Pharmacokinetics after a single dose of naloxone administered as a nasal spray in healthy volunteers

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Background: There is increasing interest in the use of intranasal naloxone to reverse adverse opioid effects during management of procedural pain in children and in adults after overdose. There are limited data on the pharmacokinetics of intranasal naloxone so in this study we aimed to detail the pharmacokinetic profile of the commercially marketed injectable solution of naloxone 0.4 mg/ml when administered as an intranasal spray.
Methods: Twenty healthy volunteers received naloxone as an intranasal spray at a dose of 10 μg/kg. Venous blood sampling was carried out for 90 min after administration to determine the time profile of the plasma concentrations of using tandem mass spectrometry. Pharmacokinetic parameters were calculated using a one-compartment model.
Results: Median time to maximum naloxone concentration (Tmax) was 14.5 (95% CI: 9.0–16.5) min, mean maximum naloxone concentration (Cmax) was 1.09 ± 0.56 ng/ml and mean $AUC_{0-90\ min}$ was 37.1 ± 15.0 ng*min/ml. Elimination half-life estimated from the median concentration data was 28.2 min.
Conclusion: Our results show a faster uptake of intranasal naloxone to maximum concentration compared with previous studies although with a marked variation in maximum concentration. The findings are consistent with our clinical experience of the time profile for reversing the effects of sufentanil sedation in children.

Editorial Comment
Intranasal naloxone can be useful to counteract undesirable opioid effects, not only in emergent pre-hospital situations, but also perioperatively where patients with potent opioid sedation may later benefit from some cautious and simply administered reversal. In this study in healthy volunteers, the authors explored the pharmacokinetics of naloxone administered intranasally, to better define the uptake profile.

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Naloxone is a competitive antagonist of the mu-opioid receptor, which has been used clinically for many years to reverse the effects of opioids. Intranasal administration avoids painful injections and has better patient acceptance, especially important aspects when treating children.

There is growing interest in intranasal administration of naloxone for the reversal of opioid effects in patients with overdose or when reversing intranasal sufentanil when used in elective painful procedures in children. Naloxone (Narcan®) has been approved as a nasal spray in 2015 by the US Food and Drug Administration (FDA). Aiming to reduce the mortality associated with opioid overdose FDA states that the approval of Narcan® nasal spray gives first responders and caregivers access to an opioid-reversal product that is easier to deliver than injectable formulations and eliminates the risk of contaminated needlestick injury. Narcan® delivers a 4-mg dose of naloxone in 0.1 ml, which is one hundred times more concentrated than solutions traditionally used clinically for intravenous administration.

At the Astrid Lindgren Children's Hospital intranasal naloxone administration has been used in more than 1000 children to reverse the sedative effect of nasally administered opioid sufentanil in the treatment of painful procedures. The use of intranasal sufentanil and naloxone has been part of our clinical routine for a decade to avoid an intravenous line for the procedure. At the end of the painful procedure naloxone is given, aiming for a faster recovery and higher patient safety. This is especially important in outpatients. In our experience the clinical effect of naloxone in reversing the effect of sufentanil has been impressive in most patients.

A good clinical effect has also been shown in a randomized clinical trial in adult patients presenting with an opioid overdose.[1] The use of intranasal naloxone has mostly been described in case reports and in treatment of opioid overdose.[2–5]

One concern regarding nasal administration is the degree of bioavailability. Nasal spray is often preferred over nasal drops because of superior absorption and thus a higher peak plasma concentration. Intranasal administration bypasses hepatic first-pass metabolism by direct absorption via the nasal mucosa which has a rich blood supply and high permeability. Intranasal drug delivery also has the potential for more direct delivery to the brain by bypassing the blood brain barrier.[6]

