

Dihydroetorphine: A Potent Analgesic: Pharmacology, Toxicology, Pharmacokinetics, and Clinical Effects

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ABSTRACT

Dihydroetorphine (DHE) is one of the strongest analgesic opioid alkaloids known; it is 1000 to 12,000 times more potent than morphine. Several *in vitro* and *in vivo* studies have shown that DHE is a selective μ -opioid receptor (OP_3) agonist that also binds and activates all human recombinant μ -, δ -, and κ -opioid receptors (OP_3 , OP_1 , and OP_2). The onset of the analgesic effect of DHE in rodents is rapid, 5 to 15 min after parenteral administration; the duration of action is short, the analgesic effect disappears within 120 min after administration. By oral administration much higher doses of DHE are required to produce analgesic effects. These characteristics are accounted for by the pharmacokinetic properties of DHE in the rat, namely, by rapid distribution of DHE from the injection site to the brain and rapid metabolism by glucuronidation in the gut and liver followed by elimination into the bile. Continuous infusion and repeated administration of DHE lead to the development of tolerance to analgesia, physical dependence, and a rewarding effect in normal rats but not in animals with formalin-induced inflammation. Although formalin-induced inflammation is only one type of pain stimulus, these findings suggest that DHE addiction would be observed only in the case of pain-free conditions. Clinical reports in China show that sublingual doses of DHE, 20 to 180 μ g, produce a potent analgesic effect with only mild side effects, including dizziness, somnolence, nausea, vomiting, constipation, and shortness of breath. To improve the short-lasting effect following sublingual administration, transdermal delivery of DHE via a patch has been investigated. The patch formulation of DHE produces continuous analgesic effect with minimal physical dependence and rewarding effect in rats suffering from chronic pain. This patch formulation, which is very suitable for DHE, may be viable for the treatment of severe pain and is likely to improve patients' quality of life.