Received: 23 November 2020 | Revised: 22 February 2021 | Accepted: 28 February 2021

DOI: 10.1111/pan.14175

RESEARCH REPORT

Pediatric Anesthesia WILEY

Rapid systemic uptake of naloxone after intranasal administration in children

Eva Malmros Olsson[1,2] | Per-Arne Lönnqvist[3] | Carl-Olav Stiller[4] | Staffan Eksborg[3,5] | Stefan Lundeberg[1,2]

[1]Pediatric Pain Treatment Service, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

[3]Pediatric Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden

[4]Clinical Pharmacology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

[5]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Correspondence
Eva Malmros Olsson, Pediatric Pain Treatment Service, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Karolinska Universitetssjukhuset, Smärtbehandlingsenheten Barn, S3:03 Norrbacka, 171 76 Solna, Sweden.
Email: eva.malmros-olsson@sll.se

Section Editor: Brian Anderson

Abstract

Background: Naloxone has a high affinity for the μ-opioid receptor and acts as a competitive antagonist, thus reversing the effects of opioids. Naloxone is often administrated intravenously, but there is a growing interest in the intranasal route in treating patients with opioid overdose, and in reversing effects after therapeutic use of opioids. As administration is painless and no intravenous access is needed, the intranasal route is especially useful in children.

Aim: The aim of this study was to investigate the uptake of naloxone 0.4 mg/ml during the first 20 min after administration as a nasal spray in a pediatric population, with special focus on the time to achieve maximum plasma concentration.

Methods: Twenty children, 6 months–10 years, were included in the study. The naloxone dose administered was 20 μg/kg, maximum 0.4 mg, divided into repeated doses of 0.1 ml in each nostril. Venous blood samples were collected at 5, 10, and 20 min after the end of administration.

Results: All patients had quantifiable concentrations of naloxone in venous blood at 5 min, and within 20 min, peak concentration had been reached in more than half of the children. At 20 min after intranasal administration, the plasma naloxone concentrations were within the range of 2–6 nanogram/ml.

Conclusion: This study confirms the clinical experience that the rapid effect of naloxone after intranasal administration in children was reflected in rapid systemic uptake to achieve higher peak plasma concentrations than previously reported in adults.

KEYWORDS
children, intranasal, naloxone, pediatric, pharmacokinetic, uptake

What is already known about the topic?

Intranasal administration of drugs is sometimes an alternative in situations where intravenous access is not applicable or lacking. Intranasal naloxone is an attractive option for treating opioid side effects when intravenous access is lacking for various reasons. It has previously been shown that intranasal naloxone has a rapid systemic uptake in the early phase after administration in healthy adults.

What new information this study adds

In anesthetized children, there is a rapid, within minutes, systemic uptake of intranasal naloxone when using the commercially available solution of 0.4 mg/ml administrated as

a spray. This implies there is a possibility of using the 0.4 mg/ml solution of naloxone for treating children with unwanted side effects of opioids in situations where intravenous access is lacking.

1 | INTRODUCTION

Naloxone has a high affinity for the μ-opioid receptor and acts as a competitive antagonist reversing the effects of opioids. Naloxone is often administrated intravenously, but there is a growing interest in the intranasal route, mainly in treating patients with opioid overdose.[1,2] There are only a few previous studies describing the pharmacokinetics of intranasal naloxone, and in these, the concentration of naloxone used is higher than in the commonly marketed solution.[3–6] In children, there are only case reports on the use of intranasal naloxone.[7] Our group has previously shown that in adult healthy volunteers, intranasal administration of the commonly marketed solution of naloxone, 0.4 mg/ml, has a bioavailability that is comparable to intramuscular injection.[8] Using the commonly marketed solution of naloxone, 0.4 mg/ml, has advantages since it is available at any emergency department or hospital ward, and therefore, it gives more possibilities to individualize the dose based on the size of the patient.

