

Population Pharmacokinetics and Pharmacodynamics of Dexmedetomidine in Children Undergoing Ambulatory Surgery

María-Gabriela Pérez-Guillé, MD,* Alejandra Toledo-López, PHC,* Liliana Rivera-Espinosa, MSc,* Radames Alemon-Medina, PhD,* Chiharu Murata, MSc,† Ismael Lares-Asseff, PhD,‡ Juan Luis Chávez-Pacheco, PhD,* Josefina Gómez-Garduño, Biol.§ Ana-Lilia Zamora Gutiérrez, MD,|| Claudia Orozco-Galicia, MD,|| Karina Ramírez-Morales, MD,|| and Gustavo Lugo-Goytia, PhD¶

BACKGROUND: Dexmedetomidine (DEX) is an α -2 adrenergic agonist with sedative and analgesic properties. Although not approved for pediatric use by the Food and Drug Administration, DEX is increasingly used in pediatric anesthesia and critical care. However, very limited information is available regarding the pharmacokinetics of DEX in children. The aim of this study was to investigate DEX pharmacokinetics and pharmacodynamics (PK–PD) in Mexican children 2–18 years of age who were undergoing outpatient surgical procedures.

METHODS: Thirty children 2–18 years of age with American Society of Anesthesiologists physical status score of I/II were enrolled in this study. DEX (0.7 μ g/kg) was administered as a single-dose intravenous infusion. Venous blood samples were collected, and plasma DEX concentrations were analyzed with a combination of high-performance liquid chromatography and electrospray ionization-tandem mass spectrometry. Population PK–PD models were constructed using the Monolix program.

RESULTS: A 2-compartment model adequately described the concentration–time relationship. The parameters were standardized for a body weight of 70 kg by using an allometric model. Population parameters estimates were as follows: mean (between-subject variability): clearance (Cl) (L/h \times 70 kg) = 20.8 (27%); central volume of distribution (V1) (L \times 70 kg) = 21.9 (20%); peripheral volume of distribution (V2) (L \times 70 kg) = 81.2 (21%); and intercompartmental clearance (Q) (L/h \times 70 kg) = 75.8 (25%). The PK–PD model predicted a maximum mean arterial blood pressure reduction of 45% with an IC_{50} of 0.501 ng/ml, and a maximum heart rate reduction of 28.9% with an IC_{50} of 0.552 ng/ml.

CONCLUSIONS: Our results suggest that in Mexican children 2–18 years of age with American Society of Anesthesiologists score of I/II, the DEX dose should be adjusted in accordance with lower DEX clearance. (Anesth Analg 2018;127:716–23)

KEY POINTS

- **Question:** What are the pharmacokinetics and pharmacodynamics of dexmedetomidine in Mexican children?
- **Findings:** The pharmacokinetics of dexmedetomidine was explained by a 2-compartment model with a clearance of 20.8 L-hour⁻¹ 70 kg, lower than that reported in the literature in other populations, and an IC_{50} (ng/mL) for heart rate and mean arterial blood pressure of 0.552 and 0.501, respectively.
- **Meaning:** The clearance of dexmedetomidine is lower in our population of Mexican Mestizo children, as compared with other populations, suggesting an adjustment in the dosage to obtain a target plasma concentration.

Dexmedetomidine (DEX) is a highly selective agonist of α -2 adrenergic receptors. DEX activity in the locus coeruleus and spinal cord results in sedative and analgesic

effects with minimal respiratory depression.¹ These effects reduce postoperative agitation and analgesic requirements^{2–5}; therefore, DEX usage may be beneficial in outpatient surgical procedures.

From the *Departamento de Farmacología, Instituto Nacional de Pediatría, México; †Departamento de Metodología de la Investigación, Instituto Nacional de Pediatría, México; ‡Instituto Politécnico Nacional CIIDIR Durango, México; §Laboratorio de Toxicología Experimental, Instituto Nacional de Pediatría, México; ||Departamento de Anestesiología, Instituto Nacional de Pediatría, México; and ¶Departamento de Anestesiología y Medicina Crítica, Instituto Nacional de Ciencias Médicas y Nutrición, México;

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DOI: 10.1213/ANE.00000000000003413

and Respiratory Intensive Care Unit, Instituto Nacional de Enfermedades Respiratorias, México.

Accepted for publication March 27, 2018.

Funding: None.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgia.org).

Reprints will not be available from the authors.

Address correspondence to Gustavo Lugo-Goytia, PhD, Departamento de Anestesiología y Medicina Crítica, Instituto Nacional de Ciencias Médicas y Nutrición, México; and Respiratory Intensive Care Unit, Instituto Nacional de Enfermedades Respiratorias, México. Address e-mail to lugogoy@yahoo.com.mx.

Although DEX is not Food and Drug Administration–approved for use in children, it is being increasingly used in pediatric anesthesia and intensive care.^{2–7} However, very limited information is available concerning the pharmacokinetics (PK) and pharmacodynamics (PD) of DEX in children, especially in the Mexican population. Information about the PK–PD behavior of DEX in this specific population can contribute to the design of safer and more effective dosing regimens.

Therefore, in this study, we aimed to characterize the PK–PD of DEX in healthy Mexican children 2–18 years of age who underwent outpatient surgical interventions.

METHODS

Study Design and Patient Population

This study was approved by the local Institutional Review Board (#062/2014), and written informed consent was obtained from all subjects participating in the trial. After approval was granted, 30 children 2–18 years of age with an American Society of Anesthesiologists (ASA) physical status score of I/II who were scheduled to undergo outpatient surgical procedures were enrolled in this prospective study. Written informed consent was obtained from the children’s parents after they were informed of the objectives and risks, and consent was obtained from children >9 years of age. Exclusion criteria were the use of drugs with an enzyme-inducing effect, history of arrhythmias, delayed neurological development, or malnutrition. This manuscript adheres to the applicable Consolidated Standards Of Reporting Trials (CONSORT) guidelines.

