Computer-controlled Infusion of Intravenous Dexmedetomidine Hydrochloride in Adult Human Volunteers

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Background: This investigation extended the pharmacokinetic analysis of our previous study, of intravenous dexmedetomidine in 10 healthy male volunteers, and prospectively tested the resulting compartmental pharmacokinetics in an additional six subjects using a computer-controlled infusion pump (CCIP) to target four different plasma concentrations of dexmedetomidine for 30 min at each concentration.

Methods: A three-compartment mamillary pharmacokinetic model best described the intravenous dexmedetomidine concentration versus time profile following the 5 min intravenous infusion of 2 μg/kg in our previous study. Nonlinear regression was performed using both two-stage and pooled data techniques to determine the population pharmacokinetics. The pooled technique allowed covariates, such as weight, age, and height of the subjects, to be incorporated into the nonlinear regression to test the hypothesis that these additional covariates would reduce the residual error between the measured concentrations and the predicted values.

Results: The addition of age, weight, lean body mass, and body surface area as covariates of the pharmacokinetic parameters did not improve the predictive value of the model. However, the model was improved when subject height was a covariate of the volume in the central compartment. The residual error in the pharmacokinetic model was markedly lower with the pooled versus the two-stage approach. The following pharmacokinetic values were obtained from the pooled analysis of the zero-order dexmedetomidine infusion: \( V_1 = 8.05, V_2 = 12.4, V_3 = 175 \) (L), \( Cl_f = (0.0101 \times \text{height (cm)}) - 1.33 \), \( Cl_t = 2.05 \text{, and } Cl_s = 2.0 \text{ (L/min)}. \) Prospective evaluation of the pooled pharmacokinetic parameters using a computer-controlled infusion in six healthy volunteers showed the precision (average [absolute error]/measured concentration) of the CCIP to be 31.5% and the bias (average [error/measured concentration]) to be -22.4%. A pooled regression of the combined CCIP and zero-order data confirmed that the covariates, height (cm), was related in linear fashion to \( Cl_f \). A striking nonlinearity of dexmedetomidine pharmacokinetics related to concentration was observed during the CCIP infusion. The final pharmacokinetic values for the entire data set were: \( V_1 = 7.99, V_2 = 13.8, V_3 = 187 \) (L), \( Cl_t = (0.00791 \times \text{height (cm)}) - 0.927, Cl_s = 2.26, \) and \( Cl_f = 1.99 \text{ (L/min)}. \)

Conclusions: Pharmacokinetics of dexmedetomidine are best described by a three-compartment model. Addition of age, weight, lean body mass, and body surface area do not improve the predictive value of the model. Additional improvement in CCIP accuracy for dexmedetomidine infusions would require modification of the model based on the targeted concentration. (Key words: Anesthetic techniques: computer-controlled drug administration. Pharmacokinetics: dexmedetomidine. Sympathetic nervous system, \( \alpha_2 \) agonists: dexmedetomidine.)

THE toxicity of many intravenous anesthetic medications occurs during the first few minutes following bolus injection before distribution into peripheral tissues has lowered the plasma concentration. Dexmedetomidine demonstrates such a phenomenon with biphasic blood pressure alterations typical of \( \alpha_2 \) agonists.1,2 To most accurately administer dexmedetomidine, it is necessary to characterize its pharmacokinetic profile including the early distribution phases. We analyzed the data presented in our preceding study1 using parametric techniques and evaluated the performance of the resulting pharmacokinetic parameters in an additional six volunteers. The prospective evaluation was performed with a computer-controlled infusion pump.

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(CCIP). We then investigated whether the pharmacokinetics of dexmedetomidine administered by CCIP were consistent with the pharmacokinetics of dexmedetomidine administered as a zero-order infusion.

Methods

Clinical Methodology

Following approval by the Stanford University Investigational Review Board, six healthy male volunteers were recruited for prospective testing of our pharmacokinetic description of dexmedetomidine. Men between the ages of 18 and 50 yr, weight less than 100 kg, and ASA physical status 1 and 2, were eligible for study. Pre-study screening included a history, physical examination, 20-panel serum chemistry, complete blood count, clotting times, electrocardiogram, and urine drug screen. The six volunteers had an average age of 31.5 yr (range 27–40) and an average weight of 82 kg (range 71–98).

