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Absorption pharmacokinetics of clonidine nasal drops in children

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Summary

Background: The α2 agonist clonidine has become a popular drug for premedication in children. Effects and pharmacokinetics after oral, rectal, and intravenous administration are well known. The aim of this study was to investigate the absorption pharmacokinetics of clonidine nasal drops in children.

Methods: Thirteen ASA I pediatric patients received after induction of anesthesia 4 mcg·kg^{-1} of clonidine by the nasal route. Blood samples were taken during a 12-h period and plasma levels of clonidine were analyzed by liquid chromatography–mass spectrometry. Data were calculated by a computer-aided curve-fitting program.

Results: Plasma pharmacokinetics following administration of clonidine nasal drops showed a considerable interindividual variability and absorption was delayed and limited. A total of 95% confidence intervals for maximum plasma concentration and time to achieve maximum plasma concentration were 0.4–0.6 ng·ml^{-1} and 1.4–3.0 h, respectively.

Conclusions: Clonidine nasal drops are erratically absorbed from the nasal mucosa and, thus, this mode of drug administration is not recommended for premedication purposes.

Keywords: clonidine; pharmacokinetics; children

Introduction

Clonidine, an α2-adrenoceptor agonist, has been used for premedication in children since 1993 (1) and it has been suggested to be superior to midazolam in this setting (2). It is well absorbed after oral and rectal administration with nearly 100% bioavailability (3,4). However, the relative slow onset of action is a major drawback with the routine use of oral or rectal clonidine for premedication. It therefore needs to be given well in advance in order to obtain a good clinical effect.

One opportunity to reduce the time to adequate clinical effect might be to administer clondine by the nasal route. Potts *et al.* recently reported a comprehensive study of the populations pharmacokinetics

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(PK) of clonidine in children, including data from various studies and administration routes (5). However, this populations PK study did not include data following nasal administration and can, thus, not help to explain why administration of clonidine as nasal drops was not found to significantly differ from regular oral administration concerning preoperative sedation or the quality of anesthetic induction, as previously reported by Almenrader (6). This lack of efficacy of nasal drops also differs from the results of a rodent study showing peak plasma concentrations within 10 min of nasal administration of clonidine (7).

In an attempt to elucidate this lack of difference between oral and nasal administration we decided to investigate the absorption PK of clonidine administered as nasal drops in children undergoing general anesthesia.

Methods

This study was approved by the local Ethics Committee and informed parental consent was obtained before the patients were enrolled into the study. Only patients with an anesthetic risk classified as ASA I were eligible for this study participation.

Children requiring nose, throat or dental surgery, gastric or airway endoscopy and those suffering from any kind of nasal pathology were excluded from this study.

Patients

Thirteen pediatric patients (10 boys and three girls, ASA I, age 22–84 months, weight 10–25 kg) scheduled for infraumbilical surgical procedures such as inguinal herniorraphy, orchidopexy, hypospadia or hydrocele repair participated in this study. Patients received 5 $mg \cdot kg^{-1}$ of oral ibuprofen 30 min prior to anesthesia induction. Anesthesia was induced by face mask with sevoflurane in a mixture of oxygen and nitrous oxide using a Jackson Rees T-piece. As soon as loss of eyelid reflex was obtained, two intravenous catheters (BD Saf-T-Intima, Becton Dickinson Italia S.p.A, Buccinasco, Italy) were inserted. One intravenous catheter was inserted in an antecubital vein and was used for blood sampling only. Anesthesia was maintained with sevoflurane in a mixture of oxygen and air. All patients were breathing spontaneously through a laryngeal mask airway. Analgesia was provided by a caudal block or peripheral nerve block according to the surgical procedure. All patients received a loading dose of rectal paracetamol 30–40 $mg \cdot kg^{-1}$.

Drug administration

A dose of 4 $mcg \cdot kg^{-1}$ of an intravenous clonidine solution (Catapresan 150 $mcg \cdot ml^{-1}$; Boehringer Ingelheim, Ingelheim, Germany) was given undiluted after anesthesia induction and insertion of the two intravenous catheters. The predetermined dose of clonidine was drawn up in equal volumes into two 1 ml syringes. The dose was then administered into both nostrils with the patient supine, the head in the neutral position and breathing spontaneously through the laryngeal mask airway. The patient's head remained in the neutral position for the entire length of surgery. All nerve blocks requiring a change in position were performed before the administration of this study drug. The solution was retained in the nostrils without external leakage in all patients.