Electrocardiogram, pulse oximetry, capnography, and temperature were recorded continuously during surgery. Heart rate (HR) and systolic, diastolic, and mean arterial blood pressure (MAP) were recorded every 5 minutes during surgery. A standardized anesthetic regimen was used, consisting of induction via inhalation of a mixture of sevoflurane and oxygen. On loss of consciousness, 2 venous catheters were placed: 1 for the administration of fluids and medications, and another in the contralateral arm for the collection of samples for DEX concentration measurements. After catheters were placed, fentanyl was administered, and endotracheal or laryngeal mask insertion was facilitated with intravenous (IV) propofol. Anesthesia was maintained with sevoflurane, which was adjusted according to surgical stimuli and patient response. At the end of the surgery, the patients were transferred to the postanesthetic care unit. Vital signs were recorded at admission, every 5 minutes for the first 30 minutes after admission, and then every hour until discharge. The patients were discharged after they met the following standard criteria of the unit: stable vital signs, no pain, awake, tolerating oral fluids, and Aldrete score >8.

Blood Sampling and Sample Handling

After insertion of an IV catheter, a control blood sample was obtained; thereafter, DEX (Precedex; Hospira, Inc, Lake Forest, IL) was administered as a single-dose IV infusion over 10–15 minutes (0.7 µg/kg). Venous blood samples (1 mL each) were obtained at the following time points after the end of the infusion: 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 300, 420, and 600 minutes. Each child contributed 2–5 samples; sampling times were randomly assigned.

The heparinized blood samples were centrifuged within 30 minutes of collection, and the supernatant plasma was stored in plastic vials at –80°C until analysis.

Determination of DEX Concentration

The plasma concentration of DEX was analyzed using a validated, sensitive, and selective high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry method as described previously.⁸ The assay exhibited a linear dynamic range of 55,000 pg/mL with a correlation coefficient above 0.9995. The lower limit of quantification was 5 pg/mL with a relative standard deviation of <15%. The intraday and interday coefficients of variation ranged between 5.6% and 11.2%.

Population PK Analysis

A population PK approach with a nonlinear mixed-effect model was implemented using the software program Monolix (version 4.4, Lixoft, Antony, France, <http://www.lixoft.com/>), which combines the stochastic expectation maximization algorithm and a Markov Chain Monte Carlo procedure for likelihood maximization.^{9,10}

Model Building

Structural Model. The DEX concentration–time data were described using compartmental PK modeling. One- and 2-compartment models with zero-order input and first-order elimination were analyzed. The exact infusion time was recorded for each patient and was used as input to the PK model. The model’s fit was visually inspected by generating diagnostic plots. Models were further selected on the basis of the precision of the parameter estimates, decrease in the Bayesian information criteria (BIC), and between-subject variability (BSV).

Interindividual and Error Models. Interindividual variability in PK parameters was ascribed to an exponential model according to the equation $\theta_j = \theta_p \times \exp(\eta_j)$, where θ_j is the estimate for a PK parameter in the *j*th patient as predicted by the model, θ_p is the typical population PK parameter value, and η_j is a random variable from a normal distribution with zero mean and variance ω^2 , which is estimated. The covariance between 2 elements of η is a measure of the statistical association between the variables (eg, CI–V1, CI–Q, where CI is clearance, V1 is central volume of distribution, and Q is intercompartmental clearance); its correlation was estimated from the elements of variance–covariance matrix according to the following formula: $R = \text{covariance} / (\omega_{\theta_1}^2 + \omega_{\theta_2}^2)^{1/2}$. The likelihood ratio test including the log-likelihood, the Akaike information criterion, and the BIC was used to test different hypotheses with respect to the structure of the variance–covariance matrix for the BSV parameters. Residual variability, which includes intraindividual variability, measurement errors, and model misspecification, was estimated using additive and proportional error models $C_{ij} = P_{ij} + \varepsilon$ and $C_{ij} = P_{ij}(1 + \varepsilon_p)$, where C_{ij} and P_{ij} are the observed and predicted concentrations of DEX for the *j*th patient at the time *i*, respectively, and ε and ε_p represent the error, a

random variable with normal distribution and zero mean and variance σ^2 and σ_p^2 .

Covariate Analysis

Once the basic model was determined, we only evaluated the relevance of the covariates age and weight because they are the 2 primary factors affecting PK in children.¹¹ The problems due to collinearity between these variables were addressed by using an allometric scale for the initial standardization of the parameters to the weight. Age was used later to explore a model of maturation of the clearance.¹²

The values of the parameters were standardized for a body weight of 70 kg by using the allometric model: $\theta_j = \theta_{std} \times (W_i / W_{std})^{PWR}$, where θ_j is the parameter in the j th individual, W_i is the weight in the j th individual, and θ_{std} is the parameter in an individual with a weight (W_{std}) of 70 kg. The parameter power exponent (PWR) was 0.75 for elimination and intercompartmental clearances, and 1 for central and peripheral volumes of distribution.¹¹ Also, the following proportional weight model was analyzed: $\theta_j = \theta_{std} \times (W_i / W_{std})$, where θ_j is the parameter in the j th individual, W_i is the weight in the j th individual, and θ_{std} is the parameter in an individual with a weight (W_{std}) of 70 kg.

