

Pharmacologic and Clinical Considerations of Nalmefene

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Nalmefene is a pure opioid antagonist structurally similar to naltrexone that can serve as an alternative antidote for reversing respiratory depression associated with acute opioid overdose. Nalmefene is also known as 6-methylene naltrexone. Its main features of interest are its prolonged duration of action that surpasses most opioids and its ability to serve as an antidote for acute opioid overdose.

Keywords: nalmefene ; opioid overdose ; naloxone ; harm reduction ; antidote

1. Introduction

The primary drug for combatting acute opioid overdose has been naloxone. In overdose situations and for clinical uses, the respiratory depression and sedative effects of opioids can occur for several hours after administration ^{[1][2]}. This requires more hours of patient monitoring for signs of respiratory depression and potential repeated administration of naloxone, as the duration of action (DOA) of naloxone is generally 64 min ^[3]. This brings light to the pertinent issue associated with naloxone: its DOA is less than that of most frequently abused opioids ^{[4][5]}.

This central issue with naloxone has led much research toward an alternative opioid antagonist with a longer DOA. Nalmefene is a pure opioid antagonist structurally similar to naltrexone that can serve as an alternative antidote for reversing respiratory depression associated with acute opioid overdose. The key feature of nalmefene is its increased DOA being several hours longer than naloxone and its ability to serve as an antidote during acute opioid overdose, unlike naltrexone. This can help patients be discharged earlier and decrease nursing observation by 2–4 h ^{[3][4]}. An alternative opioid overdose antidote on the market is further beneficial with the marked rise in opioid overdose deaths.

On 13 March 2019, the U.S. Food and Drug Administration (FDA) granted Fast Track designation for Purdue Pharma L.P.'s Nalmefene HCl injections to treat known or suspected opioid overdose ^[6]. Reasons for Fast Track designation include the marked rise in opioid overdoses in the U.S. and the subsequent need for more reversal agents of similar or better efficacy than naloxone.

Though nalmefene has displayed efficacy in treating alcohol dependence in humans ^[7], this review will focus on nalmefene's implications with opioid use disorder (OUD) and opioid overdose. This study was designed to analyze the efficacy and practicality of nalmefene treatment in OUD and suspected opioid overdose cases by reviewing the history of nalmefene research in human subjects.

2. Nalmefene

Nalmefene HCl is a pure opioid receptor antagonist and is considered the longest-acting parenteral opioid antagonist commercially available for OUD and opioid overdose. It is a white crystalline substance, and its chemical name is 17-(cyclopropylmethyl)-4,5-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt. It can be used to prevent or counter the various consequences of opioid overdose or post-surgery opioid effects, such as respiratory depression and sedation. Desirable outcomes of nalmefene administration include alleviation of respiratory depression, nerve center depression, and hypotension associated with prolonged opioid receptor activation ^[8]. A pill form of nalmefene is manufactured in Japan, England, and other European countries under the brand name of Selincro ® for the treatment of alcohol dependence in decreasing alcohol intake ^[9].

In 1995, nalmefene HCl was granted approval by the U.S. FDA to treat known or suspected opioid overdose and was sold under the brand name Revex ® . Nalmefene can be administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC). Nalmefene is currently sold in two doses, with the concentration being dependent on postoperative or overdose use. Nalmefene is available in a blue-labeled ampul containing 1 mL at a concentration of 100 µg/mL for

postoperative use. For opioid overdose reversal, nalmeferene is available in a green-labeled ampul containing 2 mL at a 1 mg/mL concentration, being ten times more concentrated than the postoperative formulation [10]. An initial dose of 0.5 mg/70 kg for opioid overdose reversal is recommended and can be followed up 2–5 min with a 1.0 mg/70 kg dose [10]. Intravenously administration of nalmeferene generally takes 2 min for initiation of opioid reversal [10]. If nalmeferene is administered via intramuscular (IM) or subcutaneous (SC) routes, it may take 5–15 min for a 1 mg dose to be effective [8].