Intranasal sufentanil is used routinely at Astrid Lindgren Children's Hospital in the treatment of children undergoing painful or stressful procedures when intravenous access is lacking. The intranasal route has advantages since it can be used without pain or discomfort and avoids intravenous access, which may be unpleasant. To reverse the residual effects of intranasal sufentanil, we have used intranasal naloxone successfully for 10 years. With intranasal administration, first-pass metabolism of naloxone is avoided where oral naloxone would lead to extensive first-pass metabolism. An oral solution would also be much more difficult to administer, and unsafe, in a sedated patient.

The aim of this study was to validate our clinical experience by investigating the pharmacokinetic profile of naloxone 0.4 mg/ml administered as a nasal spray in a pediatric population, with special interest in the time to achieve maximum plasma concentration. This is, to our knowledge, this is the first study performed in children looking at the initial pharmacokinetic properties after intranasal administration of naloxone, and this study contributes to new knowledge in this field. Our study also confirms the observation made in our clinical practice of adequate effect of the commercially available solution of naloxone, 0.4 mg/ml, used as a nasal spray. This information can be valuable to any physician in need of treating sedative side effects of opioids.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

The study was approved by the regional research ethics committee in Stockholm, Sweden (Ethical protocol number 2014/1354-31/4, November 19, 2014), and the Swedish Medical Product Agency (EudraCT number 2017–000379–96). The study was performed according to the Declaration of Helsinki. Good Clinical Practice standards, which included regular monitoring of all procedures and protocols, were followed.

Twenty previously healthy children undergoing minor surgery at an outpatient surgical unit were included. Written consent was obtained from the parents during the assessment interview prior to the surgery. The patients were enrolled consecutively with 26 interviewed patients, 24 gave their consent to participate and two declined. In the group giving consent, the first 20 consecutive patients that appeared for surgery were enrolled in the study. The predominance of boys reflects the surgical selection. Anesthesia was induced with intravenous propofol, and no opioids were used during the anesthesia induction according to the anesthetic protocol selected presurgery. Anesthesia was maintained with inhaled sevoflurane and corticosteroids, and paracetamol and local anesthetic blocks were routinely used as adjuvant analgesics. Naloxone was given as a nasal spray using a Mucosal Atomizing Device (Wolfe Tory Medical Inc, Salt Lake City, USA) and was administered approximately 10 min after induction of anesthesia. The MAD-nipple has advantages when the patient is in supine position and the dosing is easier since it makes it possible to use a graded syringe, compared with using a spray bottle. A separate venous access was established for blood sampling before naloxone administration. The intended dose of naloxone administered intranasally was 20 μg/kg (corresponding to 0.39 – 0.70 mg/m^2), divided into repeated doses of 0.1 ml in each nostril according to the established practice, a method chosen to optimize conditions for mucosal absorption. The total dose was not allowed to exceed a maximum of 0.4 mg. The total administration time was approximately 2 min. The naloxone solution used was the solution registered for intravenous or intramuscular injection (naloxone 0.4 mg/ml; Hameln Pharma Plus GmbH, Hameln, Germany).

Venous blood samples were collected at 5, 10, and 20 min after the end of administration. Blood samples were initially stored in a refrigerator and centrifuged within 1 h. The separated blood plasma was then frozen at −80°C until analysis.

2.2 | Naloxone analysis

A 100 μl aliquot of plasma and a standard specimen was mixed with 250 μl acetonitrile/methanol (vv 50:50) mixture. 25 μl of internal standard naloxone-D5 (conc. 5 ng/ml) was then added to both the plasma sample and the standard. The specimens were shaken vigorously for 10 s and centrifuged for 10 min at 3500 rpm. The supernatant was thereafter transferred to new vials, and 5 μl was subsequently injected into LC-MS/MS system (liquid chromatography-mass spectrometry/mass spectrometry system).

The LC-MS/MS system consisted of a Waters Acquity ultra-performance liquid chromatograph connected to a Xevo TQS Micro tandem mass spectrometer (Waters Co, Milford, MA, USA). The electrospray interface was used with the instrument operating in the positive ion mode. Chromatography was performed using a 1.9 µm, 100 × 2.0 mm (inner diameter) YMC-Triart C8 column (YMC Co, Japan).

