EDITORIAL

Opioid Harm Reduction Strategies: Focus on Expanded Access to Intranasal Naloxone

Daniel P. Wermeling, Pharm.D., FCCP, FASHP

Key Words: opioids, antidote, naloxone, overdose.
(Pharmacotherapy 2010;30(7):627–631)

In 2008, both prescription and illicit opioids, alone or in combination with other intoxicants, led to over 20,000 overdose deaths in the United States.[1–4] This statistic is generated through reports originating from emergency departments and does not include information from coroner reports. Thus, this number is likely to be conservative. In addition, over the past decade, incremental increases in the number of overdose deaths have been demonstrated each year.[5] In 2006, opioid overdose surpassed firearms as the second leading cause of accidental injury death in the United States, and rates of mortality from poisoning were higher than from motor vehicle accidents among adults aged 34–56 years. The average U.S. mortality rate related to opioid overdose in 2006 was approximately 7.8/100,000 persons.[5] In rural Appalachia, during the past 5 years, over 75% of fatalities were related to the use of prescription methadone, hydrocodone, and oxycodone.[5–9] Many states and large metropolitan areas consider opioid-related mortality to be a public health crisis.[3, 4, 9]

The Opioid Antidote Naloxone

Naloxone hydrochloride, known chemically as 17-allyl-4,5α,-epoxy-3,14-dihydroxymorphinan-6-one-hydrochloride, is a potent μ-receptor antagonist and antidote for opioid overdose.[10–12] Naloxone was approved by the U.S. Food and Drug Administration (FDA) in 1971 and was first marketed by Endo Pharmaceuticals (Chadds Ford, PA) as Narcan injection. It has subsequently become a multisource generic drug manufactured by International Medication Systems, Ltd. (South El Monte, CA) and Hospira, Inc. (Lake Forest, IL). Naloxone injection is available in two strengths: 0.4 mg/ml and 1.0 mg/ml. Current formulations of naloxone are approved for intravenous, intramuscular, and subcutaneous administration.[10] The initial adult dose for known or suspected narcotic overdose is 0.4–2 mg, which may be repeated, up to a total dose of 10 mg.[10]

The standard of care for emergency services personnel is to have naloxone available in ambulances and emergency drug kits for reversal of suspected opioid overdose, whether accidental or intentional, in the field. Hospital emergency departments also use this drug routinely for this purpose. Naloxone is also indicated as a reversal agent when the effects of therapeutic use of opioids are no longer medically necessary, such as in reversal of opioid effects after general anesthesia.[11, 12] The drug produces a rapid reversal of narcosis and central nervous and respiratory system depression. Patients and opioid abusers who may be physically dependent on opioids may experience short-lived withdrawal symptoms, which rarely are severe. Opioid withdrawal, while highly uncomfortable, is not a life-threatening phenomenon.

Harm Reduction Strategies for Pain Management

Morbidity and mortality related to opioid overdose are not limited to the illicit use of prescription drugs or heroin. Clearly, our patients are prescribed increasingly complex pharmacologic regimens for the treatment of malignant and nonmalignant

From the Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, Kentucky.

The opinions expressed in this editorial are those of the author and do not necessarily represent the position of *Pharmacotherapy* or the American College of Clinical Pharmacy. Invited editorials are not peer reviewed.

For reprints, visit http://www.atypon-link.com/PPI/loi/phco. For questions or comments, contact Daniel P. Wermeling, Pharm.D., FCCP, FASHP, Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, 789 South Limestone Street, Lexington, KY 40536; e-mail: dwermel@uky.edu.

chronic pain. Other central nervous system depressant drugs are frequently prescribed in conjunction with opioids, often by several physicians who are simultaneously treating the patient. Concurrent use of alcohol and other substances such as marijuana are common cointoxicants found in patients who have died from opioid overdose. Thus, serious consideration should be given to prescribing naloxone to patients who are at high risk of an inadvertent opioid overdose. Potential indications for prescribing naloxone and the patient populations targeted could include the following:

