

# Development of a Safe and Effective Pediatric Dosing Regimen for Sotalol Based on Population Pharmacokinetics and Pharmacodynamics in Children With Supraventricular Tachycardia

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<b>OBJECTIVES</b>	The objective of this study was to develop age-specific dosage guidelines for sotalol in children with supraventricular tachycardia (SVT) based on a population pharmacokinetic covariate analysis, clinical trial simulations, and pharmacodynamics.
<b>BACKGROUND</b>	A rapid onset of an effective and safe antiarrhythmic sotalol therapy, especially for infants and neonates, is frequently delayed because of age-dependent interpatient variability in pharmacokinetics and pharmacodynamics.
<b>METHODS</b>	Pediatric patients with SVT (mean age 3.51 years [range 0.03 to 17 years]) were analyzed after oral sotalol doses of 1.0 to 9.9 mg/kg/day using population pharmacokinetic analysis and clinical trial simulation (n = 76), pharmacokinetic/pharmacodynamic modeling for QT interval prolongation (n = 32), and for the concentration–antiarrhythmic–response relationship (n = 15).
<b>RESULTS</b>	Inter-individual differences in oral clearance and volume of distribution could largely be attributed to size and weight differences, with an additional age effect on clearance in children younger than one year. Neonates showed a higher sensitivity toward QTc interval prolongation compared with older patients. In a subgroup of 15 patients, one-half of the patients converted into sinus rhythm at sotalol trough levels of 0.4 µg/ml and more than 95% at 1.0 µg/ml. Dosing recommendations derived for different age groups based on these findings were starting dose and target dose of 2 and 4 mg/kg/day for neonates, 3 and 6 mg/kg/day for infants and children <6 years, and 2 and 4 mg/kg/day for children >6 years.
<b>CONCLUSIONS</b>	This study provides an example for rational drug dosage in children that copes with interpatient variability and can be easily switched to an individually guided therapy based on effective sotalol trough levels. (J Am Coll Cardiol 2005;46:1322–30) © 2005 by the American College of Cardiology Foundation

The performance of clinical drug investigations is currently a subject of intense debate focusing on issues related to moving a traditional paradigm of confirmatory hypothesis testing toward a learning-based new paradigm (1). This new paradigm incorporates pharmacostatistical cutting-edge technology such as population pharmacokinetic (PK) and pharmacodynamic (PD) analyses and clinical trial simulation to build a scientific framework for more rational, efficient, and informative clinical drug investigations (1).

For drug investigations in the pediatric population, these issues are critically important and urgent. The pediatric

population is characterized by a limited number of patients, a broad age range with different developmental stages, age-restricted windows for diagnostic and treatment strategies, and an age-dependent sensitivity toward pharmacologic and toxicologic effects (2). All these burdens apply to the drug treatment of children with supraventricular tachycardia (SVT), which is the most common symptomatic tachycardia in childhood (3). The peak incidence of SVT is found in neonates and infants, who are particularly prone to developing congestive heart failure during persistent SVT (4). Pharmacotherapy is the first-line intervention in neonates and infants.

The antiarrhythmic sotalol is highly effective (80%) in the treatment of various subtypes of SVT in children (5). As a first step, intense investigations were performed on sotalol pharmacokinetics, showing that sotalol follows the maturation process of renal function in the developing child with higher drug exposure in neonates and young infants (6–8). One dosing option derived was a dosing recommendation calculated on the basis of body surface area (BSA) with an additional adjustment for children below a BSA of 0.33 m<sup>2</sup>

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Manuscript received January 13, 2005; revised manuscript received June 4, 2005, accepted June 13, 2005.

#### Abbreviations and Acronyms

AV	=	atrioventricular
BSA	=	body surface area
COES	=	COncentration Efficacy of Sotalol study
ECG	=	electrocardiogram
GFR	=	glomerular filtration rate
PD	=	pharmacodynamic
PK	=	pharmacokinetic
SVT	=	supraventricular tachycardia

(6). According to the guidelines of the International Conference on Harmonization, however, pediatric dosing recommendations should be based on body weight (9) because of practicability and safety, as calculation errors of BSA are not uncommon in smaller children and infants. Body weight-based dosing is recommended for other commonly used antiarrhythmics in pediatric therapy, such as digoxin, propranolol, amiodarone, and flecainide (10) and is also desirable for sotalol.

