is a synthetic analgesic that is a racaemic mixture of two enantiomers that bind to the MOP receptor with low (10 μM) affinity (Volpe et al., 2011). After systemic administration, tramadol is metabolized in the liver by the enzyme CYP2D6, to its O-demethylated M1 metabolite, a potent μ-opioid agonist that contributes to its analgesic actions (Subrahmanyam et al., 2001). The (-)-enantiomer of tramadol mainly inhibits noradrenaline reuptake in the central nervous system (CNS) to augment descending inhibition of pain transmission in the spinal cord whereas the (+)-enantiomer preferentially inhibits serotonin reuptake (Reimann & Hennies, 1994). Thus, the pharmacology of tramadol is complex with its analgesic action being due to the combined effects of its two enantiomers and the M1 metabolite. For this reason, the US Food and Drug Administration (FDA) has classified tramadol as a nontraditional, centrally acting analgesic (Grond & Sablotzki, 2004).

For the relief of post-operative pain relief, tramadol is regarded as a "weak" opioid analgesic with potency at ~10% that of morphine but it does not produce significant constipation or respiratory depression and it has low abuse potential (Grond & Sablotzki, 2004). When tramadol is given in doses larger than the recommended doses, or if it is co-administered with medications that lower the seizure threshold such as selective serotonin reuptake inhibitors, tricyclic antidepressants and antipsychotic drugs, seizures may be induced (Gardner et al., 2000).

5. Strong opioid analgesics

5.1 Morphine

Morphine (7,8-didehydro-4,5,-epoxy-17-methyl-(5α,6α)-morphinan-3,6-diol) is extracted from opium due to its relatively high abundance at ~10-15% by weight (Boerner, 1975). Morphine was first isolated from opium in 1805 by Freidrich Sertűrner, a German pharmacist who named it "morphium" after Morpheus the Greek God of Dreams (Milne et al., 1996).

Morphine is the prototypic strong opioid analgesic that binds with high affinity (K_i = 1.2 nM) at the MOP receptor (Volpe et al., 2011). After oral administration in humans, morphine has low oral bioavailability at ~20% due to extensive first-pass metabolism in the liver to two major metabolites, viz morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) that account for ~10% and >50% of each dose, respectively (Milne et al., 1996). Morphine has a short elimination half-life at ~2 h consistent with its short duration of action at ~4 h (Mather & Smith, 1998).

M6G, like morphine, binds with high affinity at the MOP receptor and it is a more potent analgesic than morphine when given by central routes (Smith & South, 2001). By contrast, supraspinally administered M3G evokes dose-dependent neuro-excitatory effects and its

actions generally oppose those of morphine in animal studies (Smith, 2000). The elimination half-lives of M3G and M6G are in the range 3-4 h (Mather & Smith, 1998).
After administration of single doses of morphine to patients with clinical pain, the plasma and CSF concentrations of M3G exceed those of morphine by several-fold (Hasselström & Säwe, 1993) and after chronic dosing, the plasma M3G concentrations exceed the corresponding morphine levels by as much as 10-20 fold (Smith et al., 1999). In patients with renal impairment, M6G and M3G may accumulate in the plasma and CSF, thereby increasing the risk of M6G-induced respiratory depression (Smith & South, 2001) and/or M3G-induced neuro-excitation (Smith, 2000).
Morphine is available in immediate-release and sustained-release oral tablet and capsule formulations as well as oral mixtures, rectal suppositories and sterile ampoules for parenteral administration by the intramuscular, intravenous, subcutaneous, epidural and intrathecal routes (Argoff & Silvershein, 2009). The duration of action for immediate-release oral morphine preparations is approximately 3-4 h whereas for oral sustained-released morphine tablets and capsules, the duration of action is 12-24 h (Mather & Smith, 1998). The convenience of once or twice daily dosing provided by sustained-release formulations improves patient compliance and pain relief outcomes (Argoff & Silvershein, 2009).