The chromatographic elution was carried out with a mobile phase consisting of the components 10 mmoL/L ammonium formate and methanol (pH 4.8). The total run time was 3 min, and the injected volume was 5 µl. The acquisition was performed in multiple reaction monitoring (MRM) mode with transition 328 >310 for naloxone and 333 >315 for naloxone-D5, respectively. For quantitation were used the following standard concentrations: 0 ng/ml, 0.05 ng/ml, 1.0 ng/ml, 2.5 ng/ml, 5.0 ng/ml, 7.5 ng/ml, and 10.0 ng/ml. As quality controls were used the following concentration levels: 0.1 ng/ml and 2.0 ng/ml. The limit of quantitation was 0.05 ng/ml.

2.3 | Statistics

Correlation was established by the Spearman rank correlation test. Two independent groups of samples were compared using the Mann-Whitney *U* test. Statistics were evaluated by MS Excel (Microsoft Corporation, Redmond, Washington USA) and GraphPad Prism version 5.04 (GraphPad Software Inc. San Diego, USA). *p*-values <.05 were considered statistically significant. Reported p-values are from two-sided tests. Data are presented as median values and interquartile range (IQR).

Plasma concentrations of naloxone were divided by the dose in µg/kg or µg/m^2 to normalize for different sizes of the patients and differences in the administered doses.[9,10] The body surface area (BSA) was determined according to Boyd in this study and according to Mosteller in our previous study on adults.[11,12]

3 | RESULTS

Patient characteristics are shown in Table 1. The surgical procedures were outpatient inguinal surgery (Table 1) that was associated with insignificant blood loss.

The individual plasma concentrations are displayed in Figure 1. All patients had quantifiable concentrations at 5 min, and within 20 min, more than half (14) of them had reached their observed peak concentration (Figure 1). The median plasma concentrations were 3.67 (IQR: 2.66–5.42), 3.98 (IQR: 2.98–5.28), and 3.58 (IQR: 2.72–4.77) ng mL^{-1} at 5, 10, and 20 min, respectively.

Dose-normalized observed maximum concentration of naloxone as a function of age is shown in Figure 2. The dose-normalized observed C_{max} by body weight (Cmax/µg/kg) increased with increasing

TABLE 1 Patient characteristics

Patient No	Age (years)	Sex	Body weight (kg)	Naloxone (µg)	Naloxone (µg/kg)	Naloxone µg/m^2	Surgery
1	0.5	Girl	8.5	170	20.0	387	IHR
2	8.8	Boy	25.5	400	15.7	427	IHR
3	7.3	Boy	20.0	400	20.0	505	OP
4	1.9	Boy	12.0	240	20.0	430	IHR
5	3.8	Boy	15.7	320	20.0	477	IHR
6	2.7	Boy	17.5	350	20.0	484	IHR
7	8.3	Boy	24.4	400	16.4	440	IHR
8	9.9	Boy	42.0	400	9.5	305	OP
9	1.6	Girl	13.0	260	20.0	441	IHR
10	10.1	Boy	47.0	400	8.5	283	OP
11	3.1	Boy	17.0	340	20.0	479	HC
12	4.5	Boy	22.0	400	18.2	473	IHR
13	2.5	Boy	12.0	240	20.0	430	IHR
14	3.6	Boy	16.0	320	20.0	470	IHR
15	4.2	Girl	16.0	320	20.0	470	IHR
16	2.5	Boy	15.0	300	20.0	461	IHR
17	2.0	Boy	12.0	240	20.0	430	OP
18	2.2	Boy	10.4	210	20.0	416	IHR
19	1.7	Boy	12.0	240	20.0	430	OP
20	8.4	Boy	56.0	400	7.1	251	OP

Abbreviations: HC, hydrocele repair; IHR, inguinal hernia repair; OP, orchidopexy.

