Pharmacokinetics of a novel, approved, 1.4 mg intranasal naloxone formulation for reversal of opioid overdose- a randomised controlled trial.

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Declarations of Interest

The formulation described has been approved by 12 European countries from 16th June 2018 under the name of Ventizolve (Respinal in Sweden), produced by Sanivo Pharma AS. Sponsor of this trial was AS Den Norske Eterfabrikk.

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Ola Dale (OD) was engaged by AS Den Norske Eterfabrikk as Principle Investigator in this study for which OD receives no personal honorarium. OD´s employer Norwegian University of Science and Technology (NTNU) and its subsidiary Technical Transfer Office have signed cooperation and licensing contracts with dne pharma as to seek commercialisation of this nasal naloxone formulation. This regulates potential royalties for OD through NTNU. dne pharma as has compensated OD for business travels from Trondheim to Oslo.
Arne Kristian Skulberg (AKS) has signed a non- compete contract with AS Den Norske Eterfabrikk lasting the duration of his PhD program at NTNU (estimated 2018). This does not limit AKS right to publish results. AKS has received no honorarium from AS Den Norske Eterfabrikk or dne pharma as and will receive no financial benefit from the licence agreement between dne pharma as and NTNU.
Anders Åsberg (AÅ) has received consultant honorarium from dne pharma as in relation to the naloxone formulation presented.
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Abstract

Background and aims

Intranasal (IN) naloxone is an established treatment for opioid overdose. Anyone likely to witness an overdose should have access to the antidote. We aimed to determine whether an IN formulation delivering 1.4 mg naloxone hydrochloride would achieve systemic exposure comparable to that of 0.8 mg intramuscular naloxone.

Design

Open, randomised four-way crossover trial

Setting

Clinical Trials Units in St. Olav´s Hospital, Trondheim, and Rikshospitalet, Oslo, Norway

Participants

22 healthy human volunteers, ten women. Median age 25.8 years.

Intervention and comparator

One and two doses of IN 1.4 mg naloxone compared with intramuscular (IM) 0.8 mg and intravenous (IV) 0.4 mg naloxone

Measurements

Quantification of plasma naloxone was performed by liquid chromatography tandem mass spectrometry. Pharmacokinetic non-compartment analyses were used for the main analyses. A non-parametric pharmacokinetic population model was developed for Monte Carlo simulations of different dosing scenarios.

Findings

AUC0-last for IN 1.4 mg and IM 0.8 mg were 2.62 ±0.94 and 3.09 ±0.64 h*ng/mL, respectively (p=0.33). Cmax was 2.36 ±0.68 ng/mL for IN 1.4 mg, and 3.73 ±3.34 for IM 0.8 mg (p=0.72). Two IN doses showed dose linearity and achieved a Cmax of 4.18 ±1.53 ng/mL. Tmax was reached after 20.2 ±9.4 min for IN 1.4 mg and 13.6 ±15.4 min for IM (p=0.098). The absolute bioavailability for IN 1.4 mg was 0.49 (±0.24), while the relative IN/IM bioavailability was 0.52 (±0.25).

Conclusion

Intranasal 1.4 mg naloxone provides adequate systemic concentrations to treat opioid overdose, compared with intramuscular 0.8 mg, without statistical difference on maximum plasma concentration, time to maximum plasma concentration or area under the curve.

Simulations support its appropriateness both as peer administered antidote and for titration of treatment by professionals.

Key words

Administration, intranasal; Administration, Intravenous; Administration, intramuscular; Drug Overdose, Substance-Related Disorders, Naloxone, Narcotic Antagonists, Antidotes

Introduction

The increasing number of deaths from opioid overdoses is extensively documented (1-3). Opioid overdoses are reversed by naloxone. The maximum recommended initial dose of naloxone is 2.0 mg, but starting doses of 0.4 - 0.8 mg intramuscularly are favoured. The WHO guideline of 2014 warns that start doses exceeding 0.8 mg may increase the risk of triggering acute opioid withdrawal (2). Acute opioid withdrawal is rarely fatal, but is harmful to the patients. Withdrawal may hinder the further medical and social follow up required by these patients. Restoring ventilation and oxygenation, as well as careful titration of naloxone without overshooting the mark, are the goals of naloxone reversal (4, 5). The lowest safe naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation (6).

Originally initiated by activist organisations, the distribution of naloxone to lay people has now become an important public health care strategy (7). Intranasal naloxone has been preferred due to its simple administration and reduced risk of exposure to blood. After years of using various off-label, improvised, naloxone formulations without marketing authorisation, several intranasal (IN) naloxone formulations are now licenced in Europe and the US. They are all low volume/high concentration, and are characterised by absorption rates that deliver systemic exposure within the recommended range in one actuation.

In this setting—treatment of a life-threatening condition where titration is the cornerstone—pharmacokinetic (PK) knowledge of the formulation used is important to optimise dosing. The previous use of various dilute naloxone formulations given IN in improvised devices has

been criticised (8, 9). Dilute Take Home Naloxone (THN) formulations typically have low bioavailability, ranging from 0.10 to 0.15 (10, 11). The corresponding dose absorbed of a 2.0 mg dose would then be 0.2-0.3 mg; 50-75 % of the lowest recommended starting dose (12). The off-label use of IN naloxone was the only alternative, until FDA approved the Narcan 40 mg/mL nasal spray in 2015, with later additions to the market, both in the US and Europe.

