Comparison of a New Intranasal Naloxone Formulation to Intramuscular Naloxone: Results from Hypothesis-generating Small Clinical Studies

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Easy-to-use naloxone formulations are needed to help address the opioid overdose epidemic. The pharmacokinetics of i.v., i.m., and a new i.n. naloxone formulation (2 mg) were compared in six healthy volunteers. Relative to i.m. naloxone, geometric mean (90% confidence interval [CI]) absolute bioavailability of i.n. naloxone was modestly lower (55%; 90% CI, 43–70% vs. 41%; 90% CI, 27–62%), whereas average (±SE) mean absorption time was substantially shorter (74 ± 8.8 vs. 6.7 ± 4.9 min). The opioid-attenuating effects of i.n. naloxone were compared with i.m. naloxone (2 mg) after administration of oral alfentanil (4 mg) to a separate group of six healthy volunteers pretreated with 240 mL of water or grapefruit juice. The i.m. and i.n. naloxone attenuated miosis by similar extents after water (40 ± 15 vs. 41 ± 21 h*%) and grapefruit juice (49 ± 18 vs. 50 ± 22 h*%) pretreatment. Results merit further testing of this new naloxone formulation.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE OF THE TOPIC?
✔ Parental naloxone is the definitive treatment for opioid overdose, a burgeoning public health concern. New naloxone products are under development for administration by first responders, yet the need for a cost-effective, noninvasive, and highly bioavailable formulation remains.

WHAT QUESTION DID THE STUDY ADDRESS?
✔ Two small clinical studies were conducted to compare the pharmacokinetics and opioid attenuating effects of a new i.n. naloxone formulation with i.m. naloxone.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ The first study suggested that the absolute bioavailability of the new i.n. naloxone formulation was comparable to i.m. naloxone, with i.n. naloxone showing more rapid absorption. The second study suggested that whether or not the pharmacokinetic enhancer grapefruit juice was administered prior to alfentanil, i.n. naloxone was nearly as effective as i.m. naloxone in attenuating alfentanil-induced pupil miosis.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ These two small clinical studies suggest the new i.n. naloxone formulation as a viable candidate that warrants further evaluation as a potential rescue therapy for opioid overdose.
An i.n. naloxone product (Narcan Nasal Spray®) recently received marketing approval after Fast Track Designation and Priority Review by the US Food and Drug Administration that partially addresses issues of cost and availability (average wholesale price approximately US $75 per kit). Despite this improvement, many public health organizations and emergency responders continue to use a more cost-effective i.n. administration option that combines the currently approved parenteral formulation (average wholesale price approximately US $15) with a luer lock nasal atomization device (average wholesale price approximately US $5). However, the bioavailability of naloxone associated with i.n. administration of the parenteral formulation is only ~4%.10 Development of a more cost-effective i.n. naloxone formulation with higher bioavailability would further help allay public health concerns regarding opioid overdose.

The objective of this work was to assess the pharmacokinetics of a new i.n. formulation of naloxone. The primary aim was to compare the absolute and relative bioavailability of two i.n. naloxone formulations with that of i.m. naloxone. The secondary aim was to compare i.n. to i.m. naloxone in attenuating central opioid effects. The opioid receptor agonist and cytochrome P450 3A probe substrate, alfentanil, was selected due to a straightforward plasma concentration-effect relationship and short duration of effect.11 Pupil miosis, a sensitive measure of central opioid effect,12 was selected as a noninvasive end point. Grapefruit juice, shown to enhance alfentanil-induced miosis,11 was selected to evaluate attenuation of central opioid effect in the presence of a readily available intestinal cytochrome P450 3A inhibitor used illicly to enhance the central effects of prescription and over-the-counter opioids.13,14 Two hypothesis-generating small clinical studies were conducted to evaluate the pharmacokinetics and opioid attenuating effects of the i.n. naloxone formulation. Results provide a foundation for further testing of this new i.n. formulation as rescue therapy for opioid overdose.

METHODS
Clinical study protocols
The Washington State University Institutional Review Board reviewed and approved the study protocols and consent forms prior to subject enrollment to ensure compliance with appropriate ethical standards for conducting human research. Potential subjects provided written informed consent and Health Insurance Portability and Accountability Act authorization before undergoing screening, which consisted of a medical history, physical examination, liver function tests, complete blood count, and urinalysis that included a 14-panel drug test (14-panel T-cup; Confirm Biosciences, San Diego, CA) to ensure that potential subjects were not taking any opioids. All women underwent a serum pregnancy test. Subjects were eligible to participate based on screening results and inclusion/exclusion criteria (Supplementary Table S1).

