NINTH EDITION

Goldfrank's Toxicologic Emergencies

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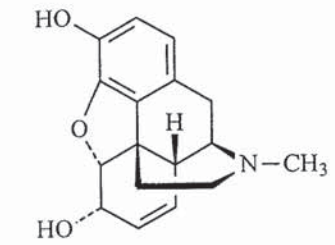
ANTIDOTES IN DEPTH (A6)

OPIOID ANTAGONISTS

Mary Ann Howland and Lewis S. Nelson



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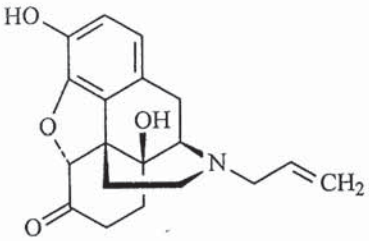
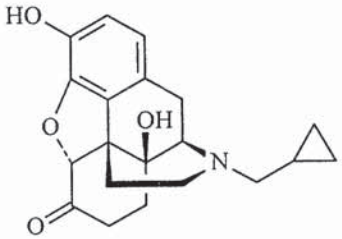
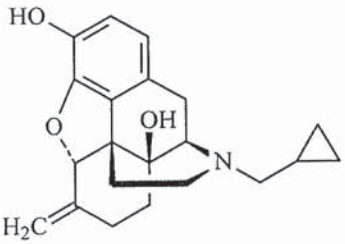


Naloxone



Naltrexone



Nalmefene

Naloxone, nalmefene, naltrexone, and methylnaltrexone are pure competitive opioid antagonists at the mu (μ), kappa (κ), and delta (δ) receptors. Opioid antagonists prevent the actions of opioid agonists, reverse the effects of both endogenous and exogenous opioids, and cause opioid withdrawal in opioid-dependent patients. Naloxone is primarily used to reverse respiratory depression in patients manifesting opioid toxicity. The parenteral dose should be titrated to maintain adequate airway reflexes and ventilation. By titrating the dose, beginning with 0.04 mg and increasing as indicated to 0.4 mg, 2 mg, and finally 10 mg, abrupt opioid withdrawal can be prevented. This method of administration limits withdrawal-induced adverse effects, such as vomiting and the potential for aspiration pneumonitis, and a surge in catecholamines with the potential for cardiac dysrhythmias and acute lung injury (ALI). Because of its poor oral bioavailability, oral naloxone may be used to treat patients with opioid-induced constipation. Methylnaltrexone is a parenteral medication and alvimopan an oral capsule that fail to enter the central nervous system (CNS) and are uniquely effective in reversing opioid-induced constipation. Naltrexone is used orally for patients after opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence. Nalmefene is available for parenteral use with a duration of action between those of naloxone and naltrexone.

HISTORY

The understanding of structure–activity relationships led to the synthesis of many new molecules in the hope of producing potent opioid agonists free of abuse potential. Although this goal has not yet been achieved, opioid antagonists and partial agonists resulted from these investigations. *N*-Allylnorcodeine was the first opioid antagonist synthesized (in 1915), and *N*-allylnormorphine (nalorphine) was synthesized in the 1940s.[39,83] Nalorphine was recognized as having both agonist and antagonist effects in 1954. Naloxone was synthesized in 1960, and naltrexone was synthesized in 1963.

CHEMISTRY

Minor alterations can convert an agonist into an antagonist.[38] The substitution of the *N*-methyl group on morphine by a larger functional group led to nalorphine and converted the agonist levorphanol to the antagonist levallorphan.[35] Naloxone, naltrexone, and nalmefene are derivatives of oxymorphone with antagonist properties resulting from addition of organic or other functional groups.[35,42] Relatedly, nalmefene is a 6-methylene derivative of naltrexone.