The volunteers were fasted from midnight before the study and were asked to abstain from caffeine and alcohol consumption for the preceding 24 h. On arrival at the study site, an 18-G intravenous cannula was inserted and 500 ml normal saline was infused rapidly, followed by an infusion at 125 ml/h. A 20-G catheter was inserted into the radial artery to sample blood for analysis of plasma dexmedetomidine concentrations. Dexmedetomidine was infused via a CCIP** targeting the plasma concentrations of 0.49, 0.65, 0.81, and 0.97 ng/ml for 30 min at each concentration. These concentrations were chosen to represent 60%, 80%, 100%, and 120%, respectively, of the peak plasma dexmedetomidine concentrations following a 2 μg/kg intramuscular injection.††

Blood Sampling

During the evaluation of the pharmacokinetic model by CCIP administration of dexmedetomidine, concentrations were determined 5 and 25 min after targeting the new concentration and at 10, 20, 30, 45, 60, 90, and 120 min after termination of the infusion as shown in figure 1. The 5-ml K2EDTA anti-coagulated samples were centrifuged and the plasma frozen at −40 °C until the dexmedetomidine concentration was assayed.

Dexmedetomidine Assay

The plasma samples were assayed using a gas chromatograph with mass spectroscopy detection by Famos, LTD (Turku, Finland), as previously described.†

Pharmacokinetic Analysis

Employing the data derived from the 10 patients described in the preceding paper,† parametric analysis was performed on the concentration versus time data from our initial zero-order infusion (n = 10). Similar analysis of the CCIP infusion data (n = 6) and the combined set of data was performed using a standard three-compartment mamillar pharmacokinetic model. The extended least squares nonlinear regression package MKMODEL†† was used to fit the volume and clearance parameters.

Two methods were used to estimate the pharmacokinetics in our population, the traditional two-stage technique and the pooled technique. In both analyses, we estimated the three volume and three clearance pharmacokinetic parameters (V1, V2, V3, Cl1, Cl2, and Cl3) of a standard three-compartment mamillary pharmacokinetic model. V1 represents the initial volume of distribution and Cl1, the elimination clearance. V2 and V3 represent the shallow and deep distribution

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** The software, STANPUMP, is available at no charge from the author (S.L.S.). STANPUMP is written in C and runs on any 8088-compatible MS-DOS computer with a serial port. A mathematics co-processor is not required. STANPUMP currently supports the Harvard Pump 22.

†† Available from Nicholas Holford, M. Sc., M.R.C.P.(UK), F.R.A.C.P., Department of Pharmacology and Clinical Pharmacology, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand.
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compartments, and Cl_2 and Cl_3 are the respective intercompartmental clearances. All doses were assumed to be administered into V_1. In the first stage of the two-stage data analysis, we estimated the volume and clearance parameters that best fit the concentration versus time profile of each of the 10 individuals studied in the preceding paper. In the second stage of the two-stage analysis, we calculated the population values as the arithmetic mean among individuals for each of the volumes and clearances.

In the pooled technique the concentration versus time data for the 10 subjects were fit simultaneously by the MKMODEL program to produce a single best estimate of the three-compartment pharmacokinetic parameters of the entire sample population. Pooled data analysis allowed the incorporation of individual subject covariates (age, weight, height, lean body mass, and body surface area) into the model. Body surface area was calculated as:

\[ BSA = \text{Weight}^{0.425} \times \text{Height}^{0.725} \times 0.007184, \]

and lean body mass for men as:

\[ \text{LBM} = 1.1(\text{Weight}) - 128(\text{Height})^2. \]

The covariates were incorporated into each parameter (P) in serial fashion with a floating intercept:

\[ P = (\text{Slope}_{\text{Parameter}} \times \text{Covariate}) + \text{Intercept}_{\text{Parameter}}. \]

All linear combinations of these covariates and the pharmacokinetic parameters were examined to determine the optimal pharmacokinetic model. Log likelihood was the objective function used to evaluate the goodness of fit and choose between the original model and the new model with one additional covariate. When the models differ by one parameter, twice the log of the likelihood ratio conforms to the chi-square distribution with one degree of freedom. It then follows that, if twice the difference in log likelihood is greater than 3.84, the full model with its increased complexity would be considered better with 95% confidence. We conservatively used a log likelihood difference of 4 as the cutoff for a significant difference between the two models.

