Altered Cisatracurium Pharmacokinetics and Pharmacodynamics in Patients with Congenital Heart Defects

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ABSTRACT

The neuromuscular blocking agent cisatracurium is frequently used adjunctively in anesthesia to facilitate endotracheal intubation and to provide muscle relaxation during surgery. We aimed to determine the pharmacokinetics (PK)/pharmacodynamics (PD) of cisatracurium in patients with congenital heart defects (CHDs), such as ventricular septal defects and atrial septal defects, and to assess the effects of CHDs on the PK/PD profiles of cisatracurium. A modified two-compartment model with drug clearance from both compartments was best fitted to the PK data to determine the PK parameters. The model suggested that septal defects significantly lowered the rate of cisatracurium distribution from the central to peripheral compartment. The intercompartment rate constants $k_{12}$ and $k_{21}$ were significantly reduced (35%–60%, $P < 0.05$) in patients with ventricular septal defects and in patients with atrial septal defects compared with control patients. Consistently, septal defects caused a marked increase (160%–175%, $P < 0.001$) in the distribution half-life. Furthermore, significantly delayed pharmacodynamic responses to cisatracurium were observed in patients with septal defects. The onset time (i.e., the time to maximal neuromuscular block) was prolonged from 2.2 minutes to 5.0 minutes. PK/PD modeling suggested that reduced concentrations of cisatracurium in the effect compartment due to poorer distribution were the main cause of lagged pharmacodynamic responses. In conclusion, cisatracurium PK/PD were significantly altered in patients with septal defects. Our study should be of use in clinical practice for the administration of cisatracurium to patients with CHDs.

Introduction

Cisatracurium (marketed as Nimbex; AbbVie Inc., North Chicago, IL) is the $R$-cis, $R$-etis isomer of atracurium (Kisor and Schmith, 1999). Both cisatracurium and atracurium act as nondepolarizing neuromuscular blocking agents. However, cisatracurium is approximately 3-fold more potent as a muscle relaxant compared with atracurium (Bryson and Faulds, 1997). Furthermore, it has less propensity to elicit histamine release, the major adverse effect of atracurium (Belmont et al., 1995). Cisatracurium has been frequently used adjunctively in anesthesia to facilitate endotracheal intubation and to provide muscle relaxation during surgery (Bryson and Faulds, 1997). The drug spontaneously degrades at physiologic pH and temperature via Hofmann elimination, which is subsequently metabolized to a number of conjugated metabolites (Dear et al., 1995; Welch et al., 1995; Weidlmayr-Goettel et al., 1998). Therefore, elimination of cisatracurium most likely occurs in both plasma and tissues. Although Hofmann elimination is the main mechanism for cisatracurium clearance in the body, plasma esterase-mediated hydrolysis also plays a role (Kisor et al., 1996).

Congenital heart defects (CHDs) are an abnormality in the structure of the heart, resulting in a change in the normal flow of blood through the heart (Garg, 2006). CHDs are one of the most common types of birth defects, affecting 8 of every 1000 newborns (Mozaftari et al., 2015). It is reported that more than 35,000 infants in the United States are born with CHDs every year (Mozaftari et al., 2015). Cardiac septal defects, characterized by holes in the septum, are the main type of CHD (Garg, 2006). Furthermore, there are two types of septal defects—namely, ventricular septal defects (VSDs) and atrial septal defects (ASDs) (McDaniel, 2001). CHDs can be repaired with a high success rate via catheter procedures or surgery (Pace Napoleon and Gargiulo, 2007; Blanche et al., 2013). However, numerous adult patients in developing countries are still suffering from CHDs because these individuals fail to receive timely treatment in their childhood.

Cisatracurium is a commonly used muscle relaxant in anesthesia (Bryson and Faulds, 1997). It is frequently used in anesthesia during repair surgery for patients with CHDs (Pinard et al., 2003; Mirinejad et al., 2007). However, the pharmacokinetics (PK) and pharmacodynamics (PD) of cisatracurium in patients with CHDs remain underexplored. The lack of PK/PD information in this specific population raises serious concerns about administration of cisatracurium with a regular dose (0.15 mg/kg). The objectives of this study were to determine the