Population PK–PD Analysis

To construct the PK–PD models, we used a sequential approach that consisted of constructing the PK model first, and then keeping the PK parameters fixed to the individual estimates, the parameters of the PD model were estimated.^{13,14}

The mean arterial pressure and HR response MAP(t) and HR(t), were related to DEX concentrations by means of a maximal immediate response inhibition model (Imax):

$$\text{Effect}(t) = \text{So} - \text{Imax} \left(C(t) / C(t) + \text{IC}_{50} \right)$$

$$\text{Effect}(t) = \text{So} - \text{Imax} \left(C(t)^\gamma / C(t)^\gamma + \text{IC}_{50}^\gamma \right)$$

Here, So is the basal effect (fixed to 1), Imax is the maximum decrease of MAP or HR expressed as a percentage of baseline values, IC_{50} is the concentration that induces 50% of the maximal effect on MAP or HR, and γ is the Hill exponent that describes the steepness of the concentration versus effect curve.

Model Evaluation

The accuracy and robustness of the models were evaluated by applying the resampling statistical techniques of bootstrapping and prediction-corrected visual predictive checks (pc-VPCs).^{15–17}

Sample Size and Statistics Analysis

The sample size was considered based on criteria such as patient availability, number of patients included in previous studies, and available economic resources. However, it is important to have an a priori hypothesis because this allows calculate the sample size necessary to estimate the parameters of the model with an appropriate accuracy and precision. We estimated the power of our study a posteriori based on the size of our sample, applying the methodology suggested by Ogungbenro and Aarons.¹⁸ Thus, with our sample size of 30 patients, >80% of the 95% confidence

intervals included the sample population elimination clearance value with 20% accuracy, which is considered by the Food and Drug Administration to be appropriate for population pharmacokinetic studies in children.¹⁹ We justify the selection of the elimination clearance to calculate the power of the study (a posteriori) because this parameter is the most important to establish an infusion dose regimen.

Hemodynamic changes at different time points were also analyzed to test the differences with respect to the baseline values, using a statistical model of 1-way analysis of variance for repeated measurements if Kolmogorov–Smirnov and Shapiro–Wilk test for normality were not significant, otherwise the nonparametric Friedman test was applied. Post hoc analysis was performed using Student t test or the Wilcoxon signed-rank test, with Bonferroni correction. A P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 21 (IBM corporation, Chicago, IL).

RESULTS

Patient Data

Thirty children 2–18 years of age were enrolled in this study, and their clinical and demographic characteristics are shown in Table 1. The average patient age was 11 ± 5 years (70% male and 30% female), and all had ASA score of I/II. The most frequent procedures were plastic, urology, and otorhinolaryngology surgeries. The average duration of the procedures was 45 ± 15 minutes. Administration of atropine or ephedrine was not required for any patient, and no adverse effects were reported that required hospitalization or prolonging their stay in the recovery unit.

DEX PK and Model Validation

One- and 2-compartment models were used for the evaluation of DEX PK. A 2-compartment open model with linear elimination described the temporal course of DEX concentrations better than a 1-compartment model (Bayesian Information Criterion [ΔBIC], 175) did. The PK parameters were clearance (Cl), central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2). The parameter values were estimated for a standard body weight of 70 kg by using an allometric weight-normalized model and also a weight-normalized model. Introduction of allometric and weight-normalized size standardization improved the objective function

Table 1. Demographic and Clinical Characteristics of Patients, Mean (\pm SD)

Variable	Mean \pm SD
Age (y)	11 \pm 5
Weight (kg)	43 \pm 19
Height (cm)	132 \pm 42
Sex (F/M)	9/21
ASA (I/II)	28/2
Type of procedure	
Urologic	6
ORL	12
Plastic	8
General	4
Mean duration of anesthesia (min)	77 \pm 15

Abbreviations: ASA, American Society of Anesthesiologists; F, female; M, male; ORL, otorhinolaryngology; SD, standard deviation.

Table 2. Population Pharmacokinetic Parameters and Bootstrap Validation

Pharmacokinetic Parameters Allometric Model ^a	Estimate	RSE (%)	Bootstrap (Median)	2.5th, 97.5th Percentiles
θ_{Cl} (L-hour ⁻¹ 70 kg)	20.8	10	21.0	20.5, 21.5
β_{Cl}	0.75 (fixed)	NA	—	—
θ_{V1} (L × 70 kg)	21.9	17	21.8	19.9, 24.1
β_{V1}	1.0 (fixed)	NA	—	—
θ_Q (L-hour ⁻¹ × 70 kg)	75.8	12	74.1	65.7, 80.4
β_Q	0.75 (fixed)	NA	—	—
θ_{V2} (L × 70 kg)	81.2	9	81.7	79, 83.5
β_{V2}	1 (fixed)	NA	—	—
Interindividual variability				
ω^2_{Cl} (CV%)	0.275	17	0.275	0.259, 0.289
ω^2_{V1} (CV%)	0.202	52	0.161	0.089, 0.263
ω^2_Q (CV%)	0.253	48	0.248	0.186, 0.289
ω^2_{V2} (CV%)	0.218	35	0.218	0.199, 0.247
Residual variability (%)				
σ^2 proportional	14.2	13	14.5	13.9, 15.4
Pharmacokinetic Parameters Proportional Model ^b	Estimate	RSE (%)	Bootstrap (Median)	2.5th, 97.5th Percentiles
θ_{Cl} (L-hour ⁻¹ 70 kg)	21.6	10	21.1	19.6, 22.4
β_{Cl}	1 (fixed)	NA	—	—
θ_{V1} (L × 70 kg)	15.7	29	14.4	12.5, 16.5
β_{V1}	1 (fixed)	NA	—	—
θ_Q (L-hour ⁻¹ × 70 kg)	66	17	66.4	60.7, 72.4
β_Q	1 (fixed)	NA	—	—
θ_{V2} (L × 70 kg)	72	7	73	71.4, 75.1
β_{V2}	1 (fixed)	NA	—	—
Interindividual variability				
ω^2_{Cl} (CV%)	0.466	16	0.453	0.416, 0.493
ω^2_{V1} (CV%)	0.801	29	0.835	0.724, 0.950
ω^2_Q (CV%)	0.520	23	0.495	0.450, 0.539
ω^2_{V2} (CV%)	0.165	37	0.168	0.135, 0.197
Residual variability (%)				
σ^2 proportional	14.4	12	14.5	13.9, 15.4

Abbreviations: Cl, clearance; CV%, percentage coefficient of variation; NA, not applicable; Q, intercompartmental clearance; RSE, relative standard error; V1, central volume of distribution; V2, peripheral volume of distribution; Wt, weight.