The weighted residual of each technique was calculated as:

\[ \%WR = \frac{\text{Predicted} - \text{Measured}}{\text{Predicted}} \times 100\%. \]

The median absolute weighted residual was calculated as the median of the weighted residuals for all the concentrations in the data set. Examination of the percent weighted residual (%WR) between the measured dexmedetomidine concentration and that predicted by the nonlinear regression was facilitated by plotting the %WR against a log time axis. This allowed the errors to be spread out for visual inspection. This type of error plot allows rapid identification of model misspecification through consistent deviations above or below the horizontal line of zero error. Time points showing a larger deviation in the errors serve to identify portions of data poorly described by the model.

In all cases, log likelihood was the objective function used to evaluate the goodness of fit of the nonlinear regression, and the squared error was weighted by the reciprocal of the predicted concentration squared. Based on previously described techniques, plasma concentration recovery curves were constructed using the method of Shafer and Varvel. Context-sensitive half-times, that is, the time required for the plasma concentration to decline by one-half following termination of an infusion, were determined as described by Hughes et al.

Results

The three volume and three clearance parameters that best described the individual nonlinear regression were averaged and are presented in table 1 as the two-stage analysis of zero-order data. The pooled analysis of the same data with and without covariates also is presented in table 1. Height was the only covariate that significantly improved the log likelihood of the nonlinear regression. The improvement in predictive error between the two-stage and the pooled analysis with covariates is easily appreciated with comparison of the residual errors in figures 2 and 3. Between 7 and 20 min and 100 and 400 min, the concentration predicted by the two-stage analysis is higher than the measured concentration as evidenced by the asymmetric distribution of errors with an upward bias about the line of zero %WR. These systematic errors are eliminated by the pooled analysis.

Figure 4 shows the plasma dexmedetomidine concentrations predicted by the two-stage and pooled parameter sets following a unit bolus (i.e., the unit disposition function), overlaid on the graph of the unit disposition function predicted by numeric deconvolution. The unit disposition function produced
through numeric deconvolution is closest to that obtained through pooled analysis.

Figure 5 uses the pooled pharmacokinetic parameters and depicts the projected time required for the plasma concentration of dexmedetomidine to decline by a given percentage following administration of such an infusion designed to hold the plasma dexmedetomidine concentration constant. This recovery curve profile is similar to that seen after administration of fentanyl.7 The context-sensitive half-times8 for dexmedetomidine using our pooled pharmacokinetic parameters are shown in table 2.

Figure 6 shows the performance of the CCIP using the pooled pharmacokinetic parameters to hold four target plasma dexmedetomidine concentrations. The hollow circles represent the mean measured concentrations (±SD). The CCIP underestimated the dose required to achieve the lower target concentrations (i.e., the mean is consistently below the target) while performing reasonably well at the subsequent higher concentrations. The precision of the CCIP was 31.5%, and the bias was −22.4%. In an attempt to refine the pharmacokinetic model further, we fit the parameters of a mamillary pharmacokinetic model to the CCIP data us-

<table>
<thead>
<tr>
<th>Analysis (Data)</th>
<th>Two-stage (Zero Order)</th>
<th>Pooled (Zero Order)</th>
<th>Pooled with Covariates (Zero Order)</th>
<th>Pooled with Covariates (CCIP)</th>
<th>Pooled with Covariates (CCIP and Zero Order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L) (±SD)</td>
<td>8.09 ± 2.2</td>
<td>8.06</td>
<td>8.05</td>
<td>30.3</td>
<td>7.99</td>
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<tr>
<td>V2 (L) (±SD)</td>
<td>37.9 ± 35</td>
<td>12.6</td>
<td>12.4</td>
<td>70.1</td>
<td>13.8</td>
</tr>
<tr>
<td>V3 (L) (±SD)</td>
<td>229 ± 173</td>
<td>178</td>
<td>175</td>
<td>NA</td>
<td>187</td>
</tr>
<tr>
<td>Cl1 (L·min⁻¹) (±SD)</td>
<td>0.453 ± 0.085</td>
<td>0.445</td>
<td>(0.0101±HT)−1.33</td>
<td>3.31−(0.0119±HT)</td>
<td>(0.0079±HT)−0.927</td>
</tr>
<tr>
<td>Cl2 (L·min⁻¹) (±SD)</td>
<td>2.71 ± 1.7</td>
<td>2.06</td>
<td>2.05</td>
<td>1.51</td>
<td>2.26</td>
</tr>
<tr>
<td>Cl3 (L·min⁻¹) (±SD)</td>
<td>1.47 ± 0.93</td>
<td>1.99</td>
<td>2.00</td>
<td>NA</td>
<td>1.99</td>
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<td>% WR</td>
<td>+7.7</td>
<td>−0.5</td>
<td>−0.1</td>
<td>17.0</td>
<td>−0.9</td>
</tr>
<tr>
<td>% MDAWR</td>
<td>+24.4</td>
<td>+22.2</td>
<td>+22.5</td>
<td>14.4</td>
<td>+23</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>−168</td>
<td>−123</td>
<td>−118</td>
<td>70</td>
<td>−91</td>
</tr>
</tbody>
</table>