- Any methadone prescription
- High-dose opioid prescriptions (e.g., high-potency, extended-release products)
- Patients released after an opioid poisoning
- People with a suspected history of illicit or nonmedical use of opioids
- Concurrent use of opioids with antidepressants, benzodiazepines, or alcohol
- Opioid use in patients with major organ dysfunction (renal, hepatic, cardiac, or pulmonary)
- Patients released from opioid detoxification programs

An interesting dilemma that arises from the notion of prescribing naloxone to patients at risk of overdose is that they are very unlikely to be able to rescue themselves should they be overcome by the effects of an opioid. Thus, a bystander, family member, or caregiver will likely by the first to witness the overdose and have the first opportunity to respond. Even though the patient would be prescribed naloxone, it is clearly those closely surrounding the patient who need to be trained on overdose recognition and treatment (administering naloxone, calling 911, and rescue breathing for the patient [if apneic]). The ability to enable such a program that consists of at-home, triage-related emergency medicine requires that an exemption be made in most state pharmacy, medicine, and nursing practice acts to permit a layperson to administer the antidote to another person. Similar statutes exist for the administration of epinephrine for anaphylaxis and glucagon for insulin shock. Needle-free drug delivery systems (discussed below) would also facilitate layperson rescue.

Naloxone Nasal Drug Delivery by Emergency Medical Technicians

Federal and state agencies, the pharmaceutical industry, and others are adopting prevention and intervention strategies in an attempt to reduce opioid overdose mortality while protecting the health of emergency medical services staff.[13–18] Initially, injection-based naloxone served as the standard of care. However, many emergency medical services programs have now moved toward intranasal administration of naloxone injection since about 80% of the injection-drug abuse population is hepatitis C or human immunodeficiency virus positive, particularly in large metropolitan areas.[15, 17, 18] The emergency medical services program has created an intranasal naloxone administration system (Figure 1). The system combines an FDA-approved naloxone injection product with a Luer-fitted tip without a needle and an approved medical device—a disposable nasal solution atomizer—called the Mucosal Atomization Device (MAD; Wolfe Tory Medical, Salt Lake City, UT). Emergency medical services programs in Boston, Denver, and San Francisco use this drug administration technique as the standard of care.[19–22]

An additional reason to advocate intranasal delivery of naloxone is that there are different tiers of responsibility and professional scopes of practice within the emergency medical services staff. For example, paramedics are authorized to start intravenous lines and administer injections whereas emergency medical technicians (EMTs) are not. Moreover, EMTs more commonly provide emergency medical services in rural regions of the United States. Thus, providing a mechanism so that EMTs can administer naloxone seems to be warranted.

A group of authors first demonstrated the use of intranasal delivery of naloxone in a study published in 2002.[19] Thirty patients in Denver encountered by paramedics received 2 mg/2 ml of naloxone injection used with the MAD nasal spray atomizer. One ml was administered into each naris on initial contact. Eighty-three percent of the patients with a suspected opioid overdose responded to intranasal naloxone, with an average response time of 3.4 minutes. Sixty-four percent of the patients did not require intravenous line placement. These authors were the first to suggest that nasal naloxone rescue administered by emergency medical services can work in practice.

Th same group of authors published an expanded version of their study 3 years later (2005).[20] Response rates to treatment remained similar. Additional data on time to first patient contact, time to drug administration, and time to achieve a spontaneous respiratory rate of at least 10 breaths/minute were reported. The average time

to clinical response was slightly longer with intranasal compared with intravenous administration. Of importance, however, was that the time from first contact to clinical response was not different between intravenous and intranasal administration, as the time spent starting an intravenous line is saved with intranasal administration. Given the same elapsed time until patient outcome in most circumstances, and the hazards of needlesticks in this population, there is a strong argument for use of nasal delivery.

A similar randomized trial, also reported in 2005, comparing intranasal naloxone 2 mg with intramuscular naloxone 2 mg produced similar results.[21] Two other reports published in 2005 and 2009 compared intravenous naloxone with intranasal naloxone in the "prehospital" setting of the San Francisco emergency medical services area.[22, 23] One hundred fifty-four patients were enrolled; 100 received intravenous and 54 received intranasal treatment. Time to clinical response to naloxone was reported to be the same between groups. Similar to the findings of one of the previous studies,[20] the mean time from patient contact to clinical response was not different (20.3 min for intranasal versus 20.7 min for intravenous). The authors concluded that intranasal naloxone is a viable alternative rescue treatment given the hazards associated with obtaining intravenous access in this patient population.