Blood sampling

Blood samples for clonidine analysis were taken at 10, 25, 40, 60, and 90 min and 3, 6, and 12 h after administration of nasal clonidine. Each blood sample consisted of 2 ml of blood. All blood samples were immediately anticoagulated with heparin; plasma was separated by centrifugation and stored at a temperature of −70°C until assay.

Drug analysis

Plasma levels of clonidine were determined by liquid chromatography–mass spectrometry. Clonidine-d4 was used as internal standard. Samples were prepared by a solid phase extraction. The clonidine analysis was performed on a Waters ultra-pressure liquid chromatography (UPLC)–MS/MS system (Waters Sverige AB, Sollentuna, Sweden) consisting of an ACQUITY UPLC coupled to a Quattro Premier XE mass spectrometer operated in the selected reaction monitoring mode. The analysis was performed at an accredited laboratory in the

Department of Pharmacology at Karolinska, University Hospital–Huddinge certified according to good laboratory practice.

The detection limit of the assay was 0.1 ng·ml^{-1}. The interassay coefficient of variation (CV) was 6.0% and the intraassay CV was 5.2% for the low concentration quality control. The interassay CV was 5.2% and the intraassay CV was 4.1% for the high concentration quality control.

Pharmacokinetics

The PC NONLIN program (version 2.0, Statistical Consultants Inc, Lexington, Kentucky, USA) was used for the pharmocokinetic modeling of the plasma concentration data.

The maximum plasma concentration (Cmax) and time to achieve maximum plasma concentration (Tmax) were evaluated from the fitted curves. The area under the curve (AUC) was calculated by numeric integration of the plasma concentration – time (12 h) curve for each patient.

Statistics

All numerical data are reported as median. Calculation of nonparametric 95% confidence intervals (CI) were based on Wilcoxon signed ranks test.

Results

In three patients 12-h blood sampling was incomplete because of clotting of the intravenous catheter. In one patient the generated data did not produce an acceptable curve fit and was therefore excluded from final analysis. Thus, data from 9/13 patients were included into the final analysis. Demographic and pharmacokinetic data are shown in Table 1. The plasma absorption PK of clonidine nasal drops 4 mcg·kg^{-1} was slow and modest and showed a considerable interindividual variability (Figure 1).

The median Cmax was 0.53 ng·ml^{-1} (95% CI 0.42–0.64 ng·ml^{-1}) and the median Tmax was 2.22 h (95% CI 1.45–2.99 h). The median AUC for data from 0 to 12 h was found to be 7.24 ng·h·ml^{-1} (95% CI 5.63–8.85 ng·h·ml^{-1}).

The median elimination half-life time (K10-HL) was 7.69 h (95% CI 5.22–10.16 h). Thus the PK of clonidine administered as nasal drops showed a substantial variability.

Discussion

Premedication with clonidine has been reported to be superior to benzodiazepines in children (1,2) and effective preoperative sedation can be achieved by the oral (1) and rectal (4) route. However, the onset of action by the oral route can take as long as 105 min (1).

A study on rodents suggested nasal administration of clonidine to be an alternative route to intravenous administration as Cmax were reached after 10 min (7). Intranasal administration is a practical, non-invasive, rapid, and simple method to reduce the time from drug delivery to peak plasma concentrations compared with oral or rectal administration. The highly vascularized nasal mucosa with its large surface area enhances both

Table 1
Demographic and pharmacokinetic data.

Patient No	*Sex*	*Age (months)*	*Weight (kg)*	*AUC (ng·h·ml^{-1})*	*K10-HL (h)*	*Tmax (h)*	*Cmax (ng·ml^{-1})*
1	Female	68	22	2.35	1.64	2.34	0.36
2	Female	54	20	7.70	8.41	2.22	0.52
3	Male	27	13	8.52	7.68	1.23	0.69
4	Male	37	17	9.55	4.42	4.42	0.76
5	Male	41	17	10.38	12.96	4.15	0.44
6	Male	51	17	7.24	12.8	1.64	0.35
8	Male	26	10	5.29	3.88	1.33	0.74
10	Male	27	12	4.4	4.03	1.03	0.66
11	Male	25	12	5.31	8.19	2.85	0.35
Median		37	17	7.24	7.69	2.22	0.53
95% CI				5.6–8.8	5.2–10.2	1.4–3.0	0.4–0.6

AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to achieve maximum plasma concentration; K10-HL, median elimination half-life time CI, confidence intervals.