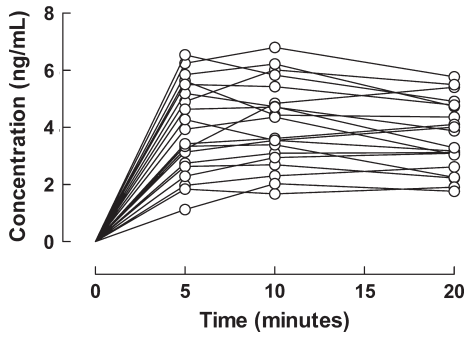

FIGURE 1 Individual concentration of naloxone

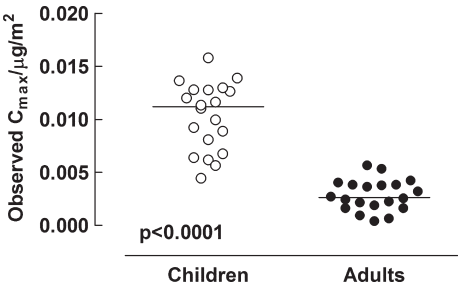

FIGURE 3 Comparison of observed maximum naloxone concentration after intranasal administration in children and adults (8). Dose normalized for body surface

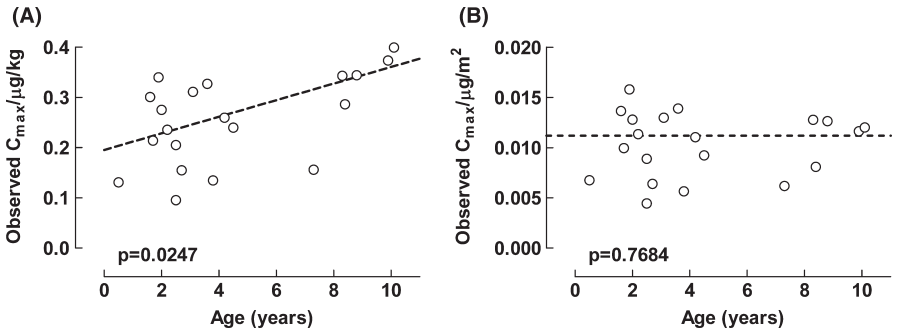

FIGURE 2 Dose-normalized observed maximum concentration of naloxone as a function of age

age (Figure 2A). In contrast, dose-normalized observed C_{max} by body surface area (Cmax/µg/m^2) was unaffected by age (Figure 2B).

The observed maximum concentrations of naloxone were dose-normalized by body surface area (Cmax/µg/m^2). The observed maximum concentrations of naloxone, normalized by body surface area, were higher in children as compared to our previous adult data as shown in Figure 3.8

4 | DISCUSSION

The main finding of this study was that effective plasma concentrations of naloxone were observed within 10 min after intranasal administration of 20 microgram per kg body weight in children. The plasma concentrations were, after normalization for body surface area, generally higher than previously reported in adults receiving intranasal naloxone.

Intranasal sufentanil may be used as a powerful analgesic in association with short painful procedures in children (eg, reduction in minor fractures, burn dressing changes, lumbar puncture, rheumatic joint injection) when intravenous access is not present. The residual effects of sufentanil, such as sedation and respiratory depression, may need to be reversed after the procedure is ended.

The intranasal route for administration of naloxone is painless, and no intravenous access is needed. This is a special advantage in children since the insertion of a venous cannula is for many children a painful and stressful event.[13]

The currently marketed products for intranasal administration of naloxone are not customized for children and often contain a 10-fold higher concentration than the common solution registered for intravenous and intramuscular administration. In clinical practice, this enables only use of a fixed dose, without possibilities for dose adjustment based on the size of the patients, which could be hazardous in small children.[14,15] However, the commonly marketed solution of naloxone (0.4 mg/ml) is easily accessible in hospital wards and emergency departments, is affordable, and does not introduce the risk of incorrect dosing by using the wrong concentration of naloxone. The naloxone dose used in the present study was 20 µg/kg, which represents the standard dosage used in our clinical protocol to reverse residual opioid effects following procedural sedation and analgesia. It is also a dose we have experienced to be sufficient to reverse the residual sedative effects of sufentanil in clinical practice. Although we have a positive experience with regard to using the commonly marketed solution of naloxone (0.4 mg/ml), there has hitherto been a lack of relevant pharmacokinetic data associated with this practice.