5.2 Oxycodone

Oxycodone ((5α-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one) is a strong opioid analgesic that is a semi-synthetic derivative of the abundant opium alkaloid, thebaine (Lenz et al., 1986). After oral administration, the bioavailability of oxycodone is high at 60-87% (Leow et al., 1992; Lalovic et al., 2006). Oxycodone is extensively N-demethylated by the enzyme, CYP3A4, to the analgesically inactive metabolite, noroxycodone (Poyhia et al., 1992; Davis et al., 2003; Lalovic et al., 2004, 2006) with up to another 10% of each dose undergoing CYP2D6-catalyzed O-demethylation to the high affinity MOP receptor agonist oxymorphone (Lalovic et al., 2006). However, metabolically-derived oxymorphone does not contribute significantly to the analgesic actions of oxycodone for the relief of clinical pain because its circulating plasma concentrations are very low (~1 ng/mL) in both extensive metabolisers (EMs) and PMs (0.3 ng/mL) as it is rapidly further metabolized to its analgesically-inactive glucuronide conjugate (Lalovic et al., 2006; Zwisler et al., 2010). For patients with post-operative pain, there is no difference in analgesic outcomes between PMs and EMs (Zwisler et al., 2010), affirming earlier work by others showing that the analgesic effects of oxycodone are attributable to the parent opioid alone (Heiskanen et al., 1998; Lalovic et al., 1996).
Radioligand binding studies show that oxycodone has relatively low affinity (Ki = 26 nM) at the cloned MOP receptor (Volpe et al., 2011) and that it has a distinctly different binding profile from morphine in rat brain homogenate (Nielsen et al., 2007). This likely underpins the low extent of cross-tolerance between oxycodone and morphine in rodents (Nielsen et al., 2000) and the success of opioid rotation from morphine to oxycodone for the restoration of analgesia with tolerable opioid-related side-effects in humans (Narabayashi et al., 2008).
The potency of intravenous and oral oxycodone for the relief of both post-operative and chronic cancer pain is ~1.5 times that of morphine (Kalso et al., 1991; Heiskanen & Kalso, 1997; Bruera et al., 1998). However, when given by the epidural route for the relief of post-operative pain, the potency of oxycodone is much lower than that of morphine at ~11% (Backlund et al., 1997).

Oxycodone, like morphine, is available in immediate-release and sustained-release tablet formulations as well as in oral mixtures, rectal suppositories and ampoules for parenteral administration (Argoff & Silvershein, 2009).

5.3 Methadone

Methadone, 6-dimethylamino-4,4-diphenyl-heptan-3-one, is a synthetic, strong opioid analgesic that is a racaemic mixture of two enantiomers. The analgesic efficacy of methadone is multi-faceted as the R-enantiomer is a high affinity MOP receptor agonist (Ki = 3.4nM) whereas the S-enantiomer augments descending noradrenergic inhibition to block nociceptive signaling in the spinal cord, and both enantiomers have NMDA receptor antagonist activity (Davis and Walsh, 2001).

In humans, methadone has high but unpredictable oral bioavailability at ~80% (range 41-99%) with peak plasma concentrations observed at 2-4 h post-dosing (Trescot et al., 2008; Modesto-Lowe et al., 2010). There is a large degree of inter-individual variability in its long elimination half-life (12-150 h) (Trescot et al., 2008). These properties make it difficult to use for the relief of acute pain or for pain that is poorly controlled where rapid dose adjustments are needed (Davis & Walsh, 2001). Further adding to these difficulties, methadone is metabolized by CYP3A4-catalyzed N-demethylation to the analgesically inactive metabolite, normethadone, such that methadone is potentially subject to a large number of metabolic drug-drug interactions as many clinically used drugs are either CYP3A4 inhibitors or inducers (Fishman et al., 2002).

Apart from its use as a strong opioid analgesic for relief of moderate to severe pain, methadone is also widely used for opioid maintenance therapy in patients with heroin addiction (Fishman et al., 2002). Commercially available methadone formulations include oral tablets and mixtures, rectal suppositories and ampoules for parenteral administration (Manfredi et al., 2003). When converting patients from a strong opioid analgesic such as morphine to methadone, caution needs to be exercised. This is because morphine-methadone analgesic ratios vary significantly according to the previous morphine dosing regimen (Mancini et al., 2000).