Preparation of intranasal naloxone, oral alfentanil, and grapefruit juice
Naloxone hydrochloride, polysorbate 20, and sodium lauryl sulfate were purchased from PCCA (Houston, TX). The i.n. mucosal atomization devices (MAD Nasal) were provided by Teleflex (Research Triangle Park, NC). Millex GP 0.22 μm sterile syringe filter units (Merck Millipore, Darmstadt, Germany) and 5 μm filter needles (Becton, Dickinson and Company, Franklin Lakes, NJ) were purchased from Fisher Scientific (Waltham, MA). Sterile saline 0.9% (Becton, Dickinson and Company) and alfentanil 1 mg/2 mL ampules (Hospira, Lake Forest, IL) were purchased from McKesson Corporation (San Francisco, CA). Grapefruit juice frozen concentrate (Great Value) was purchased from a local store (Walmart, Post Falls, ID; lot nos. LOC4N and LOC1N).

The i.n. naloxone was prepared by suspending naloxone hydrochloride powder in a vehicle consisting of 5% polysorbate 20 and 1% sodium lauryl sulfate dissolved in sterile saline, yielding 5 or 10 mg naloxone/mL. Two concentrations were tested in the pharmacokinetic study to evaluate the impact of dosing volume and concentration on naloxone pharmacokinetics. The solutions were sterilized by filtration before transferring to syringes for administration (0.23 mL per syringe to deliver 0.1 or 0.2 mL [1 mg] per nostril, allowing for 0.13 mL dead space in the MAD Nasal). Syringes were sealed with sterile caps and dispensed in UV protective amber bags. Due to lack of data to support formulation stability, i.n. naloxone was administered within 24 h of admixture. Alfentanil was prepared immediately prior to oral administration by removing 2 mL from each of 4 ampules using a syringe with filter needle (total dose, 4 mg in 8 mL) and diluting into 50 mL of water. The contents from each can of grapefruit juice were thawed and pooled, and an aliquot was saved for quantitation of the marker constituent, 6',7'-dihydroxybergamottin, by high performance liquid chromatography.15 Grapefruit juice was diluted with water to achieve a final 6',7'-dihydroxybergamottin concentration of ~60 μM. The diluted juice was divided into 240-mL aliquots and stored in light-protective containers at −20°C until use; the contents of each container were thawed at 4°C the evening before each study day.

Pharmacokinetic study
Healthy volunteers (5 men and 1 nonpregnant woman), aged 23–29 years, were enrolled in a four-phase, sequential, open-label study (Figure 1a); a sequential design was selected for both logistical and cost purposes. None of the subjects were selecting concomitant medications. Weight and blood pressure were obtained at the beginning of each study day. Naloxone (2 mg) was administered i.v. or i.m. (2 mg/2 mL prefilled syringe, International Medication Systems, El Monte, CA) or i.n. (10 mg/mL, 100 μL/nostril or 5 mg/mL, 200 μL/nostril designated i.n.-100 and i.n.-200, respectively). Blood (10 mL) was collected serially via an indwelling i.v. catheter at 5, 10, 15, 30, 45, 60, 90, 120, and 240 min after naloxone administration. Plasma was harvested and quantified for naloxone by liquid chromatography tandem mass spectrometry as described previously; intra-day and inter-day variability were within 15%.16 A minimum washout of 12 h elapsed between each of the four study days to ensure sufficient elimination of naloxone (terminal half-life [t1/2] <1 h).
Alfentanil effect study
Healthy volunteers (3 men and 3 nonpregnant women), aged 20–32 years, were enrolled in a six-phase, sequential, open-label study (Figure 1b); as with the pharmacokinetic study, a sequential design was selected for both logistical and cost purposes. None of the subjects were taking concomitant medications or dietary/herbal supplements except for one woman who was taking bupropion regularly for >2 months prior to study initiation. Subjects were administered 240 mL water (study days 1–3) or grapefruit juice (study days 4–6) 30 min prior to a single oral dose of alfentanil (4 mg; Figure 1c). Naloxone (2 mg) was administered i.m. (study days 2 and 5) or as i.n. (study days 3 and 6) 1 h after alfentanil administration (alfentanil time of maximum plasma concentration \( t_{\text{max}} \), \( t_{\text{max}} \approx 1 \) h\(^{11}\); Figure 1c). Pupil diameter of the right eye was measured, at least in triplicate (coefficient of variation \( \leq 3.3\% \)), before and 5, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 min after alfentanil administration using a NeurOptics VIP-200 pupillometer with a resolution of 0.1 mm (San Clemente, CA). The light intensity of the room, measured using a Sper Scientific 840021 light meter (Scottsdale, AZ), was always <1 lux. Vital signs (oxygen saturation, pulse, and blood pressure) were obtained concurrent with pupil diameter to ensure safety by monitoring for respiratory depression or adverse reactions to the study drugs. In the event of an adverse reaction to alfentanil, an extra dose of parenteral naloxone and supplemental oxygen were available. Promethazine (Actavis, Parsippany, NJ) and epinephrine (Mylan, Basking Ridge, NJ) were available as anti-nausea and anti-anaphylaxis medications, respectively. A minimum washout of 12 h elapsed between study days 1 and 4 to ensure sufficient elimination of naloxone and alfentanil (\( t_{\text{1/2}} \approx 90 \) min); a minimum washout of 7 days elapsed between study days 4 and 6 to allow for recovery of intestinal cytochrome P450 3A\(^{17}\).

