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RESEARCH ARTICLE

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Absorption pharmacokinetics and feasibility of intranasal dexmedetomidine in patients under general anaesthesia

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Abstract

Background: The use of intranasal dexmedetomidine is hampered by a limited understanding of its absorption pharmacokinetics.

Methods: We examined the pharmacokinetics and feasibility of intranasal dexmedetomidine administered in the supine position to adult patients undergoing general anaesthesia. Twenty-eight patients between 35 and 80 years of age, ASA 1–3 and weight between 50 and 100 kg, who underwent elective unilateral total hip or knee arthroplasty under general anaesthesia were recruited. All patients received 100 μg of intranasal dexmedetomidine after anaesthesia induction. Six venous blood samples (at 0, 5, 15, 45, 60, 240 min timepoints from dexmedetomidine administration) were collected from each patient and dexmedetomidine plasma concentrations were measured. Concentration-time profiles after nasal administration were pooled with earlier data from a population analysis of intravenous dexmedetomidine ($n = 202$) in order to estimate absorption parameters using nonlinear mixed effects. Peak concentration (C_{MAX}) and time (T_{MAX}) were estimated using simulation ($n = 1000$) with parameter estimates and their associated variability.

Results: There were 28 adult patients with a mean (SD) age of 66 (8) years and weight of 83 (10) kg. The mean weight-adjusted dose of dexmedetomidine was 1.22 (0.15) μg kg^{-1}. C_{MAX} 0.273 μg L^{-1} was achieved at 98 min after intranasal administration (T_{MAX}). The relative bioavailability of dexmedetomidine was 80% (95% CI 75–91%). The absorption half-time ($T_{ABS} = 120$ min; 95% CI 90–147 min) was slower

than that in previous pharmacokinetic studies on adult patients. Perioperative haemodynamics of all patients remained stable.

Conclusions: Administration of intranasal dexmedetomidine in the supine position during general anaesthesia is feasible with good bioavailability. This administration method has slower absorption when compared to awake patients in upright position, with consequent concentrations attained after T_{MAX} for several hours.

KEYWORDS
alpha2-agonists, extravascular administration, intranasal administration, pharmacokinetics

Editorial Comment

This study in normal sized adults provided a standardised dose of nasal dexmedetomidine during general anaesthesia and in the supine position. The relative bioavailability of dexmedetomidine was found to be 80%, identifying a peak blood concentration estimate for this dose, along with an estimated time to achieve this of 98 min, which was slower than has been previously reported.

1 | INTRODUCTION

The highly selective alpha-2-adrenoceptor agonist dexmedetomidine is indicated for procedural and intensive care sedation in adult patients. In addition to its sedative properties, dexmedetomidine has been shown to have an analgesic effect and diminish postoperative opioid consumption.[1] Other possible benefits of perioperatively administered dexmedetomidine include a lower incidence of postoperative delirium,[2] nausea,[3] anti-inflammatory effects[4] and organoprotective effects.[5]

Intravenous and sublingual routes[6] are the only approved administration routes for dexmedetomidine. Alternative extravascular routes, such as intranasal administration, have gained popularity in recent years. Intranasal administration of dexmedetomidine is currently still considered off-label although it has been found to be safe and effective.[7,8] The main benefits of intranasal administration are non-invasiveness and ease of administration. It avoids hepatic first-pass metabolism and has thus improved bioavailability compared with oral administration. Furthermore, intranasal administration may reduce acute hemodynamic changes after dexmedetomidine administration compared with rapid intravenous administration.[8–10]

Pharmacokinetics of intranasal dexmedetomidine have been previously studied mainly in children,[11–15] although adult studies exist.[8,16–19] Dexmedetomidine was administered to awake adults in the upright or semi-recumbent position in previous studies. Absorption parameters for intranasal dexmedetomidine have not been studied in anaesthetised adult patients, although this administration routine has been reported in both children[13] and adults.[20,21] We investigated the absorption pharmacokinetics of intranasal dexmedetomidine in adult patients under general anaesthesia after administration in the supine position. We also describe the intraoperative haemodynamics and requirement for other anaesthetics and vasoactive medication.

2 | METHODS

2.1 | Ethical considerations

This prospective pharmacokinetic study was registered at clinicaltrials.gov (NCT05065775). The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, Turku, Finland (80/1800/2021) (Chairperson MD, PhD Sirkku Jyrkkiö) on 17 August 2021 and by the national drug regulatory authority; Finnish Medicines Agency (Fimea). Written informed consent was obtained from each patient.

2.2 | Study outline

An open, exploratory study design was used. Patients scheduled for elective unilateral total knee arthroplasty (TKA) or total hip arthroplasty (THA) under general anaesthesia were recruited. Data were collected prospectively at Turku University Hospital between November and December 2021.