For individuals receiving chronic methadone treatment for opioid dependence, cardiotoxicity characterized by prolonged QTc intervals are associated with methadone dose and concurrent stimulant use (Modesto-Lowe et al., 2010; Mayet et al., 2011). For individuals receiving methadone at doses exceeding 60 mg/day together with tricyclic antidepressants or other drugs that inhibit methadone metabolism, the QTc interval is lengthened thereby initiating Torsades de Pointes (Krantz et al., 2002, Ehret et al., 2007). QT prolongation with methadone is also influenced by other factors including hypokalaemia, hepatic failure and pre-existing heart disease (Ehret et al., 2007). Unfortunately, the general lack of awareness of the long and highly variable elimination half-life of methadone together with its many metabolic drug-drug interactions, has led to a dramatic increase in methadone-associated deaths (Trescot et al., 2008).

5.4 Hydromorphone

Hydromorphone, 4,5 alpha-epoxy-3-hydroxy-17-methyl morphinan-6-one, is a semi-synthetic opioid analgesic (Murray & Hagen, 2005) that binds with high affinity (Ki = 0.37 nM) at the MOP receptor (Volpe et al., 2011) and to a lesser extent at the δ-opioid (DOP) receptor but not at the κ-opioid (KOP) receptor (Murray & Hagen, 2005). Orally

administered hydromorphone undergoes extensive first-pass metabolism in the liver to hydromorphone-3-glucuronide (H3G) that accounts for more than 50% of each dose. Although H3G, like M3G, is analgesically inactive, it produces dose-dependent neuro-excitatory effects after supraspinal administration in rodents with a potency ~2.5-fold higher than M3G (Wright et al., 2001). Chronic administration of hydromorphone in patients with renal impairment will result in H3G accumulation, raising the risk that neuro-excitatory side-effects will be produced (Smith, 2000; Mercadante & Arcuri, 2004).
The analgesic potency of parenteral hydromorphone is ~ 5-fold higher than that of morphine for the alleviation of moderate to severe acute pain (Bruera et al., 1996; Dunbar et al., 1996; Quigley, 2002; Horn & Nesbit, 2004) whereas for chronic cancer pain, the analgesic potency of hydromorphone is similar to that of morphine (Murray & Hagen, 2005).
Hydromorphone is available as immediate-release and controlled-release oral formulations (Guay, 2010) as well as ampoules for parenteral administration by either the epidural or intrathecal routes (Lee et al., 2011; Liu et al., 2011).

5.5 Buprenorphine

Buprenorphine, ((2S)-2-[(-)-(5R,6R,7R,14S)-9α-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol), is also a semi-synthetic derivative of thebaine. Buprenorphine binds with high affinity (K_i = 0.2nM) at the MOP receptor (Volpe et al., 2011) and functionally it is a partial agonist (Pick et al., 1997). Buprenorphine also has antagonist actions at the κ-opioid (KOP) receptor and it interacts with the nociceptin (ORL-1) receptor (Pick et al., 1997). Buprenorphine produces dose-dependent analgesia with potency at ~25-50 times higher than morphine (Evans & Easthope, 2003). The slow onset and long duration of buprenorphine's pharmacodynamic actions are thought to be due to its slow binding to and dissociation from the MOP receptor (Evans & Easthope, 2003).
Consistent with its partial agonist activity at the MOP receptor, sublingual buprenorphine administered to healthy male volunteers in doses up to 70-fold higher than the recommended analgesic dose (0.3 mg) and 4-8 fold higher than doses (4-8 mg) used to treat opioid addiction, produced ceiling responses for subjective measures of drug liking in doses at 8 to 16 mg (Walsh et al., 1994). In the same subjects a ceiling effect for respiratory depression was observed at 16mg (Walsh et al., 1994). Because buprenorphine exhibited linear pharmacokinetics across the dose range tested, dose-limited sublingual absorption is not responsible for the ceiling effects (Walsh et al., 1994). The KOP antagonist activity of buprenorphine is thought to contribute to its good tolerability characterized by limited dysphoria or psychotomimetic effects (Johnson et al., 2005).
After oral administration, buprenorphine undergoes extensive first-pass metabolism in the liver catalyzed by the enzymes, CYP3A4 and CYP2C8 to produce the active N-dealkylated metabolite, norbuprenorphine (Picard et al., 2005). Consequently the oral bioavailability is low at ~14% and so buccal, sublingual, intranasal and transdermal formulations of buprenorphine have been developed that effectively by-pass first-pass metabolism and increase bioavailability to 30-60% (Evans & Easthope, 2003; Johnson et al., 2005; Davis, 2005).
Due to its long half-life (~26 h) and ceiling pharmacodynamic effects, buprenorphine is used as an alternative to methadone for opioid maintenance therapy in opioid-dependent individuals (Robinson, 2002; Johnson et al., 2005). A combination product containing buprenorphine and naloxone in a 4:1 ratio respectively is available in some countries as a deterrent to illicit use of buprenorphine tablets for parenteral injection (Harris et al., 2004).

