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REVIEW ARTICLE

A response to the opioid overdose epidemic: naloxone nasal spray

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Abstract Opioid overdose morbidity and mortality is recognized to have epidemic proportions. Medical and public health agencies are adopting opioid harm reduction strategies to reduce the morbidity and mortality associated with overdose. One strategy developed by emergency medical services and public health agencies is to deliver the opioid antidote naloxone injection intranasally to reverse the effects of opioids. Paramedics have used this route to quickly administer naloxone in a needle-free system and avoiding needlestick injuries and contracting a blood-born pathogen disease such as hepatitis or human immunodeficiency virus. Public health officials advocate broader lay person access since civilians are likely witnesses or first responders to an opioid overdose in a time-acute setting. The barrier to greater use of naloxone is that a suitable and optimized needle-free drug delivery system is unavailable. The scientific basis for design and study of an intranasal naloxone product is described. Lessons from nasal delivery of opioid analgesics are applied to the consideration of naloxone nasal spray.

Keywords Intranasal · Naloxone · Opioid · Overdose · Antidote

Introduction

In 2008, poisoning surpassed motor vehicle accidents as the leading cause of "injury deaths" in the USA [1]. Nearly 90 % of poisoning deaths are caused by drugs. During the past three decades, the number of drug poisoning deaths increased sixfold from about 6,100 in 1980 to 36,500 in 2008. Of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose. In 2008, the overall death rate in the USA was 4.8 per 100,000 for nonmedical use of prescription opioids [2, 3].

The opioid overdose crisis is a worldwide phenomenon crossing sovereign, cultural, and socio-economic boundaries. The US Centers for Disease Control considers prescription drug overdose in epidemic proportions, in particular, the morbidity and mortality associated with use, abuse, and misuse of prescription opioids [4]. Hospitalizations from prescription opioid poisoning increased by over 50 % from 1999 to 2006, paralleling the increased prescribing of these medications for the treatment of pain [5, 6]. Although many deaths are associated with drug abuse, there is also a growing trend of therapeutic misadventures for pain patients prescribed powerful analgesics, including opioids. Chronic cancer and nonmalignant pain pharmacotherapy regimens frequently involve combinations of medications with additive or synergistic central nervous system depression adverse effects.

Injection drug use, principally heroin, is one of the most significant correlates to opiate use mortality. Eurasia, Australia, Canada, Italy, and Great Britain, among others, all describe significant injection drug use populations that experience drug overdose with similar rates of mortality regardless of socioeconomic status [7–12].

Government and nongovernment public health agencies, the pharmaceutical industry, and others are adopting prevention and intervention strategies in an attempt to reduce opioid overdose mortality. One "harm-reduction" strategy has been to provide education and training on opioid overdose recognition and emergency treatment to addicts and their close daily contacts [13]. In addition, the addict and their loved ones are trained to rescue breathe, call emergency medical services, and to administer the opioid antidote naloxone.

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Naloxone is the drug of choice to reverse respiratory and central nervous system depression caused by opioid overdose [14]. Naloxone injection has been marketed in the USA for 41 years, initially under the trade name Narcan®. Naloxone hydrochloride (HCl), known chemically as 17-Allyl-4,5α,-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride, is a potent mu-receptor antagonist. It has subsequently become a multisource prescription generic drug manufactured by International Medication Systems, Limited and Hospira, Inc. [15, 16]. Ampoules of naloxone injection are also available in many countries. The injection is available in two strengths, 0.4 and 1.0 mg/mL. Naloxone is a standard drug carried by emergency services personnel in ambulances and medication kits for reversal of suspected opioid overdose, whether accidental or intentional. Hospital emergency departments also use this medication routinely for this purpose. The initial adult dose of naloxone in known or suspected narcotic overdose is 0.4–2 mg, which may be repeated to a total dose of 10 mg. The current formulations of naloxone are approved for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration, with IV being the recommended route [17, 18]. 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 in general anesthesia [15, 16]. Lastly, naloxone is coformulated with buprenorphine as an oral product providing an abuse-deterrent formulation for opioid maintenance in opioid dependent patients.