V1 = central volume of distribution; CCIP = computer-controlled infusion pump; Cl1 = elimination clearance; WR = weighted residual; MDAWR = median absolute weighted residual; HT = subject height in centimeters.
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Table 2. Context-sensitive half-times

<table>
<thead>
<tr>
<th>Infusion Duration</th>
<th>Context-sensitive Half-times (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>3.52</td>
</tr>
<tr>
<td>1 h</td>
<td>25.1</td>
</tr>
<tr>
<td>3 h</td>
<td>204</td>
</tr>
<tr>
<td>8 h</td>
<td>249</td>
</tr>
<tr>
<td>Infinite</td>
<td>251</td>
</tr>
</tbody>
</table>

dexmedetomidine concentrations and a positive bias at the higher concentrations. This nonrandom error pattern in the residuals suggests the possibility that dexmedetomidine influences its own pharmacokinetics. Specifically, the positive bias at higher concentrations is consistent with dexmedetomidine-induced decrease in clearance and initial mixing volumes.

The CCIP data set used low-resolution sampling following each increment in target concentration. In an effort to evaluate the result of using our CCIP parameters outside the original sample times, we applied these parameters to the measured concentrations from the zero-order data set, and the weighted residuals are plotted in figure 7. For reference purposes, we have included the weighted residuals from the zero-order data set shown in figure 3. It can be seen that the CCIP parameters performed at least as well as the zero-order parameters over the time span of 5–60 min. Unfortunately, there is enormous bias before 5 min and after 60 min.

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To generate a single set of pharmacokinetic parameters that would provide the best performance in longer CCIP infusions, we performed a pooled regression on the combined data from both the zero-order and CCIP infusions. The results are shown in table 1 as the pooled analysis of both zero-order and CCIP data. Height was still a significant covariate of CL1. The weighted residuals using these parameters on all the data are shown in figure 8.

Discussion

For medications with concentration versus time profiles best described by a one-compartment model, or medications where chronic stable concentrations are the therapeutic goal and peak concentrations are not toxic, the clearance and volume parameters from moment analysis provide adequate information to design a dosing regimen. In anesthesia, medications with narrow therapeutic windows are administered intravenously and the distribution phase frequently governs both the therapeutic effect and drug toxicity. Moment analysis does not allow prediction of plasma concentrations over time in non-steady-state conditions unless the data can be described by a one-compartment model.

Parametric analysis is model-dependent and provides a description of the concentration versus time profile during both the distribution and elimination phases. Provided that linear pharmacokinetics apply, parametric analysis will allow prediction of plasma concentrations over time when any combination of boluses or infusions are administered. Additionally, a CCIP can use these parameters to maintain the plasma concentration at any desired target.

The traditional two-stage pharmacokinetic estimates of the volume of compartment 1 and the clearance from compartment 1 were similar to those from the pooled analysis. V1 is fixed as the dose/concentration at time zero following a bolus injection. Regardless of the chosen regression technique, the starting point of the unit disposition function is fixed, and hence there is less latitude in fitting the volume of the central compartment. This may account for the similar volumes of the central compartment with the different techniques. Peripheral compartments do not reflect any easily measured value, and one would expect greater variability in the parameter values of the peripheral compartments depending on the chosen regression technique.

Performing a two-stage analysis averages volumes and clearances from many individual parameter estimations. There are three intrinsic problems with the two-stage approach, resulting in virtual assurance that optimal parameter estimates for the population are not obtained when individual parameters are averaged.9

1. Volume and clearance terms may represent slightly different portions of the data in individual patients. Thus, the mean represents an average of parameters that should not, a priori, be averaged.

2. The computation of the mean value assumes a normal distribution of the parameters. Since clearances

Fig. 7. Percent weighted residual error zero-order data versus time, CCIP pooled analysis parameters with covariates (thick line), zero-order parameters (thin line).