Sotalol is known for its high proarrhythmic potential of torsade de pointes tachycardia (11). The QT interval used for risk assessment of a drug's proarrhythmic potential (12) prolongs linearly with increasing sotalol concentration (13). The higher sotalol exposure in young children consequently led to higher QT intervals in this age group (6). But there is evidence from animal data that developmental changes include not only the maturation of the kidney but also the maturation of myocardial potassium channels, which are the sotalol targets for the QT prolongation (5). Until now, definite data concerning QT interval as a developmental PD parameter as well as a safety parameter have been lacking (6,14). Furthermore, investigations of the relationship between sotalol concentrations and antiarrhythmic efficacy are lacking in children, but should provide a target concentration needed for successful SVT management.

Thus, the present study had three objectives: 1) to delineate developmental changes of the QT interval using a PK/PD modeling approach; 2) to define a target sotalol concentration for the effective suppression of SVTs in pediatric patients based on the concentration/antiarrhythmic effect relationship; and 3) to develop practical and age-specific dosing recommendations for SVT management in children of different age groups on the basis of body weight.

## METHODS

**Study organization.** A prospective multiple-dose PK/PD study was conducted in accordance with the Declaration of Helsinki and subsequent amendments. The institutional board at each study site approved the research protocol. Parents, legal guardians, or, when appropriate, patients older than seven years gave written informed consent.

**Patients.** Children older than one week and below 18 years of age with incessant or periodic SVT due to Wolff-Parkinson-White syndrome, concealed accessory pathway, atrioventricular (AV) node reentry, or atrial ectopic or

junctional ectopic tachycardia who required long-term antiarrhythmic intervention were included in the study. The patients had to have two or more episodes of SVT. Failure to respond to antiarrhythmics other than beta-receptor blockers or sotalol in the past was not considered an exclusion for this study. Patients were excluded or sotalol therapy was discontinued if any of the following criteria were present or developed: marked left ventricular dysfunction (ejection fraction below 25%, shortening fraction below 15%); sinoatrial node dysfunction with age-inappropriate resting sinus bradycardia below 100 beats/min for newborns, 80 beats/min for infants, and 60 beats/min for children and adolescents; sinus pauses lasting longer than 2.5 s; AV block grade 2 or 3 unless paced; PR >0.24 s, QRS >0.18 s, QTc prolongation (15) of more than 470 ms (16); increased frequency and duration of tachycardia phases with increasing dose; doubling of serum creatinine from the start any time through the end of sotalol therapy; any abnormal concentrations of serum potassium, sodium, calcium, or magnesium (reference values in mmol/l: 3.5 to 4.8, 135 to 150, 2.2 to 2.65, and 0.75 to 1.05, respectively); significant underlying renal, hepatic, gastrointestinal, or hematopoietic dysfunction; infectious diseases; obstructive airway disease; allergies related to medication; inability to tolerate age-appropriate food or the required study procedures (e.g., maintaining vascular access for repeated blood sampling); prescription of drugs that influence QT-interval such as amiodarone, quinidine, disopyramide, or procainamide; drugs influencing AV conduction such as verapamil or diltiazem; any beta-receptor blocker; and digitalis intoxication. Digoxin was accepted as comedication if the patient had already received digoxin before starting the inpatient monitoring phase. The following laboratory tests were performed for all children before the PK investigations: complete blood count with differential blood count, blood urea nitrogen, serum creatinine, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, alkaline phosphatase, total bilirubin, serum albumin, potassium, sodium, calcium, and urinalysis. An analysis of all concurrent medications for possible drug interactions with sotalol was made before patient enrollment.

**Study design and treatment.** Hospitalized patients at the university hospitals in Hamburg and Göttingen received sotalol orally with a starting dose of 2 mg/kg/day divided in three equal parts every 8 h. All patients were hospitalized for at least 3 days before the PK investigation to ensure regular medication intake. In the morning, each patient was given an age-appropriate breakfast in amount and composition consisting of at least milk, tea or coffee, two slices of bread, or two rolls with jelly 30 min before sotalol administration. Breastfed pediatric patients received oral sotalol either 30 min before or 2 h after the breastfeeding. Patients received their morning dose of oral sotalol as a single capsule in patient-specific strength. These capsules were prepared out of Sotalex tablets (Bristol-Myers Squibb GmbH, Munich, Germany) and lactose by the hospital pharmacy and were

provided during the whole hospital stay. The content of the sotalol capsule was administered to the patient with an age-appropriate amount of water or tea. Complete ingestion of the study medication was ensured by inspection of the oral cavity and close supervision of the patient by the research fellow (J. P. E.).