There are limited data on the pharmacokinetics of intranasal naloxone. In a study of intranasal naloxone (0.4 mg/ml) in volumes of 2 and 5 ml, bioavailability was low at 4%.[7] The total volume was divided equally in each nostril and there was a significant amount lost either from the nose or swallowed. Intranasal administration of a more concentrated naloxone formulation containing 2–8 mg in a small volume of 0.1–0.2 ml resulted in a relative bioavailability of 50% when compared with the intramuscular route.[8] In a recent, a new nasal formulation of naloxone with a concentration of 8 mg/ml and a dosing of 0.1 or 0.2 ml (0.8 or 1.6 mg respectively) demonstrated an absolute bioavailability of 50%.[9] In our study the aim was to evaluate the pharmacokinetic profile of naloxone in plasma after intranasal administration using the standard solution of naloxone 0.4 mg/ml marketed in many countries. Of particular interest in our study was the variability in the time to maximum plasma concentration. The results will be used to design future pharmacokinetic and pharmacodynamic studies in children.

Methods

This pharmacokinetic study was approved by the regional research ethics committee in Stockholm, Sweden (Ethical protocol number 2014/1354-31/4, November 19, 2014) as well as by the Swedish Medical Product Agency (Eudra CT number 2013-005201-31). The study has been performed according to the Declaration of Helsinki. Good Clinical Practice standards, which include regular monitoring of all procedures and protocols, were followed.

Twenty healthy volunteers received intranasal naloxone as a spray with the Mucosal Atomizing Device (Wolfe Tory Medical Inc, Salt Lake City, USA). The spray was administered with the subject in a reclined position. A total dose of 10 μg/kg (Naloxone 0.4 mg/ml, Hameln pharma plus GmbH, Hameln, Germany) was given over a period of 2 min divided in repeated doses of 0.1 ml in each nostril. The naloxone solution used was that normally marketed for injectable use. Blood samples (5 ml, venous

blood) were collected at 3, 5, 10, 15, 20, 30, 40, 60 and 90 min after the administration of naloxone was completed. Blood samples were kept on ice and centrifuged within 1 h. Plasma was separated and kept frozen at −80°C until analysis.

Sample preparation analytical procedures

Fifty micro liter internal standard solution ($^2H_5$-Naloxone 0.0024 μg/ml in MilliQ water) and 300 μl protein precipitation solution (acetonitrile) were added to 100 μl of each study sample. The samples were then vortex mixed and centrifuged before being injected into the ultra-high performance liquid chromatography – tandem mass spectrometry (UHPLC-MS/MS) system. Concentrations of naloxone were determined in human plasma by UHPLC-MS/MS following protein precipitation in the 96-well plate format.

UHPLC-MS/MS

The analytical instrumentation consisted of an Acquity UHPLC system coupled to a Xevo-TQS tandem quadruple mass spectrometer (Waters Corp., Milford, MA, USA). The ionization technique used was positive electrospray. The chromatographic column was a Waters Acquity UHPLC BEH C18 (100 × 2.1 mm length x inner diameter, particle diameter 1.7 μm).

The chromatographic elution was carried out with a mobile phase consisting of the components *A*: 0.1% formic acid in MilliQ water and *B*: 0.1% formic acid in acetonitrile. The total run time was 3.5 min after washing and equilibrating the column. The auto-sampler was programmed to inject 10 μl of sample.

The data collection was performed in the Multiple Reaction Monitoring mode (MRM). The MRM transitions were 328 > 310 for naloxone, 333 > 315 for naloxone-d5 respectively. The chromatographic peak area ratio (analyte/internal standard) was plotted as a function of analyte concentration (μg/ml in plasma). Linear regression with a weighting factor 1/*x* in the calibration range 0.05–8.6 ng/ml was used for naloxone. The resulting functions has the format $y = Ax + B$, where y is the peak area ratio, *A* is the slope, *x* is the concentration ng/ml and *B* is the intercept. The quantitative values (*x* ng/ml) in the back-calculated calibration samples and QC samples were calculated as $x = (y - B)/A$. The limit of quantification was 0.05 ng/ml.

Pharmacokinetic evaluation

The area under the plasma concentration time cure ($AUC_{0-90\ min}$) for the individual subjects was determined by the linear trapezoidal rule using GraphPad Prism version 5.04 (GraphPad Software, Inc. La Jolla, CA, USA).