Other approved IN sprays (Narcan Nasal® and Nyxoid®) both deliver systemic exposure of naloxone higher than 0.8 mg IM. There are two reasons for the development of high-dose IN sprays. In order to receive regulatory approval, the FDA has required that administration forms alternative to 0.4 mg IM must demonstrate similar or higher blood concentrations, especially in the initial absorption phase (13). There is also concern that the naloxone doses that worked in past may be insufficient, as the opioid epidemiology changes, with the introduction of potent synthetic opioids such as fentanyl (14, 15). A meeting in the FDA in 2016 narrowly voted to increase the minimum acceptable naloxone exposure from 0.4 mg (16). The 0.8 mg naloxone comparator is the higher spectrum of the WHO recommendation, and provides increased safety for successful reversal without sparking off avoidable acute withdrawal.

The present study was conducted to demonstrate that a novel formulation delivering 1.4 mg naloxone hydrochloride would achieve systemic exposure comparable to that of 0.8 mg IM. The IN dose was chosen on the basis of previous studies with the same formulation (17-19). The formulation contains the stabiliser EDTA, the mucoadhesive substance povidone and the humectant glycerol. The licensed product will be delivered with two sprays per pack for dose titration.

Material and methods

This study was a two-centre randomised, open label, four-way crossover trial in healthy human volunteers, with 72 hours wash-out.

It was approved by the Regional Committee of Medical and Health Research Ethics (2015/1285) and by the Norwegian Medicines Agency (EudraCT number: 2015-002355-10). All procedures were in accordance with the ethical standards of the Helsinki declaration and

the ICH Good Clinical Practice guidelines. The study was registered in clinicaltrials.gov (NCT02598856). Participants were insured trough the Drug Liability Association, Norway, and compensated for each treatment visit with 1000 NOK (110 Euro/120 USD). The trial was conducted at Clinical Trials Units at St. Olavs Hospital, Trondheim, and at Rikshospitalet, Oslo, Norway between October 28th, 2015 and September 30th, 2016. Smerud Medical Research Group operated as clinical Contract Research Organisation.

The primary pharmacokinetic outcome variables were: Area under the plasma concentration versus time curve (AUC) from administration to last measured concentration ($AUC_{0\text{-}last}$), AUC from administration to infinity ($AUC_{0\text{-}inf}$), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}), compared for single dose IN, IM and IV naloxone. Secondary outcome variables were dose proportionality, by comparing systemic exposure following one and two doses of 1.4 mg of IN naloxone, and absolute and relative bioavailability.

Eligibility criteria for participants.

Healthy men and women aged 18-45 years with haemoglobin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transferase within reference values and a normal electrocardiogram (ECG) were eligible for inclusion. Regular use of medications, including herbal, were not allowed. Female participants required a negative pregnancy test, the use of high efficacy contraception from inclusion, and could not be breastfeeding during the study period. Participants with a history of previous nasal surgery, a history of drug allergies or drug addiction were excluded. A full list of inclusion and exclusion criteria is presented in the supplementary material.

Interventions:

There were six study visits, first a screening visit for consent and eligibility criteria, and last for safety follow up. The four visits in between involved the administration of study medicine. All participants were set to receive all treatments. Treatment A: Single dose IN naloxone 1.4 mg: Administered as 0.1 mL 14.0 mg/mL (1.4 mg naloxone HCl) by Aptar Unit dose device as one puff in one nostril. Treatment B: Double dose IN naloxone 1.4 mg: Administered as 2 x 0.1 mL 14.0 mg/mL (2.8 mg naloxone HCl) by Aptar Unit dose device as two puffs in the same nostril, three minutes apart. Treatment C: IM naloxone 0.8 mg: Administered as 2.0 mL Naloxon B.

Braun 0.4 mg naloxone HCl/mL in the deltoid muscle. Treatment D: IV naloxone 0.4 mg administered as 1.0 mL Naloxon B. Braun 0.4 mg naloxone HCl/mL. Adverse events were monitored at all visits. All participants underwent anterior rhinoscopy at the screening and the follow up visit.

Randomisation:

This was performed by a computerised procedure from the clinical research organization Smerud, using block randomisation without stratification. Subjects were randomised to treatment order of the four naloxone administrations.

Study procedures:

Participants were reclined fully as they received naloxone. They were monitored with oxygen saturation, ECG and non-invasive blood pressure. Participants who had taken any concomitant medication during the study period had their treatment visit rescheduled to a time where at least five half-lives of the medication had passed, or minimum 7 days, if no half-life was known.

Blood samples were drawn within 10 minutes prior to administration of naloxone, and then at 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120, 240 and 360 minutes after administration of study drug from an IV cannula placed in the antecubital fossa. Six mL blood were collected in glass tubes with K_2EDTA anticoagulant, gently mixed and centrifuged for 20 minutes at 1300 g, and 0.5 mL plasma was decanted into cryotubes and immediately frozen at -20 ºC, and stored at -80 ºC before the end of the day and until analysis.

