I. Understand the classification of opioid compounds (Casey and Parfitt 1986; Gutstein and Akil 2001; Uppington 2002).
   A. Identify and differentiate the various subclasses and specific drugs that are used clinically and are agonists at the mu-opioid receptor:
      1. Alkaloids (including semisynthetic alkaloids) such as morphine, hydromorphone, oxymorphone, codeine, oxycodone, hydrocodone, dihydrocodeine, and heroin.
      2. Synthetic opioids, including phenylpiperidine derivatives (such as fentanyl, sufentanil, alfentanil, remifentanil, and meperidine [pethidine]), diphenylheptane derivatives (such as methadone and propoxyphene), and morphinan derivatives (such as levorphanol).
   B. Identify and differentiate those opioid drugs that are used clinically and are partial agonists at the mu receptor:
      1. Semisynthetic alkaloids, including buprenorphine.
      2. Synthetic opioids, including the morphinan dezocine.
      3. Tramadol (which also has non-opioid analgesic effects).
   C. Identify and differentiate those opioid drugs that are used clinically and are known as the mixed agonists-antagonists because they possess antagonist activity at the mu-opioid receptor and agonist activity at another opioid receptor subtype (e.g., the kappa receptor):
      1. Semisynthetic alkaloids, including nalbuphine.
      2. Synthetic opioids, including benzomorphan derivatives (such as pentazocine) and morphinan derivatives (such as butorphanol).
   D. Identify and differentiate those opioid drugs that are used clinically and are pure antagonists of the opioid receptor, including:
      1. Naloxone.
      2. Naltrexone.
   E. Identify and differentiate the major classes of the endogenous opioid peptides, and know the precursor molecules for each.
      1. The precursor proopiomelanocortin yields beta-endorphin.
      2. The precursor prodynorphin yields the dynorphin peptides.
      3. The precursor proenkephalin yields the enkephalin peptides.

II. Understand those aspects of basic opioid pharmacology that are relevant to the use of opioid drugs in clinical practice for acute, chronic, and cancer-related pain.
   A. Understand the core structure shared by all opioids and how structural modifications alter binding to opioid receptors and the resultant pharmacodynamic activities of the related compounds (Casey and Parfitt 1986; Pasternak 1993; Gutstein and Akil 2001).
   B. Understand the importance of physical properties of opioid drugs (Gutstein and Akil 2001).
      1. Understand how the lipid solubility and pKa of an opioid influences transport across biological membranes and affects its pharmacokinetics (Bernards 1999).
2. Understand the particular importance of lipid solubility in determining the pharmacodynamics following intraspinal and other routes of opioid administration (Carr and Cousins 1998; Gourlay 2002).

C. Understand the major findings related to opioid receptor pharmacology (Dickenson 1994; Kieffer and Gaveriaux-Ruff 2003; Cheng et al. 2004; Fields 2004).
   1. The major types of opioid receptors: mu (MOR/OPRM), delta (DOR/OPRD) and kappa (KOR/OPRK), their subtypes, and the receptor selective actions that have been identified (Kieffer and Gaveriaux-Ruff 2003).
   2. Localization of opioid receptors in relation to sites likely to be involved in analgesia, and the concept of state-dependent opioid control of pain (Stein et al. 2003; Fields 2004).
   4. The localization of opioid receptors both inside and outside the nervous system and the implications of this localization for widespread involvement of opioid mechanisms in the modulation of mood, affect, learning, and memory acquisition and in the physiological functioning of many organ systems, including the cardiovascular, gastrointestinal, hormonal, and immune systems (Dickenson 1994; Gutstein and Akil 2001; Stein et al. 2003).
   5. The intracellular events produced by binding of the opioid receptor, including activation of second messenger systems (e.g., G protein, protein kinase C), interaction with other receptors (e.g., N-methyl D aspartate), electrophysiological outcomes (e.g., hyperpolarization due to opening of potassium channels or closing of calcium channels) (Dickenson 1994; Mayer et al. 1995; Kieffer and Gaveriaux-Ruff 2003; Eguchi 2004), and endocytosis (Finn and Whistler 2001).
   6. Understand that other receptor types have been identified, such as opioid-receptor-like 1 receptor (ORL1; Zeilhofer et al. 2003).

   1. Be able to define tolerance and physical dependence.
   2. Recognize the multiple types of tolerance (e.g., associative or behavioral vs. non-associative or pharmacological) and that tolerance can develop to many opioid effects. Some effects such as constipation and miosis are more resistant to the development of tolerance.
   3. Understand the multiple mechanisms that may be responsible for opioid tolerance or physical dependence (Akil et al. 1997).