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ABBREVIATIONS: AIC, Akaike information criterion; ASD, atrial septal defect; CHD, congenital heart defect; PD, pharmacodynamics; PK, pharmacokinetics; QTOF/MS, quadrupole time-of-flight/mass spectrometry; SNX-2112, 4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-5,7-dihydroindazol-1-yl]-2-[(4-hydroxy cyclohexyl)amino] benzamide; TOF, train-of-four; UPLC, ultra-performance liquid chromatography; VSD, ventricular septal defect.
PK/PD of cisatracurium in patients with CHDs and to assess the effects of CHDs on PK/PD profiles of cisatracurium. To this end, a clinical trial was performed with patients suffering from CHDs (i.e., VSDs and ASDs). Cisatracurium levels in plasma samples were quantified using an ultra-performance liquid chromatography (UPLC)–quadrupole time-of-flight/mass spectrometry (QTOF/MS) method. The neuromuscular block effects were measured using the train-of-four (TOF) technique. Customized PK and integrated PK/PD models were used to analyze the data. We demonstrated for the first time that PK and PD behaviors of cisatracurium were significantly altered in patients with CHDs.

Materials and Methods

Materials
Cisatracurium (≥98% pure) was purchased from Sigma-Aldrich (St. Louis, MO). SNX-2112 (4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-5,7-dihydroindazol-1-y1]-2-[4-(4-hydroxy cyclohexy1)amino] benzamide) (used as an internal standard) was kindly provided by Dr. Yifei Wang (Biomedicine Research and Development Center, Jinan University, Guangzhou, China). Mass spectrometry–grade acetonitrile was obtained from Merck (Darmstadt, Germany). H2SO4 (analytical grade) was purchased from Runhao Biologic Technology Ltd. (Guangzhou, China).

Participants
The clinical trial study of cisatracurium (no. GDREC2015297H; Supplemental Fig. 1) was approved by the Guangdong General Hospital, Guangdong Academy of Medical Sciences (Guangzhou, China). The clinical trial was performed at Guangdong General Hospital (Guangzhou, China). A total of 43 patients were included in the trial (written informed consent forms were obtained from all patients). These patients were divided into three groups—namely, control (n = 15), VSD (n = 12), and ASD (n = 15) groups. Patients in the control group were diagnosed with a gallstone or inguinal hernia but had intact cardiac function and were free of clinically significant blood, psychiatric, neurologic, or neuromuscular diseases.

Anesthesia (Cisatracurium Administration)
A peripheral catheter was inserted into the median cubital vein for administration of anesthetic agents. Approximately 1 ml of blank blood was collected for pH measurement before anesthesia execution. Blood pH was measured using a blood gas analyzer (IRMA TruPoint; LifeHealth, LLC; Roseville, MN). Anesthesia was induced with a loading dose of 0.05 mg/kg midazolam, 1–1.5 mg/kg propofol, and 5 µg/kg fentanyl. After loss of the eyelash reflex (approximately 3 to 4 minutes later), 0.15 mg/kg cisatracurium was administered by intravenous bolus injection. Anesthesia was then maintained by continuous infusion of propofol (4 mg/kg per hour) and remifentanil (0.1–0.5 µg/kg per minute). Before drug dosing, the body temperature of each patient was measured using the Primus system (Drager, Lübeck, Germany).

Neuromuscular Monitoring
The neuromuscular block response to cisatracurium was assessed using the TOF twitch technique. TOF measurements were performed with TOF-Watch SX (Organon, Dublin, Ireland) according to the manufacturer’s protocol. In brief, the skin over the ulnar at the wrist was gently abraded and then cleaned with an alcohol wipe. The negative electrode was placed on the wrist, in line with the smallest digit (1 to 2 cm below the skin crease) and the positive electrode was 2 to 3 cm proximal to the negative electrode. The adductor pollicis muscle twitch upon nerve stimulation was monitored at a 15-second interval. Single stimuli at 1 Hz were administered for 3 minutes for stabilization before switching to TOF stimulation (2 Hz every 15 seconds) prior to cisatracurium administration. The percentage of neuromuscular block was calculated using T1 (the first twitch) values as described (Bergeron et al., 2001). The onset time was defined as the time to reach maximum block (Bergeron et al., 2001).

