Opioids
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Abstract

Opioids form the cornerstone of the pharmacologic armamentarium for the treatment of pain. Despite their long history of use, much confusion and misperception still surrounds their use. This short review will focus on pharmacodynamic and physiologic considerations in the clinical use of oral and parenteral opioids.

Our knowledge of opioid pharmacology has progressed greatly in the last two decades. This enhanced understanding has, unfortunately, provided an opportunity for confusion nomenclature. Let us then take the opportunity to define several terms. The word *opium* is derived from the Greek, meaning "juice" (i.e., juice of the poppy plant). Opium is obtained from the unripe seed capsules of the poppy plant and is a dried powdered mixture containing approximately 20 alkaloids. An *opiate* is an alkaloid (i.e., any agent derived from opium). All endogenous and exogenous (natural or synthetic) compounds which possess morphine-like analgesic properties are termed *opioids*. Thus, the correct "generic" term for this class of agents is "opioid."

Structure-activity Relationship

The alkaloids of opium can be chemically subdived into two groups: the phenanthrenes and the benzylisoquinolones. Morphine, codeine, and thebaine are the principal phenthrene alkaloids derived from opium (Table 1). Papaverine (a vasodilator) and noscapine (both lakcing morphine-like properties) are the principal bensylisoquinolones.

Morphine is the prototypic opioid. The molecular skeleton of morphine is composed of five interlocked rings (Figure 1). Substitution of chemical constituents on the skeleton generates the semisynthetic opioids (Table 1). Synthetic opioids (Table 1) are created by reduction of the number of fused rings (Figure 2). Despite changes in the number of rings, a common "T-shaped" core is found in all opioids. A piperidine ring forms the crossbar (and is believed to confer "opioid-like" properties), and a hydroxylated phenyl group forms the verical axis (Figure 2).2

Endogenous Opioids and Opioid Receptors

---Receptor Type
(with subtypes) Endogenous Prototypic Ligand Exgenous Actions
---
□1 /□-endorphin /morphine /supraspinal analgesia
□2
□-endorphin
morphine
respiratory depression
cardiovascular effects
gastrointestinal tract transit
□
enkephalin
-
spinal analgesia
□
dynorphin
ketocyclazocine
spinal analgesia
sedation
□
□-endorphin
-
hormone

□

-

N-allylnormetazocine

psychotomimetic effects

dysphoria

Endogenous Opioid Peptides

The endogenous opioids3 form part of an endogenous analgesic system (containing enkephalinergic, serotonergic, and noradrenergic pathways). All endogenous opioids contain the amino acid sequence *tyrosine-glycine-glycine-phenylalanine.* They are formed by cleavage of larger precursor molecules and can be grouped accordingly.

Both met-enkephalin and leu-enkephalin are derived from proenkephalin A. Enkephalins are somatotopically localized to areas of the central nervous system (CNS) essential for antinociception. They are also found in the gastrointestinal tract, sympathetic nervous system and adrenal medulla.

ß-endorphin is the most potent of the endogenous opioids and is found in the hypothalamus, periaqueductal gray matter and locus ceruleus. ß-endorphin is generated from cleavage of pro-opiomelanocortin and is released in a one-to-one molar ratio with adrenocorticotropic hormone (ACTH) from the pituitary.

Dynorphin (the prototypic ligand of the □-receptor) and □-neoendorphin are derived from prodynorphin (Proenkephalin-B). Despite having somatotopic localization similar to that of the enkephalins, the dynorphine possess no potent analgesic properties.

Opioid Receptors

Opioids produce their analgesic effect by mimicking the actions of endogenous opioid peptides at specific receptors within the CONS. The receptor can be viewed as a common molecular site of action for a diverse group of compounds.

The receptor mediates two functions: Chemical recognition and physiologic action; these functions are localized to different physical areas of the receptor complex. Only levorotatory isomers possess analgesic activity and, therefore, the recognition site is highly specific.5 Binding affinity refers to the strength of attachment of the opioid to the receptor site, as opioids will bind to the recognition site with varying strength.6 It is possible to determine the rank order of binding affinities using various bioassay systems. These binding affinities correlate quite closely with the analgesic potencies of the opioids.7

There are several types of opioid receptors (Table 2), each of which mediates an array of pharmacologic effects.7-12 Most opioids bind to "morphine-preferring" or □-receptors. □-endorphin is the prototypic endogenous ligand, and morphine is the prototypic exogenous ligand. Using autoradiographic, □-receptors have been found in highest concentrations in areas of the brain that mediate opioid-induced analgesia. These areas include the periaqueductal gray, the nucleus raphe magnus, and the medial thalamus.13-15 Other opioid receptors which produce analgesic effects (□- and □-receptors) are found mainly in the spinal cord. While □-receptors are found at the level of the spinal cord, activation of □-receptors is largely responsible for supraspinal analgesia.