Pharmacokinetic, effect, and statistical analysis
Pharmacokinetic and effect outcomes were determined via noncompartmental methods using Phoenix WinNonlin (version 6.3; Pharsight, Mountain View, CA). Naloxone plasma concentrations below the lower limit of quantification (0.025 ng/mL) were excluded from the pharmacokinetic analysis. The terminal elimination rate constant was determined by linear regression of the terminal portion of the log-transformed concentration–time profile using at least three data points. The \( t_{\text{1/2}} \) was calculated as \( \ln(2) \)/terminal elimination rate constant. The maximum concentration (\( C_{\text{max}} \)), time to reach \( C_{\text{max}} \) (\( t_{\text{max}} \)), and last measured concentration (\( C_{\text{last}} \)) were obtained directly from the concentration–time profile. Area under the curve from time zero to the time at \( C_{\text{last}} \) (AUC\(_{\text{last}}\)) was determined using the trapezoidal method, with linear interpolation for i.v. administration and linear up/log-down interpolation for extravascular administration. AUC\(_{\text{ref}}\) was calculated as the sum of AUC\(_{\text{last}}\) and the ratio of C\(_{\text{last}}\) to terminal elimination rate constant. Absolute bioavailability was calculated as the ratio of the AUC\(_{\text{ref}}\) after extravascular to that after i.v. administration. Relative bioavailability was calculated as the ratio of the AUC\(_{\text{ref}}\) after extravascular to that after i.m. administration. Mean residence time after i.v. or extravascular extravascular administration was calculated as the ratio of AUMC\(_{\text{ref}}\) to AUC\(_{\text{ref}}\), where AUMC\(_{\text{ref}}\) denotes the area under the moment curve from time 0 extrapolated to infinite time. Mean absorption time was calculated as the difference between mean residence time after extravascular administration and after i.v. administration. Pupil diameter measurements were converted to miosis as a function of the percent change from a baseline (predose) measurement. Maximum miotic response (\( R_{\text{max}} \)) was obtained directly from the miosis–time profile. The area under the effect–time curve from 0–6 h (AUEC\(_{0-6h}\)) was determined using the trapezoidal method with linear-up/log-down interpolation.

Descriptive statistics were generated using Phoenix WinNonlin. Statistical comparisons were made using the average bioequivalence approach within Phoenix WinNonlin using a two one-sided testing procedure; a \( P \) value < 0.05 was considered significant. The reference treatment arm was assigned to alfentanil taken with water in the absence of
Table 1  Pharmacokinetics of naloxone (2 mg) after i.v., i.m., and i.n. administration to six healthy volunteers