Naloxone Analysis:

1320 (88 sessions) plasma samples were to be analysed for naloxone using liquid chromatography tandem mass spectrometry. Only subjects contributing with datasets from all visits were included in the statistical analyses. Twenty-one plasma concentrations were missing, and these were not replaced. Of the 1,299 measured plasma concentrations of naloxone, 161 were below the limit of quantification and one was above upper limit of the calibration curve. The latter was set at 47.6 ng/mL and included in analysis. Results below LOQ were not included in the analyses. Two concentrations measured before dose

administration showed values above LOQ, and these two were set to zero in the analyses. In total, 182 (7.3%) were either below LOQ or missing, thus a total of 1,138 plasma naloxone concentration measurements were used in the analyses.

The bioanalyses were performed by Vitas AS, Oslo, Norway. The analytical method used was validated in accordance with the European Medicines Agency guideline for bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). 200 µL plasma was precipitated using methanol containing a stable isotope labelled internal standard (naloxone d5). Precipitated samples were filtered using Impact protein precipitation plates (Phenomenex, Torrance CA, USA). Analysis was performed using an Agilent 1260 LC system coupled to an Agilent 6460 QQQ detector (Agilent Technologies, Palo Alto CA, USA). Separation was performed on a Phenomenex Kinetex EVO C18 (100mm x 3,0 mm x 2,6 µm) column. Quality control samples analysed in duplicate at four levels of analyte were included in each analytical run. QC samples were prepared from pools of human plasma and spiked with naloxone at levels 0.05, 0.26, 15.32 and 38.5 ng/mL. Limit of quantification (LOQ) was <0.02 ng/mL for 26 samples, <0.05 ng/mL for 41 samples and <0.1 ng/mL for 94 samples.

Drug Supply:

Nalokson DnE 14 mg/mL nasal spray was manufactured by AS Den norske Eterfabrikk, Oslo, Norway. Naloxon B. Braun 0.4 mg/mL (B. Braun Melsungen AG, Melsungen, Germany) was supplied from the Hospital Pharmacy in Trondheim, Norway.

Statistics and sample size

The significance level was set to 5%, and the sample size was scaled to not accept bioequivalence of an inferior or superior drug. The data used to assess the anticipated variation in the naloxone data were from previous studies of the same IN formulation. Based on this, it would be necessary to include 22 participants. See Supplementary Material for details. All planned analyses of the efficacy and safety variables were described in the Clinical Trial Analysis Plan. Analysis of variance were preformed using SAS software, version 9.4 (SAS Institute Inc., Cary, USA).

Pharmacokinetic calculations and simulations

Non-compartmental analysis (NCA) was applied assuming a salt factor of 1.0. Time zero concentration for IN and IM administered naloxone was set to zero, and for intravenous naloxone first measured concentration was used also as concentration at time zero. The elimination rate constant (k_{el}) was assessed from at least three concentrations in the semi logarithmic linear elimination phase. $AUC_{0\text{-}last}$ was assessed by the trapezoidal rule. $AUC_{0\text{-}inf}$ was calculated according to the following formula: $AUC_{0\text{-}last} + C_{last}/k_{el}$. Terminal half-life was calculated as $LN(2)/k_{el}$ and bioavailability (F) as $(AUC_{test,0\text{-}inf}/AUC_{reference,0\text{-}inf})*(DOSE_{reference}/DOSE_{test})$, where test was either IN or IM and reference either IV or IM administered naloxone. Clearance (CL) was calculated as $DOSE*F/AUC_{0\text{-}inf}$.

A non-parametric pharmacokinetic population model was developed for intranasal administration, and one for intramuscular administration, using Pmetrics (version 1.5.0, Laboratory for Applied Pharmacokinetics, Los Angeles, CA) (20). Details on model development, validation and simulation are presented in Supplementary Material.
The population model was used to evaluate different dosing scenarios presented in figures 3 and 4.

Results

Patients: 44 subjects were screened and gave informed consent to participate. 20 were not included, while 24 were randomised, two were withdrawn from the study after randomisation, one because of an adverse event, and one started with medication, leading to exclusion. Twenty-two participants (12 men and 10 women) were included in the final analysis, all providing evaluable data from all four visits. The two participants that received study drug and later withdrawn, were included in the safety analysis. Median age was 25.8 years (min 20.7, max 30.7) and a body mass index of median 22.5 kg/m^2 (min 20.7, max 26.0).

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The mean time-course of the plasma concentrations (0-360 min) for the IN, IM and IV administrations is seen in fig 1. As expected, the distribution and elimination phases are similar in all administrations, with both IN and IM staying above IV after 20 minutes. The real-data absorption phase is magnified in figure 2.1. The absorption rate of IM 0.8 is higher compared to IN, but plasma concentrations following IN 1.4 mg and 2.8 mg administration surpass IM after 15 and 10 minutes, respectively. Figure 2.2 shows the simulated absorption phase, comparing IN 1.4 mg to both IM 0.4 mg and 0.8 mg. Concentrations after IN 1.4 mg exceeds concentrations after IM 0.4 mg after 7.5 minutes, and remains above.