PHARMACOLOGY

The μ receptors are responsible for analgesia, sedation, miosis, euphoria, respiratory depression, and decreased gastrointestinal (GI) motility. κ receptors are responsible for spinal analgesia, miosis, dysphoria, anxiety, nightmares, and hallucinations. δ receptors are responsible for analgesia and hunger. The currently available opioid receptor

antagonists are most potent at the μ receptor, with higher doses required to affect the κ and δ receptors. They all bind to the opioid receptor in a competitive fashion, preventing the binding of agonists, partial agonists, or mixed agonist–antagonists without producing any independent action. Naloxone, naltrexone, and nalmefene are similar in their antagonistic mechanism but differ primarily in their pharmacokinetics. Both nalmefene and naltrexone have longer durations of action than naloxone, and both have adequate oral bioavailability to produce systemic effects. Methylnaltrexone can be given orally or parenterally but is excluded from the CNS and only produces peripheral effects. Selective antagonists for μ, κ, and δ are available experimentally and are undergoing investigation.[62]

In the proper doses, pure opioid antagonists reverse all of the effects at the μ, κ, and δ receptors of endogenous and exogenous opioid agonists, except for those of buprenorphine, which has a very high affinity for and slow rate of dissociation from the μ receptor.[62,63] Actions of opioid agonists that are not mediated by interaction with opioid receptors, such as direct mast cell liberation of histamine or the sodium channel-blocking effects of propoxyphene, are not reversed by these antagonists.[3] Chest wall rigidity from rapid fentanyl infusion is usually reversed with naloxone.[23] Opioid-induced seizures in animals, such as from propoxyphene, tend to be antagonized by opioid antagonists, though seizures caused by meperidine (normeperidine) and tramadol are exceptions.[6,30] The benefit in humans is less clear. A report of two newborns who developed seizures associated with fentanyl and morphine infusion demonstrated abrupt clinical and electroencephalographic resolution after administration of naloxone.[13]

Opioids operate bimodally on opioid receptors.[10] At low concentrations, μ opioid receptor agonism is excitatory and actually antianalgesic. This antianalgesic effect is modulated through a G_s protein and usually is less important clinically than the well-known inhibitory actions that result from coupling to a G_o protein at usual analgesic doses. For this reason, extremely low doses of opioid antagonists (ie, 0.25 mcg/kg/h of naloxone) enhance the analgesic potency of opioids, including morphine, methadone, and buprenorphine.[11,29,48] Naloxone also attenuates or prevents the development of tolerance and dependence.[10,29] Coadministration of these very low doses of antagonists or derivatives with the opioid also limits opioid-induced adverse effects such as nausea, vomiting, constipation, and pruritus.[97]

Opioid antagonists may reverse the effects of endogenous opioid peptides, including endorphins, dynorphins, and enkephalins. Endogenous opioids are found in tissues throughout the body and may work in concert with other neurotransmitter systems to modulate many physiologic effects.[22,84,86] For instance, during shock, the release of circulating endorphins produces an inhibition of central sympathetic tone by stimulating κ receptors within the locus coeruleus, resulting in vasodilation. Vagal tone is also enhanced through stimulation of opioid receptors in the nucleus ambiguus.

Research investigating the cardioprotective effects of opioid agonists through their action at the sarcolemmal and mitochondrial K^+ ATP (adenosine triphosphate) channels is ongoing.[64,69,73] Nonselective opioid antagonists may negate these protective effects.

PHARMACOKINETICS AND PHARMACODYNAMICS

The bioavailability of sublingual naloxone is only 10%.[5,38] In contrast, naloxone is well absorbed by all parenteral routes of administration, including the intramuscular (IM), subcutaneous (SC), endotracheal, intranasal, intralingual, and inhalational (nebulized) routes. The onset of action with the various routes of administration are as follows: IV, 1-2 minutes; SC, approximately 5.5 minutes; intralingual, 30 seconds; intranasal, 3.4 minutes; inhalational, 5 minutes; endotracheal, 60 seconds; and IM, 6 minutes.[19,43,52,58,78,94] The distribution half-life is rapid (~5 minutes) because of its high lipid solubility. The volume of distribution (Vd) is 0.8 to 2.64 L/kg.[31,33]