2.3 | Patient population

Patients were considered eligible if they were between 35 and 80 years of age, ASA (American Society of Anaesthesiologists) status 1–3 and weighted between 50 and 100 kg. The exclusion criteria were as follows: previous history of intolerance to the study drug or related compounds and additives, disease or condition affecting the patient's ability to give written informed consent, existing or recent disease that could affect absorption, distribution, metabolism, excretion, or response to the study drug, history of cardiac disease (valvular insufficiency, severe left ventricular dysfunction), pacemaker or abnormal ECG rhythm (bradycardia <50/min, 2nd or 3rd degree AV-

block), chronic opioid use or use of other analgesic adjuvants such as pregabalin, gabapentin, amitriptyline, or duloxetine, prior use of alpha-2-agonists, involvement in any other study concurrently or within a month before, clinically important abnormal findings in physical examination or laboratory screening, use of drugs or natural products known to cause enzyme induction or inhibition, pregnancy or breast-feeding, spinal anaesthesia, and preoperative systolic blood pressure <110 mmHg.

2.4 | Sample size

We aimed to recruit 30 patients for this study. Two additional patients were recruited in anticipation of dropouts or sample assay irregularities. The sample size was based on previous pharmacokinetic studies with intranasal dexmedetomidine.[13,16]

2.5 | Drug administration

Intranasal dexmedetomidine 100 μg (Dexdor® 100 μg ml^{-1}, Orion Pharma, Espoo, Finland) was administered within 5 min of anaesthesia induction according to the local protocol. Administration was performed using a 1 mL syringe with an atomizer (Teleflex MAD Nasal™). The total volume of dexmedetomidine was 1 mL, which was evenly divided into both nostrils (0.5 mL in each nare). Dexmedetomidine administration was performed by registered nurses trained in the administration technique. When dexmedetomidine was administered, patients were in the supine position with head positioned in midline, while under general anaesthesia and supraglottic airway in place.

2.6 | Anaesthetic management

Anaesthesia was conducted with total intravenous anaesthesia using propofol and remifentanil target-controlled infusions. Propofol TCI was administered with the Schnider effect-site model and remifentanil with the Minto effect-site model. Airway management was accomplished using a supraglottic airway device (either Ambu® or i-gel®). Hypotension (mean arterial pressure; MAP <65 mmHg) was treated with intravenous ephedrine bolus (6 mg). If hypotension persisted despite 1–4 ephedrine boluses, an intravenous norepinephrine infusion was initiated. Bradycardia (heart rate; HR <40/min) was treated with an intravenous (0.5–1.0 mg) atropine bolus.

2.7 | Concomitant medications during the perioperative period

For premedication, all patients received 1 g of oral acetaminophen. To enhance multimodal analgesia, intravenous corticosteroid (either intravenous hydrocortisone 125 mg or betamethasone 4 mg) was administered during surgery. Local infiltration analgesia (LIA) consisting of levobupivacaine and adrenaline was administered to all patients by the operating orthopaedic surgeon. Non-steroidal anti-inflammatory drug (intravenous ketorolac 30 mg) was administered at the end of surgery if the patient had no contraindications. To prevent postoperative nausea and vomiting, intravenous granisetron 1 mg was administered if deemed necessary. All patients received 1 g of intravenous tranexamic acid to reduce blood loss. At the end of surgery, an intravenous opioid (fentanyl or oxycodone) was administered when the remifentanil infusion was stopped. In the postoperative care unit pain was treated principally with intravenous oxycodone.

2.8 | Blood sampling

After the induction of anaesthesia, a second venous cannula was placed in the contralateral antecubital vein to obtain blood samples. Venous blood samples (2.0 mL in EDTA containing tubes) were obtained to determine the plasma concentrations of dexmedetomidine. Altogether six blood samples were obtained from each patient. One sample was taken before dexmedetomidine administration (baseline). Two venous blood samples were drawn during the assumed absorption phase (at 5 min and 15 min after drug administration), another two samples during the assumed distribution phase (at 45 min and 60 min after drug administration) and one sample during the assumed elimination phase (at 240 min after drug administration). Sampling times were based on earlier pharmacokinetic profile of intranasally administered dexmedetomidine.[8,18] The samples were chilled on ice. Blood samples were centrifuged, and plasma was separated and stored at −40 degrees until analysis.

2.9 | Dexmedetomidine plasma concentration analysis

Dexmedetomidine plasma concentrations were measured at the Bioanalytical laboratory, Institute of Biomedicine, University of Turku, using a validated liquid chromatographic/mass spectrometric method. The analytical methods used to determine the concentrations of dexmedetomidine are described in detail in the electronic supplemental file (Supplemental File 1).