The one-compartment model (i.e. mono-exponential decay) was used for the estimation of the elimination half life using the Win-Nonlin program Standard Edition version 1.5 (Pharsight Corporation, Mountain View, CA, USA), which uses nonlinear regression procedures. Mean values of the concentration were used for curve fitting procedure. The reciprocal of measured plasma concentrations were used as weights and the Gauss-Newton minimization method was used in the iterative procedure. The time to maximum concentration of naloxone was measured with T_0 at the start of the intranasal administration.

Statistics

Median values including their 95% non-parametric confidence interval (95% CI) were calculated based on the Wilcoxon Signed-Ranks Test.[10]

Results

Twenty healthy volunteers were included, 14 males and 6 females with mean weight 72.8 (range: 55–90) kg and age 37 (range: 22–64) years. Mean volume of naloxone administered as an intranasal spray was 1.8 (range 1.4–2.3) ml.

Median time to maximum concentration (Tmax) was 14.5 (95% CI: 9.0–16.5) min, mean maximum concentration (Cmax) was 1.09 ± 0.56 ng/ml, and $AUC_{0-90\ min}$ was 37.1 ± 15.0 ng*min/ml. The elimination half-life estimated from the median concentration data was 28.2 min (standard error of the mean: 3.8 min). There was no sex difference in Tmax or $AUC_{0-90\ min}$. The mean Cmax were for males 1.25

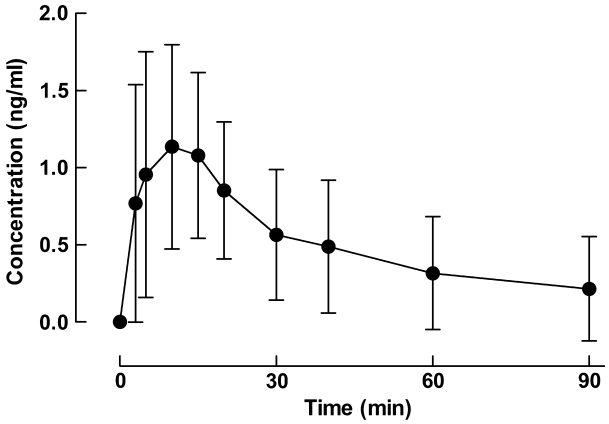

Fig. 1. Plasma concentration of naloxone after administration as a nasal spray. Data are given as mean values ± standard deviation.

and females 0.73 ng/ml, and mean $AUC_{0–90\ min}$ 40.2 and 29.7 ng*min/ml respectively.

In Fig. 1 the mean naloxone concentration ± standard deviation at the various sampling times with the solid line the result from pharmacokinetic modeling. In Fig. 2 individual Tmax, $AUC_{0–90\ min}$ and Cmax are shown.

No pain or discomfort from intranasal naloxone administration was noted. Some of the subjects experienced mucosal overload with the feeling of liquid running down the pharynx.

Discussion

This study supplies new pharmacokinetic data on the use of low concentration formulation (0.4 mg/ml) of naloxone after intranasal administration. Previous published study in humans,[8,9] used higher doses of naloxone and a higher concentration of naloxone (20 and 40 mg/ml). In both studies an intranasal spray was used but different devices were used. The results in our study shows a faster Tmax of 14.5 min compared to 18–30 min. Both studies showed a large inter-individual range in Tmax that could be due to the concentration of naloxone and the volume administered. The dose chosen in our study was based on our clinical use in children (10–20 μg/kg). In the present study in healthy adults 10 μg/kg was chosen to limit the volume. In our clinical practice we use the standard injectable solution of naloxone 0.4 mg/ml although in children a solution of 1 mg/ml would probably be advantageous in respect of a more suitable and lesser volume. A high volume given in repeated doses results in liquid running down to the pharynx and reduces the amount of naloxone absorbed. For optimal effect, using the mucosal atomizing device for nasal application, a volume of not higher than 0.1–0.15 ml is recommended in each nostril at each time and so repeated fractions may need to be given to reach the desired dose per kg.