In the last several years, the emergency medical systems (EMS) community in the USA and elsewhere has developed an interest in administering naloxone in a needleless system via the intranasal (IN) route. Some EMS programs have now moved toward intranasal administration of naloxone since many of the patients needing naloxone are injection drug users; 80 % of the injection drug user population in large metropolitan areas is hepatitis C positive or HIV positive. For example, the Denver and San Francisco EMS uses this drug administration technique as standard of care to prevent needlestick injuries to emergency medical technicians [17, 19, 20].

Some EMS programs have developed a system using existing technologies of an approved drug and an existing medical device to administer this opioid antidote, albeit in a non-Food and Drug Administration (FDA)-approved manner [19, 20]. This has been accomplished by using the injectable formulation (1 mg/mL) and administering 1 mL per nostril via a marketed nasal atomizer/nebulizer device. The system combines an FDA-approved naloxone injection product (with a Luer fitted tip, no needles) with a marketed [510(k) exempt] medical device called the Mucosal Atomization Device (MAD™ Nasal, Wolfe Tory Medical, Inc.). This initiative is consistent with the US Needlestick Safety and Prevention Act (Public Law 106–430) [21–25].

The EMS programs recognize limitations of this system, one limitation being that it is not assembled and ready to use. Although this administration mode appears to be effective in reversing narcosis, the formulation is not concentrated for retention in the nasal cavity. The 1 mL delivery volume per naris is larger than that generally utilized for intranasal drug administration. Therefore, there is loss of drug from the nasal cavity, due either to drainage into the nasopharynx or externally from the nasal cavity. An improvement would be to design a ready-to-use product specifically optimized, concentrated, and formulated for nasal delivery.

The drug abuse treatment and overdose prevention communities worldwide have also recognized the desire for a needle-free system for naloxone delivery [26]. Clients at needle-exchange centers provide kits containing naloxone, with either needles or nasal spray atomizers, and instructions for use. Such programs are well-described in the USA and Great Britain, commonly operating in conjunction with needle-exchange programs [27–33]. In May 2012, the British Advisory Council on the Misuse of Drugs published a report advocating for greater distribution of naloxone and training for administration [34]. The Council reiterates that naloxone is safe and effective, that there is evidence that take-home naloxone can be effective for reversing heroin overdoses. Cost-effectiveness of these programs is still being assessed.

An unmet medical need exists to provide greater access to the opioid antidote naloxone. A significant barrier to this goal is that naloxone is only available as an injection for IV, IM, or SC administration. A needleless system that integrates a concentrated formulation and a nasal delivery device would help satisfy this unmet need.

Nasal physiology, drug, and formulation considerations for nasal delivery

Nasal physiology

Intranasal sprays of medication intended for systemic drug absorption are generally designed to target the turbinates on the medial wall of the nasal cavity. The turbinates serve as a baffle in which inspired air is humidified and filtered. This region of the nasal cavity is covered with a thin mucus layer, a monolayer ciliated epithelium, with an abundant underlying blood supply. These conditions are ideal to permit passive diffusion (transcellular) of medications with certain chemical characteristics across cell membranes and into the bloodstream. Some medications also transit to the blood stream by passing through the tight-cell junctions between cells (paracellular) [35].

To reach the turbinates, the nasal spray device must be inserted fully into the nasal vestibule with the atomizer tip placed at the nasal valve, and then aimed laterally toward the turbinates. Activation of the device ejects the liquid as an atomized spray or plume. The bulk of the spray impacts the anterior and inferior portions of the nasal cavity as a function of straight-line impact of particles greater than 10 μm in size [36–38]. The smallest particles, less than 10 μm in size, may be carried by air currents more superiorly in the nasal cavity and impact on the superior turbinate and possibly reach the olfactory region and nerve. There is substantial evidence in animals, and some evidence in man, that the olfactory nerve can absorb or actively transport medications to the central nervous system via the olfactory bulb (nose to brain theory). Differences in animal and human nasal apparatus anatomy, and certain characteristics of the medication, seem to play roles as to whether medication is transported to the brain via this mechanism and if a pharmacologic effect is observed [39–41].

Under ideal conditions, most medication is absorbed from the nasal cavity and into the bloodstream within 15–20 min, thus generally avoiding the gut first-pass metabolism [35, 36]. Medication remaining in the nasal cavity beyond this time is subject to elimination via various enzyme systems present within the nasal mucus and by swallowing. A second absorption phase (oral) can be observed with nasally administered medications having incomplete nasal absorption that are not subject to high first pass gut metabolism.