^aAllometric weight-normalized model: $Cl = \theta_{Cl} \times (Wt/70)^{0.75}$; $V1 = \theta_{V1} \times (Wt/70)^{0.75}$; $Q = \theta_Q \times (Wt/70)^{0.75}$; $V2 = \theta_{V2} \times (Wt/70)^{0.75}$.

^bWeight-normalized model: $Cl = \theta_{Cl} \times (Wt/70)$; $V1 = \theta_{V1} \times (Wt/70)$; $Q = \theta_Q \times (Wt/70)$; $V2 = \theta_{V2} \times (Wt/70)$.

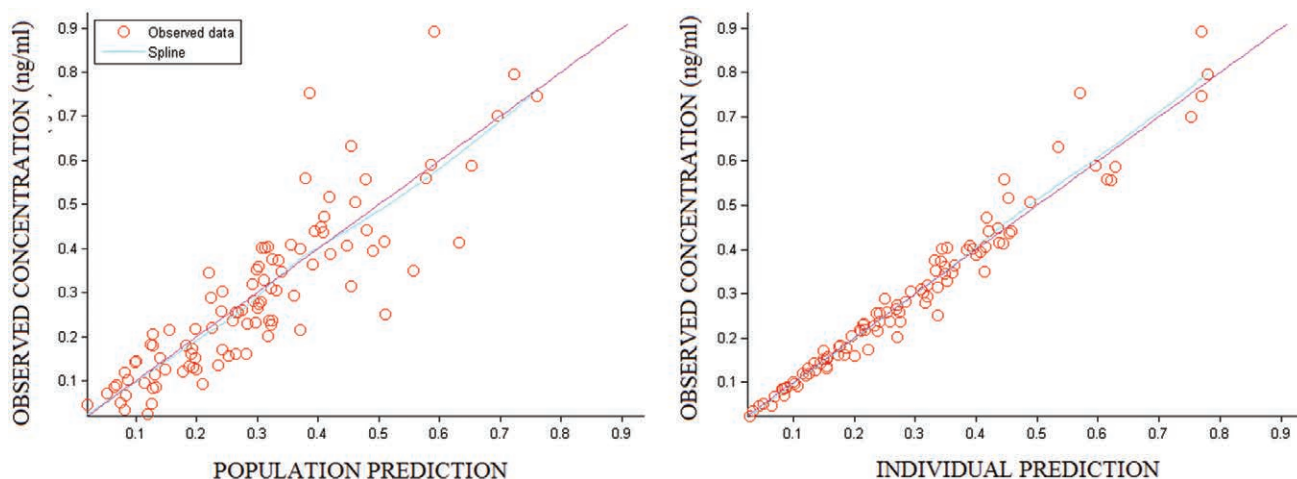


Figure 1. Population and individual predicted dexmedetomidine concentrations versus observed concentrations.

significantly: ΔBIC 57 and ΔBIC 54 respectively. The residual variability was best described by a proportional model. The introduction of patient age did not improve the value of the objective function (ΔBIC , 2.17) because it did not reach a probability value $<5\%$. Table 2 shows the estimated parameters of the final models. All parameters were estimated with good accuracy, as indicated by a standard error $<20\%$. The final PK parameters were as follows: mean (BSV): Cl (L/h

$\times 70$ kg) = 20.8 (27%), V1 (L $\times 70$ kg) = 21.9 (20%), V2 (L $\times 70$ kg) = 81.2 (21%), and Q (L/h $\times 70$ kg) = 75.8 (25%) for the allometric model. The population and individual values of predicted versus observed DEX concentrations were judged acceptable, and the trend line was close to the line of the unit (Figure 1). The normalized prediction error (NPDE) analysis revealed that the points were distributed symmetrically with respect to the zero line and that all