E. Recognize that the mechanisms that produce tolerance are not the only factors that can reduce opioid efficacy and that the following pathological processes, which have the same result, may be more important clinically (Dickenson 1994; Portenoy 1994, 2002; Mayer et al. 1999; Gourlay 2002; Desmeules et al. 2004):
   1. Increased nociception due to progression of a tissue damaging lesion.
   2. Sensitization of central nervous system neurons, rendering them less responsive to opioid mechanisms.
   3. Transmission of nociceptive information along afferent pathways that are usually non-nociceptive and are less subject to modulation by opioid mechanisms.
   4. Pharmacokinetic processes, such as the production of active metabolites that may have antianalgesic effects or pharmacokinetic interaction (induction of liver enzymes like CYP 3A4 with decreased methadone concentrations).

III. Know those aspects of clinical opioid pharmacology that are relevant to the use of opioid drugs in patient care (Lipman and Gauthier 1997; Gutstein and Akil 2001; Gourlay 2002; Uppington 2002).
A. Be able to define the terms efficacy, maximal efficacy, relative efficacy, responsiveness, potency (for acute and chronic opioid administration), and relative potency (Portenoy 1994).

B. Understand the differences in clinical effects among pure opioid agonists, partial agonists, mixed agonists-antagonists, and antagonists.
   1. Recognize that the existence of a ceiling effect for analgesia limits the utility of the partial agonist and mixed agonist-antagonist drugs for the management of chronic pain.
   2. Understand that the mixed agonist-antagonist opioids are more likely to cause psychotomimetic effects than are the pure agonist opioids.
   3. Understand that the partial agonists and mixed agonist-antagonist drugs have a ceiling effect for respiratory depression, in contrast to the pure agonist opioids.
   4. Understand that abstinence can be precipitated when a partial agonist or mixed agonist-antagonist is administered to a patient who is physically dependent on a pure agonist drug.

C. Understand the various factors that results in the great individual variability in opioid response in terms of pharmacokinetics and pharmacodynamics. This pronounced variability, combined with changes in responsiveness over time, mandates individualization of opioid doses based on a continuing process of assessment (analgesia and adverse effects) and dose titration (Bandolier Web Site; Ballantyne and Mao 2003; Kalso et al. 2004). There is a requirement to regularly reassess the dose to optimize the analgesic response and minimize adverse effects.

D. Be aware of the varied routes of administration by which opioids can be delivered and the benefits and limitations of each route (Bruera and Neumann 1999; Gourlay 2001, 2002).
   1. Systemic administration:
      a. Oral.
      b. Sublingual.
      c. Buccal.
      d. Rectal.
      e. Transdermal (and the emerging area of iontophoretic transdermal drug delivery).
      f. Subcutaneous, via intermittent injection or continuous infusion.
      g. Intramuscular, via intermittent injection.
      h. Intravenous, via intermittent injection or continuous infusion.
      i. Pulmonary.
      j. Nasal.
   2. Cerebrospinal administration:
      a. Spinal epidural, via intermittent injection or continuous infusion.
      b. Spinal intrathecal, via intermittent injection or continuous infusion.
      c. Intraventricular.
   3. Peripheral:
      a. Local/topical for inflammatory conditions such as mucositis, skin ulcerations, or arthritis (Stein et al. 2003).

E. Understand the clinical factors that influence the decision to use specific routes of administration in the management of acute and chronic pain (Carr and Cousins 1998; Gourlay 2001, 2002; Macintyre and Ready 2001; Uppington 2002; ANZCA 2005).
   1. Be aware of the efficacy and utility of noninvasive routes, particularly the oral route, when treating chronic pain.
   2. Be aware that the need for rapid onset of analgesia may justify the parenteral route.
   3. Understand that infusions can eliminate bolus effects (peak concentration toxicity or pain recurrence at the end of the dosing interval).
4. Understand that patient controlled analgesia can provide appropriate patients an effective means to continually adjust treatment to meet analgesic needs.

5. Recognize that intraspinal administration (epidural or subarachnoid) may be able to reduce the opioid adverse effects associated with systemic opioid administration.

6. Understand that slow transdermal systems are not suitable for opioid titration.

F. Understand that equianalgesic dose tables are derived from relative potency data and recognize the need to adjust doses when changing drugs or routes of administration (Bruera et al. 1996; Pereira et al. 2001). Understand the important interindividual differences in the relative equianalgesic dose conversions and the need to used different conversion ratios when switching to another opioid when the patient has already been on a high opioid dose for some time.

G. Understand major pharmacokinetic and pharmacodynamic considerations for each opioid drug and for each formulation and route of administration used clinically.

1. Know important pharmacokinetic information for each drug (Gourlay 1998, 2002; Gutstein and Akil 2001; Andersen et al. 2003).
   a. Elimination half life.
   b. Whether active metabolites exist, and their contribution to the analgesic response and/or adverse event profile; for example, meperidine [pethidine] (with its toxic metabolite, normeperidine [norpethidine]) and morphine (with its active opioid metabolite, morphine-6-glucuronide).
   c. Influence of patient characteristics, including age (changes associated with very young age and old age) and major organ dysfunction (changes associated with disease of the kidneys or liver) and the impact of concomitantly administered drugs on these pharmacokinetic parameters. There may be other conditions such as sleep apnea that render the patient more sensitive to opioids.

   a. Bioavailability.
   b. Time-action profile for a single dose, including time of onset, time to peak effect, and duration of effect.
   c. Time-action profile for repeated doses and infusions, including time of onset and time to approach steady state.