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C_{max} (table 1) was significantly different between the three administration routes (P=0.031, ANOVA), however IM 0.8 mg and IN 1.4 mg did not differ significantly (P=0.72, TukeyHSD). There was no interaction of treatment sequence on C_{max} (P=0.90, ANOVA).

$AUC_{0\text{-}last}$ (table 1) was significantly different between the three routes (P=0.0025, ANOVA). Significant differences between both IV 0.4 mg and IM 0.8 mg (P=0.008, TukeyHSD) and IN 1.4 mg (P=0.050, TukeyHSD) were seen, but not between IN 1.4 mg and IM 0.8 mg (P=0.33, TukeyHSD). Treatment sequence did not show any significant interaction with the effect (P=0.80, ANOVA). Data analysed as $AUC_{0\text{-}inf}$ showed similar differences as the $AUC_{0\text{-}last}$ data, but in these data IV 0.4 mg and IN 1.4 mg only tended to be significantly different (P=0.059, TukeyHSD). The applied sampling strategy assured coverage of 92% ±6%, 96% ±2%, 90% ±8%, 87% ±11% of the systemic exposure of $AUC_{0\text{-}last}$, compared to $AUC_{0\text{-}inf}$ for IN 1.4 mg, 2xIN 1.4 mg, IM 0.8 mg and IV 0.4 mg, respectively.

T_{max} (table 1) was not significantly different between IM 0.8 mg and IN 1.4 mg (p=0.098, t-test). Mean time to 50% of C_{max} was 10.1 min for IN 1.4 mg naloxone and 6.5 for IM 0.8 mg (p=0.061, t-test). On average, naloxone concentrations following both IN 1.4 mg and IM 0.8 mg were above 0.5 ng/mL at the first sample at 2 minutes (Figure 2).

Mean terminal elimination half-lives (table 1) of naloxone ranged from 73-85 min, and were not significantly different between the different administration forms (P=0.11, ANOVA). In the elimination phase 0.5 ng/mL has been suggested as a minimum effective concentration of naloxone (21). Figure 1 shows how IN 1.4 mg maintained its concentration above this for 88 minutes and IN 2.8 mg 118 minutes, IM 0.8 mg 118 minutes and IV 0.4 mg 45 minutes.

The absolute bioavailability for IN 1.4 mg in this study was 0.49 ±0.24, while the relative bioavailability to IM 0.8 mg was 0.52 ±0.25.

----------Please insert figure 3 here----------

Dose proportionality assessed by systemic exposure ($AUC_{0\text{-}last}$) between IN 1.4 mg and 2 x IN 1.4 mg naloxone was on average 1.09 ±0.53, and for C_{max} 1.27 ±0.57.

Results from PK simulations

A two-compartment model with five transit compartments in the absorption phase described the data well. The model was parameterised using differential equations with rate constants and volume of distribution in the central compartment, scaled for centralised (median) body weight. No covariates were retained in the final models. The intranasal and intramuscular models had 42 and 41 support points, respectively. A more detailed presentation of model development and validation is presented in supplemental material.

Simulations:

Simulation of the absorption phase in a “standard” person weighing 70 kg from respective population pharmacokinetic model, i.e. the IN- and IM-model separately, is presented in figure 2.2. IM administration is simulated as 0.8 mg and 0.4 mg. The major observation is that the lag in achieved plasma concentrations during the absorption phase between IN 1.4 mg and IM 0.4 mg is, as expected, far smaller than when compared with IM 0.8 mg.

The model is used to visualise clinical scenarios where 1.4 mg IN naloxone is administered prior to, or in addition to, injected naloxone.

----------Please insert figure 4 here----------

Panel 4.1 shows IN 1.4 mg naloxone administered 10 minutes prior to injected IM naloxone, a common scenario in THN. Plasma concentrations following IN 1.4 mg remain above the concentrations obtained by IM 0.4 mg, during the whole period. They do not reach the levels obtained by IM 0.8 mg within this 20-minutes period. Panel 4.2 simulates the shortest time IN 1.4 mg could be administered prior to IM 0.4 mg, and constantly provides higher plasma concentrations. That time is 2.25 minutes. Panel 4.3 simulates the opposite; the injection of IM 0.4 mg naloxone, 10 minutes after IN 1.4 mg is given. The C_{max} in this scenario is 3.15 ng/mL, lower C_{max} than what we find for IM 0.8 mg in our real data.

Safety and adverse events: At anterior rhinoscopy at the follow-up visit, one had abnormal colour and swelling of mucosa, one had abnormal amount and colour of secretion and one had presence of concha inferior swelling, not present prior to the study. One participant had a clinically significant increased value of ALT after treatment with IN 1.4 mg, and was withdrawn. This increase of the ALT value was deemed possibly related to the study drug. A total 31 adverse events were reported for 14 participants in the study. All adverse events reported were of mild severity, except for one abnormal haemoglobin, which was reported as moderate, but unrelated to treatment. The adverse events reported most by participants were headache and nasal congestion. For questions related to irritation in the nose, no events were reported for rhinorrhoea, itching and loss of smell sensation. Intranasal administration of 1.4 mg naloxone was found to be safe and well tolerated by healthy volunteers.