A naloxone dose of 13 μg/kg in an adult occupies approximately 50% of the available opioid receptors.[54] The duration of action of naloxone is approximately 20 to 90 minutes and depends on the dose of the agonist, the dose and route of administration of naloxone, and the rates of elimination of the agonist and naloxone.[5,21,85] Naloxone is metabolized by the liver to several compounds, including a glucuronide. The elimination half-life is 60 to 90 minutes in adults and approximately two to three times longer in neonates.[60]

Naltrexone is rapidly absorbed with an oral bioavailability of 5% to 60%, and peak serum concentrations occur at 1 hour.[34,89,93] Distribution is rapid, with a Vd of approximately 15 L/kg and low protein binding.[48] Naltrexone is metabolized in the liver to β-naltrexol (with 2%–8% activity) and 2-hydroxy,3-methoxy-β-naltrexol,[88] and undergoes an enterohepatic cycle.[93] The plasma elimination half-life is 10 hours for β-naltrexone and 13 hours for β-naltrexol,[88,92,93] with a terminal phase of elimination of 96 hours and 18 hours, respectively.[89]

Nalmefene has an oral bioavailability of 40%, with peak serum concentrations usually reached within 1 to 2 hours.[17] However, in the United States, it is currently available only in a parenteral formulation. After SC administration, peak concentrations do not occur for more than 2 hours, though therapeutic concentrations are reached within 5 to 15 minutes.[59] A 1-mg parenteral dose blocked more than 80% of opioid receptors within 5 minutes.[59] The apparent Vd is 3.9 L/kg for the central compartment and 8.6 L/kg at steady state.[59] Protein binding is approximately 45%.[16] Nalmefene has a redistribution half-life of 41 ± 34 minutes and a terminal half-life of 10.8 ± 5 hours after a 1-mg intravenous (IV) dose.[59] It is metabolized in the liver to an inactive glucuronide conjugate that probably undergoes enterohepatic recycling, accounting for approximately 17% of drug elimination in the feces. Less than 5% is excreted unchanged in the urine.

Methylnaltrexone is a quaternary amine methylated derivative of naltrexone that is peripherally restricted because of its poor lipid solubility and inability to cross the blood–brain barrier.[97] After SC administration, peak serum concentrations occur in about 30 minutes. The drug has a Vd of 1.1 L/kg and is minimally protein bound (11%–15%).[59] Although there are several metabolites, 85% of the drug is eliminated unchanged in the urine.[97]

ADVERSE DRUG EFFECTS

Pure opioid antagonists produce no clinical effects in opioid naïve or nondependent patients, even when administered in massive doses.[7]

When exposed to opioid antagonists or agonist–antagonists such as pentazocine, patients dependent upon opioid agonists exhibit opioid withdrawal reactions, including yawning, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting, diarrhea, myalgias, mild elevations in heart rate and blood pressure, and insomnia. Antagonist-precipitated withdrawal may result in an "overshoot" phenomenon, from a transient increase in circulating catecholamines, resulting in hyperventilation, tachycardia, and hypertension. Under these circumstances, there is a potential for related complications such as myocardial ischemia, heart failure, CNS injury.[45,57] Delirium, although rarely reported with gradual withdrawal, may occur when an opioid antagonist is used to reverse effects in patients dependent upon high doses of opioids or during rapid opioid detoxification.[32] Delirium is unique to these circumstances and is not described in patients withdrawing by opioid abstinence. These

severe manifestations of precipitated opioid withdrawal may occur with ultrarapid opioid detoxification, and are associated with fatalities occurring in the postadministration period.[37] This rapid form of enforced detoxification differs significantly from the opioid withdrawal associated with volitional opioid abstinence (see Chap. 14).

Case reports describe ALI, hypertension, and cardiac dysrhythmias in association with naloxone administration, generally in opioid-dependent patients.[26,56,66,72,77] The clinical complexities of the setting and case reports make it difficult to analyze and attribute these adverse effects solely to naloxone.[8] ALI occurs after heroin overdose in the absence of naloxone,[20] making the exact contribution of naloxone to the problem unclear. Rather, in certain patients, naloxone may unmask ALI previously induced by the opioid but unrecognized because of the patient's concomitant opioid-induced respiratory depression.[20]

If the patient's airway is unprotected during withdrawal and vomiting occurs, aspiration pneumonitis may complicate the recovery. Given the frequency of polysubstance abuse and overdose associated with altered consciousness, the risk of precipitating withdrawal associated vomiting should always be a concern.

