A review of naloxone
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Narcotics are some of the most commonly used drugs in anesthesia. As beneficial as these drugs are, they are not without side effects. Narcotic antagonists are frequently used to “reverse” some of these undesirable side effects. The following is a review of naloxone (Narcan®), currently the most widely used reversal agent.

The history of narcotic antagonists began over 50 years ago with the discovery that n-allyl derivatives of narcotic analgesics could “reverse” the effects of their parent compounds. In 1951, nalorphine (Nalline®) was introduced as a narcotic antagonist and levallorphan (Lorfan®) was introduced in 1956.1

Both nalorphine and levallorphan are n-allyl derivatives of narcotics obtained by substitution of an allyl group for the methyl group of the basic nitrogen of morphine.1,2 (Figure 1).

When given alone, nalorphine and levallorphan produce significant respiratory depression and also share certain “agonistic” properties with the narcotics. In addition, these drugs also produce unpleasant mental side effects such as, anxiety, “unreal” daydreams, hallucinations and a feeling of gogginess without the ability to sleep.1

Because of these shortcomings the search for a “pure” antagonist continued and naloxone (Nar- can®) was synthesized from oxymorphone by substitution of an allyl group for a methyl group.1

Usages
Naloxone is the drug of choice for the treatment of narcotic overdosage and post-anesthetic depression induced by narcotics. It is the only available narcotic antagonist that does not have any narcotic properties by itself.1,3,4

After bolus intravenous administration, the drug’s high lipid solubility, reflected in a drug distribution coefficient of 33.60, results in easy blood-brain barrier penetration and therefore a rapid onset of effects.

Little information about naloxone is available because of analytic difficulty in measuring low concentrations of the drug present in the blood. After IV administration, the drug exhibits a bi-exponential decay. The distribution half-life is 2.7 minutes and is similar to other narcotics.

Naloxone has a large volume of distribution at steady state which is similar to the narcotics. The combination of high clearance and large volume of distribution results in a very short terminal elimination half-life of 1.0-1.5 hours.3 (Figure 2.)

The duration of action of naloxone is brief due to two factors. First, the high lipid solubility results in rapid redistribution from the brain to blood and then to other tissues. Second, the short terminal elimination half-life results in rapid drug removal from the body, which maintains a high concentration gradient from the brain to the blood.
This short terminal elimination half-life also prevents a lengthening of naloxone's effect with multiple administrations.

The drug is metabolized in the liver primarily by conjugation with glucuronic acid. Other metabolites are produced in small amounts and to a minor extent. Naloxone undergoes keto reduction and/or N-dealkylation phase I reactions followed by phase II glucuronidation and possibly sulfation. Naloxone's degree of protein binding has yet to be determined.

Currently, there is virtually no information regarding the effects of altered physiologic and disease states on the drug. It must be kept in mind that any decrease in hepatic blood flow should decrease naloxone clearance and prolong the terminal elimination half-life. This should, in turn, prolong the pharmacological effect of the drug.

Naloxone's use is thus limited by its short duration of action after IV administration. It will antagonize the effect of morphine for only about 45 minutes.\(^1,^8\)

Naloxone is the narcotic antagonist of choice under most conditions. The indications for administration are excessive ventilatory and central nervous system (CNS) depression due to a narcotic analgesic.

When administered in recommended doses in the absence of a narcotic analgesic, it is devoid of depressant or other effects of its own. It is able to antagonize the actions of both pure agonists (morphine) and mixed agonist-antagonists (pentazocine).\(^1,^4,^5\)

Narcotics produce dose-dependent depression of respiration and the CNS. Small doses (0.4-0.8 mg) of naloxone prevent or promptly reverse the effects of narcotics. In patients with narcotic-induced respiratory depression, there is an increase in the respiratory rate within 1-2 minutes. Sedative effects are reversed and blood pressure, if depressed, returns to normal.\(^1,^4\)

Naloxone has been used in newborns who appeared normal in all respects except that they would not breathe spontaneously or that they appeared centrally depressed. Naloxone administration via the umbilical or a peripheral vein produces dramatic results, usually within 30 seconds after the injection. If a peripheral or umbilical vein cannot be cannulated, some authors recommend that a double dose of the drug be given IM.\(^1\)

**Side effects**

The use of naloxone involves side effects and some authors feel that the drug should be given only to antagonize a specific narcotic effect.\(^4\)

Routine administration of naloxone following anesthesia in which narcotics have been given may result in complications. Difficulty in re-establishing analgesia, hypertension, sympathetic stimulation, tachycardia, arrhythmias, nausea, vomit-

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**Figure 1**

A comparative chemical structure of naloxone

- Naloxone
- Meperidine
- Morphine
- Fentanyl

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**Figure 2**

Naloxone elimination half-life times

<table>
<thead>
<tr>
<th>Elimination half-life (hours)</th>
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</thead>
<tbody>
<tr>
<td>Meperidine</td>
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<tr>
<td>Morphine</td>
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<tr>
<td>Fentanyl</td>
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ing or retching, and both acute and severe pain may occur. There are some reports of deaths following the administration of the drug.\textsuperscript{5,6,7}

Antagonism of narcotics by naloxone is often accompanied by an “overshoot” phenomenon, whereby a depressed respiratory rate becomes higher than it was prior to the period of depression.\textsuperscript{1}

Reappearance of the narcotic effect may take place hours after naloxone was first administered. The reappearance of the narcotic effect is probably the most serious complication encountered with the drug since it can occur rapidly in patients who minutes before were alert and may have been lightly monitored.\textsuperscript{4}

Naloxone is ineffective against respiratory depression caused by barbiturates, other anesthetics, other non-narcotic drugs or pathological conditions. The drug can precipitate acute withdrawal symptoms in narcotic addicts.\textsuperscript{1,8}

Summary

In summary, naloxone is generally considered to be a safe drug; however, an understanding of its actions and side effects is necessary for its safe administration.

REFERENCES