Two subtypes of □-receptors have been demonstrated.16-18 Activation of □□-receptors is responsible for the analgesia attendant to □-receptors while activation of the □□-receptors produce respiratory depression, cardiovascular effects, and depression of gastrointestinal motility. No known opioid agonist selectively activates □□-receptors without simultaneous □□-receptor activation.

Activation of □- and □-receptors produces spinal analgesia. The prototypic ligands for the □-receptors are the enkephalins. Yaksh and coworkers19-21 demonstrated the enkephalin analogues are more potent spinal analgesics than morphine when administered into the subarachnoid space. The □-rligand [D-Ala2, D-Leu5] enkephalin (DADL) has been demonstrated to be up to five times more potent than morphine when administered into the subarachnoid space in humans.22

□-receptor activation results in a segmental (spinal) analgesia with concomitant sedation. Similar to □-receptors, analgesia is produced without respiratory compromise. Dynorphin is the prototypic endogenous agonist. Morphine also acts as a □-receptor. However, the relative affinity of morphine for the □-receptor is 200 times less than its affinity for the □-receptor. Analgesia attendant to the opioid agonist-antagonists is mainly derived from □-receptor activation.

In vitro binding studies in the rat deferens have described the □-receptor, though it is not well characterized. □-endorphin is the proposed endogenous agonist. As □-endorphin is released in a one-to-one molar ration with ATCH from the pituitary gland, the □-receptor may mediate a hormonal effect of □-endorphin.

Another poorly characterized receptor that has been proposed as an opioid receptor in the past is the □-receptor. The agonist-antagonist opioids at least partially activate the □-receptor, producing psychotomimetic effects including dysphoria and hallucinations, as well as tachycardia, tachypnea and mydriasis.

Intrinsic Activity: The Relationship Between Receptor Binding and Response

The intensity of physiologic actions produced by exogenous administration of an opioid defines its intrinsic activity. *Agonists* produce a maximal biologic response through receptor binding. *Antagonists* (naloxone) have low or no intrinsic activity and reverse or inhibit the effects of agonists by preventing receptor access.23 *Partial agonists* produce a submaximal response at the receptor even at high doses (e.g., buprenorphine's action at the □-receptor).

The previous discussion involved binding interaction at a single receptor type, but opioids can have divergent activities at different receptors, simultaneously acting as an agonist at one and an antagonist at another. These opioids are termed *agonist-antagonists* or *mixed agonist-antagonists*.24-25 Morphine is a complete agonist at □-receptors. Naloxone is devoid of agonist activity and simultaneously acts as an antagonist at □- and □-receptors. However, naloxone has greater binding affinity for the □-receptor. Pentazocine is a weak competitive antagonist at the □-receptor, a strong □-agonist, and □-agonist. Nalbuphine reverses opioid-mediated respiratory depression through □-receptor antagonism but provides analgesia through partial □-agonism.26 Table 3 lists the interactions of opioids at various receptors subtypes.

The agonist-antagonists also exhibit characteristic pharmacologic properties (1) the slope of the dose-response curve is less steep than that of a full agonist (Figure 3); (2) the dose response curve exhibits a ceiling effect (i.e., a submaximal response as compared with a full agonist) (Figure 3), and (3) concomitant administration of an agonist-antagonist and full agonist can reduce the effect of the full agonist.

Pharmacologic Considerations

The Concept of Equianalgesic Dosing

The "potency" of intensity of analgesic effect of individual opioids is dependent upon: (1) access to the receptor, and (2) binding affinity ("fit" at the receptor site). Access to the receptor for □-agonist is dependent upon physicochemical and pharmacokinetic properties: (1) partition coefficient, (2) pKa, (3) the degree of ionization, (4) unbound fraction of a dose, (5) apparent volume of distribution, (6) clearance, and (7) the route of administration. Therefore, apparent differences in potency among opioids are the result of physicochemical and pharmacokinetic differences among individual opioids not a function of pharmacodynamic distinctions. Thus, all opioids can be made equipotent or equianalgesic by adjusting for physicochemical and phamracokinetic differences by correcting for dosage and route of administration. This concept is extremely important in the clinical use of opioids.27-28

It is important to emphasize that equianalgesic conversion schemas can only be used as guidelines. Practitioners should not be dogmatic in their interpretation, as certain methodological problems are inherent in the genesis of such conversion tables.