2.10 | Population pharmacokinetics

Investigation of absorption parameters (absorption half time [T_{ABS}], absorption lag time [T_{LAG}] and relative bioavailability [F]) entailed pooling time-concentration data from this current study with those from investigations using intravenous administration. Dexmedetomidine concentration data collected in this current study were pooled with published dexmedetomidine time-concentration observations.[22–26] Analysis of these pooled data without the

additional observations from the current study are available and details of data sources, pharmacokinetic analysis and results are published.[27]

A two-compartment pharmacokinetic (PK) model with first order elimination were used to describe dexmedetomidine pharmacokinetics. The model was parameterised in terms of clearance (CL), volumes of distribution (V1, V2), and intercompartmental clearance (Q2). A depot compartment was used to model the absorption rate constant (k_a) that was expressed as an absorption half-time (T_{ABS}).

$$T_{ABS} = Logn/k_a$$

Population parameter estimates were obtained using nonlinear mixed effects models (NONMEM 7.5 ICON Development Solutions, USA) with first-order conditional estimation and a convergence criterion set to 3 significant digits. The population mean parameters, between subject variance and residual variance were estimated using the first order conditional interaction estimate method using ADVAN13 TOL = 9 of NONMEM.

PK parameters (e.g., CL, Q2, V1, V2) were standardised to an adult measure of body size with a standard weight of 70 kg using allometric scaling.[28] Population parameter variability (PPV) was accounted for using an exponential model for the random effect variables (η). This assumes a log-normal distribution and avoids parameter estimates falling below biologically plausible values. Residual unidentified variability (RUV) was modelled using both proportional and additive residual errors. The between subject variability (ηRUV,i) of the RUV was also estimated for the data.

Model selection was also based on parameter plausibility and prediction-corrected visual predictive checks (PC-VPC) plots.[29] Bootstrap methods provided a means to evaluate parameter uncertainty.[30] A total of 100 bootstrap replications were used to estimate parameter means and confidence intervals. Results from the population models are presented as parameter estimates, together with their 95% CI. Between subject parameter variability is expressed as an apparent coefficient of variation obtained from the square root of the variance estimate.

2.11 | Haemodynamics and requirement of anaesthetics and vasoactive medication

Heart rate (HR), systolic, diastolic, and mean arterial pressure (MAP) were recorded immediately prior to administration of dexmedetomidine and 5, 10, 15, 30, and 45 min, 1 h, 2 h, 3 h, and 4 h after dexmedetomidine administration. Blood pressure was measured with non-invasive blood pressure monitoring (NIBP). Intraoperative ephedrine and norepinephrine requirements as well as cumulative propofol and remifentanil doses were recorded.

2.12 | Safety and adverse events

We defined adverse events of special interest as bradycardia, hypotension, respiratory complications, and other drug reactions within 4 h of dexmedetomidine administration. Bradycardia was defined as HR lower than 40/min, including administration of atropine. Hypotension was defined as MAP lower than 65 mmHg despite adequate fluid bolus or vasoactive medication. Respiratory complications included difficulties weaning the patient from ventilator, requirement for more than 40% supplemental oxygen, requirement for non-invasive ventilator support and respiratory rate over 20/min. Other drug reactions included any allergic reactions or local symptoms related to intranasal drug administration.

TABLE 1 Patient characteristics.

	All patients ($n = 28$)
Surgery type (THA/TKA)	11/17
Age (years)	66.2 (7.6) [56–80]
Gender (F/M)	19/9
Weight (kg)	82.9 (9.6) [63–98]
Height (cm)	169.8 (8.9) [156–185]
BMI	28.9 (4.0) [21.5–37.5]
Weight-adjusted dexmedetomidine dose (μg kg^{-1})	1.22 (0.15) [1.02–1.58]

Note: Data are shown as mean (±standard deviation), [range].
Abbreviations: BMI, body mass index; F, female; M, male; TKA, total knee arthroplasty; THA, total hip arthroplasty.

3 | RESULTS

Data collection took place in November–December 2021 at Turku University Hospital. Thirty-two patients who met the eligibility criteria were enrolled to participate in this study; however, two patients were excluded from the analyses due to inadequate blood sampling and two patients were later excluded due to blood sample haemolysis. A total of 168 plasma samples were collected from 28 subjects.

The patients' characteristics are presented in Table 1. Eleven patients underwent total hip arthroplasty (THA), and seventeen patients total knee arthroplasty (TKA). Mean age of patients was 66.2 years and mean BMI 28.9. Most of patients were female, which was expected because osteoarthritis is more common in women than in men. The majority of patients were Caucasian, and only one patient was non-Caucasian (African). The dose of intranasal dexmedetomidine administered to all patients was 100 μg. The median weight-adjusted dose of dexmedetomidine was 1.22 μg kg^{-1}.

