Naloxone hydrochloride (Narcan) is a pure narcotic antagonist that is the drug of choice in the treatment of central nervous system and cardiorespiratory depression due to narcotic agonist drugs. It has virtually no agonist activity and therefore produces no narcotic effect even when administered in greater than recommended doses, in contrast to nalorphine hydrochloride and levallorphan tartrate, which have mixed agonist-antagonist activity.

In 1975 the FDA approved a dosage form of naloxone in a concentration of 0.02 mg/ml that was specifically designed for use in newborns whose mothers receive narcotic analgesics during labor and who are born with narcotic-induced respiratory depression; this drug was marketed for general prescription use. Three years after its introduction, the role of naloxone in the management of the depressed newborn merits clarification. In addition, recent information regarding opiate receptors and endogenous opioids raises questions concerning the long-term safety of naloxone in neonates. A review of available published and unpublished data pertaining to naloxone use in the newborn infant by the Committee on Drugs forms the basis for the following commentary and recommendations.

**Efficacy**

The potent narcotic antagonist activity of naloxone is well documented in infants and children as well as in adults. Naloxone has been effectively used postoperatively to reverse respiratory depression in infants and children who received narcotics for analgesia. Additional cases have been reported in which naloxone was successfully and safely used to treat children who were poisoned with narcotic agonists such as diphenoxylate hydrochloride (Lomotil), methadone hydrochloride, and propoxyphene hydrochloride (Darvon).

Most of the controlled clinical trials to study the safety and efficacy of naloxone in treating respiratory depression in the narcotic-exposed newborn have been carried out on full-term, healthy infants whose mothers received morphine or meperidine hydrochloride during labor, but who showed no overt clinical evidence of respiratory or CNS depression at birth. The parameters used to detect narcotic effect vary from study to study. These include the Apgar score, various neurobehavioral assessment scales, and physiologic measurements of respiratory function. Not only do the methods of assessment vary from study to study, but naloxone dose and route of administration are different. This makes comparison of the studies difficult and, not surprisingly, results are inconsistent.

Several controlled trials have shown statistically significant differences between narcotic-exposed infants who received naloxone and those who did not with respect to alveolar Pco2, tidal volume, and ventilatory response to breathing an increased CO2 tension. The infants in one study also demonstrated significantly improved sucking behavior and shortened time for habituation to auditory stimuli after receiving naloxone, 200 µg/kg IM (20 times the usual recommended dose). In one series of 43 newborns, the naloxone-treated infants had higher “alertness scores” and greater “response to sound” than the control infants. In none of these studies was there evidence of significant respiratory or central nervous system depression as reflected by Apgar scores. With the possible exception of one study, capillary pH and Pco2 also did not differ significantly between naloxone-treated and control group infants. Several uncontrolled studies have claimed beneficial effects due to naloxone based on subjective, nonquantitative observations such as increase in depth of respiration, improved tone, increased activity, and increased crying.

Only one controlled clinical trial (P. Lynd, J. J.
showed no difference from the control infants in the pneumonia, undefined central nervous system depression poorly or not at all and appeared to have infants seemed to respond rapidly to naloxone and scores greater than 7). The eleven infants who cotic-induced depression (Apgar score less than 6) were compared to a group of seven infants whose mothers received narcotics but who appeared normal at birth (Apgar scores greater than 7). The eleven infants who appeared depressed received 10 to 15 \( \mu \text{g} \) naloxone intralingually. Temperature, heart rate, respiratory rate, color, cry, activity, and capillary blood gases were monitored in all infants during the first six hours of life. Eight of the 11 naloxone-treated infants seemed to respond rapidly to naloxone and showed no difference from the control infants in the monitored parameters. The other three infants responded poorly or not at all and appeared to have other causes of depression including aspiration pneumonia, undefined central nervous system depression, and asphyxia following prolonged labor ending with emergency cesarean section. Two of the principal parameters used in this study, ie, Apgar score and respiratory rate, have been shown by other investigators to be crude and nondiscriminating measures of respiratory depression. No data are available regarding use of naloxone in premature infants.

The single published study of the use of naloxone administered to the mother just prior to delivery to reverse potential narcotic-induced respiratory depression of the neonate is difficult to interpret due to the poorly controlled conditions of the study. Naloxone is not recommended for administration to the parturient for this indication.

SAFETY

The immediate short-term toxicity of naloxone appears to be negligible. Even in excessive doses it does not have narcotic agonist activity or other detectable adverse effects. However, the long-term safety of naloxone has not been investigated.

The administration of naloxone to the infant of a narcotic-dependent mother may precipitate an acute withdrawal syndrome in the infant. It is, therefore, important for the physician to ascertain whether the mother may be narcotic-dependent prior to using naloxone in her infant.

Recent information regarding opiate receptors and endogenous opioid substances (endorphins and enkephalins) suggests that opiate receptors probably have physiologic roles and enkephalin and endorphin polypeptides may function as important neurotransmitters. Endogenous opioids may play important regulatory functions involving integra-
CONCLUSIONS AND RECOMMENDATIONS

1. Naloxone should be reserved for adjunctive therapy in selected infants who have not initiated or established independent respirations following ventilation, are significantly depressed, and have a high probability of being narcotized.

2. When naloxone is administered to the neonate, the 0.02 mg/ml preparation should be used. The recommended dose is 0.01 mg/kg. The initial dose may be repeated in three to five minutes if there is no response. The dose may need to be repeated in 30 to 90 minutes, depending on the degree of depression of the infant, because of the relatively short duration of action of naloxone. Naloxone should be given intravenously if possible.

3. Naloxone is not recommended for administration to the mother just prior to delivery to reverse the fetal and neonatal effects of maternally administered narcotic analgesics.

4. Naloxone should not be administered to infants of narcotic-dependent mothers as this may precipitate withdrawal in the physically dependent infant.

5. Naloxone should not be used routinely in narcotic-exposed newborns.

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