Resedation is a function of the relatively short duration of action of the opioid antagonist compared with the opioid agonist. Most opioid agonists have durations of action longer than that of naloxone and shorter than that of naltrexone; the relationship is variable with nalmefene. A long duration of action is advantageous when the antagonist is used to promote abstinence (naltrexone) but is undesired when inappropriately administered to an opioid-dependent patient.

Unmasking underlying cocaine or other stimulant toxicity may explain some of the cardiac dysrhythmias that develop after naloxone-induced opioid reversal in a patient simultaneously using both opioids and stimulants[55] (see Chap. 76).

Antagonists stimulate the release of hormones from the pituitary, resulting in increased concentrations of luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic hormone and stimulate the release of prolactin in women.[70]

USE OF OPIOID ANTAGONISTS FOR MAINTENANCE OF OPIOID ABSTINENCE

Opioid dependence is managed by substitution of the abused opioid, typically heroin or a prescription opioid, with methadone or buprenorphine or by detoxification and subsequent abstinence. Maintenance of abstinence is often assisted by naltrexone, although any pure opioid antagonist could be used. Typically, naltrexone is chosen because of its oral absorption and long duration of action compared with that of naloxone or nalmefene.[47,53]

When 1 mg of naloxone is administered IV, it prevents the action of 25 mg of IV heroin for 1 hour, whereas 50 mg of oral naltrexone antagonizes this dose of heroin for 24 hours; 100 mg has a blocking effect for 48 hours, and 150 mg is effective for 72 hours. Nalmefene antagonizes the action of 2 μg/kg of IV fentanyl with a duration of action that is similarly dose dependent: 0.5 mg IV last about 4 hours, 2 mg IV lasts about 8 hours, and 50 mg orally lasts about 50 hours.[27,28]

Before naltrexone can be administered for abstinence maintenance, the patient must be weaned from opioid dependence and be a willing participant. Naloxone should be administered IV to confirm that the patient is no longer opioid dependent and safe for naltrexone. With naloxone, opioid withdrawal, if it occurs, will be short lived instead of prolonged after use of naltrexone or nalmefene. Naltrexone does not produce tolerance, although prolonged treatment with naltrexone produces upregulation of opioid receptors.[96]

USE OF OPIOID ANTAGONISTS FOR ETHANOL ABSTINENCE

Naltrexone, particularly the IM depot form, is used as adjunctive therapy in ethanol dependence, based on the theory that the endogenous opioid system modulates ethanol intake.[65,92] Naltrexone reduces ethanol craving, the number of drinking days, and relapse rates.[68] Naltrexone induces moderate to severe nausea in 15% of these patients, possibly as a result of alterations in endogenous opioid tone induced by prolonged ethanol ingestion.[61,92]

OTHER USES

Poorly orally bioavailable opioid antagonists (eg, naloxone) and peripherally restricted opioid antagonists (eg, methylnaltrexone) are used to prevent or treat the constipation occurring as a side effect of opioid pain management.[1,50,97] Methylnaltrexone administered SC results in laxation within 4 hours in nearly half of those who receive the drug for this indication.[81,98]

Take-home naloxone programs are developing around the world. In these programs, opioid abusers are supplied naloxone to be administered to other users after opioid overdose, generally by the SC or intranasal route.[2,76] These bystander programs are credited with saving numerous lives, although concerns exist regarding proper dosing, relative safety, use in mixed overdose, attempts to overcome precipitated withdrawal, and refusal of Emergency Medical Services involvement.

Opioid antagonists are used infrequently in the management of overdoses with nonopioids such as ethanol,[18,75] clonidine,[74] captopril,[87] and valproic acid.[80] In none of these instances is the reported improvement as dramatic or consistent as in the reversal of an opioid. The mechanisms for each of these, though undefined, may relate to reversal of endogenous opioid peptides at opioid receptors.