Nalmeferene is well tolerated in human subjects for up to 24 mg of IV doses [11]. In most studies, its side effects were transient, relatively mild, and similar to naloxone's side effects. The main side effects for both are nausea, vomiting, tachycardia, hypertension, pain, fever, and dizziness [8]. However, it can produce acute withdrawal symptoms in those physically dependent on opioids [8]. Furthermore, nalmeferene is only known to have net antagonistic effects on opioid receptors and is not considered abuse potential nor cause physical dependence [12].

Nalmeferene also has a higher potency for opioid receptors than naloxone. Its potency is 4 times higher than naloxone at MOR and slightly more potent at KOR [13]. Nalmeferene also has a longer elimination half-life, ranging from 8 to 11 h, and a longer duration of action of 1–4 h [13]. The longer duration of action is also associated with the medication's slow dissociation from the opioid receptor [13].

3. Nalmeferene vs. Naloxone

Nalmeferene and naltrexone are pure opioid antagonists that block receptor activity of the mu, kappa, and delta sub receptors in the CNS [14]. Nalmeferene is a methylene analog of naltrexone that was originally approved in 1995 as a more potent analog. Nalmeferene is has a slightly slower onset of action when given IV (5–15 min compared to 1–2 min with naloxone), equipotent binding power compared to naloxone, a longer DOA, and a much longer plasma half-life (8–11 h compared to 80 min with naloxone) [15]. Both naloxone and nalmeferene are indicated in acute opioid intoxication characterized by respiratory depression, coma, or hypotension. Off-label uses for both agents include clonidine, benzodiazepine, ethanol, or valproic acid overdoses [16]. Overall, both agents are useful for acute opioid withdrawal despite a longer DOA, similar potency, and a longer onset of action is seen in nalmeferene compared to naloxone.

4. Naltrexone

Naltrexone is a pure opioid antagonist and is used for the reduction of cravings and consumption of both opioids and alcohol. Of note, naltrexone is not indicated for acute opioid intoxication. In fact, naltrexone has been implicated in acute opioid overdose deaths as it can lower the patient's tolerance to opioids. These overdoses happen after a period of abstinence and discontinuation of naltrexone [17]. This makes them more susceptible to overdose with a smaller amount of opioids used than in the past.

Naltrexone comes in an oral or a long-acting injectable form, called vivitrol. Historically, patients would have to show that oral naltrexone was tolerable without an increase in liver function enzymes prior to starting the injectable form. It is because of this that naltrexone has not been useful in an acute overdose situations since oral medicine cannot be given to someone who is unconscious. The injectable form comes with another set of barriers. Each injection is costly, at around USD 1400 a shot. It is because of this that not all pharmacies can afford to carry it, let alone have it accessible for emergency medical services. **Table 1** shows a comparison of naloxone, nalmeferene, and naltrexone.

Table 1. The comparison of naloxone, nalmeferene, and naltrexone.

Medication	Mechanism of Action	Pharmacokinetics/Dynamics	Uses	Routes of Administration
Naloxone	Antagonist of MOR	Half-life: 30–120 min Duration of Action: 1–4 h Metabolized by: Liver	Reversal of Opioid Overdose	Intranasal Subcutaneous Endotracheal Sublingual Intralungual Submental Intravenous Intramuscular
Nalmeferene	Antagonists at MOR and DOR Partial agoist at KOR	Half-life: 8–11 h Duration of action: 1–4 h Metabolized by: Liver	Reversal of Opioid Overdose	Intravenous Intramuscular Subcutaneously

Medication	Mechanism of Action	Pharmacokinetics/Dynamics	Uses	Routes of Administration
Naltrexone	Pure antagonist at the MOR, DOR, and KOR	Half life: 4 h for naltrexone and 13 h for active metabolite of 6 beta-naltrexol Duration of action: Metabolized by: Liver	Can reduce and suppress opioid and alcohol cravings Not used in opioid overdose	Oral Intramuscular

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