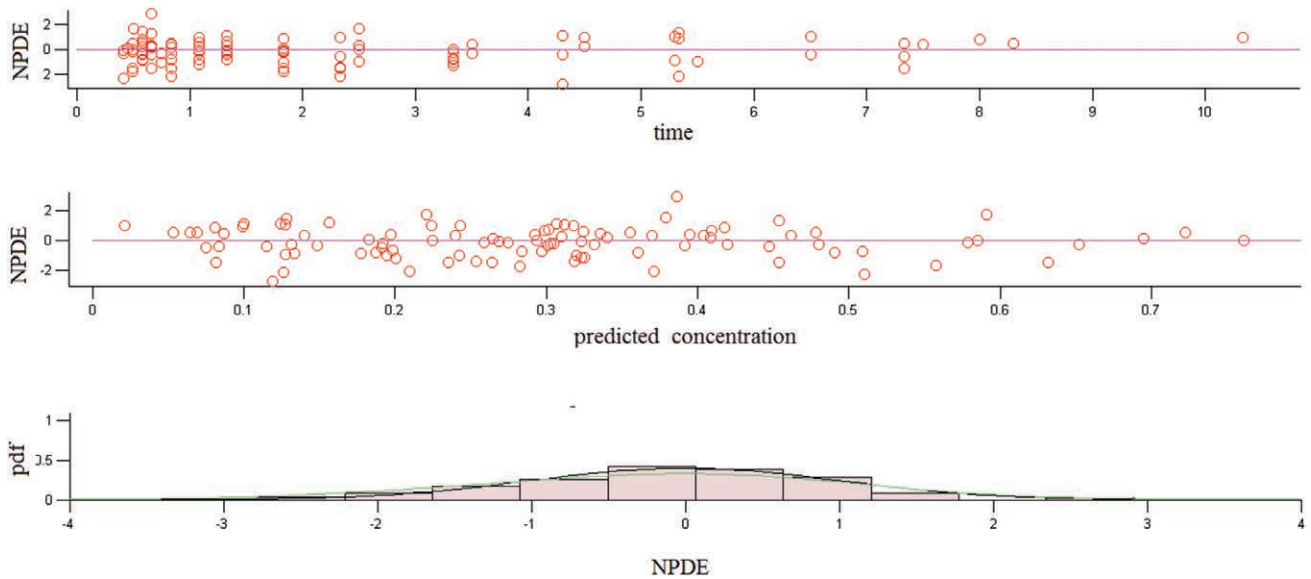


Figure 2. Results of the NPDE analysis for dexmedetomidine concentration: (A) the NPDE distributions over time, (B) against the observed concentrations, and (C) the NPDE histogram. NPDE indicates normalized prediction distribution error; pdf, probability density function.

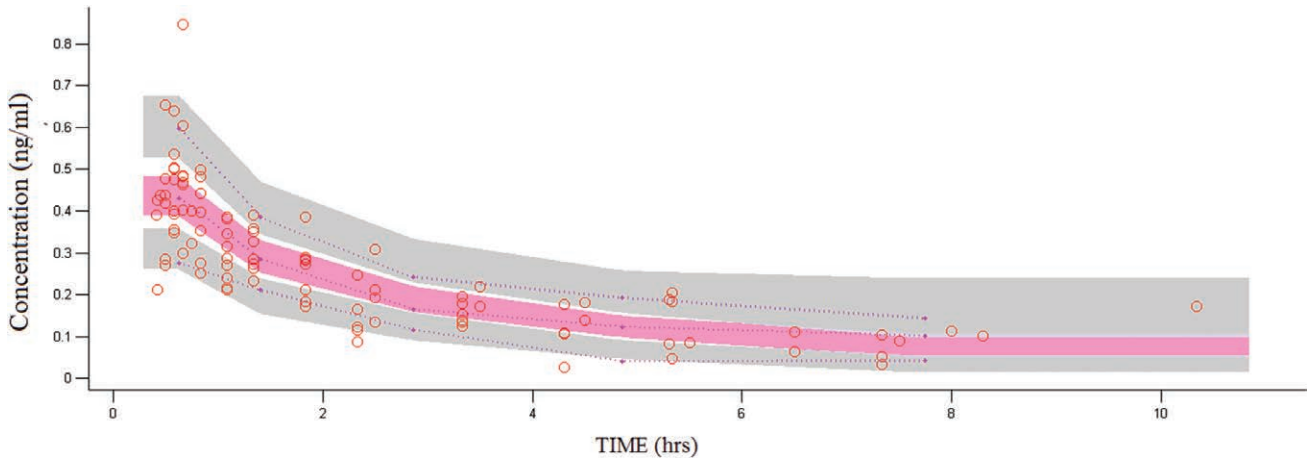


Figure 3. pc-VPC for dexmedetomidine concentrations versus time in hours. Lines represent the 5th, 50th, and 95th percentiles of the observed concentrations. Color areas represent the 95% confidence intervals for the 5th, 50th, and 95th percentiles of simulated concentrations. Circles represent the observed concentrations. pc-VPC indicates prediction-corrected visual predictive check.

points were between -3 and $+3$ units, as shown in Figure 2A, B. There was no evidence of bias because NPDE fits well to a symmetric distribution (Figure 2C). The pc-VPC plots for DEX concentrations are shown in Figure 3. Less than 10% of the observed concentrations fell outside the 10% and 90% confidence intervals of the simulated data. The median values and the 95% confidence intervals obtained by the bootstrap method are shown in Table 2. There were no significant differences with respect to the parameters estimated in the original database, and the confidence intervals included the population values of the original base. These data support the stability of the model. The graphs for the proportional weight model are shown in Supplemental Digital Content, Figures 1S–3S, <http://links.lww.com/AA/C362>.

DEX Hemodynamics

The changes in HR and MAP are expressed as a percentage of the baseline MAP and HR values for each patient. HR

and MAP decreased significantly from baseline in the first 30 minutes after infusion of DEX. Subsequently, HR and MAP increased up to 90% of baseline values at 45 minutes after the end of infusion as shown in Supplemental Digital Content, Figure 4S, <http://links.lww.com/AA/C362>.

DEX PK–PD Model

Different functional forms, I_{max} and sigmoidal I_{max} , were tested, and a sigmoidal I_{max} model related to baseline was found to best describe the relationship between the changes in MAP and HR as a function of DEX concentrations. The changes are expressed as the percentage of the baseline MAP and HR values for each patient. The PK–PD model (Table 3) predicted a maximum MAP reduction of 45% (relative standard error [RSE], 17%) and BSV 3.4%, with an IC_{50} of 0.501 ng/mL (RSE, 30%) and BSV 12%; a maximal HR reduction of 29% (RSE, 8%) and BSV 6.6%, with an IC_{50} of 0.552 ng/mL (RSE, 10%) and BSV 9.7%. Supplemental Digital

Table 3. Pharmacodynamic Models for Heart Rate and Mean Arterial Pressure and Bootstrap Validation