Take-Home Naloxone for Opioid Abusers

Several large metropolitan cities that have significant injection-based drug abuse, primarily heroin, adopted pilot studies in the 1990s to determine if addicts could be trained to rescue other individuals who may be experiencing an overdose; a summary of evidence addressing this point was published in 2001.[24] The basic premise was that needle-exchange programs commonly have repeated access by addicts. Also, it was generally understood that abuse occurs in small groups of individuals and that a fellow addict is likely to be the observer and potential first responder to a person overcome by the effects of heroin and in need of resuscitation. The initial programs developed a medical protocol in which naloxone injection was prescribed to an addict who was trained on overdose recognition and treatment. A simple kit was provided to the addict that contained naloxone injection along with a needle or nasal atomizer adaptor, a rescue breathing mask, and a message to call 911. The concept was simple—give naloxone, rescue breathe if apneic, and call for emergency medical services.

In a 2005 pilot study conducted in San Francisco, pairs of heroin users were trained to recognize overdose and complete the three-step process of naloxone administration, rescue

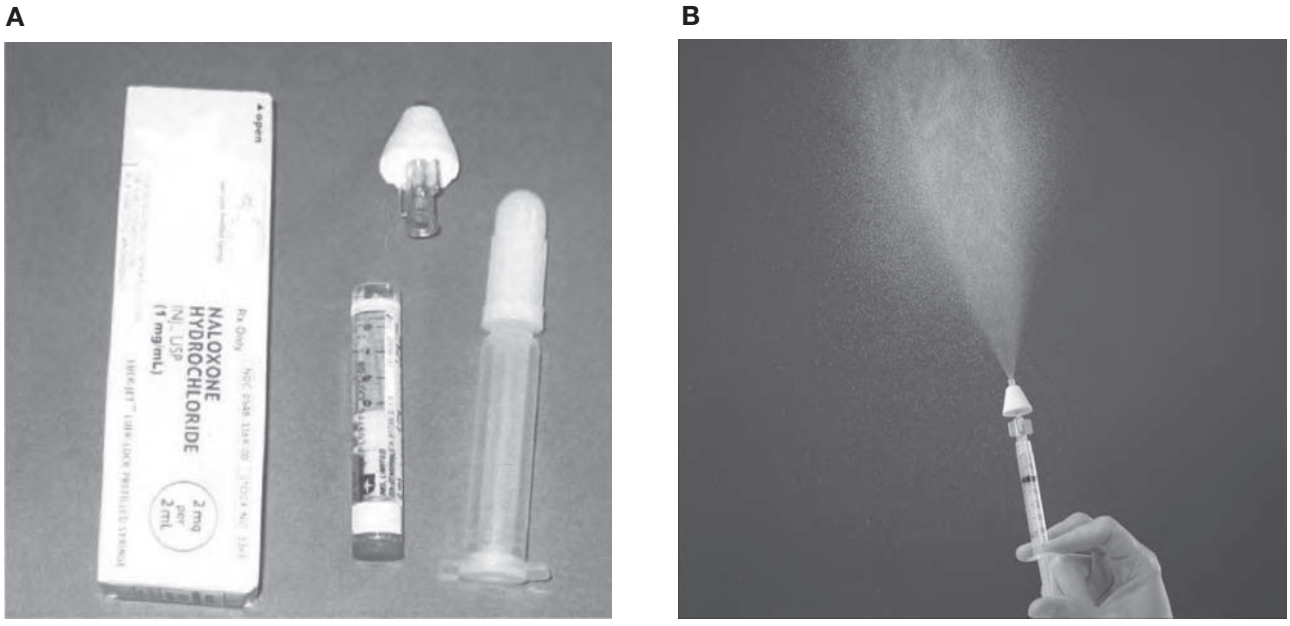

Figure 1. The intranasal naloxone administration system, which combines a naloxone injection product with a Luer-fitted tip without a needle and an approved medical device—a disposable nasal solution atomizer called the Mucosal Atomization Device (panel A); use of the system is demonstrated in panel B.

breathing, and calling 911 for help.[25] Twenty-four pairs were enrolled and were followed for 1 year after receiving training and a naloxone rescue kit. Twenty witnessed overdoses were reported, and the rescue methods were employed. All subjects survived the overdose incidents.