| Outcome                     | i.v. (90% CI)                      | i.m. (90% CI)                      | i.n., 100 μL/nostril (90% CI) | i.n., 200 μL/nostril (90% CI) |
|-----------------------------|------------------------------------|------------------------------------|--------------------------------|--------------------------------|
| AUC<sub>last</sub>, min*ng/mL | 650 (535–789)                      | 347 (310–390)                      | 266 (190–373)                  | 147 (112–194)                  |
| AUC<sub>inf</sub>, min*ng/mL | 748 (586–954)                      | 434 (386–487)                      | 282 (200–399)                  | 168 (117–240)                  |
| t<sub>1/2</sub>, min        | 81 (64–130)                        | 100 (89–111)                       | 61 (53–72)                     | 80 (56–113)                    |
| C<sub>max</sub>, ng/mL      | –                                  | 3.1 (2.3–4.2)                      | 5.7 (3.3–10.0)                 | 3.0 (1.7–5.3)                  |
| T<sub>max</sub>, min, median (range) | –                                  | 22.5 (10–60)                      | 12.5 (5–15)                    | 5 (5–15)                      |
| MAT, min, mean ± SE        | –                                  | 74 ± 8.8                           | 6.7 ± 4.9                      | 31 ± 22                       |
| F, %                       | –                                  | 55 (43–70)                         | 41 (27–62)                     | 24 (15–33)                     |
| FR, %                      | –                                  | 75 (59–96)                         | 44 (35–49)                     |                                |

AUC<sub>inf</sub>, area under the curve from time zero to infinite time; AUC<sub>last</sub>, area under the plasma concentration-time curve from time zero to the time at the last measured concentration (240 min); CI, confidence interval; C<sub>max</sub>, maximum plasma concentration; F, absolute bioavailability; FR, bioavailability relative to i.m.; i.n., intranasal naloxone, 10 mg/mL, 100 μL/nostril; i.n., 200, intranasal naloxone, 5 mg/mL, 200 μL/nostril; MAT, mean absorption time; t<sub>1/2</sub>, terminal half-life; T<sub>max</sub>, time to reach C<sub>max</sub>.
Values are geometric means (90% CIs) unless indicated otherwise.
N = 6 for each administration route.

Figure 2  Concentration-time profiles for naloxone (2 mg) following i.v., i.m., or i.n. (100 μL/nostril or 200 μL/nostril) administration to six healthy volunteers. Symbols denote geometric mean concentrations. Error bars denote 90% confidence intervals.

nalofoxone for comparison of miosis end points. These comparisons are for descriptive purposes only because the studies were hypothesis-generating in nature; thus, no formal a priori statistical analysis plan was in place.

**RESULTS**

**Pharmacokinetics of naloxone**

The pharmacokinetics of two i.n. naloxone formulations were compared with those of i.m. and i.v. naloxone. All subjects completed all four study days (Figure 1a). All administration routes were generally well-tolerated; five subjects reported a bitter taste and pharyngeal discomfort (tingling or burning sensation) after i.n. administration of at least one of the formulations that resolved within 20–30 min.

The percent of AUC<sub>inf</sub> extrapolated from the last measured time point to infinite time was <25% for all subjects and all administration routes (Table 1). The geometric mean t<sub>1/2</sub> of i.m. and i.n. naloxone was consistent with that of i.v. naloxone (Figure 2, Table 1). Geometric mean C<sub>max</sub> for i.n., 200 naloxone (5 mg/mL, 200 μL/nostril) was comparable to that for i.m. naloxone, whereas that for i.n., 100 naloxone (10 mg/mL, 100 μL/nostril) was nearly double that for i.m. naloxone. Median T<sub>max</sub> of i.m. naloxone was roughly twice that of i.n., 100 naloxone, which was roughly twice that
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Figure 3 (a–c) Mean pupil miosis-time profiles after administration of oral alfentanil (4 mg) to six healthy volunteers pretreated with water (open symbols) or grapefruit juice (closed symbols). Naloxone (2 mg) was administered i.m. (b) or i.n. (10 mg/mL, 100/nostril) (c) 1 h after alfentanil. Error bars denote SEs.

of i.n.200 naloxone. The average mean absorption time of i.n.100 and i.n.200 naloxone was ~10 and 2 times shorter, respectively, than that of i.m. naloxone. The geometric mean absolute bioavailability of i.n.100 and i.n.200 naloxone was 25% and 59% lower, respectively, than that of i.m. naloxone (Table 1). The geometric mean relative bioavailability of i.n.100 naloxone was 70% higher than that of i.n.200 naloxone (Table 1).