Discussion

The major finding in this study was that the absorption of 0.8 mg naloxone administered IM was slightly faster than for the IN 1.4 mg. There were no statistically significant differences between IN 1.4 mg and IM 0.8 mg in $C_{max,}$ $T_{max,}$ or $AUC_{0\text{-}last}$. IN naloxone showed dose linear increase in systemic exposure for two doses to the same nostril separated by three minutes, indicating that it is suited for repeated administration and titration. Simulations showed that IN 1.4 mg naloxone compares well with 0.4 mg IM naloxone, providing higher concentrations within 7.5 minutes. The present IN formulation was safe in healthy volunteers, and has

received regulatory approval in 12 European countries under the trade name Ventizolve® (Respinal® in Sweden).

This study builds on two previously published studies of a similar naloxone formulation (17, 18). The formulation shows similar dose corrected C_{max} across these studies. The absolute bioavailability was also similar, but the relative bioavailability compared to IM was lower compared to when naloxone was given together with remifentanil (18).

Several new naloxone formulations have come to the market in recent years. Nyxoid 1.8 mg IN naloxone by Mundipharma (Cambridge, UK) (22) and Narcan Nasal 2.0 mg and 4.0 mg IN naloxone (Adapt Pharma, Inc. Radnor, PA, USA) (23) are now available. These formulations and the present 1.4 mg have several pharmacokinetic characteristics in common. They can all deliver a therapeutic dose (corresponding to 0.4-2.0 mg IM) by one actuation of a 0.1 mL volume by the Aptar Unit dose device. They all have a relative bioavailability of about 50%, similar average T_{max} of 21 minutes (min 15, max 30), and similar dose corrected C_{max} (1.52 ± 0.16 ng/mL, n=9). Although the absolute C_{max} of IN 1.4 mg was 82 % and 76% of Nyxoid and Narcan, respectively, IN 1.4 mg C_{max} was 186 % compared to that of 0.4 mg IM (22). $AUC_{0\text{-}inf}$ for IN 1.4 mg was 85% of that of IM 0.8 mg, but again this exceeds by far the published AUC values of 0.4 mg IM (157% and 134% of (Narcan Nasal and Nyxoid,) respectively.

Questions have been raised about different uptake and interactions with opioids or other drugs used by patients in overdose. In a previous study of this IN naloxone formulation administered with the opioid remifentanil, the relative bioavailability to IM was 75% (18). This led to the conclusion that there may be an interaction between naloxone and remifentanil. Further studies in this direction can bridge the gap between healthy volunteers and patients presenting with opioid overdose.

The current formulation was compared with IM 0.8 mg naloxone as reference, as it represents the safe upper end of the start-dose recommendations, without undue risk of triggering withdrawal. As other regulatory studies relate to 0.4 mg IM, a population kinetic simulation was developed to examine the relations between 1.4 mg IN and 0.4 mg IM. Modelling is also used to compare different treatments in a Take Home Naloxone scenario,

where peer administered naloxone may substitute or be combined with injected naloxone by ambulance personnel. Titration is the core principle in naloxone reversal of overdose, and these simulations can guide clinical use. Part of the rationale of THN is to shorten the time from an opioid overdose is suspected to the administration of antidote. Calling for help, dispatch and transport times for ambulance personnel, securing the workplace, establishing airway and breathing control, and preparing and injecting naloxone takes considerable time. As shown in Figure 4.1; when naloxone was given 10 minutes prior to naloxone injected, the THN administration of the present formulation delivered serum concentrations above IM 0.4 mg at all times, however, below IM 0.8 mg. Calculations showed that when IN 1.4 mg was given as close as 2.25 min before IM injection of 0.4 mg, it still provided higher blood concentrations (figure 4.2). This indicates a clinical benefit by this IN formulation, even by ambulance personnel, as 2.25 minutes is comparable to the time it takes to prepare an IM injection site, fill a syringe and inject naloxone, or to establish IV access (24). Figure 4.3 shows a simulation where ambulance personnel administer 0.4 mg IM naloxone 10 minutes after 1.4 mg is given as THN. This would be relevant if a patient remained unresponsive after one dose IN, and ambulance personnel suspected opioid intoxication to be a possible cause. The C_{max} in this scenario is almost identical to the arithmetic mean of Nyxoid 1.8 mg, and is reached 5 minutes after ambulance personnel administered IM naloxone. The early administration of antidote is the rationale behind THN, and the simulations show that IN 1.4 mg has a place in this treatment model and is well suited for titration.

The safe initial dose of naloxone is debated (13), and will remain a balancing act between safe reversal and the precipitation of acute withdrawal reactions (4). Dilute formulations have shown to provide relatively low rate of repeat naloxone dosing in the field (25-27). Previously approved nasal formulations deliver systemic exposure similar to 1.0 and 2.0 mg injected naloxone, which is above the upper initial dose recommended by the WHO (2). A high initial dose will increase the likelihood of provoking acute withdrawal; the symptoms are well described (28), and experiencing withdrawal is feared among opioid abusers (29). Withdrawal and inadequate follow up may lead to death (30). Withdrawal is a part of what leads to early discharge or being left at the scene against medical advice. Both must be seen as less than ideal follow-up after non-fatal overdoses. Being left at the scene of the overdose has been debated over the years and found to be relatively safe, as death immediately after

is rare (31, 32). This may change in the future with the arrival of more potent opioids, and vary between the location and other circumstances of the overdose (33). There is conflicting evidence regarding the fentanyl-like opioids and the need for potent naloxone formulations (34, 35), but basic first aid with ventilation and antidote titration will remain treatment gold standard.