Nasal physiologic changes during pathologic conditions, such as polyposis and allergic and vasomotor rhinitis, could theoretically alter the biopharmaceutics of intranasal medications intended for systemic drug administration [35, 36, 42, 43]. Physical obstruction of the nasal passage(s) due to prior trauma and subsequent deflection of the passageways is another possibility. Concurrent use of medications with vasoconstriction or vasodilation properties may also affect drug absorption. Lastly, increases in mucus production and changes in mucociliary clearance rates could affect bioavailability [35–38].

Pharmaceutical regulatory agencies have required studies of the effect of rhinitis on nasal drug delivery biopharmaceutics [43, 44]. It has been demonstrated that there is a lack of effect of nasal mucosal inflammation on the absorption of hydromorphone, butorphanol, buserelin, and triamcinolone acetonide—an exception was reported for desmopressin. Inconsistent results have been reported on the biopharmaceutical disposition of these medications when pretreatment with oral or topical decongestant was administered [37, 43, 44]. Small but statistically measureable changes in rate or extent of absorption have been reported when decongestants were co-administered.

Drug and formulation considerations

Many intranasal delivery products are designed to serve certain purposes or unmet medical needs. Clearly, a nasal spray can remove the needle from drug administration, as is the case with the conversion of the protein calcitonin from a daily injection to a nasal spray. Furthermore, beyond just removing the needle from delivery, intranasal products are designed for rapid action, such as those products designed to treat seizures (benzodiazepines) migraine headache (sumatriptan, butorphannol, zolmitriptan, dihydroergotamine) or pain in general (fentanyl, hydromorphone) [45–49].

Successful intranasal products satisfied several design fundamentals necessary for intranasal delivery. The properties of the drug generally follow these characteristics:

- Mass of 20 mg or less per dose
- Molecular weight <1,000 Da
- Excellent water solubility
- Ionization and pH control of aqueous solutions
- Osmolality—isotonic to slightly hypertonic
- Stability in processing and storage
- Compatibility container closure and sprayer components
- Compatible with excipients (buffers, antioxidants, cosolvents, etc.)

Physical–chemical properties of the candidates must also be considered. Water solubility is important for formulation considerations. Log P, derived from the octanol/water partition coefficient, is a surrogate for lipophilicity and potential for compounds to diffuse across biologic membranes. Successful intranasal medications tend to be water soluble and have sufficient lipophilic character to readily cross biologic membranes [35, 36].

The dose must have sufficient solubility to be administered in approximately 100–200 μL (one spray per naris) of solution. The nasal cavity can retain 100–150 μL without causing immediate runoff out the front of the nose or down the nasopharynx [35, 36]. Additional solubilization strategies may be necessary including the use of organic cosolvents, excipients such as cyclodextrins or other agents to from water-soluble inclusion complexes, or preparation of emulsions. Permeation enhancers may also be necessary to enhance drug penetration through cell membranes [50].

Design of the formulation must account for other factors as well. It is useful to design the formulation to be isotonic to slightly hypertonic to optimize absorption and tolerability. Viscosity enhancing agents such as methylcellulose and others can promote retention in the nasal cavity by slowing the ciliary movement of mucus [35, 36]. Surfactants or polymers can be employed to enhance transmembrane permeation [50]. Lastly, the drug and formulation have to be stable in the device during processing, i.e., sterilization and storage, and thus may require stabilizers.

The choice of delivery device for the medication is another critical consideration. Squeeze bottles are available but have no metering device appropriate to administer potent systemic medications. Multidose bottles provide a metered dose and are available for chronic drug administration. A standard syringe with Luer fitting to accept a nasal atomizer has been used to draw up and administer injection-based drug solutions into the nasal cavity for opiate overdoses, acute pain, and to deliver midazolam injection to the nasal cavity of a seizing patient. Unit–dose devices similar to those used for migraine treatment are also available and being used in development of benzodiazepine nasal spray products. The choice of device depends upon factors such as intended clinical use, setting, stability with the drug and formulation, among others [35, 36].

Ideally, a well-designed formulation must not induce localized toxicity with acute or chronic use. For example, chronic vasoconstriction, irritation, or inflammation can induce tissue damage including ulceration, epistaxis, nasal–septal defects, and fistulae. Formulations should not cause damage to the cilia. Chronic, or daily use, of an irritating product could lead to more serious sequallae from nasal delivery [36].