Opioid attenuating effects of intramuscular and intranasal naloxone
Based on results from the pharmacokinetic study, i.n.100 naloxone was selected for comparison to i.m. naloxone in attenuating the pupil miotic effects of the test opioid, oral alfentanil, in the absence and presence of grapefruit juice. All subjects completed all six study days (Figure 1b). Naloxone, alfentanil, and grapefruit juice were generally well-tolerated; two subjects reported nausea (attributed to alfentanil and/or grapefruit juice) on all study days that resolved within 5–20 min. One of these subjects and a different subject reported pharyngeal discomfort with i.n.100 naloxone that resolved within 30 min.

Relative to baseline (prior to alfentanil administration; Figure 1c), alfentanil produced miosis in all subjects during all study days (Figure 3). When subjects were pretreated with water (days 1–3; Figure 1b), relative to control (absence of naloxone; day 1), i.m. naloxone attenuated mean alfentanil AUEC0–6h by a modestly higher extent than i.n.100 naloxone (43% vs. 30%); mean alfentanil Rmax was insensitive (Figure 4, Table 2). When subjects were pretreated with grapefruit juice (days 4–6), relative to control (day 4), i.m. naloxone attenuated mean alfentanil AUEC0–6h by a modestly higher extent than i.n.100 naloxone (58% vs. 49%); i.m. and i.n.100 naloxone attenuated mean alfentanil Rmax by similar extents (~30%; Figure 4, Table 2). Lack of a significant difference between i.m. and i.n.100 naloxone attenuation of alfentanil miosis (Table 2) should not be interpreted to infer therapeutic equivalence, as this study was not powered nor designed to support formal bioequivalence testing. Likewise, significant differences should be interpreted with caution.

DISCUSSION
Opioids are a mainstay in pain management and are common drugs of choice encountered in addiction recovery programs. Although effective, these drugs are associated with overdose, both intentional and accidental.1–4 Deaths due to opioid overdose result from illicit or licit use, either when taken alone or with concomitant medications or other xenobiotics. Parenteral naloxone is the definitive treatment for opioid overdose, but in most cases, first responders typically are lay bystanders not trained to administer naloxone parenterally. Consequently, easy-to-use naloxone products are urgently needed. Evzio and Narcan Nasal Spray are US Food and
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As anticipated, oral alfentanil elicited a pupillary response that was augmented by the readily available pharmacokinetic enhancer grapefruit juice (by 40%), which is consistent with a previous report. Whether or not grapefruit juice was administered prior to alfentanil, i.m. and i.n.100 naloxone attenuated miosis by similar extents, suggesting comparable systemic exposure to naloxone between the two routes. However, the time to maximum response tended to be achieved more rapidly in the absence of grapefruit juice. Inclusion of a grapefruit juice pretreatment arm increased the dynamic range of effect, indicating that this approach may be useful to assess the effects of additional inhibitory precipitant xenobiotics, including drugs and other natural products that may be used clinically or illicitly to enhance opioid pharmacokinetics and effects. The combination of oral alfentanil, pupillometry, and i.n.100 naloxone may also be adapted to address the need for an efficient, cost-effective method to assess opioid effect and reversal in healthy volunteers and patient populations during clinical development of new opioid analgesics and reversal agents.

Despite encouraging results from the current work, limitations are recognized yet addressable upon further study. First, given the preliminary nature of the studies, the small sample sizes precluded formal statistical comparisons between the various treatments. However, data obtained from these studies provide fundamental information for future powered studies. For example, using alfentanil AUEC0–6h as the primary end point, a power calculation indicated a cohort of 16 subjects would be needed to detect a 25% difference with 80% power and a type I error of 0.05. Second, although pupillometry is a noninvasive technique, intense sampling was not feasible with more than one subject present on a given study day due to the availability of one pupillometer. Third, intensive sampling immediately following naloxone administration and analysis of partial AUCs (e.g., AUC0–tmax) may provide additional information for comparison of formulations intended for rapid delivery. Increased resources would enable intense and simultaneous plasma and pupil diameter collection following naloxone administration, permitting a comprehensive characterization of naloxone pharmacokinetics in the early absorption phase and assessment of the reversal rate of alfentanil-induced miosis. Finally, as alfentanil is short-acting, rigorous characterization of the duration of opioid reversing effects of naloxone was not possible. As such, testing the reversing effects against long-acting opioids (e.g., methadone or extended-release opioid formulations) is of interest, warranting further clinical evaluation. With modifications, including increased subject enrollment, staffing, and instrumentation, this approach is well-suited for the "learn and confirm" paradigm used during early clinical development of new drug candidates and novel formulations.