3.1 | Pooled compartment pharmacokinetics

Parameter estimates for the pooled data determining the dexmedetomidine model are shown in Table 2. There were 2284 dexmedetomidine concentrations that were amenable for modelling in the pooled dexmedetomidine PK analysis. This pooled data analysis included 168 drug concentrations from the 28 participants administered

TABLE 2 Dexmedetomidine population pharmacokinetic parameter estimates.

	Estimate	PPV (%)	Bootstrap median	95%CI
V1 (L/70 kg)	27.3	99.8	28.8	24.8, 34.0
V2 (L/70 kg)	69.9	30.1	70.2	77.5
CL (L/min/70 kg)	0.677	39.	0.688	0.653, 0.836
Q2 (L/min/70 kg)	1.09	49.4	1.09	0.918, 1.27
F	0.80	-	-	0.75, 0.91
T_{ABS} (min)	120	22.9	120	90, 147
T_{LAG} (min)	2.75	-	2.70	1.82, 3.44
Additive residual error (μg L^{-1})	0.005	38.6	0.004	0.003, 0.006
Proportional residual error (%)	21.2	-	21.1	19.8, 22.4

Note: Bootstrap median and 95% confidence interval (CI) determined from 100 bootstrap replications. Abbreviations: CL, clearance; Q2, intercompartmental clearance; PPV%, population parameter variability; RUV_{ADD}, additive residual unidentified variability; RUV_{PROP}, proportional residual unidentified variability; V1, central volume of distribution; V2, peripheral volume of distribution.

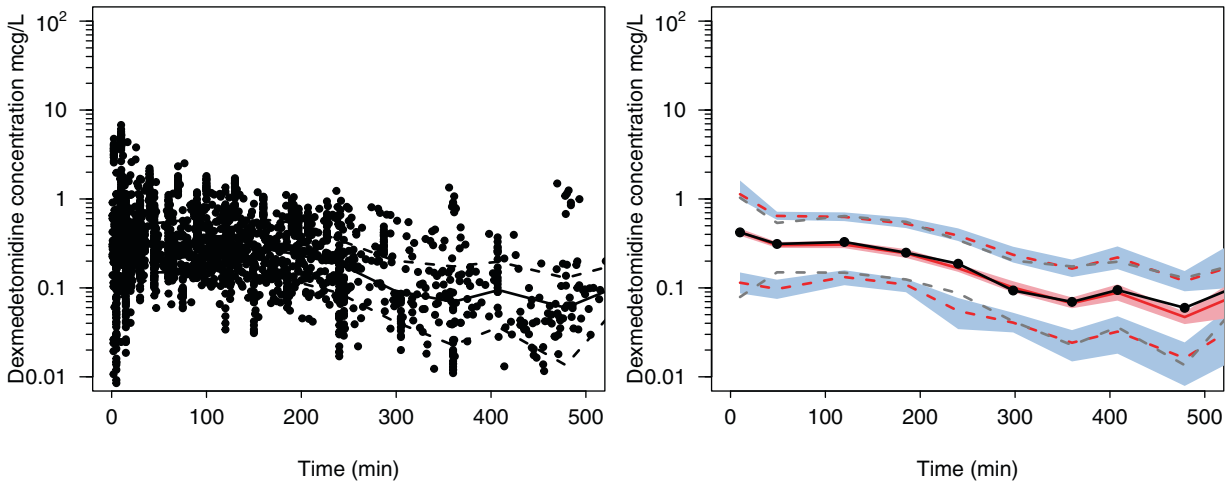

FIGURE 1 Prediction-corrected visual predictive check (PC-VPC) for pooled patients ($n = 2284$) using the universal dexmedetomidine PK parameter set. Plots show median (solid) and 90% intervals (dashed lines). The left-hand plot shows all prediction corrected observed dexmedetomidine concentrations. Right-hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (grey dashed lines) and predictions (red dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5th and 95th blue shading).

intranasal dexmedetomidine. A two-compartment PK model was adequate to describe the concentration profiles. The final model included allometric scaling of the pharmacokinetic parameters using total body weight. The PC-VPC plots for the pooled population analysis are shown in Figure 1. The absorption half time (T_{ABS}) was 120 min (CV 22.9%) with a relative bioavailability of 0.8. There was a short lag time ($T_{LAG} = 2.7$ min) between administration and the start of absorption. The PC-VPC for those patients ($n = 28$) given intranasal dexmedetomidine are shown in Figure 2. For two nested models a decrease in the minimum value of the objective function (ΔOBJ) of 3.84 points for an added parameter was considered significant at the 0.05 level.