Fig. 8. Percent weighted residual error following parameter estimation using the combined zero-order and CCIP data sets.
are nonlinear parameters in the model, it is not reasonable to expect an arithmetic mean to capture the true population value.

3. The process of calculating the mean does not account for the varying degrees of certainty among individual estimates of parameters.

In contrast, the pooled approach minimizes the residual error between the measured and predicted values in all subjects at the same time. While the pooled approach introduces an element of bias by failing to account for intraindividual variability in parameters, the decrease in systematic bias with the pooled results is evident from comparison of figures 2 and 3. This decreased bias was not dependent on the inclusion of height as a covariate.

The covariates age and body weight provided no improvement in the predictive value of the model. Our volunteers were healthy men within a narrow range of the age and weight (29–44 yr and 60–98 kg, respectively), and therefore any relationship to these covariates might be difficult to discern. Extrapolation of these data obtained in our homogeneous group of subjects to others of advanced age or in the presence of other medications might result in increases in the predictive error of the model.

Our CCIP administration targeted initial plasma dexmedetomidine concentrations a full order of magnitude lower than seen following our zero-order infusion study. Dexmedetomidine is known to have marked cardiovascular effects when administered rapidly intravenously, causing initial profound hypertension and bradycardia. If one attributes these hemodynamic alterations to a peripheral vasoconstrictive action of dexmedetomidine at high concentrations, it would be reasonable to expect a decrease in the initial volume of distribution and intercompartmental clearance until the vasoconstrictive dexmedetomidine concentrations have declined ($V_{\text{hig}}$ concentration < $V_{\text{low}}$ concentration). Figure 6 is illustrative of this concept. The CCIP programmed with $V_{\text{hig}}$ concentration but targeted to a low concentration noticeably underdosed the subjects. As the targeted concentration increased, the performance of the CCIP improved. Our refinement of the CCIP parameters also illustrates the nonlinear pharmacokinetics of dexmedetomidine. The solid line in figure 6 is the best two-compartment regression of the measured CCIP data and shows the same systematic error with underdosing at lower concentrations and overdosing at higher concentrations. The concentration-dependent nonlinearity of dexmedetomidine pharmacokinetics adds a new dimension of complexity to dosing recommendations because any single set of pharmacokinetic parameters will represent a compromise outside an average concentration attained during the original study. Optimal dosing would require that the infusion parameters be continuously modified along a currently undefined function as the dexmedetomidine concentration changes. It would be possible to provide such recommendations through the use of CCIP technology. In separate studies, a series of dexmedetomidine concentrations could be held reasonably constant by the CCIP for extended periods while high resolution sampling is performed. It would be anticipated that the parameters fit to data from studies at different concentrations would show a pattern amenable to a mathematical description incorporating concentration into the model.

Our CCIP study demonstrates that it is only possible to characterize a pharmacokinetic model over the time period in which concentrations were obtained. This is intuitive for a bolus or a single short infusion, but is not as obvious during a CCIP infusion. In a hypothetical situation, a CCIP might be infusing medication for days or weeks with targeted concentrations increasing and decreasing in response to patient needs. If plasma concentrations are only obtained 1 min after a large step up in target concentration, regardless of whether the CCIP has been infusing for minutes or weeks, one is predominately describing the distribution phase of the medication. More frequent sampling, relative to each change in target concentration, would be required to characterize the higher frequency components of the pharmacokinetics profile. Figure 7 shows the highly biased results that are possible if models are extrapolated earlier or beyond the data upon which they were derived.

In summary, the pharmacokinetics of dexmedetomidine are best described by a three-compartment model. The present data do not support weight adjustment within the range of 60–98 kg. Dexmedetomidine clearance was correlated with height in this study. There was evidence that dexmedetomidine-induced changes in systemic vascular resistance and cardiac output modestly altered dexmedetomidine pharmacokinetics. The dexmedetomidine pharmacokinetic values from our intravenous study (table 1, pooled analysis zero-order data) gave us good prospective performance when tested via computer-controlled drug
delivery but demonstrated concentration-dependent nonlinear pharmacokinetics. We anticipate that, because the pharmacokinetic parameters with the addition of the CCIP data (table 1, pooled analysis zero-order and CCIP data) show only small differences from the zero-order data alone (table 1, pooled analysis zero-order data), the performance if tested prospectively would be similar. Improvements in CCIP accuracy for dexmedetomidine infusions would require modification of the model based on the targeted concentration.

References