Hemodynamic Parameters	Estimates	RSE (%)	Bootstrap (Median)	2.5th, 97.5th Percentiles
Heart rate				
So	1 (fixed)	NA	—	—
I _{max} (%)	28.9	8	29.2	27, 36.6
IC ₅₀ (ng/mL)	0.552	10	0.569	0.505, 0.834
γ	1.86	17	1.65	1.19, 2.0
ω ² _{I_{max}}	0.066	73	0.066	0.033, 0.083
ω ² _{IC₅₀ (HR)}	0.097	87	0.112	0.050, 0.150
ω ² γ	0.38	39	0.350	0.290, 0.395
Residual variability (%)	6.5	5	6.5	6.4, 6.5
Mean arterial pressure				
So	1 (fixed)	NA	—	—
I _{max} (%)	45	17	48.3	16.1, 52.6
IC ₅₀ (ng/mL)	0.501	30	0.539	0.363, 1.07
γ	1.26	31	1.28	0.842, 1.58
ω ² _{I_{max}}	0.034	97	0.040	0.029, 0.05
ω ² _{IC₅₀ (MAP)}	0.119	93	0.115	0.072, 0.151
ω ² γ	0.242	45	0.210	0.116, 0.266
Residual variability (%)	15	4.6	15.2	14.9, 15.3

Abbreviations: HR, heart rate; I_{max}, maximum inhibition; IC₅₀, dexmedetomidine concentration producing 50% of I_{max}; MAP, mean arterial blood pressure; NA, not applicable; So, basal effect (fixed to 1); ω²_{I_{max}}, I_{max} between subject variability; ω²_{IC₅₀}, IC₅₀ between subject variability.

Content, Figure 5S, <http://links.lww.com/AA/C362>, depicts the results of the NPDE analysis for MAP and HR, and Supplemental Digital Content, Figure 6S, <http://links.lww.com/AA/C362>, depicts the pc-VPC plots. The NPDE analysis revealed that the points were distributed symmetrically with respect to the zero line and that all points were between -3 and +3 units. Moreover, the NPDE adjusted well to a normal distribution, as shown in Supplemental Digital Content, Figure 5SA-B, <http://links.lww.com/AA/C362>. The pc-VPC plots showed a reasonable fit within the 5th and 95th percentiles of the simulated data.

DISCUSSION

DEX PK

A 2-compartment model with the first-order elimination best fitted our data, as has been reported previously.^{1,7} The DEX PK parameters obtained, except for the elimination clearance, were in agreement with those reported in previous studies in children.^{1,7,20}

In our analysis using an allometric model, the DEX plasma clearance was 20.8 L × 70 kg and with the proportional model was 21.6 L × 70 kg, both lower than the values reported in other populations.^{1,20,21} Although the allometric model showed a greater reduction of the objective function, the difference with the proportional model can be considered as trivial. So, quoting Fisher and Safer:²² "There is no scientific justification for the view that human clearances are better described using weight^{0.75}. These models should only be used when weight^{0.75} rather than weight^{1.0} provides a sufficient improvement in the pharmacokinetic model and dose calculation to justify the risk of calculation error." Therefore, we reported both models. Population PK models play an important role in anesthesia for the design of dosage strategies, since they describe the behavior of a drug in a specific population, the variability expected between individuals and factors that explain part of this variability. The use of this information in simulation programs facilitates the design of individualized dosing strategies, which can be easily implemented with the current infusion

systems. An example is shown in Supplemental Digital Content, Table 1S, <http://links.lww.com/AA/C362>.

DEX is a highly lipophilic drug with extensive tissue distribution, which is consistent with the high volumes of distribution reported in adults and children. The estimated steady-state volume of distribution in our patients was similar to that reported by Potts et al²¹ and Petroz et al¹ in Canadian children, but lower than that reported by Petroz et al¹ in South African children and by Liu et al²⁰ in Chinese children. In the blood, 94% of DEX is bound to plasma proteins, primarily albumin and α1-acid glycoprotein. Decreases in the concentrations or affinity of these plasma proteins because of age, or genetic or pharmacological factors, could increase the free DEX fraction and explain these discrepancies between study results.^{23,24} Supplemental Digital Content, Table 2S, <http://links.lww.com/AA/C362>, shows the population pharmacokinetic parameters reported in different studies in children as compared with those obtained in our population.

Because most previous studies were in children with congenital heart disease undergoing cardiac surgery, we expected a greater clearance in our population of healthy patients, in view of the reported relationship between cardiac output and DEX clearance.²⁵ Unexpectedly, however, the clearance in our patients, allometrically extrapolated to a 70-kg adult, was significantly lower than that in similar patients (ASA score of I/II) in other studies. DEX is almost completely biotransformed by the hepatic enzymes uridine 5'-diphospho-glucuronosyltransferase (UDPG) and cytochrome P4502A6 (CYP2A6) to inactive metabolites, which are excreted in bile and through renal pathways. The expression and activity of these enzyme systems are related to age in children.^{26,27} In a study by Potts et al²¹ in 45 children 4 weeks to 14 years of age who received DEX after cardiac surgery, DEX clearance was 15.5 L/h/70 kg at birth and a maturational half-life of 47.5 weeks of postmenstrual age, reaching 87.5% of the adult values at 1 year of age (39.2 L/h × 70 kg). This finding is consistent with the lack of an age effect on DEX plasma clearance in the present study. Thus, it is unlikely that the immaturity of the enzyme system caused

the decreased DEX clearance in our population. Genetic factors, sex, and environmental factors may affect the metabolic activity of CYP2A6, an enzyme responsible for the aliphatic hydroxylation of DEX. In a study in critically ill adult patients, Kohli et al²⁸ found no relationship between DEX clearance and metabolizing genotype (fast, intermediate, and slow metabolizers) based on CYP2A6 allelic variants. However, the results are difficult to extrapolate to populations of different ethnicity and age. In addition, the role of glucuronidation, which is a more important biotransformation pathway than aliphatic hydroxylation by CYP2A6, was not considered. Uridine 5'-diphospho (UDP)-glucuronosyltransferases catalyze the glucuronidation of various endogenous and exogenous lipophilic substances, including environmental toxins and drugs, to produce water-soluble glucuronides. Direct glucuronidation of DEX to G-dex1 and G-dex2 conjugates accounts for approximately 34% of its metabolism.²⁸ Genetic variations in UDP-glucuronosyltransferases influence the activity of these enzymes^{28,29}; however, no information is available on this enzyme's activity on DEX. Polymorphisms and epigenetic variations could explain this phenotypic variation in DEX metabolism in our study population.