The maximum concentration (C_{MAX}) and time to maximum concentration (T_{MAX}) of intranasal dexmedetomidine could not be determined from observational methods because they fell unexpectedly between 60 min and 480 min. Time-concentration profiles were simulated (1000 replications) with current parameter estimates (Table 2) for nasal dexmedetomidine 100 μg using differential equations in Berkeley Madonna™ modelling and simulation software (Robert Macey and George Oster of the University of California Berkeley, USA) and are shown in Figure 3. According to the simulation, a mean C_{MAX} of 0.273 μg L^{-1} was achieved at a T_{MAX} of 98 min after intranasal administration. This figure also demonstrates the time concentration profile in a typical patient given 100 μg dexmedetomidine intravenously over 15 min. Simulated concentrations were greater after nasal delivery at 4 h than those predicted after intravenous administration. The C_{MAX} prediction attained after nasal delivery is sustained for 2 h due to slow absorption (T_{ABS} 2 h).

3.2 | Haemodynamics and requirement of anaesthetics and vasoactive medication

Intranasal dexmedetomidine dose of 100 μg was haemodynamically well tolerated. The median (IQR) dose of intravenous ephedrine was 6 mg (0–12 mg). None of the patients required norepinephrine infusion to treat hypotension. No bradycardia was reported. Figure 4A,B

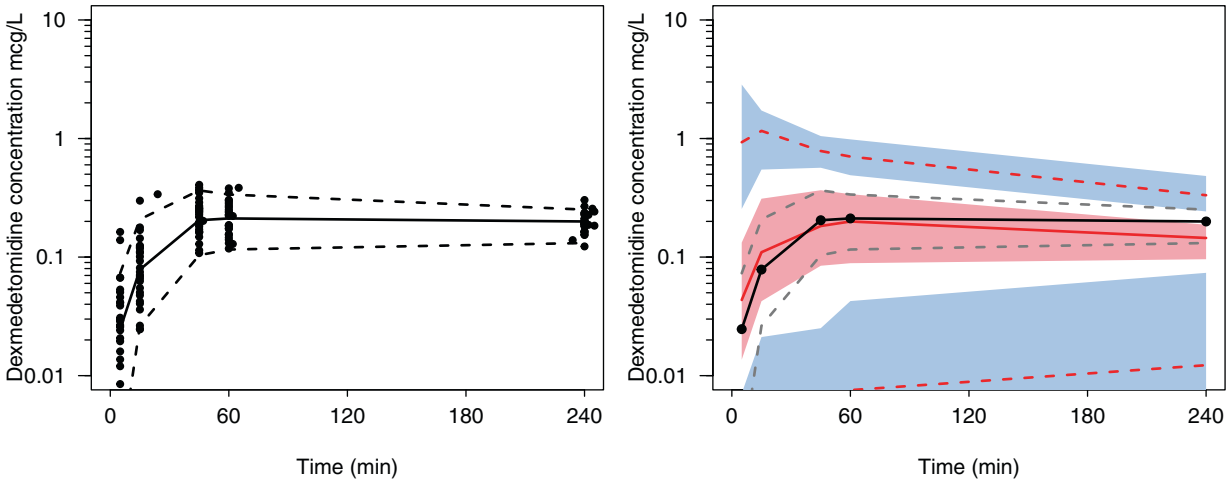

FIGURE 2 Prediction-corrected visual predictive check (PC-VPC) of for those patients ($n = 28$) given intranasal dexmedetomidine. Plots show simulation-based median (solid) and 90% intervals (dashed lines). The left-hand plot shows all prediction corrected observed dexmedetomidine concentrations. Right-hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (grey dashed lines) and predictions (red dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5th and 95th blue shading).

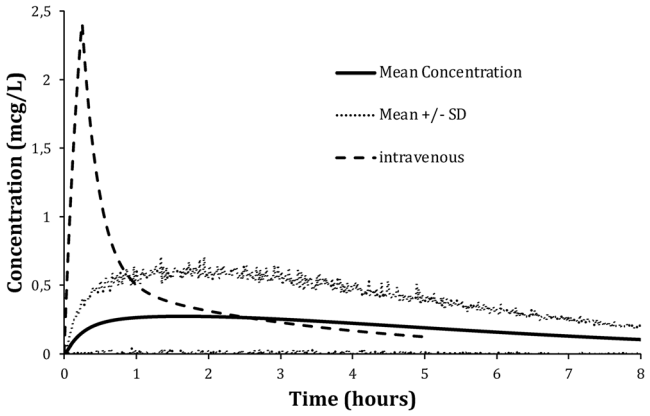

FIGURE 3 Plasma concentration–time curve. Concentrations of intravenously administered 100 μg dexmedetomidine over 15 min (dashed) and intranasally administered 100 μg dexmedetomidine (black). A mean C_{MAX} of 0.273 μg L^{-1} was achieved at a T_{MAX} of 98 min after intranasal administration. Concentrations are sustained around this C_{MAX} over 2 h.