3. Understand that individual variation in metabolic processes may be genetically determined and the impact on the efficacy and/or toxicity of opioid drugs (Poulsen et al. 1996; Eckhardt al, 1998; Desmeules et al. 2004).
   a. Genetic variability in the activity of the cytochrome P450 2D6 enzyme influences the endogenous conversion of codeine to morphine and oxycodone to oxymorphone and the impact this variability has on pharmacodynamics in terms of analgesia and side effects.
   b. Understand the extensive role of cytochrome P450 3A4 in the metabolism of opioids (e.g., methadone) and a multitude of other drugs that can be administered concomitantly (Gourlay 2002).
      i. That levels of this enzyme can be induced by concomitantly administered drugs, resulting in reduced blood opioid concentrations, and the impact this might have on the pharmacodynamic response.
      ii. That blood opioid concentrations can be significantly increased by the co-administration of other drugs that are also metabolized via cytochrome P450 3A4 (competitive inhibition); the concomitantly administered drugs are not necessarily analgesic drugs.

2. Understand that variability in the glucuronidation of morphine influences the ratio of active glucuronidated metabolites to the parent compound (Faura et al. 1998).
a. Understand the difference in glucuronide ratios in neonates compared to older children and adults.
b. Understand the impact of renal impairment on metabolite ratios.
c. Understand the routes of administration that bypass hepatic first pass metabolism (i.v., i.m.,
transdermal, rectal, local, epidural, and intrathecal) have lower metabolite production compared
to oral, buccal, and sublingual.
d. Understand that duration of morphine therapy does not influence morphine glucuronidation
ratios (Andersen et al. 2004).

H. Understand the potential for additive analgesic effects but not adverse effects that can occur with the
combination of opioids and other drugs.
1. Systemic opioids combined with nonopioid analgesics or adjuvant analgesics (such as ketamine; Bell et al. 2003).
2. Intraspinal opioids combined with local anesthetics and/or alpha-2-adrenergic agonists (Walker et al. 2002).

I. Recognize that specific clinical guidelines have been recommended for different patient populations
and that the techniques needed for optimal therapy differ for the following conditions:
3. Chronic nonmalignant pain (Kalso et al. 2003; Pain Society 2004).
4. Chronic or recurrent pain due to medical illness such as sickle cell anemia (Jacobson et al. 1997),
   headache (Bach 1999).

J. Understand the potential adverse effects and toxicities of opioid drugs (Carr and Cousins et al. 1998;
Bruera and Neumann 1999; Gutstein and Akil 2001; Gibson 2003; Kalso et al. 2004).
1. Know the clinical presentation and management strategies for common adverse effects, including
   constipation, nausea, somnolence, mental clouding, and urinary retention.
2. Know that respiratory depression is rare during chronic opioid use.
3. Know that tolerance develops to the psychomotor effects of opioids.
4. Be aware that adverse effects and toxicity may be more likely with specific patient characteristics
   such as advanced age, major organ dysfunction (e.g., renal disease, chronic encephalopathy,
   chronic obstructive pulmonary disease, sleep apnea), and with concurrent centrally acting drugs
   (e.g., benzodiazepines).
5. Be aware that chronic opioid prescription may reduce hormonal levels (notably testosterone),
   which may effect libido, particularly in men (Roberts et al. 2002; Ballantyne and Mao 2003).

K. Understand the use of naloxone to treat acute opioid overdose (Manfredi et al. 1996; Wanger et al.
1998).
1. Know the risks associated with naloxone administration to patients receiving chronic opioid
   therapy, including abstinence and recurrent pain, and understand the value of careful titration using
   a dilute solution of naloxone.
2. Be aware that naloxone should only be given to patients receiving chronic opioid therapy to
   reverse respiratory depression or impending respiratory depression.
3. Know that naloxone has a short half-life and that repeated injections or an infusion are usually
   needed to effectively treat opioid overdose.

L. Understand that the risk of abstinence mandates dose tapering after a few days of frequent dosing with
an opioid drug, and be aware of the techniques used to discontinue these drugs safely, including the
rate of the taper, substitution withdrawal with a long half-life opioid, and the use of clonidine to
prevent abstinence (Gowing et al. 2003; Umbricht et al. 2003).
M. Know the definitions of addiction (i.e., loss of control over drug use, compulsive use, and continued use despite harm), physical dependence (withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist), psychological dependence (dependence on opioid drugs for their psychic effects), and tolerance (state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time); understand the implications of the therapeutic use of a potential drug of abuse (Portenoy 1994; Savage 2002, Savage et al. 2003). (See also Section I for guidelines.)

1. Understand the need to monitor the patient for the appearance of aberrant drug-related behavior during chronic therapy.
2. Be aware of the various diagnoses that may account for aberrant drug-related behavior and understand the assessment that is needed to accurately characterize the patient’s response.

REFERENCES