Limitations

This is study is conducted in healthy volunteers, that may differ from patients being treated for opioid overdose. Our participants did not use concomitant medication, so interactions with other drugs, prescription or illegal, are not assessed. The conclusions in this study is based on plasma concentrations, not relevant clinical end-points.

Conclusion

IN 1.4 mg naloxone provides adequate systemic concentrations compared to IM 0.8 mg, without statistical difference on maximum plasma concentration, time to maximum plasma concentration or area under the curve. The naloxone exposure following administration by this formulation far exceeds more dilute “off-label” formulation often used in Take Home Naloxone programs. Compared to the higher doses in other nasal sprays, IN 1.4 mg can reduce the risk for withdrawal, while still safe, as it reaches relevant plasma concentrations fast. It exceeds IM 0.4 mg after 7.5 minutes. Simulations support that it has a place both as peer administered antidote and for titration of treatment by professionals. However, only randomised clinical trials on real opioid overdoses can determine whether IN naloxone can compare with IM naloxone.

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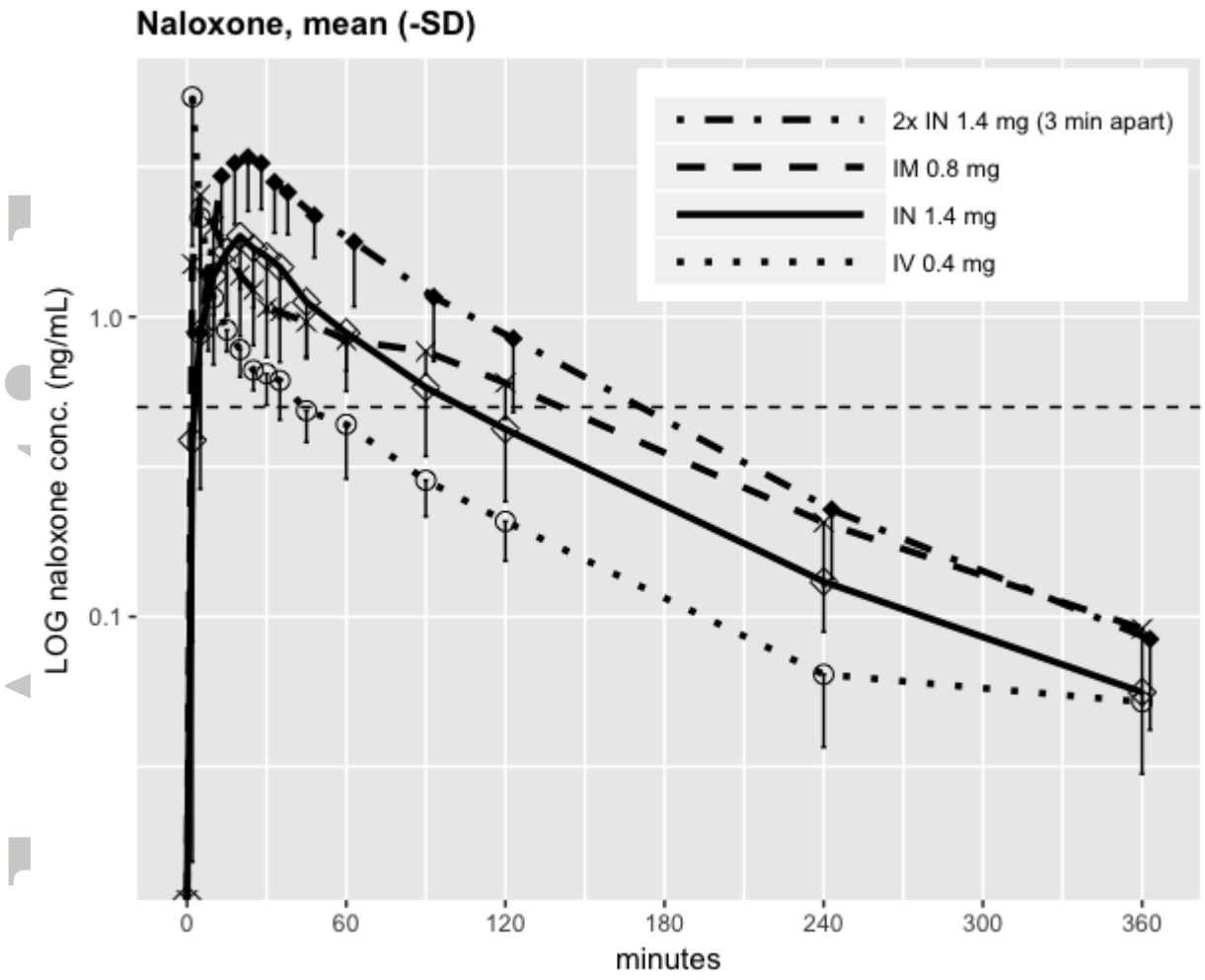

Figure 1: Time course of plasma concentrations 0-360 minutes (mean ±SD) of naloxone after intranasal (1.4 and 2.8 mg), intramuscular 0.8 mg and intravenous (0.4 mg) administration in healthy human volunteers (n=22). Dashed horizontal line indicates 0.5 ng/ml, a proposed minimum effective concentration in the elimination phase.