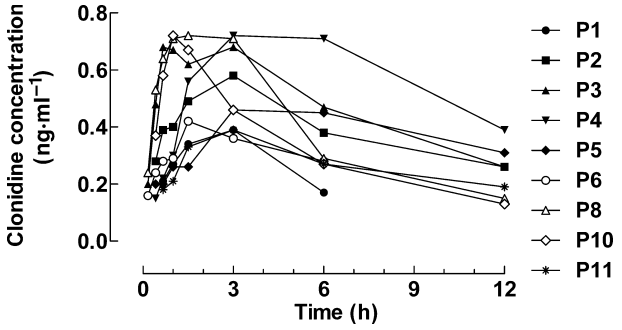

Figure 1
Plasma pharmacokinetics (PK) of nasal clonidine in children. Plasma concentration – time curves of nine patients are included.

drug absorption and the onset of therapeutic action (8). Clonidine does possess many attributes of the ideal nasal drug candidate such as absence of nasal irritation or toxic nasal metabolites, no offensive odors, suitable stability characteristics, and appropriate nasal absorption properties in the animal experiment (7,8).

In a recent study on clonidine premedication in children, we failed to show any advantage of the nasal route over the oral route in terms of onset of action (6). We therefore decided to investigate the absorption PK of clonidine nasal drops.

Before commenting on our results, we would like to draw the reader's attention to the special circumstances regarding the administration of the nasal drops in this study. Galinkin *et al*. have previously shown that nasal fentanyl, administered after induction of anesthesia, does result in adequate and timely plasma levels (9). Against this background we decided to use this approach to optimize the conditions for plasma sampling. However, the administration of nasal drops after induction of anesthesia does in fact differ from the administration to the awake child as the awake child is most often sitting up and is breathing at least partly through the nose, something that may enhance the distribution of the drug across the nasal mucosa and favor retention of the drug in the nasopharynx. Contrary to the Galinkin study (spontaneous ventilation via a face mask) no nasal breathing was possible in our study due to the laryngeal mask airway and this combined with a supine position may have increased the likelihood of a substantial part of the administered dose to rapidly trickle down into the oro-and hypo-pharynx.

Due to the unexpected absorption pattern associated with our administration technique the number of blood sampling time points was limited at the time when Cmax and Tmax values actually did occur. This does render our estimates of Cmax and Tmax somewhat imprecise but does not alter the conclusion that nasal administration as nasal drops cannot be recommended due to the great interindividual variability of absorption associated with this administration technique.

Plasma concentrations in this study were found to be within the range of plasma concentrations associated with clinical effects regarding sedation in children (10) (0.3 $ng \cdot ml^{-1}$) and adults (3,11,12) (0.2–2.0 $ng \cdot ml^{-1}$). However, plasma concentrations were lower than those found after rectal (4) or epidural (10) clonidine administration. Furthermore, time to achieve maximum plasma concentration was approximately 2 h and therefore 20 times longer than in the rodent study (7) and more than twice as long as the time to achieve the maximum sedative effect in our previous clinical study (6).

Despite the previous report by Galinkin *et al*. (9) of successful nasal administration of fentanyl after the induction of anesthesia the most probable explanation for the delayed and limited absorption of clonidine nasal drops seen in our study is most likely the method of drug administration as outlined above. In fact, in the study on rodents the nasopalatine passage was artificially closed to prevent drainage of the drug from the nasal cavity to the mouth (7).

In conclusion, the results from this study together with our previous clinical findings underline that clonidine nasal drops are not sufficiently absorbed from the nasal mucosa and hence a direct transport of the drug into the systemic circulation does not occur in a predictable way. Based on these findings we cannot recommend clonidine premedication delivered as nasal drops.

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