Properties of naloxone hydrochloride dihydrate

Naloxone is supplied as naloxone HCl dihydrate. The empirical formula of naloxone HCl dihydrate is $C_{19}H_{22}ClNO_4$, $2H_2O$ and its molecular weight is 399.9 g/mol. The structural formula for naloxone is described in Fig. 1a [15, 16].

Naloxone HCl has a physical form of white, or almost white, crystalline powder, and is hygroscopic. Its melting point is 200–205 °C. Naloxone HCl is freely soluble in water and 96 % alcohol, but practically insoluble in toluene. It is also slightly soluble in alcohol and practically insoluble in ether or chloroform. The dissociation constant pKa of naloxone is 7.9 and the log P is 1.92. These physical–chemical characteristics suggest a naloxone aqueous solution is likely feasible [36].

Given its high water solubility, naloxone HCl is an excellent candidate to consider for intranasal delivery and satisfies many criteria necessary for this route. Naloxone is a high first-pass metabolism medication; oral bioavailability is reported to be ≤5 %. The parenteral dose is 2 mg or less; it is highly potent when injected [14–16].

Nasal sprays of compounds chemically related to naloxone have been described. Medications studied include the opioid antagonist naltrexone, and the opioid agonists hydromorphone and butorphanol (Fig. 1b–d). Examination of the formulation methods and human biopharmaceutics of other chemically related compounds will be instructive for considerations of a naloxone nasal spray [36, 45, 48, 49].

Translation of intranasal opioid formulations to naloxone nasal spray

Naturally occurring and semi-synthetic opioids and antagonists share the core structure of thebaine [51]. The addition of functional groups to the core structure imparts different physical–chemical and pharmacologic properties. However, the molecular weights and pKa values are roughly similar and the acid salts tend to be freely soluble in water. Certain cogeners have relatively higher log P as compared to others and so transmembrane delivery may be more accommodative for these molecules [36]. Functional group changes also impart pharmacological properties of being a full mu-receptor agonist, partial agonist, or antagonist. Similarly, these changes may affect the degree of first-pass metabolism upon oral administration. Many of these cogeners are also quite potent—doses may range from 0.5 to 10 mg.

A recent manuscript has provided a comprehensive review on intranasal delivery of opioids [36]. Tables on physical–chemical properties and biopharmaceutics of various agents are provided. Data for naltrexone, hydromorphone, and butorphanol are provided (Table 1). These molecules may be of particular interest since the intravenous and intranasal dosing appears to be similar and the molecules share chemical characteristics to naloxone. Table 2 provides a comparison of the biopharmaceutics of nasally administered naltrexone, hydromorphone and butorphanol. Interestingly, the clinical doses of these drugs (dose normalized for naltrexone) are comparable to that of naloxone injection. Concentration–time profiles for naltrexone, hydromorphone, and butorphanol are provided in Fig. 2 (dose normalized). These data may suggest the likely outcome of an intranasally delivered concentrated solution of naloxone HCl. A 2 mg nasal solution dose will likely have a C_{max} of 3–5 ng/mL and a t_{max} of approximately 20 min, similar to naltrexone and hydromorphone [48]. The greater absorption of butorphanol is likely related to its higher Log P and ability to diffuse across biologic membranes.

Biopharmaceutics of intranasal naloxone

The nasal administration of ^{3}H-naloxone to anesthetized male rats (n=3/group) at a single dose of 30 μg (0.1 mg/kg, based on their average weight of 270 g/rat) in 0.1 mL was compared to a similar dose in 0.1 mL given by the intravenous and intraduodenal routes [52]. Nasally administered naloxone was rapidly and completely absorbed (Fig. 3). The plasma elimination half-life of radioactivity was found to be 40–45 min. The nasal bioavailability for naloxone calculated from the ratio of the $AUC_{0\text{-}INF}$ (nasal/intravenous=1,517.5/1,498.7 ng·h/mL) was 101 %. The intraduodenal bioavailability for naloxone was only 1.5 % (intraduodenal/intravenous=22.0/1,498.7 ng·h/mL).