In 2006, the multiyear experience of the Chicago Recovery Alliance, a program similar to the San Francisco pilot study, was reported.[26] Over several years, the Alliance distributed over 3500 vials of naloxone injection to addicts. The study reported 319 incidents of overdose reversals by their peers. During the study period, the Cook County medical examiner reported a 20% decrease in opioid deaths in the first year and an additional 10% reduction for each of the second and third years of implementation.

Similar programs have been described for Boston, New York City, Baltimore, and the state of New Mexico[27]; one article explained how to establish medical programs for heroin overdose prevention in other locales.[28] In 2008, an evaluation of six different naloxone training and distribution programs in the United States was published,[29] followed by additional critical considerations for training on intervention and preventing overdoses.[30, 31] It is a simple notion that family caregivers—meaning a spouse, loved one, girlfriend or boyfriend, or any family member in close contact with an addict—should be trained on recognition of suspected overdose and what to do if it occurs. A family member of an addict is likely to be the first responder and can provide rescue until arrival of emergency medical services.

In 2009, experience with intranasal delivery of naloxone injection and training of addicts on drug overdose prevention in Boston was described.[17] The article further outlines the regulatory and legal barriers that must be overcome to establish a harm reduction program. In the most recent summary of expanded access to naloxone, a global overview of the opioid overdose epidemic, the nature of programs in existence, and how additional considerations of FDA regulatory status—including developing and approving a naloxone product designed for nasal delivery, and over-the-counter status for naloxone—could help expand access, are provided.[18]

The Role of the Pharmacist

A tremendous opportunity exists for pharmacists in helping to reduce opioid-related morbidity and mortality. The paradigms discussed above related to therapeutic use of opioids in pain management, emergency medicine, and the abusing population deserve consideration. Pharmacists can take a leading role in developing legislation that is permissive of naloxone rescue. Clearly, pharmacists can assist in the training and dissemination of information regarding the proposed rescue program with their local community emergency medical services staff. Finally, pharmacy organizations should take a leading role in designing opioid harm reduction strategies, research studies, and operational models for pharmacists in their communities.

References

1. **Warner M**. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006. Centers for Disease Control and Prevention, no. 22, September 2009. Available from http://www.cdc.gov/nchs/data/databriefs/db22.htm. Accessed March 15, 2010.
2. **Drug Abuse Warning Network**. Dawn report: emergency department visits involving nonmedical use of selected pharmaceuticals. Available from http://dawninfo.samhsa.gov/files/tndr/2006-07r/tndr07edvisitsnonmedicaluse.htm. Accessed October, 2009.
3. **Szabo L**. Prescriptions now biggest cause of fatal drug overdoses. USA Today. October 1, 2009:D1.
4. **Potter M**. Prescription drug abuse ravages state's youth. MSNBC.com. Available from http://www.msnbc.msn.com/id/31707246/ns/health-addictions/print/1/displaymode/1098. Accessed July 6, 2009.
5. **Paulozzi LJ, Budnitz DS, Xi Y**. Increasing deaths from opioid analgesics in the U.S. Pharmacoepidemiol Drug Saf 2006;15:618–27.
6. **Hall AJ, Logan JE, Toblin RL, et al**. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 2008;300:2613–20.
7. **Havens JR, Walker R, Leukefeld CG**. Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. Drug and Alcohol Dependence 2007;87:98–102.
8. **Paulozzi LJ, Ryan GW**. Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med 2006;31:506–11.
9. **Wunsch MJ, Nakamoto K, Behonick G, Massello W**. Opioid deaths in rural Virginia: description of the high prevalence of accidental fatalities involving prescribed medications. Am J Addict 2009;18:5–14.
10. **International Medication Systems, Ltd**. Naloxone hydrochoride injection package insert. South El Monte, CA; April 2006.
11. **McEvoy GK, ed**. Naloxone hydrochloride. In: AHFS drug information 2009. Bethesda, MD: American Society of Health-System Pharmacists, 2009:2251–4.
12. **Hardman JG, Limbird LE, eds**. Goodman and Gilman's the pharmacologic basis of therapeutics, 10th ed. New York: McGraw-Hill, 2001:569–620.
13. **Sporer KA, Kral AH**. Out of hospital treatment of opioid overdoses in an urban setting. Acad Emerg Med 1996;3:660–7.
14. **Belz D, Lieb J, Rea T, Eisenberg MS**. Naloxone use in a tiered response emergency medical services system. Prehosp Emerg Care 2006;10:468–71.
15. **Kerr D, Dietze P, Kelly A**. Intranasal naloxone for the treatment of suspected heroin overdose. Addiction 2008;103:379–86.
16. **Wanger K, Brough L, Macmillan I, Goulding J, MacPhail I, Christenson JM**. Intravenous versus subcutaneous naloxone for out of hospital management of presumed opioid overdose. Acad Emerg Med 1998;5:293–9.
17. **Doe-Simpkins M, Walley A, Epstein A, et al**. Saved by the