summarise the intraoperative haemodynamics of the patient population. Mean (SD) dose of intravenous propofol and remifentanil were 15 (3.6) mg kg^{-1} and 8 (2.4) μg kg^{-1} respectively.

3.3 | Safety

No adverse or serious adverse effects were reported.

4 | DISCUSSION

Our primary aim in this study was to evaluate the pharmacokinetics of intranasal dexmedetomidine in adult patients under general anaesthesia after administration in the supine position. Prior studies have established the pharmacokinetic profile of intranasal dexmedetomidine in awake adult patients after administration in the upright position and in anaesthetised children after administration in the supine position. We questioned whether patient position and general anaesthesia impacted absorption parameter estimates. Our current findings suggest that either the position in which intranasal dexmedetomidine is administered, or concomitant general anaesthesia or both, might influence observed time-concentration profiles.

In previous studies conducted on anaesthetised children in the supine position, time-concentration profiles of intranasal dexmedetomidine were similar to those in the current study,[11,14] but compared with pharmacokinetic studies conducted on awake adult patients in the upright position, marked differences could be observed. Pharmacokinetic parameters in previously published adult studies are summarised in Table 3 for comparison. In this study the median time to reach maximum concentration (T_{MAX}) was approximately 90 min, which is notably longer than that in prior adult studies. The peak concentrations (C_{MAX} of 0.273 μg L^{-1}) were similar to previous findings, but absorption half-time (T_{ABS}) of 2 h and sustained concentrations around T_{MAX} for 2–3 h, markedly differ from earlier studies.

Some individual time-concentrations demonstrated an early rapid absorption phase and a later slower absorption phase. Supine position during dexmedetomidine administration may lead to slower absorption and delayed onset of action because medication drips into the oesophagus and is absorbed from both the nasopharynx and gastrointestinal tract. However, in the current study, the supraglottic airway device acted as a mechanical obstacle that prevented drug from lower gastrointestinal absorption. The pharmacokinetics of intranasal dexmedetomidine in intubated children are consistent with our findings, indicating that the position may affect the absorption of intranasally administered dexmedetomidine.[14] Relative bioavailability was higher than that in earlier adult studies (Table 3),[8,16] which also speaks