5.6 Fentanyl

Fentanyl, *N*-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenyl-propanamide, is a synthetic opioid analgesic (Horn & Nesbit, 2004) that binds with high affinity (Ki = 1.3 nM) at the MOP receptor (Volpe et al., 2011). Fentanyl is metabolized by CYP3A4 to its N-dealkylated metabolite, norfentanyl that is pharmacologically inactive (Horn & Nesbit, 2004).

After parenteral dosing, fentanyl is ~80-100 fold more potent than morphine with a rapid onset of action but only a short duration at < 60 min (Horn & Nesbit, 2004; Pasero, 2005; Stanley, 2005). For post-operative pain relief, fentanyl may be given by spinal routes whereas for breakthrough or procedural pain, the sublingual, transmucosal, intra-nasal, inhaled or parenteral routes are preferred (Lennernas et al., 2005; Hair et al., 2008; Peng & Sandler, 1999).

Fentanyl has high lipophilicity making it suitable for transdermal delivery. To this end, there are several transdermal patch formulations of fentanyl available for clinical use that effectively overcome fentanyl's short duration of action (Cachia & Ahmedzai, 2011). There is now a large body of evidence to support the use of fentanyl patches for the management of moderate to severe chronic cancer pain, with data suggesting improved pain relief and reduced opioid-related side-effects compared with sustained release oral morphine (Cachia & Ahmedzai, 2011).

5.7 Tapentadol

Tapentadol, [(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol], is a recently approved centrally acting analgesic with two complementary modes of action, viz moderate affinity activity at the MOP receptor (Ki = 0.1 μM) together with inhibitory effects on the NET transporter (Ki = 0.5 μM) to block the re-uptake of norepinephrine in the CNS and so augment descending inhibition to attenuate pain at the level of the spinal cord (Tzschentke et al., 2007; Hartrick, 2009; Wade & Spruill, 2009). After oral dosing, the oral bioavailability of tapentadol is relatively low at ~32% (Tzschentke et al., 2006) due to significant first-pass metabolism in the liver to the inactive glucuronide metabolite, tapentadol-O-glucuronide (Terlinden et al., 2010).

The immediate-release (IR) formulation of tapentadol was approved by the FDA in 2008 for the management of moderate-to-severe acute pain as the first new analgesic developed in over 25 years (Vadivelu et al., 2011). When compared with oxycodone in a head-to-head clinical trial for the relief of post-operative pain in patients following bunionectomy, tapentadol provided non-inferior analgesia to oxycodone with a superior gastrointestinal adverse effect profile characterized by significantly less nausea, vomiting, and constipation when compared with oxycodone (Hartrick, 2009; Vadivelu et al., 2011).

More recently, the FDA has approved an extended-release (ER) formulation of tapentadol for twice-daily oral administration for the management of moderate to severe chronic pain in adult patients (Vadivelu et al., 2011). In patients with end-stage joint disease administered IR tapentadol for two weeks followed by the ER formulation for a further 4-weeks, the superior gastrointestinal tolerability of tapentadol relative to oxycodone, was affirmed (Etropolski et al., 2011). Mechanistically, this may be due to an 'opioid-sparing' effect of the inhibitory actions of tapentadol at the NET transporter (Tzschentke et al., 2006).

5.8 Ultra-short acting opioid analgesics

For patients with cardiovascular instability, ultra-short acting structural analogues of fentanyl such as remifentanil, alfentanil and sufentanil are preferred for use as part of balanced analgesic regimens during anaesthesia (Horn & Nesbit, 2004).

5.8.1 Remifentanil

Remifentanil, 3-[4-methoxycarbonyl-4-[1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester) is a synthetic derivative of fentanyl with an ester function in its structure that makes it susceptible to hydrolysis by non-specific blood and tissue esterases (Egan et al., 1993). The very rapid metabolism of remifentanil to the inactive remifentanil acid metabolite by non-specific esterases underpins its activity as an ultra-short acting MOP agonist (Egan et al., 1993).