Blood Sampling
Arterial blood samples (approximately 4 ml) were collected from the patients before (time 0) and at 1, 2, 4, 8, 12, 16, and 20 minutes after cisatracurium administration. Blood samples were transferred to centrifuge tubes containing heparin and were centrifuged (4°C) at 9,000 × g for 2 minutes. The supernatant (plasma) was collected and immediately mixed with 100 µl H2SO4 (1 mM). The plasma samples were stored at −80°C until analysis.

After the addition of the internal standard (SNX-2112), plasma samples (200 µl) were deproteinized using acetonitrile (800 µl). The resulting mixture was vortexed for 3 minutes and was centrifuged at 15,000 × g for 15 minutes. The supernatant was collected and dried using Eppendorf Concentrator Plus (Hamburg, Germany). The residue was reconstituted in a solution of water/acetonitrile [50:50 (v/v)]; 200 µl) and centrifuged at 15,000 g for 15 minutes (4°C). A 5-µl aliquot of the supernatant was injected into the UPLC-QTOF/MS system for drug quantification.

Quantification of Cisatracurium by UPLC-QTOF/MS Analysis
Quantification of cisatracurium was performed using an UPLC-QTOF/MS system equipped with an Acquity UPLC device and a Xevo G2 QTOF mass...
spectrometer (Waters, Milford, MA). Instrument configuration and parameter settings were described in our previous publication (Liu et al., 2014). In brief, chromatographic separation was performed on a BEH column (2.1 × 50 mm, 1.7 μm; Waters). A gradient elution was applied using formic acid (0.1%) in water (mobile phase A) versus acetonitrile (mobile phase B) at a flow rate of 0.45 ml/min. The gradient elution program was 5% B at 0 to 1 minute, 5% to 85% B at 1 to 3 minutes, 85% B at 3 to 3.5 minutes, and 85% to 5% B at 3.5 to 4 minutes. Quantitation was performed based on the full scan analysis and extracted ion chromatograms using MassLynx software (version 4.1; Waters) as described (Liu et al., 2014).

**Pharmacokinetic Modeling**

**Model Selection.** Two conventional PK models (i.e., one-compartment and two-compartment models) and a modified two-compartment PK model (Fig. 1A) were used to describe the pharmacokinetic data of cisatracurium. In conventional models, the drug is cleared from the central compartment only (Fig. 1A).

**Fig. 2.** Representative extracted ion chromatograms of cisatracurium and SNX-2112 (the internal standard) from UPLC-QTOF/MS analysis. (A) Extracted ion chromatogram of cisatracurium. (B) Extracted ion chromatogram of SNX-2112. ES+, Electrospray (positive mode); IS, internal standard; MS, mass spectrometry.

**Fig. 3.** Plasma concentration versus time curves of cisatracurium in various types of patients after intravenous administration of cisatracurium (0.15 mg/kg). (A) Individual plasma concentration versus time curves for 15 control patients. (B) Individual plasma concentration versus time curves for 12 patients with VSDs. (C) Individual plasma concentration versus time curves for 15 patients with ASDs.
By contrast, the modified model assumed that drug clearance occurred in both central and peripheral compartments (Fig. 1A). Elimination of cisatracurium from both compartments was highly possible because Hofmann degradation (the primary clearance route of the drug) was organ independent. It was noted that several studies had indicated that the pharmacokinetic data of cisatracurium were well described by this modified PK model (Kisor et al., 1996; Schmith et al., 1997; Bergeron et al., 2001).

The mean plasma concentrations (at different time points) for three groups of patients were obtained by averaging the data of all individuals in each group. Each of the three PK models was fitted to the data of mean plasma concentrations versus time. Model construction and data fitting were performed using MATLAB software (MathWorks Inc., Natick, MA). Goodness of fit was assessed by the Akaike information criterion (AIC) and dialogistic plots. The model with the smallest AIC value was regarded as the best model.

Estimation of PK Parameters. The best PK model was fitted to individual PK data to derive PK parameters for each subject. The mean value of each parameter for each study group was obtained by averaging the values derived from the individuals. This method of parameter derivation allowed for adequate assessment of the intersubject variability of PK parameters. Model building and parameter estimation were performed using MATLAB software (MathWorks Inc.).