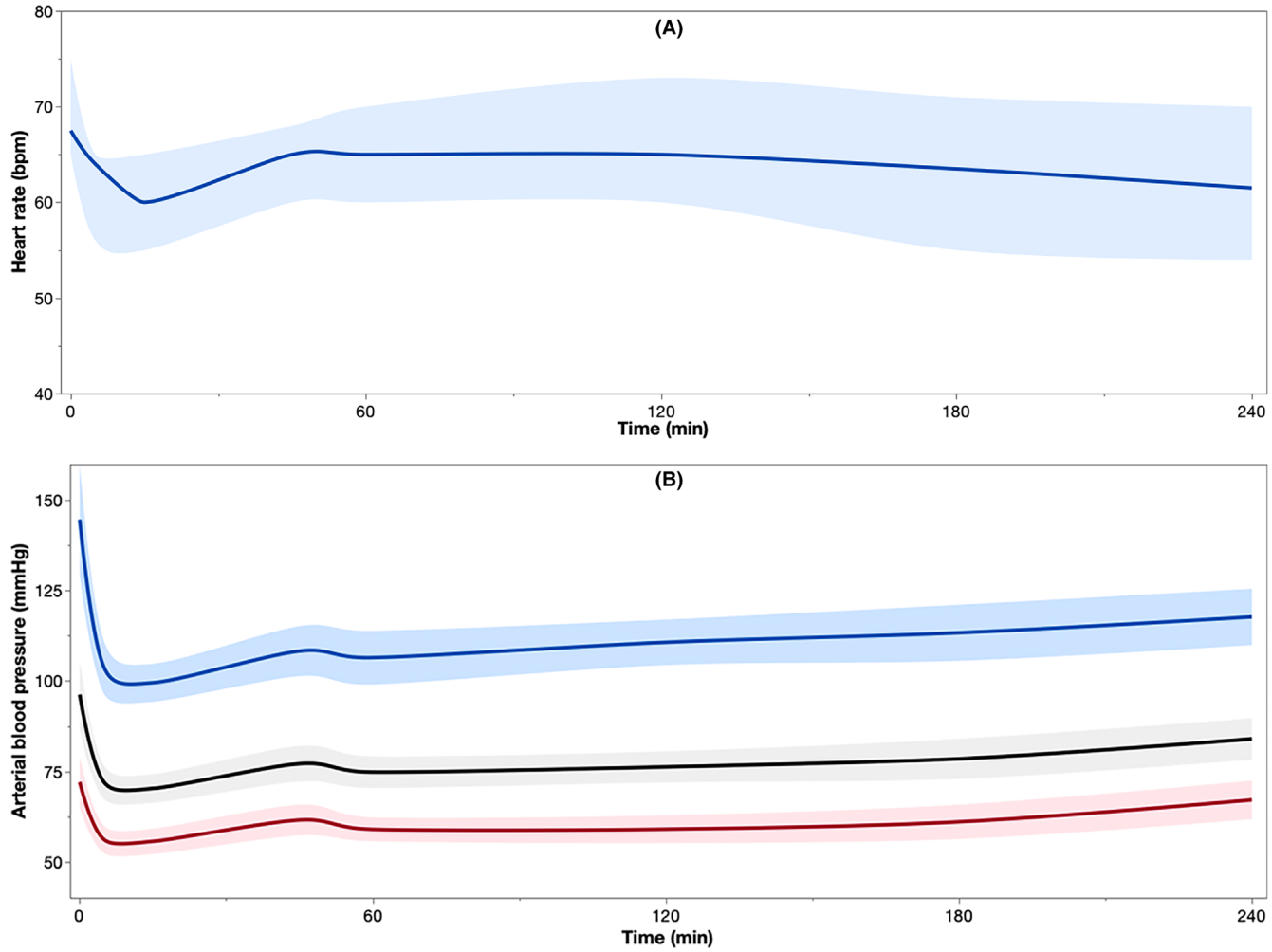

FIGURE 4 (A) Heart rate (bpm; beats per minute) and (B) mean blood pressure (black), systolic arterial pressure (blue) and diastolic arterial pressure (red); expressed as median and 95% confidence interval (lighter band) after administration of 100 μg intranasal dexmedetomidine.

TABLE 3 Pharmacokinetic parameters of intranasal dexmedetomidine administration in previously published adult studies.

	Current study	Li et al.[16]		Wu et al.[19]	Kuang et al.[17]	Iirola et al.[8]	Yoo et al.[18]
Administration method and solution	**Nasal atomizer**	**Nasal atomizer**	**Nasal drops**	**Nasal drops**	**Specialised nasal spray**	**Spray Pump VP7/100S, highly concentrated veterinary solution**	**Spray Pump VP7/100S, highly concentrated veterinary solution**
F (%)	80	40,6	40.7		85	65	82
T_{MAX} (min)	98	47.5	60	13.2	30	30	30
C_{MAX} (ng ml^{-1})	0.273	0.28	0.25		0.556	0.34	0.314
k_a (h^{-1})	0.424	0.855	0.725				0.94

Abbreviations: C_{MAX} maximum concentration; F, bioavailability; k_a, absorption rate constant; T_{MAX}, time to reach maximum concentration.

against absorption from the gastrointestinal tract where bioavailability is lower due to first-pass metabolism.[31] This could possibly indicate that slow absorption might be a result of pooling in the nasopharynx and absorption from oral mucosa, since absorption parameters after buccal administration resemble those observed in our study.[31] Absorption differences could be contributed by different absorption characteristics in different anatomical parts of the nasopharynx. Sampling times were too sparse in this current analysis to determine this more complex absorption profile.

The optimal position for intranasal drug administration is unknown. Intranasal drug deposition is affected by posture.[32] Posture affects the nasal cycle, which in turn influences the absorption of intranasally administered medications. In the supine position, nasal obstruction may be more prominent.[33] Posture may also decrease the

rate of venous return from the head region.[34] On the other hand, no drug will be lost externally in the supine position. In the present study, we used a nasal atomiser for administration, which is advertised to atomise in any position.[35] However, previous research has shown that even with a nasal atomiser, the head position affects drug distribution in the nasal cavity.[36]

Another potential reason affecting drug metabolism is the concomitant administration of anaesthetic agents. Co-administration of various other medications related to general anaesthesia may influence dexmedetomidine pharmacokinetics. However, clearance in the current cohort was consistent with that reported in other studies. Dexmedetomidine is extensively metabolised by glucuronidation (UGT 2B10, UGT1A4) with lesser contribution by cytochrome P450 (CYP) enzymes (mainly CYP2A6).[37] Pharmacokinetic interactions are unlikely, with only a few reported in the literature[38,39] due to several metabolising enzymes and because UGT clearance capacity is large. Haemodynamics may influence dexmedetomidine elimination through altered liver blood flow.[40] In the current study, mean arterial pressure was reduced from baseline after the induction of general anaesthesia but remained stable in all patients without the need for norepinephrine infusion. Clearance estimates were unchanged from those others in the pooled data analysis.