Naloxone has been used to reverse the effects of endogenous opioid peptides in patients with septic shock, although the results are variable. Treatment is often ineffective and may result in adverse effects, particularly in patients who are opioid tolerant.[15,82] Naloxone may have a temporizing effect via elevation of mean arterial pressure.[36]

Although promising in animal models of spinal cord injury, an investigation of naloxone at doses approximately 100 times greater than those used in the management of overdoses failed to demonstrate improvement in neurologic recovery in humans.[7]

Opioid antagonists are used for treatment of morphine-induced pruritus resulting from systemic or epidural opioids[41,46] and for treatment of pruritus associated with cholestasis.[14,79]

DOSING

The initial dose of antagonist is dependent on the dose of agonist and the relative binding affinity of the agonist and antagonist at the opioid receptors. The presently available antagonists have a greater affinity for the μ receptor than for the κ or δ receptors. Some opioids, such as buprenorphine (see below), require greater than expected doses of antagonist to reverse the effects at the μ receptor.[85,95] The duration of action of the antagonist depends on many drug and patient variables, such as the dose and the clearance of both antagonist and agonist.

A dose of naloxone 0.4 mg IV will reverse the respiratory depressant effects of most opioids and is an appropriate starting dose in nonopioid- dependent patients. However, this dose in an opioid-dependent patient usually produces withdrawal, which should be avoided if

possible. The goal is to produce a spontaneously and adequately ventilating patient without precipitating significant or abrupt opioid withdrawal. Therefore, 0.04 mg is a practical starting dose in most patients, increasing to 0.4 mg, 2 mg, and finally 10 mg. If the patient has no response to 8 to 10 mg, then an opioid is not likely to be responsible for the respiratory depression. The dose in children without opioid dependence is essentially the same as for adults. However, for those with the possibility of withdrawal or recrudescence of severe underlying pain, more gentle reversal with 0.001 mg/kg, with concomitant supportive care, is warranted. Although both the adult and pediatric doses recommended here are lower than those conventionally suggested in other references, the availability of safe and effective interim ventilatory therapy lower the acceptable risk of precipitating withdrawal.

The use of low doses of IV naloxone to reverse opioid overdose may prolong the time to improvement of ventilation, and during this period, assisted ventilation may be required. The same limitation exists with SC naloxone administration, and the absorbed dose is more difficult to titrate than when administered IV.[94] Naloxone can also be administered intranasally, although this route results in the delivery of unpredictable doses. In the prehospital setting, the time to onset of clinical effect of intranasal naloxone is comparable to that of IV or IM naloxone, largely because of the delay in obtaining IV access and slow absorption, respectively.[4,43] Intranasal naloxone is not currently recommended as first-line treatment by healthcare providers.[44] Nebulized naloxone (2 mg is mixed with 3 mL of 0.9% sodium chloride solution) has similar limitations in dose accuracy and is further limited in patients with severe ventilatory depression, the group most in need of naloxone. These patients are not optimal candidates for inhalation therapy because delivery of a sufficient reversal dose may not occur. Although needleless delivery is a clear prehospital advantage, there is little role for inhospital use of intranasal or nebulized naloxone.

Evaluation for the redevelopment of respiratory depression requires nearly continuous monitoring. Resedation should be treated with either repeated dosing of the antagonist or, in some cases, such as after a long-acting opioid agonist, with another bolus followed by a continuous infusion of naloxone. Two-thirds of the bolus dose of naloxone that resulted in reversal, when given hourly, usually maintains the desired effect.[33] This dose can be prepared for an adult by multiplying the effective bolus dose by 6.6, adding that quantity to 1000 mL, and administering the solution IV at an infusion rate of 100 mL/h. Titration upward or downward is easily accomplished as necessary to both maintain adequate ventilation and avoid withdrawal. A continuous infusion of naloxone is not a substitute for continued vigilance. A period of 12 to 24 hours often is chosen for observation based on the presumed opioid, the route of administration, and the dosage form (eg, sustained release). Body packers are a unique subset of patients who, because the reservoir of drug in the GI tract, require individualized antagonist management strategies (see Special Considerations: SC-4 Internal Concealment of Xenobiotics.