**PK/PD Modeling**

**Model Selection.** Three PK/PD models (i.e., model 1, indirect link $E_{\text{max}}$ model; model 2, indirect link sigmoid $E_{\text{max}}$ model; and model 3, direct link sigmoid $E_{\text{max}}$ model) were established by linking an effect compartment to the best PK model (Fig. 1B; Table 4). The effect compartment represented the site of cisatracurium action. In the indirect link models, the rate constant $k_0$ described the transfer of drug molecules from the central compartment to the effect compartment. In the sigmoidal $E_{\text{max}}$ models, the slope factor ($\gamma$) was a parameter describing steepness of the response curve. In all models, $E_{\text{max}}$ was the maximal effect. EC$_{50}$ was the drug concentration required to produce one-half of the maximal effect.

**Estimation of PD Parameters.** The best PK/PD model was fitted to individual PK/PD data to derive PD parameters for each participant. PD parameters were obtained following a two-step fitting procedure as described above. The only difference was that the individual data were used here. The mean value of each PD parameter for each study group was obtained by averaging the values derived from the individuals. Again, this method of parameter derivation allowed for adequate assessment of the intersubject variability of modeled parameters. Model building and parameter estimation were performed using MATLAB software (MathWorks Inc.).

### TABLE 2

Pharmacokinetic parameters and statistics derived from fitting of each of three pharmacokinetic models (Fig. 1A) to the average data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>VSD</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-compartment V (ml/kg)</td>
<td>84.2 ± 8.3</td>
<td>67.3 ± 6.9</td>
<td>61.7 ± 7.1</td>
</tr>
<tr>
<td>$K_{10}$ (1/min)</td>
<td>0.10 ± 0.02</td>
<td>0.12 ± 0.02</td>
<td>0.13 ± 0.02</td>
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<tr>
<td>$K_{10}$ (1/min)</td>
<td>86.6</td>
<td>87.1</td>
<td>88.2</td>
</tr>
<tr>
<td>Two-compartment $V_{\text{c}}$ (ml/kg)</td>
<td>57.2 ± 6.23</td>
<td>54.7 ± 4.98</td>
<td>52.8 ± 5.92</td>
</tr>
<tr>
<td>$K_{10}$ (1/min)</td>
<td>0.12 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td>$K_{12}$ (1/min)</td>
<td>0.25 ± 0.02</td>
<td>0.16 ± 0.01</td>
<td>0.15 ± 0.02</td>
</tr>
<tr>
<td>$K_{21}$ (1/min)</td>
<td>0.25 ± 0.03</td>
<td>0.17 ± 0.02</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td>AIC</td>
<td>61.2</td>
<td>59.7</td>
<td>62.6</td>
</tr>
<tr>
<td>A modified model $V_{\text{c}}$ (ml/kg)</td>
<td>50.1 ± 2.18</td>
<td>48.9 ± 2.17</td>
<td>47.2 ± 2.11</td>
</tr>
<tr>
<td>$K_{10}$ (1/min)</td>
<td>0.09 ± 0.01</td>
<td>0.08 ± 0.01</td>
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</tr>
<tr>
<td>$K_{20}$ (1/min)</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.02</td>
<td>0.04 ± 0.02</td>
</tr>
<tr>
<td>$K_{12}$ (1/min)</td>
<td>0.23 ± 0.01</td>
<td>0.17 ± 0.01</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>$K_{21}$ (1/min)</td>
<td>0.24 ± 0.01</td>
<td>0.16 ± 0.01</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>AIC</td>
<td>49.6</td>
<td>48.3</td>
<td>50.1</td>
</tr>
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</table>

**A**Two-compartment model with drug elimination from central compartment.

**B**Two-compartment model with drug elimination from both central and peripheral compartment.

**Fig. 4.** Comparisons of mean plasma concentration versus time curves between the control and CHD groups. (A) A comparison of mean plasma concentration versus time curves between the control group and VSD groups. (B) A comparison of mean plasma concentration versus time curves between the control and ASD groups. Solid lines were predicted data from the modified two-compartment PK model (Fig. 1A). Statistically significant differences in plasma concentrations between the control and CHD groups at specific time points were indicated by asterisks ($^{*}P < 0.01$; $^{**}P < 0.001$).

