Pharmacology of Opiates

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Introduction

There are three major opioid receptors in the central nervous system: mu, kappa, and delta, the genes for which have been cloned. There are also possible subtypes within each class, although separate genes have not yet been cloned for any subtypes. Opioids are both the natural opiates and their synthetic congeners which are the class of agonist and antagonist drugs with primarily morphine-like activity mostly at the mu opioid receptor, and also the other naturally occurring endogenous and synthetic opioid peptides, which act also at the other receptor types.

In general, opioids are well absorbed from the gastrointestinal tract after oral dosing, with a longer duration of action than following parenteral administration. However, most opioids (but not all, e.g., methadone) have reduced systemic bioavailability and thus reduced effect after oral versus parenteral administration, due to first-pass metabolism in the liver (Reisine & Pasternak, 1996). Natural opiates and their synthetic congeners are also well absorbed after subcutaneous or intramuscular injection and, depending on degree of lipophilicity, may be administered through the nasal or buccal mucosa (Weinberg et al., 1988) or transdermally (Portenoy et al., 1993). This chapter reviews the disposition, metabolism, pharmacokinetics, and excretion of four opioids that are particularly important in the area of illicit opioid abuse and its treatment: heroin, morphine, methadone, and levo-alpha-acetylmethadol (LAAM).

Diacetylmorphine or heroin is a synthetic derivative of a natural opiate which has a rapid onset of action and a very short half-life which has greatly contributed to its popularity as a drug of abuse. Heroin is increasingly abused intranasally, both due to recent concerns regarding risk of HIV-1 transmission with the more potent but less safe intravenous route, and also due to the recent increased availability of higher-purity street heroin (about 70% purity in some geographic regions, compared with less than 30% in the recent past years). Heroin is rapidly metabolized first to monoacetylmorphine and then primarily metabolized to morphine, an opioid with a somewhat longer half-life that is used primarily for pain relief.

Methadone is an orally administered long-acting opioid that was developed in the 1960s as an effective treatment for heroin addiction, and levo-alpha-acetylmethadol (LAAM) is a longer-acting and also orally effective opioid which was recently also approved for clinical use in the United States by the Food and Drug Administration as a treatment for opioid addiction.

Heroin

Diacetylmorphine was originally synthesized in 1874 and marketed in 1898 by the Bayer company under the name “Heroin,” and
is more water soluble and potent than morphine (Sawynok, 1986). Heroin is derived from morphine by acetylation of morphine both at the 3 and 6 position. When catabolized, heroin is deacetylated to 6-mono-acetylmorphine and then, mostly in the liver, metabolized to morphine. Heroin is not available for therapeutic use in the United States.

To date, there have been only a few well-designed studies of heroin pharmacokinetics. Kaiko, Wallenstein, Rogers, Grabinski, and Houde (1981) used visual analog scales to measure pain relief in comparing intramuscular heroin to intramuscular morphine in cancer patients, and found that heroin was about twice as potent as morphine (on average 4.8 mg of heroin was equivalent to 10 mg of morphine) with faster onset (average 1.2 vs. 1.5 hr, respectively) but more transient effects. Inturrisi and colleagues (1983) performed opiate binding studies using rat brain to determine the relative abilities of heroin, 6-acetylmorphine, and morphine to displace tritiated (\(^{3}H\)-naltrexone) from opiate binding sites. Heroin did not bind to the rat brain opiate receptor, while morphine and 6-acetylmorphine clearly did, suggesting that heroin lacks intrinsic opioid activity, and is actually a lipid soluble pro-drug with two active metabolites.

In a later clinical study extending these earlier findings, Inturrisi and colleagues (1984) observed the pharmacokinetics of heroin in 11 patients with chronic pain, using high-performance liquid chromatography (HPLC) to measure differences in the areas under the curve after parenteral (intravenous bolus, continuous infusion, and intramuscular) heroin versus oral heroin administration. Heroin and morphine given orally were also compared. The time-course of appearance of heroin and its metabolites, 6-acetylmorphine and morphine, in venous blood was measured in relation to the onset of pain relief and sedation. The authors found that with intravenous administration, heroin has a mean half-life of 3.0 min. Steady state blood levels were achieved with continuous infusion of heroin, with doubling of blood levels when the infusion rate was double, thus demonstrating that elimination kinetics remain linear with infusion rates given up to 333 \(\mu g/min\). Oral heroin was found to have complete first-pass metabolism to morphine, but morphine itself given orally at the same dose as heroin yielded 20% higher blood levels of morphine than heroin. However, both heroin and morphine have very low systemic bioavailability with oral administration, as compared with methadone and LAAM. The blood clearance rate of heroin (2,134 ml/min) was greater than the maximal rate of hepatic blood flow (1,500 ml/min) in humans. Thus, it is likely that other organs besides the liver are involved in the biotransformation and elimination of heroin, such as the gastrointestinal wall and the kidney. The onset of pain relief between 15 and 45 min after the start of the heroin infusion was coincident with the presence of heroin and 6-acetylmorphine in the blood prior to the appearance of morphine. The half-life of 6-acetylmorphine has not been precisely determined in humans, but appears to be around 2 hr. Weinberg and colleagues (1988) used high-performance liquid chromatography to compare sublingual versus oral absorption of selected opioid analgesics in normal subjects, subtracting the percentage of opioid recovered from the oral cavity (upon expectoration after 10 min) from 100%. The more lipid-soluble drugs (buprenorphine, fentanyl, methadone, and heroin) were absorbed to the greatest degree. Drug absorption was independent of concentration of opioid, with greater absorption permitting greater potential systemic bioavailability of the opioid. However, in comparison with morphine sulfate with 18% absorption, heroin was not significantly better absorbed via the sublingual route.

Further work needs to be done in order to better determine the contribution of 6-acetylmorphine to the pharmacokinetics of parenteral heroin, particularly in terms of its faster onset of action and greater potency compared with morphine.

**Morphine**

Morphine, relatively selective for the mu opioid receptor, is the opioid agonist with