In summary, new easy-to-use naloxone formulations and products are under development, yet the need for a cost-effective, noninvasive, and highly bioavailable formulation remains. The current preliminary pharmacokinetic study demonstrated that the absolute bioavailability of i.n.100 naloxone was comparable to i.m. naloxone, with i.n.100 naloxone showing more rapid absorption. These results prompted a second preliminary study to compare the opioid-attenuating

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**Table 2** Effects of i.m. and i.n.100 naloxone (2 mg) on pupil miosis after oral administration of alfentanil (4 mg) to six healthy volunteers pretreated with 240 mL water or grapefruit juice

| Pretreatment           | Absence of naloxone (control) | Presence of naloxone, i.m. | Presence of naloxone, i.n.100 |
|------------------------|-------------------------------|---------------------------|-------------------------------|
|                        | AUEC0–6h, h*%                 | Rmax, %                   | AUEC0–6h, h*%                 | Rmax, %                   |
| Water                  | 70.0 ± 16.8                   | 27.0 ± 10.5               | 40.0 ± 15b                    | 25.3 ± 12.7               |
| Grapefruit juice       | 96.8 ± 50.0\(^a\)             | 36.5 ± 10.9\(^a\)         | 40.6 ± 21\(^b\)              | 26.8 ± 12.0\(^b\)         |

AUEC0–6h: area under the effect (miosis) vs. time curve from 0 to 6 h; i.n.100, 10 mg/mL, 100 μL/nostril; \(R_{\text{max}}\), maximum pupillary response from baseline. Values denote means ± SEs.

\(^{a}\) P < 0.05 compared with water.

\(^{b}\) P < 0.05 compared with the absence of naloxone. Statistical comparisons of the data are for descriptive purposes only, as the studies were hypothesis-generating in nature; thus, no formal a priori statistical analysis plan was in place.

Drug Administration approved for in-field use by nonmedically trained personnel, but the relatively high costs of these products may limit widespread use. The more cost-effective parenteral naloxone formulation has been administered i.n. in the field with mixed success\(^{5,6,18-23}\) due in part to a low absolute bioavailability (~4%).\(^{10}\) Collectively, these observations prompted evaluation of the pharmacokinetics and opioid attenuating effects of a new i.n. naloxone formulation.

Selection of a test i.n. naloxone formulation was based on the pharmacokinetic study in which i.v., i.m., and i.n. naloxone were administered to six healthy subjects. The pharmacokinetics of i.v. naloxone were consistent with the literature.\(^{10}\) The absolute bioavailability of i.m. naloxone was higher (54% vs. 35%), whereas \(t_{\text{max}}\) and terminal \(t_{1/2}\) were similar to previously reported values.\(^{10}\) Absolute bioavailability of i.n.100 naloxone was substantially greater than previously published i.n. formulations (40% vs. ~4%\(^{6,10}\)). The improved bioavailability was attributed to differing combinations and concentrations of surfactants, which are believed to enhance i.n. drug permeation via interruption of the nasal epithelium\(^{24-27}\); use of surfactant combinations to enhance nasal delivery of poorly bioavailable drugs has been evaluated extensively.\(^{27}\) A detailed physicochemical evaluation of the new formulation, including formulation stability and physiological surfactant effects, would be required for further development. The absolute bioavailability of i.n.200 naloxone was superior to previous i.n. formulations but was approximatively half that of i.n.100 naloxone, which likely reflected a larger fraction of the dose lost via pharyngeal drainage due to a larger administration volume. The \(t_{1/2}\) of i.n.100 was shorter than that of i.m. naloxone (61 vs. 100 min) and shorter than that reported for the recently approved Narcan Nasal Spray (126 min). However, the relative bioavailability of i.n.100 naloxone compared with i.m. was higher than the reported dose normalized relative bioavailability for Narcan Nasal Spray (75% vs. ~45%\(^{9}\)). Based on these results, i.n.100 was selected for testing in the clinical effect study.
effects of i.n.100 to i.m. naloxone using oral alfentanil as the model opioid. Whether or not the pharmacokinetic enhancer, grapefruit juice, was administered prior to alfentanil, the i.n.100 formulation appeared to be nearly as effective as i.m. naloxone in attenuating alfentanil-induced pupil miosis. Taken together, these two small clinical studies suggest i.n.100 naloxone as a viable candidate formulation that warrants further preclinical (e.g., stability) and clinical testing as a potential rescue therapy for opioid overdose, an ever-growing public health concern.

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