### TABLE 3

Pharmacokinetic parameters estimated from fitting the modified PK model (Fig. 1A) to individual data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>VSD</th>
<th>ASD</th>
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</thead>
<tbody>
<tr>
<td>$V_{\text{c}}$ (ml/kg)</td>
<td>42.2 ± 6.72</td>
<td>50.5 ± 11.1</td>
<td>41.3 ± 6.56</td>
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<tr>
<td>$K_{10}$ (1/min)</td>
<td>0.10 ± 0.05</td>
<td>0.08 ± 0.002</td>
<td>0.09 ± 0.003</td>
</tr>
<tr>
<td>$K_{12}$ (1/min)</td>
<td>0.37 ± 0.17</td>
<td>0.14 ± 0.04**</td>
<td>0.16 ± 0.04**</td>
</tr>
<tr>
<td>$K_{21}$ (1/min)</td>
<td>0.23 ± 0.08</td>
<td>0.15 ± 0.06*</td>
<td>0.14 ± 0.06*</td>
</tr>
<tr>
<td>AIC</td>
<td>0.03 ± 0.01</td>
<td>0.04 ± 0.02</td>
<td>0.04 ± 0.02</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>1.31 ± 0.05</td>
<td>2.29 ± 0.08***</td>
<td>2.08 ± 0.05***</td>
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<tr>
<td>MRT (min)</td>
<td>19.3 ± 6.78</td>
<td>21.2 ± 7.08</td>
<td>21.0 ± 7.42</td>
</tr>
<tr>
<td>AUC (min × μg/ml)</td>
<td>23.8 ± 5.18</td>
<td>28.6 ± 6.7*</td>
<td>30.5 ± 6.65**</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CL, clearance; MRT, mean residence time; $t_{1/2}$, distribution half-life; $t_{1/2}$, elimination half-life; $V_{\text{c}}$, volume of the central compartment; $V_{\text{c}}$, steady-state volume of distribution.

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (compared with the control group).
Statistical Analysis

Data are presented as means ± S.D. The unpaired t test was used to analyze the significant differences in PK or PD parameters between the control and CHD groups. The level of significance was set at $P < 0.05$, $P < 0.01$, and $P < 0.001$.

Results

Study Participants

A total of 43 patients, divided into one control group and two CHD groups (i.e., VSD and ASD groups), were included in this clinical trial (Table 1). These patients were randomized to maximize the similarity in demographic features (e.g., age, sex, race, and body mass index) between the control and CHD groups (Table 1). The main clearance pathway for cisatracurium was Hoffman degradation that was pH and temperature dependent (Kisor et al., 1996). Hence, it was necessary to measure the blood pH and body temperature for all patients. The results showed that there were no significant differences in pH or body temperature values between any two of the three groups (Table 1).

Quantification of Plasma Cisatracurium by UPLC-QTOF/MS

Concentrations of cisatracurium in plasma were quantified using UPLC-QTOF/MS with a 4-minute elution gradient. Cisatracurium and SNX-2112 (used as an internal standard) were eluted at 2.61 and 2.88 minutes, respectively (Fig. 2). We selected SNX-2112 as an internal standard because this compound was rather stable and showed a high response in the UPLC-QTOF/MS system. The analytical method were rigorously validated with respect to linearity (50–5000 ng/ml), precision (relative standard deviation < 10%), and accuracy (within 90%–110%). The limit of quantification was estimated at 12.5 ng/ml.

Altered Cisatracurium PK in Patients with Cardiac Septal Defects

The plasma concentrations of cisatracurium versus time curves were determined for all individuals (Fig. 3). All pharmacokinetic curves clearly showed two distinct phases—namely, the distribution and elimination phases. Mean plasma concentrations versus time curves for the control and CHD groups were plotted and compared (Fig. 4). It was found that mean plasma concentrations of cisatracurium at early time points (≤4 minutes) were significantly higher ($P < 0.01$) in the CHD group than in the control group (Fig. 4). The results suggested that cardiac septal defects were associated with an elevation in the plasma level of cisatracurium in the distribution phase. This was accounted for by altered drug distribution in patients with CHDs (discussed below).