The majority of the previous pharmacokinetic research on adults has been conducted on healthy volunteers. Pharmacokinetics in healthy individuals may differ significantly from those in patients with comorbidities. Only one earlier study by Wu et al. examined intranasal dexmedetomidine pharmacokinetics on actual patients,[19] but in that study patient population was considerably younger (43 years vs. 66 years), thinner (median BMI 22 vs. 29), and healthier (ASA 1 vs. ASA 1–3) compared with our study. Earlier studies have suggested that comorbidities and weight may influence dexmedetomidine pharmacokinetics.[37] However, clearance in the current study was standardised for size using allometry. We were unable to detect any changes in clearance with age.

It is noteworthy that previous studies used different dexmedetomidine solutions (Table 3), which could explain some of the differences. No commercial solution specifically designed for intranasal administration is available at the moment, although one earlier study used a dexmedetomidine nasal spray, which was specifically intended for intranasal administration.[17] When administering dexmedetomidine intranasally in practice, an intravenous preparation with concentration 100 μg ml^{-1} is typically used. Because the amount of liquid that can be dosed intranasally is limited (10–150 mcL/nostril),[41] there is a need for stronger dexmedetomidine preparation. The optimal volume in studies has been less than 0.2–0.3 mL, but in practice doses up to 0.5 mL are used.[42] Drug volumes should be kept to a minimum because mucosal surfaces can become saturated, resulting in runoff into the oropharynx and reduced absorption. In the upright or semi-recumbent position large drug volumes also lead to running nose. In addition to more concentrated dexmedetomidine, another possible option is to use repeated small doses to achieve the desired effect in larger patients. Different concentration and therefore different amount of liquid may affect the pharmacokinetic profile.

Although intranasal administration of dexmedetomidine is off-label, it has been widely adapted in clinical practice and considered safe in earlier studies.[7,8] Previous research has found no adverse effects associated specifically with dexmedetomidine administered through the intranasal route.[8,43] Dexmedetomidine has a biphasic effect on blood pressure. There is direct early vasoconstriction associated with plasma concentration, however central mediated vasoconstriction occurs later.[25] Thus, intravenous bolus administration may be associated with labile haemodynamics. Intranasal administration has slow absorption and these haemodynamic effects are less obvious.[9] We reported cardiovascular stability during the period of sustained concentrations after T_{MAX} (Figure 4). Intranasal administration provides longer sustained concentrations (Figure 3) and concentrations are actually higher in the nasal group at 4 h compared with intravenous administration, while avoiding cardiovascular instability caused by abrupt concentration changes. Some concern has been raised about intranasal dexmedetomidine administration in older adults, since hemodynamic alterations may be more pronounced and deleterious in this patient population.[44] In the current study, no adverse or serious adverse events were recorded. Most patients required 6–12 mg of intravenous ephedrine for intraoperative hypotension, which is common after intravenous general anaesthesia induction. None of the patients experienced bradycardia.

4.1 | Limitations

The major limitation of this study is the paucity of samples during the absorption phase, which disallowed a comprehensive investigation of absorption characteristics. Delayed sampling for assay out to three half-lives would have been useful to better characterise clearance. Slow absorption contributed to higher than anticipated concentrations at 4 h. However, pooling of data allowed the assessment of parameter estimates using nonlinear effects models.

4.2 | Future prospects

We would suggest that further studies should be aimed to investigate the impact of age on dexmedetomidine clearance, to better understand absorption within the nasopharynx, and competitive or inhibitory effects of agents commonly used in anaesthesia on clearance.

5 | CONCLUSIONS

In conclusion, our study demonstrated that intranasal dexmedetomidine is well absorbed in anaesthetised adult patients. Administration during general anaesthesia in the supine position resulted in slower absorption and sustained concentrations when compared with intranasal administration in the upright position or intravenous administration. Intranasal dexmedetomidine is a feasible anaesthetic adjuvant

for adult patients undergoing unilateral THA or TKA under general anaesthesia.

AUTHOR CONTRIBUTIONS

Study design: PU, TIS; Supervision: PU, TIS; Data collection: SMT, ER; Figures and tables: SMT, PU, BJA; Interpretation of results: SMT, BJA, AT, MTE, PU; Writing of the manuscript: All authors.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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