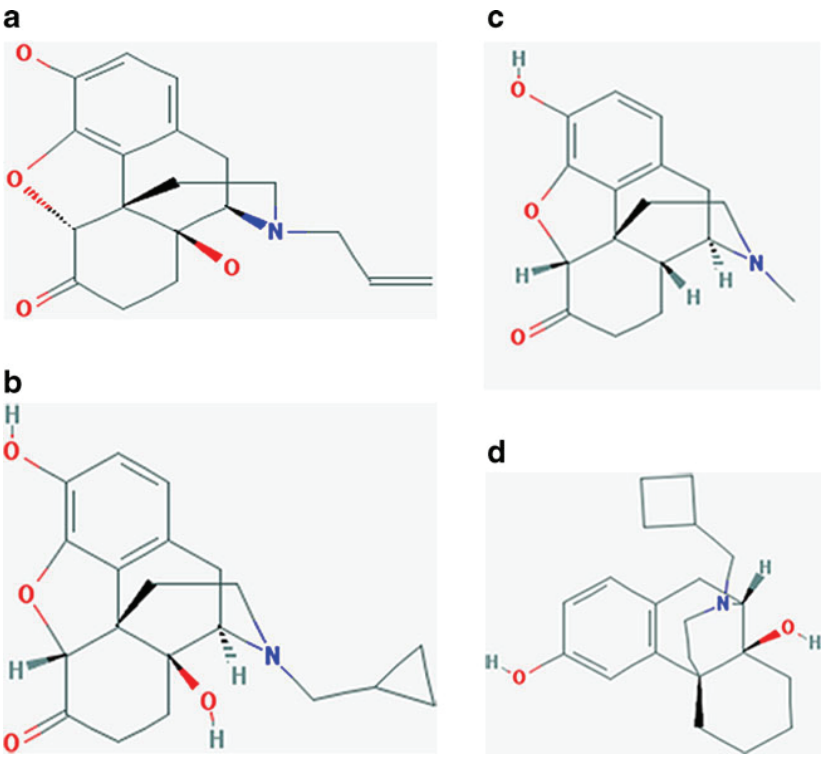

Fig. 1 Chemical structure of naloxone (**a**), naltrexone (**b**), hydromorphone (**c**) and butorphanol (**d**) (Pub Chem, pubchem.ncbi.nlm.nih.gov)

These results established the nasal route for the administration of naloxone in rats was equivalent to the parenteral route.

The pharmacokinetic properties of intranasal naloxone in humans are not well described. A literature review found there are no papers describing the human pharmacokinetics of intranasal naloxone using what might be considered a highly concentrated nasal solution formulation. One paper describes pharmacokinetics of nasal administration of commercial injectable naloxone in man [53]. The intranasal formulation employed was an injection in which 0.8 mg was administered in a volume of 2 mL (1 mL/naris) even though it is commonly understood the nasal cavity can retain only 100–200 μL per naris. The study compared intravenous and intramuscular administration to intranasal administration. The reported intranasal bioavailability of 4 % is dependent upon this non-optimized delivery volume, as it can be assumed that much of the medication ran away from the site of absorption. Therefore, the report may be misleading regarding predicting nasal naloxone absorption in humans using a solution concentrated and designed to accommodate the absorptive surface of the naris.

A recent publication provides a more relevant examination of the possible pharmacokinetic profile of a formulated naloxone nasal spray. The study provides information regarding the nasal absorption of naloxone in humans from a *powder* obtained from crushed Suboxone® (buprenorphine and naloxone sublingual tablets) [54]. After administration of 2 mg (naloxone) nasal powder, the absolute bioavailability was 30 %, with a t_{max} of 20 min and a C_{max} of 1.6 ng/mL. A powder will behave somewhat differently than a solution administered intranasally because dissolution must occur during the time that the naloxone powder is present in the nasal cavity and before the ciliated epithelia sweep the

Table 1 Chemical properties of naloxone, naltrexone, hydromorphone, and butorhpanol [36]

Drug name	Molecular weight	pKa	Log P
Naloxone	327	7.9	2
Naltrexone	341	8.1	1.9
Hydromorphone	285	8.5	1.8
Butorphanol tartrate	327	8.6	3.77

Table 2 Biopharmaceutics of intranasal naltrexone, hydromorphone and butorphanol [48, 49]

Drug and dose	C_{max} (ng/mL)	T_{max} (minutes)	Bioavailability (%)
Naltrexone HCl, 10 mg	14.9	22	600 (to oral)
Hydromorphone HCl, 2 mg	3.5	20	50–60
Butorphanol tartrate, 2 mg	5.5	10	60–70

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