nose: bystander administered intranasal naloxone hydrochloride for opioid abuse. Am J Public Health 2009;99:788–91.
18. **Kim D**, **Irwin KS**, **Khoshknod K**. Expanded access to naloxone: options for critical response to the epidemic of opioid overdose and mortality. Am J Public Health 2009;99:402–7.
19. **Barton ED**, **Ramos J**, **Colwell C**, **Benson J**, **Baily J**, **Dunn W**. Intranasal administration of naloxone by paramedics. Prehosp Emerg Care 2002;6:54–8.
20. **Barton ED**, **Colwell CB**, **Wolfe T**, **et al**. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the pre-hospital setting. J Emerg Med 2005;29: 265–71.
21. **Kelly AM**, **Kerr D**, **Dietze P**, **Patrick I**, **Walker T**, **Koutsogiannis Z**. Randomized trial of intranasal versus intramuscular naloxone in prehospital treatment of suspected opioid overdose. Med J Aust 2005;182:24–7.
22. **Robertson GW**, **Stroh G**, **Shalit M**. Intranasal vs intravenous naloxone for prehospital narcotic overdose [abstract]. Acad Emerg Med 2005;12(5 suppl 1):166.
23. **Robertson TM**, **Hendey GW**, **Stroh G**, **Shalit M**. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehospital Emerg Care 2009;13:512–15.
24. **Baca CT**, **Grant KJ**. Take-home naloxone to reduce heroin death. Addiction 2001;100:1823–31.
25. **Seal KH**, **Thawley R**, **Gee L**, **et al**. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. J Urban Health 2005;82:303–11.
26. **Maxwell S**, **Bigg D**, **Stanczykiewicz K**, **Carlberg S**. Prescribing naloxone to actively injection heroin users: a program to reduce heroin overdose death. J Addictive Dis 2006;25:89–96.
27. **Piper TM**, **Rudenstine S**, **Stancliff S**, **et al**. Overdose prevention for injection drug users: lessons learned from naloxone training and distribution programs in New York City. Harm Reduction J 2007;4:1–8.
28. **Sporer KA**, **Kral AH**. Prescription naloxone: a novel approach to heroin overdose prevention. Ann Emerg Med 2007;49:172–7.
29. **Green TC**, **Heimer R**, **Grau LE**. Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and distribution programs in the US. Addiction 2008;103:979–89.
30. **Strang J**, **Manning V**, **Mayet S**, **et al**. Family carers and the prevention of heroin overdose deaths: unmet training need and overlooked intervention opportunity of resuscitation training and supply of naloxone. Drug Education, Prevention and Policy 2008;15:211–18.
31. **Sherman SG**, **Gann DS**, **Tobin KE**, **et al**. "The life they save may be mine": diffusion of overdose prevention information from a city sponsored programme. Int J Drug Policy 2009;20:137–42.