In the present study, we found that intranasal administration in children according to our protocol resulted in measurable plasma concentrations of naloxone already 10 min after administration and that more than half of the patients had reached their observed Cmax before 20 min (Figure 1). This finding corroborates our prior clinical experience. Our results also showed an age dependence regarding dose-normalized observed maximum concentration when dosing is based on body weight (ie, µg/kg, Figure 2A), whereas no such effect was observed when dosing is based on body surface area (ie, µg/m^2, Figure 2B). However, in clinical practice, dosing of intranasal naloxone based on body weight appears to be sufficiently accurate but may result in under-dosing in infants.

When comparing our previous published data in adults, after correcting the dose for body surface, with our present pediatric data, we find that the median plasma level is about twice as high in our pediatric cohort (Figure 3). The reason for this finding remains to be clarified but could potentially be due to the higher cardiac output and therefore higher mucosal blood flow in children that may result in better absorption of naloxone from the nasal mucosa. There is also a possibility that the mucociliary clearance is diminished during anesthesia, which could lead to a greater absorption in our study population compared with the adult group that were awake.

In our clinical practice, we have set a maximum dose of 1 ml (0.4 mg), independent of patient weight, since it has shown to be efficient, and a larger dose results in an uncomfortable volume of fluid and leads to oropharyngeal run-off. However, it can be repeated if necessary. A slightly higher concentration of 1 mg/ml could be desirable to enable optimizing the volume even further, but in the clinical context, we have found the concentration of 0.4 mg/ml to be fully usable.

The majority of the enrolled patients are boys but we have not found any data in the literature suggesting there is a gender difference in nasal blood flow or mucosal uptake in prepubertal children.

4.1 | Study limitations

Patient numbers were small, and there was a wide range of ages, but the pharmacokinetic profile of individuals seen in Figure 1 is quite similar in shape, although observed Cmax concentrations did vary between approximately 2 and 6 ng ml-1. Pharmacodynamic/pharmacokinetic relationships could not be evaluated in this study design. Some patients received less than the intended dose of 20 µg/kg (Table 1), due to our choice of a maximum dose of 0.4 microgram and maximum volume of 1.0 milliliter, respectively. It has previously been shown in adults that the maximal volume that can be given with each individual spray into one nostril to avoid run-off into the oropharynx is approximately 150 microliter, which is the reason that the spraying needs to be divided into multiple episodes between both nostrils.[16] This may explain the wide range of observed Cmax values.

A previous study by Nielsen et al has shown that plasma levels of sufentanil are declining after 30 min following intranasal administration in children.[17] We have therefore opted to administer intranasal naloxone approximately 40–45 min after the initial dose of sufentanil to avoid any potential rebound effect of sufentanil regarding respiratory depression. This practice reduces the need for extended observation and monitoring of the child and allows for more rapid discharge if the procedure is performed on an outpatient basis. The use of intranasal naloxone can obviously be used to reverse other opioids in similar settings (eg, prehospital use of intranasal fentanyl), but then, the timing needs to be adapted to the pharmacokinetics of the opioid used.[18]

5 | CONCLUSION

In conclusion, intranasal administration of naloxone is painless for the pediatric patient and has several advantages with respect to patient safety and comfort. This study confirms the clinical experience that there is a rapid uptake of naloxone after intranasal administration and suggests that the nasal uptake of naloxone is higher in children than in healthy adults.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Eva Malmros Olsson https://orcid.org/0000-0001-9893-890X
Per-Arne Lönnqvist https://orcid.org/0000-0002-8586-1429