Incomplete Cross-tolerance

Patients can become tolerant to the analgesic effects of a given opioid. In such cases another opioid can be substituted in order to provide better analgesia, as opioids exhibit incomplete cross-tolerance.29-30 Clinical experience shows that one-half of the equianalgesic dose of the new opioid may be used for initial dosing and suggests that the relative potency of some opioids may increase with repetitive dosing.27

The Oral to Parenteral Potency Ratio

Opioid Equianalgesic Dosing Equivalentsa

Opioid	Route	Equinalgesic Doseb
Morphine	Parenteralc	
Oral	10 mg	
30 mg		
Codeine	Parenteral	
Oral	130 mg	
200 mg		
Oxycodone	Parenteral	
Oral	15 mg	
30 mg		
Levorphanol	Parenteral	
Oral	2 mg	
4 mg		
Hydromorphone	Parenteral	
Oral	1.5 mg	
7.5 mg		
Meperidine	Parenteral	
Oral	75 mg	
300 mg		
Methadone	Parenteral	
Oral	10 mg	
20 mg		
Fentanyl	Parenteral	
Oral	100 □g	
not available		

a Based on single-dose studies in which an IM dose of each drig was compared to morphine to establish relative potency. Comparison using multiple-dose IV-PCA may be a beter methodology

b Incomplete cross-tolerance (see text) was not used in determining conversion of dosage among the different opioids.

c The oral to parenteral potency ratio for morphine is 1:6 for acute and postoperative pain and single dosing. The oral to parenteral potency ratio may decrease to 1:2 or 1:3 with repetetive dosing and the treatment of chronic pain. Adapted from Foley.27

The bioavailability of oral morphine varies between 15 and 64% with an average oral bioavailability of 38%.31 Bioavailability with parental administration is approximately 100% (see below) when converting from oral to parenteral administration. Therefore, morphine has significant first pass metabolism which must be taken into account when converting from oral to parenteral administration.32

For acute pain and single doses, the oral to parenteral potency ratio for morphine is 1:6.33 For chronic pain and multiple doses, the oral to parenteral potency ratio for morphine is 1:2 or 1:3.31,34,35 These ratios have been empirically adopted for oral to parenteral conversion for other opioids.

The Equivalence of Potency Among Parenteral Routes

The intramuscular (IM), subcutaneous (SC) and intravenous (IV) routes of administration are assumed to be equipotent in many conversion schemes, thereby assuming equivalent bioavailability among the three

routes of administration.(Table 4) Little data exist to validate this assumption, however, and several authors have questioned it. In a study by Urquhart, et al.,36 patients receiving hydromorphone via subcutaneous-PCA in comparison to IV-PCA had significantly higher dosage requirements, thereby suggesting unequal bioavailability. According to Urquhart, et al.,36 the subcutaneous to intravenous potency ratio is 1:1.5 or 1:2.

Physiologic Considerations

Respiration

All □-agonists and partial agonist buprenorphine produce a dose-dependent reduction in the responsiveness of brain stem respiratory centers to increases in carbon dioxide tension (PCO2).37,38 This reduction in responsiveness is characterized by an increase in resting PCO2 and displacement of the CO2 response curve to the right.39 Equianalgesic doses of □-agonists will produce a similar degree of respiratory depression and an equivalent shift of the CO2 response curve to the right.39-41 Opioid agonists also depress the pontine and medullary centers involved in regulating the rhythmicity of breathing. Depression of these centers results in prolonged apnea between breaths, delayed exhalation, and periodic breathing.37,38

Mixed agonist-antagonist opioids do not produce dose-related respiratory depression but exhibit a limited or "ceiling" effect.25 Agonist-antagonist displace the CO2 response curve to the right, but the curve is characteristically "bell-shaped" when these opioids are given in increasing doses.25

Changes in Cognition, Alertness, and Mood

Opioids cause alteration in mood. Patients report feelings of warmth, drowsiness and sometimes well-being or euphoria. Alterations in mood are believed to mediated through the limbic system.42

At sufficiently high doses, opioids may eventually produce sleep. However, unconsciousness is not a certainty even at high or "anesthetic" doses. Arousal may still be produced by noxious stimulation.43 Moreover, at equianalagesic dosages, opioids differ in their intrinsic potential to produce sleep.44

Tolerance, Physical Dependence, Addiction

Continued exposure of the receptor to high concentrations of opioids will cause tolerance. Tolerance refers to the progressive decline in potency of an opioid with continued use, so that increasingly higher concentrations are required to achieve the same analgesic effect. The phenomenon is characteristic of opioids as a class of analgesics and is receptor-mediated. When tolerance develops to a particular opioid, cross-tolerance to other opioids concomitantly develops though such tolerance is incomplete.

