Intranasal Naloxone and Opioid Overdose

Naloxone is a safe, easy-to-use, and effective medication that stops the effects of heroin and other opioids on the brain, and reverses opioid overdose. For the past decade, harm reduction programs have provided training and naloxone to drug users, pain patients, and their families, so that bystanders are prepared to use it as a first aid response to overdose. In the United States, bystanders have used naloxone to reverse more than 10,000 opioid overdoses (Wheeler et al., 2012), and community naloxone programs operate in countries as varied as Kazakhstan, the UK, and China. Globally, most programs provide materials for injectable naloxone, though a few distribute kits that allow responders to spray the medication in the victim's nostrils (called intranasal, or IN, administration).

Injectable naloxone is currently a much cheaper option, available at less than $2 a dose in many countries. Since naloxone has been used extensively for decades in medical settings, there is also a well-established body of evidence of the medication's safety and efficacy (Jasinski et al., 1967; Evans, et al., 1974). Naloxone is on the World Health Organization's Model List of Essential Medicines. There are, however, some barriers to use of the injectable medication. Some people do not feel comfortable performing an injection, or fear needle-stick injuries. In certain jurisdictions, only some medical professionals are allowed to administer injections. Drug users are sometimes reluctant to carry a needle and syringe, fearing that police will use these as evidence of criminal activity.

Many emergency medical workers in the United States administer naloxone intranasally, inserting a cartridge into a syringe and attaching an atomizer to spray the liquid into an overdose victim's nose. In some jurisdictions, intranasal administration has been the protocol in pre-hospital settings for nearly a decade. In the U.S., the states of Massachusetts, New York, and New Mexico now distribute naloxone and an intranasal dispensing device to drug users and methadone patients. North Carolina will soon make intranasal naloxone available statewide through its Medicaid health insurance program to patients who are prescribed opioids for pain management and others at risk of an opioid overdose. The U.S. Army is distributing intranasal naloxone to active duty soldiers who are at risk of overdose from prescription opioids or heroin, as part of a pilot project on one of its largest bases.

Intranasal naloxone and the atomizer required to dispense it are relatively expensive in the U.S., at about $20 per kit. This high cost, coupled with other factors, makes intranasal naloxone unavailable in many countries that face high rates of opioid overdose, particularly in Eastern Europe and Asia. In order for intranasal naloxone to become accessible in such contexts, a low cost intranasal device must be developed.

Evidence for Intranasal Naloxone

In the United States, giving naloxone through the nose to reverse an overdose is considered an "off-label use," meaning that the Food and Drug

Administration has not determined the safety and efficacy of intranasal administration with the particular products that are available on the market. While doctors can prescribe the medication for intranasal use, manufacturers are not approved to market naloxone to be used intranasally. Atomizers are sold separately, requiring responders to put the atomizer on a syringe during an emergency. Evidence from emergency responders and state programs, however, suggests that once administered, intranasal naloxone is effective at reversing opioid overdoses (Ashton and Hassan, 2006).

Randomized controlled trials in emergency medical settings comparing intranasal and injectable naloxone have shown that intranasal naloxone works well (Kelly et al., 2005 and Kerr et al., 2009). Kelly and colleagues found no statistically significant difference between the two groups in the proportion of patients requiring rescue medication (an additional dose of naloxone administered intramuscularly if the initial dose did not work). However, the authors were surprised to find that those who had received naloxone intranasally were less likely to be agitated upon recovery than those who were injected with naloxone intramuscularly—even though they received the same dose. This finding may be due to the slower absorption of the intranasal formulation in the body (and therefore, a less abrupt withdrawal from the effect of the opioids).

The 2009 study by Kerr and colleagues found similar response times for overdose reversal for the two routes of administration. However, paramedics were nearly five times more likely to administer a second, "rescue" dose of naloxone to patients in the intranasal group. The study suggests that this might be due to paramedics' apprehension about the effectiveness of intranasal treatment.

A new randomized controlled trial that began in January 2012 compares intranasal and intramuscular naloxone in a supervised injecting facility in Sydney, Australia. In this double-blind study, individuals who overdose are given both intranasal and intramuscular administrations; however, only one is naloxone while the other dose is a placebo. This removes the bias that overdose responders may have for one method over the other and allows researchers to more accurately evaluate the efficacy of naloxone administration methods. The study results are forthcoming.

Limited information is available on the use of intranasal naloxone by non-medical personnel. One article reports on a program offering intranasal naloxone for layperson administration (Doe-Simkins et al., 2009). In 15 months, this Boston, Massachusetts-based program provided a 15-minute training and intranasal naloxone to 385 participants. Seventy-four successful reversals were reported, and problems were uncommon: In four overdose cases, however, responders had trouble connecting the atomizer to the syringe (but were still able to reverse the overdose, either by administering the naloxone by another method or performing rescue breathing until medical professionals arrived).

Potential Improvements for Intranasal Naloxone

Naloxone is manufactured in a number of concentrations, most commonly 0.4mg (of the active ingredient) per mL and 1mg per mL, both of which are effective for intramuscular use. Programs that use naloxone intranasally generally use the more concentrated form in a volume of 2mL; though naloxone is absorbed rapidly through the nasal mucosa, there is a limit to the amount of liquid that these membranes can absorb (roughly 0.5mL of liquid per nostril), so some of the naloxone dribbles out of the nose. While this concentration and dose

appear effective, no tests have been published identifying the optimal nasal dose.

Further, some participants report that assembling the atomizer and syringe currently available for intranasal administration is cumbersome. Studies should be done to determine if a nose-spray or other one-piece applicator could be easier to use and as effective as the current device. The U.S. National Institute on Drug Abuse has provided funding for early development of a naloxone nasal spray, with the intention that this will become available in the U.S. market (NIDA, 2010).

Increasing Options and Saving Lives

There is an urgent need to broaden access to naloxone to prevent overdose deaths: In many countries, the great majority of opioid users report witnessing or experiencing overdoses, and in at least one study, nearly three-quarters of drug users (73 percent) had personally seen someone die from a heroin overdose (Saucier, 2011). Community enthusiasm for intranasal naloxone is high: A study among 99 injecting drug users in Melbourne, Australia found that three quarters (74 percent) would prefer intranasal naloxone to other administration methods, including intramuscular or intravenous (Kerr et al., 2008).

Wider access to affordable, easy-to-administer intranasal naloxone could help overdose response programs save even more lives. Research into how to improve intranasal delivery devices and efforts to expand the pool of manufacturers and distributors will help get an effective opioid overdose antidote to the hundreds of thousands in need.

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