A modified two-compartment model (Fig. 1) was best fitted to the pharmacokinetic data according to the AIC value (Table 2). Best fitting of this custom model to the data was also justified by the diagnostic plots (Supplemental Figs. 4 and 5). The predicted values from the model were closest to the observed ones (Supplemental Fig. 4). Furthermore, the model generated the smallest and randomly distributed residuals (Supplemental Fig. 5). The mean value of each parameter for each study group was obtained by averaging the values derived from the individuals (Table 3). Cardiac septal defects led to obvious alterations in drug transfer between the central and peripheral compartments (Table 3). The rate constants $k_{12}$ and $k_{21}$ were significantly reduced (35%–60%, $P < 0.05$) in the VSD and ASD groups compared with the control group (Table 3). Consistently, septal defects caused significant increases (160%–175%, $P < 0.001$) in the distribution half-life value. Taken together, the modeling results indicated that ASD and VSD defects delayed distribution of cisatracurium to the peripheral compartment, leading to higher levels of the drug in the central compartment (or plasma) in the distribution phase. By contrast, none of other parameters, including the volume of the central compartment, steady-state volume of distribution, elimination rate constant ($k_{10b}$), elimination half-time, and mean residence time, were changed by cardiac septal defects (Table 3).

Altered Cisatracurium PD in Patients with Cardiac Septal Defects

The profiles of neuromuscular block effect versus time were determined for all individuals (Fig. 5). By using the individual data, the mean neuromuscular block effects versus time curves for three study groups were plotted and compared (Fig. 6). It was clear by visual inspection that cardiac septal defects delayed the pharmacodynamic...
effects of cisatracurium (Fig. 6). Furthermore, the pharmacodynamic data were best described by PK/PD model 2 consisting of the modified PK model and an indirect link sigmoidal $E_{\text{max}}$ model (Figs. 1B and 6; Table 4). Best fitting of this integrated model to the data was also justified by the diagnostic plots (Supplemental Figs. 6 and 7). The predicted PD values from the model were closest to the observed ones, suggesting that in addition to Hofmann elimination, the drug was also cleared via a strong PK/PD basis for rational dosing of cisatracurium in patients with septal defects to achieve a desired pharmacodynamic response.

The estimated pharmacodynamic parameters were summarized (Table 5). The mean $K_{\text{so}}$ value was 30.8%–38.5% smaller ($P < 0.001$) in patients with cardiac septal defects than in control patients, suggestive of slower distribution of drug molecules to the effect compartment from blood in patients with septal defects. The onset time (i.e., the time to maximal neuromuscular block effect) was significantly prolonged to 5.0 minutes ($P < 0.001$) in septal patients (Table 5). By contrast, septal defects did not cause changes in any of the other parameters (i.e., $E_{\text{max}}$, $E_{\text{max}}$, or $\gamma$) (Table 5), indicating that drug potency and binding affinity to the target remained unchanged.

Cisatracurium concentrations in the effect compartment were simulated based on PK/PD model 2 (Fig. 7). The delayed onset of cisatracurium effects was associated with reduced concentrations of cisatracurium in CHD groups due to poorer distribution (Fig. 7). This suggested that the differences in drug distribution may explain the distinct pharmacodynamic effects in patients with CHDs. Dose-dependent pharmacodynamic effects in patients with VSDs and in patients with ASDs were also simulated (Fig. 8). It was predicted that an escalation of dose from 0.15 to 0.20 mg/kg would result in an equal pharmacodynamic effect in patients with septal defects compared with control patients (Fig. 8).

**Discussion**

In this study, we, for the first time, determined the PK and PD of cisatracurium in patients with two common types of CHDs (i.e., VSDs and ASDs). The results suggested that septal defects significantly altered the kinetics and extent of drug distribution from the central to peripheral compartments, resulting in a higher drug level in the central compartment (plasma) during the distribution phase (Fig. 4). Furthermore, significantly delayed pharmacodynamic responses to cisatracurium were observed in patients with septal defects (Fig. 6). PK/PD modeling suggested that reduced concentrations of cisatracurium in the effect compartment due to poorer distribution may be the main cause of the lag in pharmacodynamic response (Fig. 7). Therefore, our study provided a strong PK/PD basis for rational dosing of cisatracurium in patients with septal defects to achieve a desired pharmacodynamic response.

A modified two-compartment model (Fig. 1A) with elimination from both central and peripheral compartments was best fitted to the pharmacokinetic data of cisatracurium herein. The pharmacokinetic data of cisatracurium were also well described by the same model in previous studies (Schmith et al., 1997; Bergeron et al., 2001). This model was highly relevant to cisatracurium because Hofmann elimination as the main elimination route of the drug was organ independent (Fisher et al., 1986). The conventional two-compartment models with elimination from the central compartment alone would result in an underestimation of the steady-state volume of distribution and an inadequate description of the concentration versus time curve (Kisor et al., 1996). The derived $K_{10}$ values (0.08–0.10 min$^{-1}$) were larger than the $K_{20}$ value (0.03–0.04 min$^{-1}$). This was in line with the fact that in addition to Hofmann elimination, the drug was also cleared via other pathways such as renal excretion (Kisor et al., 1996). Nevertheless, the custom model was an empirical model due to the lack of mechanistic justification using the peripheral compartment data.