DEX Hemodynamics and the PK-PD Model

Previous studies in children have reported a dose-dependent effect of DEX on MAP and HR.¹ In 1- to 7-year-old children requiring sedation for magnetic resonance imaging, administration of 1 µg/kg DEX in 10 minutes followed by a 0.5 µg·kg⁻¹·hour⁻¹ infusion resulted in maximal MAP and HR decreases of 16% and 15%, respectively.³⁰ In 0.3- to 6-year-old children who required sedation for computed tomography or magnetic resonance imaging, 2 µg/kg DEX infusion boluses followed by 1 µg·kg⁻¹·hour⁻¹ infusions resulted in an 18% decrease in HR without changes in MAP.³¹ However, the cardiac index decreased and vascular resistance increased significantly, indicating that the vascular response was important for maintaining MAP. Thus, the use of inhaled anesthetics may accentuate the decrease of MAP by DEX due to its vasodilator effect. In a study by Deutsch and Tobias³² in 40 children 1–12 years of age anesthetized with sevoflurane, the maximum decreases in HR and MAP 15 minutes after administering 0.7 µg/kg DEX were 24.6% (22.7%–28%) and 14.8% (12.6%–19.3%), respectively. In 1- to 6-year-old children undergoing orchidopexia or inguinal hernioplasty who were premedicated with DEX and receiving anesthesia with sevoflurane and caudal block, HR and MAP decreased by 28% and 28.5%, respectively. At a dose of 0.7 µg/kg, similar to that used by Deutsch and Tobias³² in sevoflurane-anesthetized children, the HR and MAP decreases were greater in our patient population. Uncontrolled factors such as sevoflurane concentrations, hydration status, and type of surgical procedure could explain these differences. However, because we could not find studies reporting the IC₅₀ of DEX in children to compare with our results, it is difficult to support the hypothesis of greater susceptibility.

Although a biphasic MAP response has been reported after bolus administration of DEX,³³ we did not observe this effect in our patients, potentially because of the infusion time and coadministration of IV and inhaled anesthetics. Moreover, this effect is generally observed at concentrations higher than 1 µg/L,³³ whereas DEX concentrations were <1 µg/L in all our patients.

Limitations of the Study

A potential limitation of our study is the small sample size. Our study was considered by us as explanatory and as such without a clear hypothesis, so we do not initially estimate a sample size. However, as previously established, our sample size allows us to estimate the clearance with adequate power to suggest dosage recommendations in our population.

Another limitation of our study is that the PK/PD models for MAP and HR only describe the first 45 minutes after infusion, representing the interaction of anesthetic effects and surgical stimulation. However, these changes represent the expected response in a real-world clinical setting, wherein DEX is used as a coadjuvant. Finally, although the model was internally validated, external validation is still necessary.³⁴

In conclusion, this is the first study to report a PK-PD model of DEX in a population of 2- to 18-year-old Mexican children with ASA score of I/II. The clearance, normalized to 70 kg with an allometric weight model and a proportional weight model, in this pediatric population was lower than that reported in other populations. These results suggest that the DEX dosage needs to be corrected in the Mexican Mestizo population because of the lower DEX clearance. In addition, the influence of ethnic or racial, genetics and epigenetic, differences in PK/PD should be considered in future studies. ■

ACKNOWLEDGMENTS

The authors thank Editage (www.editage.com) for English language editing.

DISCLOSURES

Name: María-Gabriela Pérez-Guillé, MD.

Contribution: This author helped collect and analyze the data, and draft the manuscript.

Name: Alejandra Toledo-López, PHC.

Contribution: This author helped collect the data and revise the manuscript.

Name: Liliana Rivera-Espinosa, MSc.

Contribution: This author helped collect and analyze the data, and draft the manuscript.

Name: Radames Alemon-Medina, PhD.

Contribution: This author helped in critically revising the manuscript for important intellectual content.

Name: Chiharu Murata, MSc.

Contribution: This author helped in critically revising the manuscript for important intellectual content.

Name: Ismael Lares-Asseff, PhD.

Contribution: This author helped in critically revising the manuscript for important intellectual content.

Name: Juan Luis Chávez-Pacheco, PhD.

Contribution: This author helped collect the data and revise the manuscript.

Name: Josefina Gómez-Garduño, Biol.

Contribution: This author helped collect and revise the manuscript.

Name: Ana-Lilia Zamora Gutiérrez, MD.

Contribution: This author helped collect the data and revise the manuscript.

Name: Claudia Orozco-Galicia, MD.

Contribution: This author helped collect the data and revise the manuscript.

Name: Karina Ramírez-Morales, MD.

Contribution: This author helped collect the data and revise the manuscript.

Name: Gustavo Lugo-Goytia, PhD.

Contribution: This author helped analyze the data, draft the manuscript, and helped in critically revising the manuscript for important intellectual content.

This manuscript was handled by: James A. DiNardo, MD, FAAP.