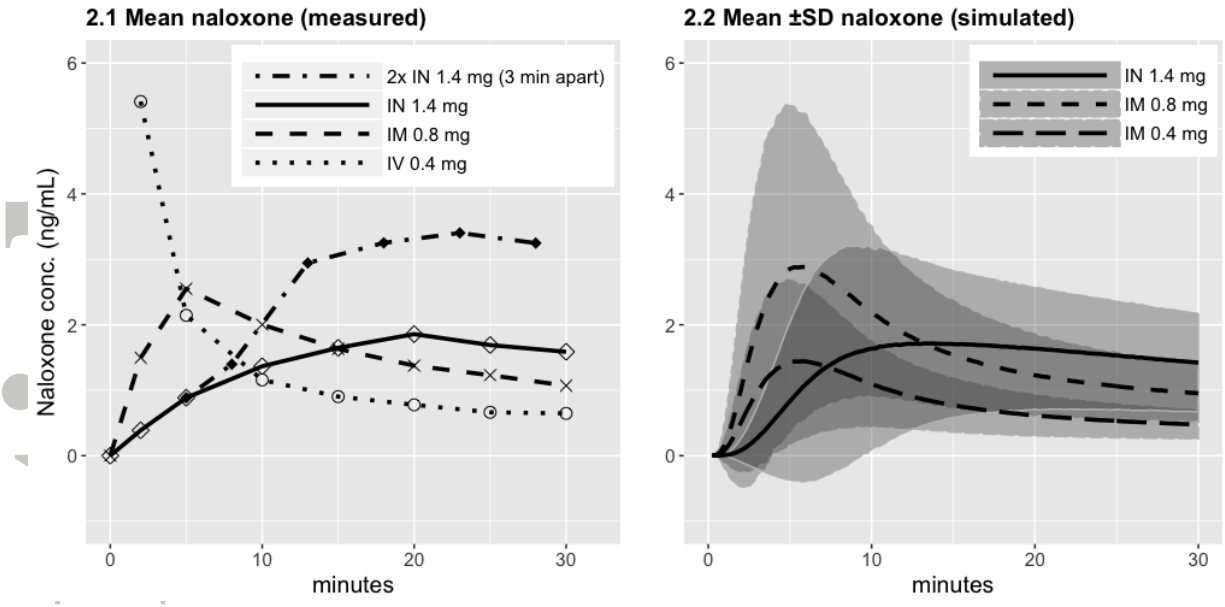

Figure 2: 2.1: Time-course of plasma concentrations 0-30 minutes (mean values, variability removed for clarity) of naloxone after intranasal (1.4 and 2.8 mg), intramuscular 0.8 mg and intravenous (0.4 mg) administration in healthy human volunteers (n=22).

2.2: Simulated time course of plasma concentrations 0-30 minutes (mean ±SD as shaded area) of naloxone after intranasal 1.4 mg and intramuscular 0.4 mg and 0.8 mg.