### Table 4

<table>
<thead>
<tr>
<th>Model</th>
<th>Control</th>
<th>VSD</th>
<th>ASD</th>
</tr>
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<tbody>
<tr>
<td>$E_{\text{max}}$ ($\mu$g/ml)</td>
<td>628 ± 428</td>
<td>999 ± 898</td>
<td>989 ± 986</td>
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<td>$E_{\text{max}}$ ($\mu$g/ml)</td>
<td>2.45 ± 32.1</td>
<td>5.75 ± 19.8</td>
<td>5.57 ± 15.5</td>
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<tr>
<td>$K_{\text{so}}$ (1/min)</td>
<td>0.14 ± 0.05</td>
<td>0.08 ± 0.02</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>AIC</td>
<td>219</td>
<td>227</td>
<td>225</td>
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### Table 5

<table>
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<tr>
<th>Parameter</th>
<th>Control</th>
<th>VSD</th>
<th>ASD</th>
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<tr>
<td>$E_{\text{max}}$ ($\mu$g/ml)</td>
<td>102 ± 2.16</td>
<td>103 ± 2.78</td>
<td>104 ± 3.12</td>
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<tr>
<td>$E_{\text{max}}$ ($\mu$g/ml)</td>
<td>0.22 ± 0.03</td>
<td>0.24 ± 0.04</td>
<td>0.27 ± 0.05</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>5.18 ± 0.78</td>
<td>6.12 ± 0.46</td>
<td>6.56 ± 0.78</td>
</tr>
<tr>
<td>$K_{\text{so}}$ (1/min)</td>
<td>0.12 ± 0.02</td>
<td>0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>AIC</td>
<td>112</td>
<td>92.4</td>
<td>107</td>
</tr>
</tbody>
</table>

*Onset time was experimentally measured.

**Table 4** Pharmacodynamic parameters and statistics derived from fitting of each of three PK/PD models (Fig. 1B) to the average data

*Data presented as estimated values ± S.D.*

**Table 5** Pharmacodynamic parameters estimated from fitting the PK/PD model 2 (Fig. 1B) to individual data

*The mean value of each parameter for each study group was obtained by averaging the values derived from the individuals. Data presented as means ± S.D.*
The PK and PD of cisatracurium were best described by an integrated PK/PD model (i.e., PK/PD model 2) with an effect compartment linked to the central compartment (Fig. 1B). The same model was successfully used to analyze the PK and PD of cisatracurium in patients with other types of diseases (e.g., end-stage liver disease and severe sepsis) (De Wolf et al., 1996; Liu et al., 2012). Our study and previous studies highlighted that the pharmacodynamic effects of cisatracurium were directly related to the drug concentrations in the site of action (Mellinghoff and Diefenbach, 1997). Hence, the first-order rate constant $K_{e0}$, characterizing the transfer of the drug from the central to the effect compartment, was a key determinant of the onset time of cisatracurium (Minto and Schnider, 2008). Because of a decrease in $K_{e0}$ value, the onset time of cisatracurium was significantly prolonged in patients with CHDs and in patients with ASDs compared with control patients (Fig. 6).

Fig. 8. Comparison of the predicted PD effect versus time curves derived from PK/PD model 2 (Fig. 1B). (A) A comparison of the predicted PD effect versus time curves between the control (at intravenous dose of 0.15 mg/kg) and VSD groups (at an intravenous dose of 0.15 mg/kg, 0.2 mg/kg, and 0.25 mg/kg). (B) A comparison of the predicted PD effect versus time curves between the control (at an intravenous dose of 0.15 mg/kg) and ASD groups (at intravenous dose of 0.15 mg/kg, 0.2 mg/kg, and 0.25 mg/kg).