REFERENCES

1. Dietze P, Jauncey M, Salomon A, et al. Effect of intranasal vs intramuscular naloxone on opioid overdose: a randomized clinical trial. *JAMA Netw Open*. 2019;2(11):e1914977.
2. Yousefifard M, Vazirizadeh-Mahabadi MH, Neishaboori AM, et al. Intranasal versus intramuscular/intravenous naloxone for prehospital opioid overdose: a systematic review and meta-analysis. *Adv J Emerg Med*. 2019;4(2):e27.
3. Ryan SA, Dunne RB. Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: a systematic review. *Pain Manag*. 2018;8(3):231-245.
4. Krieter PA, Chiang CN, Gyaw S, McCann DJ. Comparison of the pharmacokinetic properties of naloxone following the use of FDA-approved intranasal and intramuscular devices versus a common improvised nasal naloxone device. *J Clin Pharmacol*. 2019;59(8):1078-1084.
5. Krieter P, Chiang N, Gyaw S, et al. Pharmacokinetic properties and human use characteristics of an FDA-approved intranasal naloxone product for the treatment of opioid overdose. *J Clin Pharmacol*. 2016;56(10):1243-1253.
6. McDonald R, Lorch U, Woodward J, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: phase I healthy volunteer study. *Addiction*. 2018;113(3):484-493.
7. Lebin JA, Chen BC, Valento MJ. Reversal of pediatric opioid toxicity with take-home naloxone: a case report. *J Med Toxicol*. 2019;15(2):134-135.
8. Vanky E, Hellmundt L, Bondesson U, Eksborg S, Lundeberg S. Pharmacokinetics after a single dose of naloxone administered as a nasal spray in healthy volunteers. *Acta Anaesthesiol Scand*. 2017;61(6):636-640.
9. Lundeberg S, Stephanson N, Stiller CO, Eksborg S. Pharmacokinetics after a single intravenous dose of the opioid ketobemidone in neonates. *Acta Anaesthesiol Scand*. 2012;56:1026-1031.
10. Lundeberg S, Stephanson N, Lafolie P, Olsson GL, Stiller CO, Eksborg S. Pharmacokinetics after an intravenous single dose of the opioid ketobemidone in children. *Acta Anaesthesiol Scand*. 2010;54:435-441.
11. Boyd E. *The growth of the surface area of the human body*. Minneapolis, Min: University of Minnesota. The Institute of Child Welfare. In: Monograph series, No. X. London: Oxford University Press; 1935.
12. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098.
13. Kennedy RM, Luhmann J, Zempsky WT. Clinical implications of unmanaged needle-insertion pain and distress in children. *Pediatrics*. 2008;122(Suppl 3):S130-S133.

14. Hasan RA, Benko AS, Nolan BM, Campe J, Duff J, Zureikat GY. Cardiorespiratory effects of naloxone in children. *Ann Pharmacother*. 2003;37(11):1587-1592.
15. Farkas A, Lynch MJ, Westover R, et al. Pulmonary complications of opioid overdose treated with naloxone. *Ann Emerg Med*. 2020;75(1):39-48.
16. Constantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: physicochemical and therapeutic aspects. *Int J Pharm*. 2007;337(7):1-24.
17. Nielsen BN, Friis SM, Rømsing J, et al. Intranasal sufentanil/ketamine analgesia in children. *Paediatr Anaesth*. 2014;24(2):170-180.
18. Tanguay A, Lebon J, Hébert D, Bégin F. Intranasal fentanyl versus subcutaneous fentanyl for pain management in prehospital patients with acute pain: a retrospective analysis. *Prehosp Emerg Care*. 2020;23:1-9.

How to cite this article: Malmros Olsson E, Lönnqvist P-A, Stiller C-O, Eksborg S, Lundeberg S. Rapid systemic uptake of naloxone after intranasal administration in children. *Pediatr Anaesth*. 2021;00:1–6. https://doi.org/10.1111/pan.14175