REFERENCES

- Petroz GC, Sikich N, James M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. *Anesthesiology*. 2006;105:1098–1110.
- Yao Y, Qian B, Lin Y, Wu W, Ye H, Chen Y. Intranasal dexmedetomidine premedication reduces minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion and emergence delirium in children: a prospective, randomized, double-blind, placebo-controlled trial. *Paediatr Anaesth*. 2015;25:492–498.
- Ibacache ME, Muñoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg*. 2004;98:60–63.
- Guler G, Akin A, Tosun Z, Ors S, Esmoğlu A, Boyacı A. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Paediatr Anaesth*. 2005;15:762–766.
- Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. *Paediatr Anaesth*. 2002;12:171–175.
- Díaz SM, Rodarte A, Foley J, Capparelli EV. Pharmacokinetics of dexmedetomidine in postsurgical pediatric intensive care unit patients: preliminary study. *Pediatr Crit Care Med*. 2007;8:419–424.
- Mason KP, Lerman J. Review article: dexmedetomidine in children: current knowledge and future applications. *Anesth Analg*. 2011;113:1129–1142.
- Li W, Zhang Z, Wu L, Tian Y, Feng S, Chen Y. Determination of dexmedetomidine in human plasma using high performance liquid chromatography coupled with tandem mass spectrometric detection: application to a pharmacokinetic study. *J Pharm Biomed Anal*. 2009;50:897–904.
- Chan PL, Jacqmin P, Lavielle M, McFadyen L, Weatherley B. The use of the SAEM algorithm in MONOLIX software for estimation of population pharmacokinetic-pharmacodynamic-viral dynamics parameters of maraviroc in asymptomatic HIV subjects. *J Pharmacokinet Pharmacodyn*. 2011;38:41–61.
- Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. *Comput Stat Data Anal*. 2005;49:1020–1038.
- Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008;48:303–332.
- Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modelling covariate effects. *Eur J Pediatr*. 2006;165:819–829.
- Zhang L, Beal SL, Sheiner LB. Simultaneous vs sequential analysis for population PK/PD data I: best-case performance. *J Pharmacokinet Pharmacodyn*. 2003;30:387–404.
- Zhang L, Beal SL, Sheiner LB. Simultaneous vs sequential analysis for population PK/PD data II: robustness of methods. *J Pharmacokinet Pharmacodyn*. 2003;30:405–416.
- Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci*. 1986;1:54–77.
- Yafune A, Ishiguro M. Bootstrap approach for constructing confidence intervals for population pharmacokinetic parameters. I: a use of bootstrap standard error. *Stat Med*. 1999;18:581–599.
- Comets E, Brendel K, Mentre F. Model evaluation in nonlinear mixed effect models, with applications to pharmacokinetics. *J Soc Fr Statistique*. 2010;151:106–128.
- Ogungbenro K, Aarons L. How many subjects are necessary for population pharmacokinetic experiments? Confidence interval approach. *Eur J Clin Pharmacol*. 2008;64:705–713.
- Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. *J Clin Pharmacol*. 2012;52:1601–1606.
- Liu HC, Lian QQ, Wu FF, et al. Population pharmacokinetics of dexmedetomidine after short intravenous infusion in Chinese children. *Eur J Drug Metab Pharmacokinet*. 2017;42:201–211.
- Potts AL, Anderson BJ, Warman GR, Lerman J, Diaz SM, Vilo S. Dexmedetomidine pharmacokinetics in pediatric intensive care—a pooled analysis. *Paediatr Anaesth*. 2009;19:1119–1129.
- Fisher DM, Shafer SL. Allometry, shallometry! *Anesth Analg*. 2016;122:1234–1238.
- McNamara PJ, Alcorn J. Protein binding predictions in infants. *AAPS PharmSci*. 2002;4:E4.
- Zhang T, Deng Y, He P, He Z, Wang X. Effects of mild hypoalbuminemia on the pharmacokinetics and pharmacodynamics of dexmedetomidine in patients after major abdominal or thoracic surgery. *J Clin Anaesth*. 2015;27:632–637.
- Dutta S, Lal R, Karol MD, Cohen T, Ebert T. Influence of cardiac output on dexmedetomidine pharmacokinetics. *J Pharm Sci*. 2000;89:519–527.
- Raunio H, Rautio A, Gullstén H, Pelkonen O. Polymorphisms of CYP2A6 and its practical consequences. *Br J Clin Pharmacol*. 2001;52:357–363.
- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349:1157–1167.
- Kohli U, Pandharipande P, Muszkat M, et al. CYP2A6 genetic variation and dexmedetomidine disposition. *Eur J Clin Pharmacol*. 2012;68:937–942.
- Ji QC, Zhou JY, Gonzales RJ, Gage EM, El-Shourbagy TA. Simultaneous quantitation of dexmedetomidine and glucuronide metabolites (G-Dex-1 and G-Dex-2) in human plasma utilizing liquid chromatography with tandem mass spectrometric detection. *Rapid Commun Mass Spectrom*. 2004;18:1753–1760.
- Koroglu A, Demirebilek S, Teksan H, Sagir O, But AK, Ersoy MO. Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. *Br J Anaesth*. 2005;94:821–824.
- Wong J, Steil GM, Curtis M, Papas A, Zurakowski D, Mason KP. Cardiovascular effects of dexmedetomidine sedation in children. *Anesth Analg*. 2012;114:193–199.
- Deutsch E, Tobias JD. Hemodynamic and respiratory changes following dexmedetomidine administration during general anesthesia: sevoflurane vs desflurane. *Paediatr Anaesth*. 2007;17:438–444.
- Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colincio MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;93:382–394.
- Meibohm B, Laer S, Panetta JC, Barrett JS. Population pharmacokinetic studies in pediatrics: issues in design and analysis. *AAPS J*. 2005;7:E475–E487.