It was a novel finding that cardiac septal defects, the most common types of congenital heart diseases, led to significant alterations in both PK and PD of cisatracurium. The PK/PD model suggested that altered (delayed) pharmacodynamic effects may be due to reduced drug exposure in the effect compartment caused by poorer distribution. The exact reasons remained unknown as to why cisatracurium distribution from the central/blood to the peripheral/effect compartment was altered in patients with septal defects. Nevertheless, septal defects allow blood shunting between the atria and ventricles, resulting in marked changes in hemodynamics (Penny and Vick, 2011; Geva et al., 2014). Hemodynamic changes are known to be associated with pulmonary hypertension, tricuspid valve regurgitation, and mitral valve regurgitation in patients with septal defects (Penny and Vick, 2011; Geva et al., 2014). Therefore, it was reasonable to speculate that the hemodynamic changes in patients with septal defects underlie poorer distribution of cisatracurium to the tissues from blood.

Pharmacokinetic analyses showed that the elimination rate constants $K_{10}$ and $K_{20}$ remained unchanged in patients with CHDs compared with control patients (Table 3). Since the main elimination pathway for cisatracurium is Hoffman degradation (Kisor et al., 1996; Schmith et al., 1997; Bergeron et al., 2001), the unchanged $K_{10}$ and $K_{20}$ may imply that degradation of cisatracurium by Hoffman reaction was not altered in patients with CHDs. This was supported by the fact that the pH and body temperature (two critical factors determining the rate of cisatracurium degradation) of patients with CHDs were identical to those of control patients (Table 1). Since it was unlikely that CHDs caused a difference in the rate of metabolite production, there was a very low possibility that metabolite production would affect the cisatracurium PD in patients with CHDs.

Determination of PK and PD of cisatracurium in subpopulations assumed great importance in the formulation of a population-specific dosage regimen to achieve optimized therapy. Accurate dosing of cisatracurium contributed to improvement of patient safety during anesthesia (Merry et al., 2009). Failing to perform endotracheal intubation at the peak of the muscle-relaxing effect (i.e., at the onset time point) will compromise the hemodynamic stability of patients and cause a disturbance in surgical operation, thereby increasing the rate of anesthetic accidents. In clinical practice, anesthetists usually perform intubation 2 minutes after intravenous injection of 0.15 mg/kg cisatracurium (Bryson and Faulds, 1997). However, such treatment would cause tissue damage in patients with septal defects due to a lag in the onset of neuromuscular block. It was suggested that intubation should be performed approximately 5.0 minutes after cisatracurium administration. Alternatively, the dose should be escalated to approximately 0.2 mg/kg to achieve a regular pharmacodynamic effect (Fig. 8).

In summary, we have, for the first time, established an integrated PK/PD model for cisatracurium in patients with cardiac septal defects. The effects of septal defects on cisatracurium PK and PD were fully assessed. PK modeling suggested that septal defects significantly lowered the rate of cisatracurium distribution from the central to peripheral compartment, resulting in a higher drug level in the central compartment (plasma) during the distribution phase. Furthermore, significantly delayed pharmacodynamic responses to cisatracurium were observed in patients with septal defects. PK/PD modeling suggested that reduced concentrations of cisatracurium in the effect compartment due to poorer distribution may be the main cause of the lag in pharmacodynamic response. Our study should be of use in clinical practice for the administration of cisatracurium to patients with CHDs.

Authorship Contributions

Participated in research design: Z. Wu, Wang, Peng, B. Wu.
Contributed new reagents or analytic tools: Wang, Peng.
Wrote or contributed to the writing of the manuscript: Z. Wu, Wang, Peng, B. Wu.

References


Supplemental data

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Drug Metabolism and Disposition
**Figure S1. Approval letter of the Research Ethics Committee**

![Image of the approval letter](image-url)
Figure S2. Echocardiograms of ventricular septal defects patients
Figure S3. Echocardiograms of atrial septal defects patients
Figure S4. Observation versus prediction plots generated from fitting of the data to each of the three PK models

1-Comt model

2-Comt model

A modified model
Figure S5. Residual plots generated from fitting of the data to each of the three PK models

1-Comt model

2-Comt model

A modified model
Figure S6. Observation versus prediction plots generated from fitting of the data to each of the three PK/PD models

PK/PD model 1

PK/PD model 2

PK/PD model 3
Figure S7. Residual plots generated from fitting of the data to each of the three PK/PD models.