Physical dependence does not in any way imply addiction. Physical dependence is a physiologic state characterized by withdrawal (abstinence syndrome) after discontinuation of the opioid. Yawning, diaphoresis, lacrimation, coryza and tachycardia are the initial manifestations of the abstinence syndrome. Later, abdominal cramps, nausea and vomiting occur and peak at approximately 72 hours. Tolerance to the opioid is quickly lost during withdrawal.

Addiction is defined by the World Health Organization as:

> A state, psychic and sometimes also physical, resulting from the interactions between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present.45

In the popular mind, addiction is a compulsion to obtain a drug in order to experience its psychic effects. The definition of the World Health Organization closely approximates such as conception. Once again, it is important to emphasize that addiction implies compulsive behavior and psychologic dependence. Tolerance

(a pharmacologic property of a class of drugs) and physical dependence (a physiologic effect also characteristic of this class of drugs) are conceptually and phenomenologically distinct from addiction.

Can administration of opioids iatrogenically cause addiction? A prospective study has examined the incidence of opioid addiction in 12,000 hospitalized patients receiving at least one strong opioid.46 Only four reasonably well-documented cases of subsequent addiction were demonstrated in patients without a prior history of drug abuse. Thus, opioid addiction may be a rare iatrogenic event, particularly when opioids are used to treat pain.

Effects Upon the Gastrointestinal Tract Stomach, Small and Large Intestines

The propulsive peristaltic contractions of both the small and large intestines are decreased by opioids. At the same time, the amplitude of nonpropulsive, rhythmic, segmental contractions is enhanced. In the upper gastrointestinal tract, opioids cause decreased gastric motility while increasing antral tone. With concomitant enhanced tone in the first part of the duodenum, delayed gastric emptying may result. Sphincteric tone is increased by opioids in the pyloric and anal sphincters and ileocecal valve. Increased transit time is produced by coupling decreased propulsive activity with enhanced sphincteric tone. Constipation results from the delay in passage of intestinal contents, allowing for greater absorption of water, increased viscosity and desiccation of bowel contents.

The peripheral and central mechanisms underlying the effects of opioids upon bowel motility are unclear.47 With respect to peripheral mechanisms, opioids affect cholingergic, serotonergic and enkephalinergic receptors located in the myenteric plexus of the intestine. With respect to central mechanisms, the effects of neuraxial administration of opioids are not inhibited by systemic ganglionic blocking agents or the removal of the extrinsic innervation of the bowel.48 Moreover, injection of morphine into the cerebral ventricles inhibits bowel motility. Intraventricular administration of naloxone or vagotomy can inhibit or reverse this effect.47 Thus, there is substantial evidence to suggest that both local and central mechanisms are involved in opioid-induced changes in bowel motility.

Biliary Tract

□-agonists produce a marked increase in biliary tract pressure. Pressure within the common bile duct may increase ten-fold after the subcutaneous injection of 10 mg of morphine.41 A much less marked increase in biliary pressure is seen after administration of agonist-antagonist.49 Moreover, nalbuphine has been reported to actively reverse sphincter of Oddi spasm. However, analgesia is still maintained (□-receptor analgesia).50

Cardiovascular Effects

Opioids produce chronotropic, inotropic and peripheral vascular changes. Opioids produce a dose-dependent bradycardia due to central stimulation of the vagal nucleus in the medulla.51,52 As the bradycardia is vagally mediated, it can be blocked with atropine.53 (The exception to this phenomenon is the administration of meperidine which may cause tachycardia. Meperidine is structurally similar to atropine).

The negative inotropic effects of meperidine may be seen at doses as low as 2.0-2.5 mg/kg.54,55 Otherwise, opioids maintain normal myocardial contractility at clinically useful dosages. All opioids can produce direct myocardial depression, 54,56,57 but this effect is often not seen even with anesthetic dosages.

Morphine has both a direct effect on vascular smooth muscle and an indirect effect through is release of histamine. Arteriolar dilation and venodilation are thereby produced.58-60 Histamine release is believed to be the primary mechanism underlying vasolidation with morphine. Meperidine and codeine also release histamine. Fentanyl and sufentanil do not.61,62

Conclusion

The literature pertaining to opioid pharmacology is extensive and relevant to the clinical use of these drugs. Recent reviews are available and can provide rich detail about basic and applied considerations.[1,25,63,64]