Parenteral remifentanil has a rapid onset of action (~1 min) and a rapid offset of action following discontinuation (~3–10 min) (Stroumpos et al., 2010) and it is indicated for the relief of pain associated with surgical procedures (Mesolella et al., 2004, Kucukemre et al., 2005).

Remifentanil's pharmacokinetics favour its use as an analgesic during labour (Leong et al., 2011), a notion supported by the findings of two recent clinical studies (Buehner et al., 2011; Ng et al., 2011). In the first study, 94% of 244 consecutive women in a small maternity unit who received remifentanil by patient-controlled analgesia (PCA) for relief of labour pain rated their analgesic outcomes as excellent, very good or good (Buehner et al., 2011). The safety profile of remifentanil was also good as the Apgar scores of neonates born to these women did not differ significantly from those for neonates born by normal vaginal delivery to women who received no analgesia (Buehner et al., 2011). In the second study, maternal satisfaction was higher in laboring women who received PCA remifentanil for analgesia compared with intramuscular pethidine (Ng et al., 2011) with no difference in the safety profile between these two opioid analgesics in the newborn infants (Ng et al., 2011).

6. Opioid rotation

For patients experiencing poor pain relief and intolerable opioid-related side-effects on one strong opioid analgesic, switching to a second strong opioid analgesic often results in restoration of satisfactory pain relief with tolerable opioid-related adverse effects (Knotkova et al., 2009; Vissers et al., 2010). The starting dose of the second opioid is selected to minimize potential risks whilst ideally restoring analgesic efficacy and must be informed by an estimate of its potency relative to the first opioid (Fine et al., 2009; Mercadante & Caraceni, 2011).

Both pharmacokinetic and pharmacodynamic factors may contribute to the clinical success of opioid rotation. For opioid analgesics such as morphine and hydromorphone that are avidly metabolized to the neuro-excitatory 'anti-analgesic' glucuronide metabolites, M3G and H3G respectively, opioid rotation facilitates clearance of these metabolites from the body enabling restoration of analgesia with the second opioid and resolution of neuro-excitatory side-effects (Smith, 2000). Additionally, opioid rotation exploits incomplete cross-tolerance between opioids possibly underpinned by subtle differences in their modulation of MOP receptor function (Smith, 2008; Slatkin, 2009).

7. Peripherally selective opioid antagonists for improving opioid-induced constipation

In patients receiving opioid analgesics for treatment of chronic pain, constipation is a very common side-effect that impairs quality of life and has a prevalence of >80% despite proactive laxative use (Clemens & Mikus, 2010; Diego et al., 2011). A recent approach to the treatment of opioid-induced constipation involves the recent development of quarternary

ammonium opioid antagonists such as alvimopan and methylnaltrexone that have limited absorption across the gastrointestinal mucosa and do not cross the blood-brain-barrier, as well as products that incorporate low-dose oral naloxone that has very low oral bioavailability at 2% (Diego et al., 2011). These products selectively target opioid receptors in the gastrointestinal tract without affecting centrally-mediated analgesic mechanisms (Diego et al., 2011).

7.1 Alvimopan

Alvimopan, 2-([(2S)-2-([(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl) -3-phenylpropanoyl]amino)acetic acid, is an orally active synthetic MOP receptor antagonist that is unable to cross the blood-brain-barrier due to the presence of a quaternary ammonium group in its chemical structure that is fully ionized at physiological pH (Foss et al., 2008; Diego et al., 2011). Thus after oral administration, its actions are confined to peripheral sites such as the gastrointestinal tract and it does not reverse centrally mediated analgesia (Foss et al., 2008; Karuppiah & Farrah, 2011). Alvimopan has been approved by the FDA for short-term use (maximum of 15 doses at twice-daily intervals) in hospitals to treat post-operative ileus that may be caused or exacerbated by opioid analgesics (Diego et al., 2011). Alvimopan accelerates the time to upper and lower gastrointestinal recovery following partial large or small bowel resection with primary anastomosis and decreases the time to hospital discharge by approximately one day (Diego et al., 2011; Karuppiah & Farrah, 2011).