Naloxone is a pregnancy Category C drug.[60] A risk-to-benefit analysis must be considered in pregnant women, particularly those who are opioid tolerant, and their newborns. Inducing opioid withdrawal in the mother probably will induce withdrawal in the fetus and should be avoided. Likewise, administering naloxone to newborns of opioid-tolerant mothers may induce neonatal withdrawal[40] (see Chaps. 30, 31, and 38).

Use of longer-acting opioid antagonists, such as naltrexone and nalmefene, places the patient at substantial risk for protracted withdrawal syndromes. The use of a long-acting opioid antagonist in acute care situations should be reserved for carefully considered special indications, together with extended periods of observation or careful follow-up. An oral dose of 150 mg of naltrexone generally lasts 48 to 72 hours and should be adequate as an antidote for the majority of opioid-intoxicated patients. Discharge of opioid-intoxicated patients after successful administration of a long-acting opioid antagonist, while theoretically attractive, is not well studied. There are concerns about attempts by patients to overcome opioid antagonism by administering high doses of opioid agonist, with subsequent respiratory depression as the effect of the antagonist wanes.

Naltrexone is administered orally in a variety of dosage schedules for treatment of opioid dependence. A common dosing regimen is 50 mg/day Monday through Friday and 100 mg on Saturdays. Alternatively, 100 mg every other day or 150 mg every third day can be administered. The IM extended-release suspension is injected monthly at a recommended dose of 380 mg.[47]

The initial IV dose of nalmefene is 0.1 mg in a 70-kg person in whom opioid dependency is suspected. If withdrawal does not ensue, 0.5 mg can be given, followed by 1 mg in 2 to 5 minutes as necessary. If IV access is unavailable, the IM or SC route can be used, but the onset of action is delayed by 5 to 15 minutes after a 1-mg dose. For reversal of postoperative opioid respiratory depression, a starting dose of 0.25 μg/kg is used followed by incremental doses of 0.25 μg/kg every 2 to 5 minutes to the desired effect or to a total of 1 μg/kg.

Methylnaltrexone SC dosing for opioid-induced constipation is weight based.[98] The dose is 0.15 mg/kg for patients who weigh less than 38 kg and more than 114 kg. For patients who weigh between 38 and less than 62 kg, 8 mg is administered, and for those between 62 and 114 kg, 12 mg is provided. Dosing for patients with renal failure is required at half the recommended dose.

MANAGEMENT OF OVERDOSE

Although the opioid antagonists are all safe in overdose, excessive administration to an opioid-dependent patient will predictably result in opioid withdrawal. When induced by naloxone, all that is generally required is protecting the patient from harm and reassuring the patient that the effects will be short lived. Symptomatic care may be necessary on occasion. After inadvertent administration of nalmefene or naltrexone, the expected duration of the withdrawal syndrome generally mandates the use of pharmacologic intervention.[25,51] Overcoming the opioid receptor antagonism is difficult, but if used in titrated doses, morphine or fentanyl may be successful. Adverse effects from histamine release from morphine and chest wall rigidity from fentanyl should be expected. If more moderate withdrawal is present, the administration of metoclopramide, clonidine, or a benzodiazepine is usually adequate.[45]

What constitutes an appropriate observation period depends on many factors. After IV bolus naloxone, observation for 2 hours should be adequate to determine whether sedation and respiratory depression will return. Although no fatalities were identified in medical examiner records after the rapid prehospital release of patients who had presumably overdosed with heroin and were administered naloxone, the true safety of this practice remains questionable.[9] Although the matched pharmacokinetics of heroin and naloxone suggests potential utility for such a practice, the high frequency of methadone or sustained-release oxycodone use in many communities raises concerns. That is, the pharmacokinetic mismatch of both methadone and sustained-release oxycodone with naloxone results in recurrent opioid toxicity and prevents widespread implementation of this program.[90] Similarly, patients on continuous naloxone infusion must be observed for ≥2 hours after its discontinuation to ensure that respiratory depression does not recur.

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