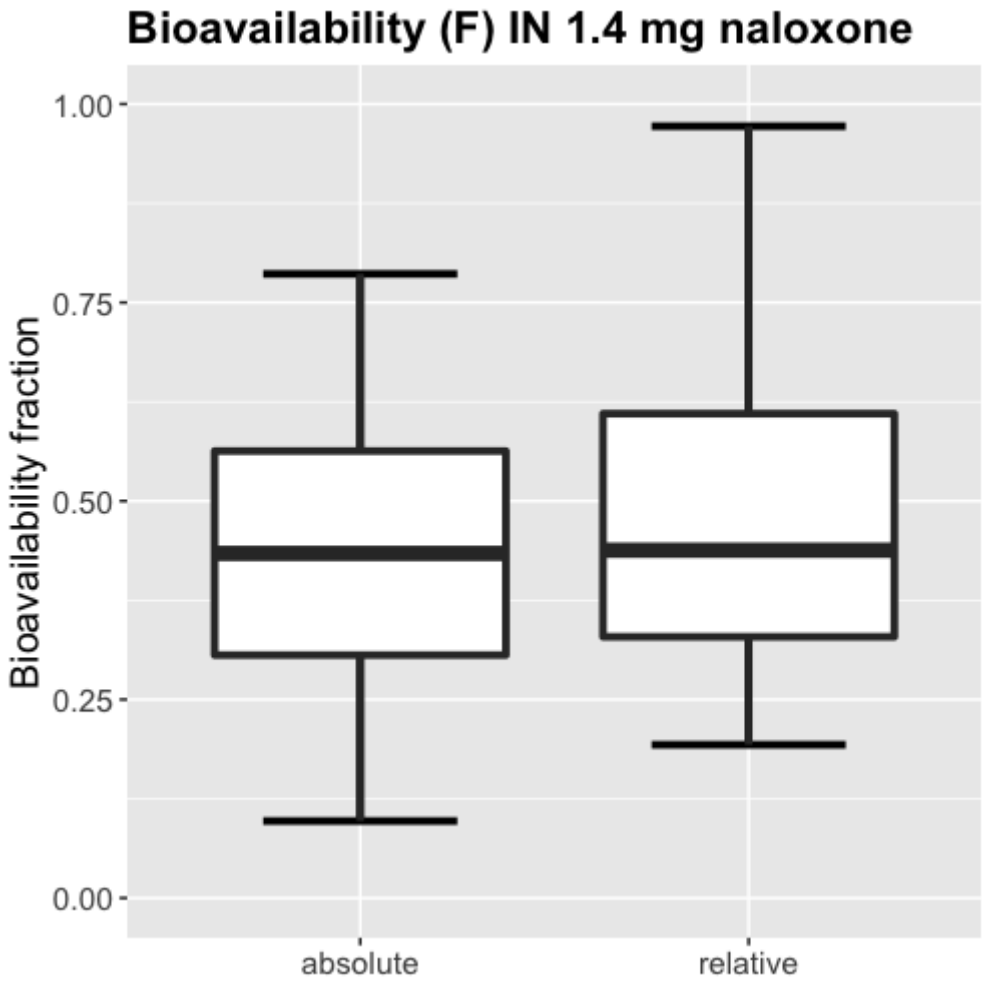

Figure 3: Box plot of absolute and relative bioavailability of IN 1.4 mg naloxone. Bold line is median, box is 75% percentiles, and whiskers are 95% percentiles.

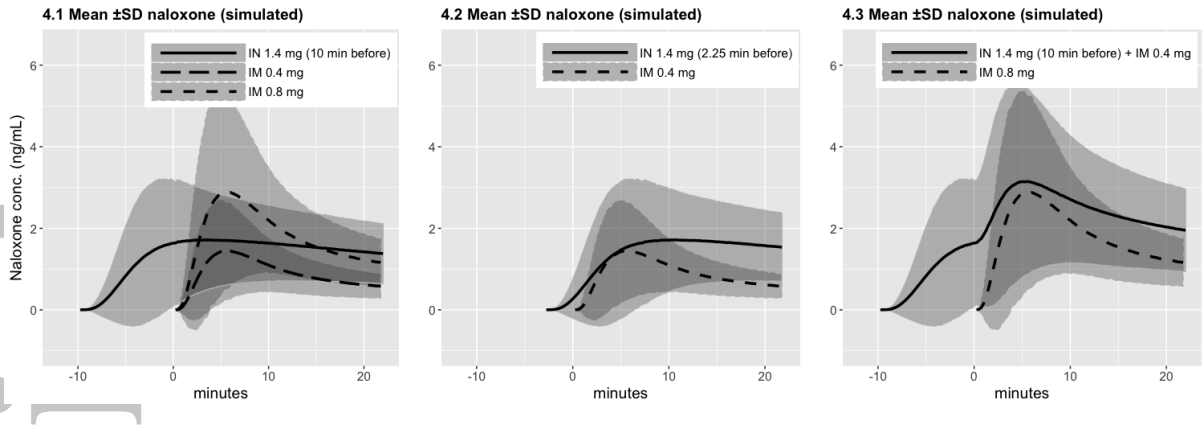

Figure 4: Simulated time courses of mean naloxone concentrations (line) and standard deviations as shaded area. 0 minutes indicate a time of administration of injected naloxone.

4.1 shows IN 1.4 mg naloxone administered 10 minutes prior to injected naloxone (0.4 and 0.8 mg).

4.2 shows the simulation of the shortest time (2.25 min) beneficial to give IN, rather than wait for naloxone to be injected.

4.3 simulates a situation where IM 0.4 mg naloxone is injected to a patient already given IN 1.4 mg 10 minutes before.

Table 1. Pharmacokinetic variables (mean values ±SD) n= 22 healthy volunteers after intranasal, intravenous and intramuscular administration of naloxone in an open, randomised four-way-way crossover trial.

Treatment	Cmax (ng/ml)	Tmax (min)	AUClast (h*ng/ml)	AUC0- inf (h*ng/ml)	Terminal half-life (min)	Cl (L/h)
1.4 mg IN	2.36 ±0.68[§]	20.2 ±9.4[§]	2.62 ±0.94[§]	2.84 ±0.94[§]	73.0 ±20.2[§]	239 ±68
2.8 mg IN	4.18 ±1.53	20.7 ±9.54	5.23 ±1.79	5.47 ±1.89	69.8 ±12.8	250 ±66
0.8 mg IM	3.73 ±3.34	13.6 ±15.4	3.09 ±0.64	3.43 ±0.66	84.8 ±26.5	236 ±68
0.4 mg IV	7.44 ±9.67	3.5 ±4.2	1.84 ±1.49	2.09 ±1.47	74.3 ±32.1	223 ±58

Abbreviations: Cmax: maximum concentration, Tmax: time to maximum concentration,
AUClast: area under the curve until last measurement. AUC0- inf: area under the curve until infinity, Cl: clearance
IN 2.8 mg is administered as IN 1.4 mg naloxone 3 minutes apart in the same nostril
[§]not statistically significant different to 0.8 mg IM (p>0.05)