The recommended dosing regimen for alvimopan is 12 mg at 0.5-5 h pre-surgery followed by 12 mg twice daily for a maximum of 15 doses (Karuppiah & Farrah, 2011). Alvimopan is generally well-tolerated when administered for seven days or less (Karuppiah & Farrah, 2011). However, with long-term use (e.g. 12 months) there is an increased risk of myocardial events (Bader et al., 2011; Karuppiah & Farrah, 2011).

7.2 Methylnaltrexone

Methylnaltrexone, (5α)-17-(cyclopropylmethyl)-3,14-dihydroxy-17-methyl-4,5-epoxymorphinanium-17-ium-6-one, is a quaternary ammonium derivative of the opioid receptor antagonist, naltrexone (Bader et al., 2011; Diego et al., 2011). Due to the quaternary ammonium group in its chemical structure that is ionized at physiological pH, methylnaltrexone does not cross the blood-brain-barrier and so centrally mediated analgesia is not reversed (Bader et al., Diego et al., 2011).

Methylnaltrexone has 8-fold and 120-fold higher binding affinity at the MOP receptor relative to the KOP and DOP receptors respectively (Bader et al., 2011). Following administration by the subcutaneous route at 0.15-5 mg/kg in humans, mean peak plasma concentrations of methylnaltrexone are observed at 0.5 h post-dosing and the elimination half-life is in the range 8-9 h (Rotshteyn et al., 2011). The mean bioavailability is high at 82% with minimal metabolism and so it has low potential for drug-drug interactions (Rotshteyn et al., 2011).

Methylnaltrexone is approved by the FDA and the European Medicines Agency (EMA) to treat opioid induced constipation in patients with advanced disease where other laxative regimens have failed (Iskedjian et al., 2010; Bader et al., 2011). Methylnaltrexone causes laxation in at least 50% of patients in less than 24 h over the first two weeks of treatment without impairing analgesia or causing serious adverse events (Bader et al., 2011).

7.3 Oral naloxone

Naloxone, (1*S*,5*R*,13*R*,17*S*)-10,17-dihydroxy- 4-(prop-2-en-1-yl)-12-oxa-4-azapentacyclo [9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7(18),8,10-trien-14-one, is a non-selective opioid receptor antagonist (Lenz et al., 1986). In the clinical setting, parenteral naloxone is used to reverse life-threatening opioid agonist-induced respiratory depression (Diego et al., 2011). However, as naloxone crosses the blood-brain-barrier, it also reverses centrally mediated analgesia (Diego et al., 2011).

After oral administration, the bioavailability of naloxone is very low at 2% due to extensive first-pass metabolism which makes it possible to obtain a highly localized opioid antagonist action in the gastrointestinal tract whilst sparing the centrally mediated opioid analgesic effects of oral oxycodone (Leppert, 2010; Diego et al., 2011). The negligible oral bioavailability of naloxone is exploited in an oral prolonged-release tablet that contains oxycodone in combination with naloxone in a fixed 2:1 ratio resulting in less constipation and less laxative consumption relative treatment with oxycodone alone (Leppert, 2010).

The oxycodone plus naloxone oxycodone tablet is available in four tablet strengths; 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg oxycodone/naloxone respectively (Leppert, 2010).

8. Conclusion

Moderate to severe acute and chronic pain continues to be managed with opioid analgesics according to the principles succinctly summarized by Steps 2 and 3 of the WHO 3-step Analgesic Ladder. Weak opioid analgesics are added to non-opioid analgesics for the management of moderate pain with adjuvants added if pain has a neuropathic component. For moderate to severe pain, strong opioid analgesics are recommended with the addition of non-opioids and adjuvants, as required.

9. References

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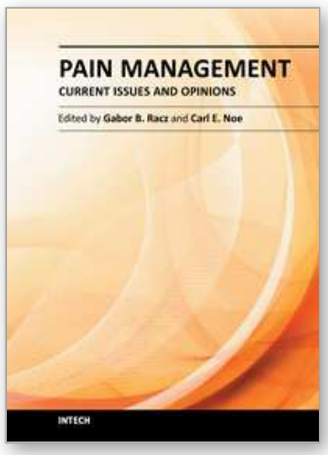
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Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

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