It is not possible to directly compare the $AUC_{0–90\ min}$, and Cmax values between our study and others but comparing the concentration-time curve in Fig. 1 there is a similarity

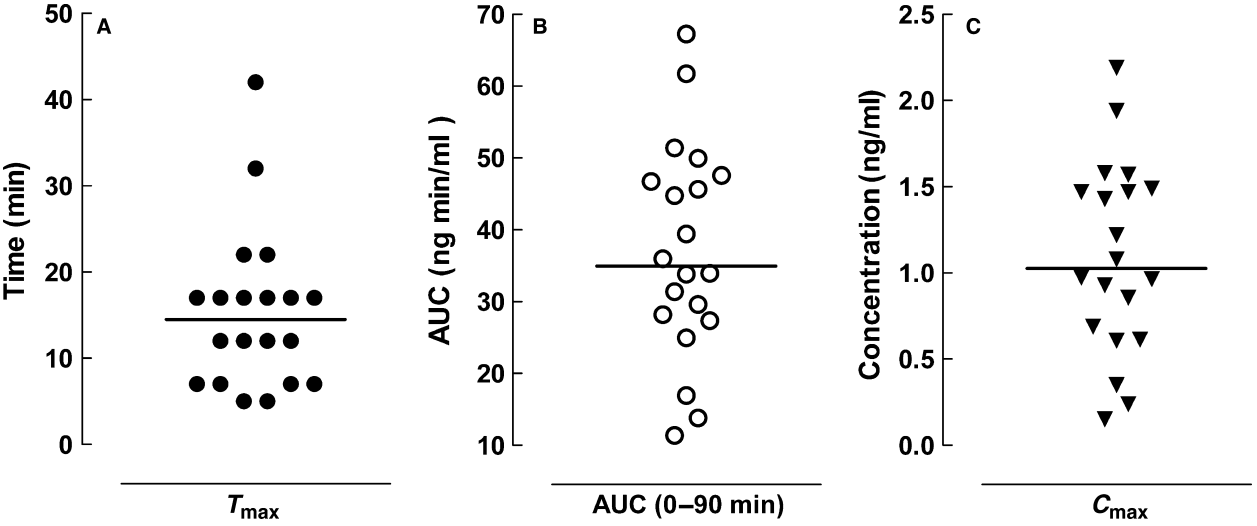

Fig. 2. Time to maximum concentration (Tmax), $AUC_{0–90\ min}$ and maximum concentration (Cmax) for each individual, median indicated as a bar in figure.

in concentration profiles although there was no variability shown in previous reports.[8]

Our results emphasize the fact that the bioavailability of intranasal naloxone is higher than previously reported,[7] and after dose correction, is comparable to an intramuscular injection.[8] In our clinical experience we usually notice a clear effect within 10 min when reversing the sedative effect of sufentanil with intranasal naloxone, but some patients do show a slower onset which reflects the pharmacokinetic results in our study. The uptake of naloxone, using the commonly marketed solution of naloxone 0.4 mg/ml, has not been shown. More concentrated solutions which are not practical for pediatric use since low doses needed would result in too small a volume to be administered with sufficient accuracy. However, the pharmacokinetic results from our study in healthy adult volunteers cannot be translated to a younger population even though our clinical experience in pediatric patients using intranasal naloxone to reverse the effect of sufentanil is convincing. We are therefore now exploring in more detail certain pharmacokinetic parameters and pharmacodynamic effects after intranasal administration of naloxone in the pediatric population.

Conclusion

Our results show a tendency to faster absorption to maximum plasma concentration following intranasal administration compared with previous studies although with a marked variation in maximum concentration. The findings are consistent with our clinical experience when used in pediatric patients who are administered intranasal naloxone to reverse the effect of previous given intranasal sufentanil. As in earlier studies there is a rather large variability in the time to maximum plasma concentration. Furthermore our results show a clear uptake using a less concentrated naloxone solution that is more suitable for pediatric use. No pain or discomfort of intranasal naloxone administration was noted.

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