The dose was increased every third day by 2 mg/kg until treatment was considered partially or completely effective or if 10 mg/kg/day was reached. All patients were kept on continuous electrocardiogram (ECG) monitoring throughout their hospital stay. A subset of 15 patients (COES: COncentration Efficacy of Sotalol study) with the same inclusion criteria as the other patients were started on 1 mg/kg/day and treated with smaller incremental dosages of 1 mg/kg every third day. In addition to the routine continuous ECG monitoring, 12-lead ECGs were recorded every day to document frequency of arrhythmia. A 24-h ECG was obtained before start of therapy and after conversion into sinus rhythm. The maximum dosage was 10 mg/kg/day when no limiting side effects occurred. Pharmacokinetics of sotalol were evaluated at the fourth day by performing a plasma concentration profile. Serum creatinine concentrations and electrolytes were regularly monitored before and during therapy.

**End points and assessments.** Complete effectiveness was defined as conversion of arrhythmia into sinus rhythm. The criterion for partial effectiveness in patients was a lowering of the heart rate to age-appropriate values. These end points had to be maintained for a minimum of three days. The target outcome parameter in the COES study patients was complete effectiveness. The QT-interval prolongation was assessed from 12-lead ECGs before treatment and in 30-min intervals during the 12-h plasma concentration profile. A single research scientist read all recordings and a second cardiologist was blind to the patient identification and to the sequence of ECGs. No differences were noted using a Bland-Altman test between the two readings (15,16).

**Sample collection and procedures.** The plasma concentration profile started at 8:00 AM. Blood samples of 300 to 500  $\mu$ l were collected before drug administration and at 1, 2, 3, 4, 6, 8, and 12 h following the oral dose. During that day, one dose in between the 12-h profile was skipped. Sotalol was determined by a non-stereoselective high-performance liquid chromatography assay with fluorimetric detection (17).

**PK/PD modeling of the QT interval.** The QT intervals of lead II were averaged from three to five consecutive sinus beats at each recording time. The same electrocardiographic apparatus was used in both institutions (Cardiovit AT-2 Plus, Schiller, Switzerland) at a chart speed of 50 mm/s and an amplitude of 10 mm/mV. Patients had rested for 10 min in the supine position. Tracings with irregular RR interval, flat T-wave, and motion artifacts were excluded. There were no patients with pre-excitation syndromes for the ECG analysis. End of the T-wave was determined by manual

drawing of a tangent to the steepest portion of the down-sloping T-wave. The tangent's intersection with the isoelectric line marked the end of the T-wave.

Because heart rate is elevated in the neonatal and infant period, neither Bazett's (18) nor Fridericia's (19) formula might suffice for correcting the QT interval for short cardiac-cycle length. According to the formula  $QT = QT_c \cdot RR^b$ , a population-derived correction mode ( $QT_{CPOP}$ ) was fitted to the baseline neonatal/infant (up to 2 years) and to children/adolescents (>2 years) data with  $b = 0.51$  and  $b = 0.37$ , respectively, and compared to Bazett's ( $QT_{CB}$ ) and Fridericia's formula ( $QT_{CF}$ ). Basal  $QT_{CPOP}$  intervals (in ms) and corresponding heart rates (in beats/min) were  $401 \pm 19$  and  $124 \pm 13$  (neonates,  $n = 9$ ),  $411 \pm 26$  and  $130 \pm 29$  (infants,  $n = 6$ ),  $387 \pm 15$  and  $78 \pm 11$  (children,  $n = 10$ ), and  $403 \pm 10$  and  $84 \pm 22$  (adolescents,  $n = 3$ ). All relations between corrected QT intervals and sotalol concentrations were best described by a linear PK/PD model (20). The slope of the linear effect model gave the individual increase in the  $QT_c$  interval per 1  $\mu$ g/ml sotalol in plasma as a measure for the individual sensitivity ( $dQT_c$ ).

**Development of the dosing schedule.** Patient covariates predictive for individual PK parameters of sotalol were identified by a population PK approach simultaneously analyzing the 76 sotalol plasma concentration-time profiles. Pharmacokinetic parameters were estimated by nonlinear mixed effects modeling (NONMEM V, Globomax, Hanover, Maryland) with first-order conditional estimation (FOCE) and  $\eta$ - $\epsilon$  interaction. After assessing a base model, the following covariates were entered by stepwise forward regression and backward elimination: age, weight, height, BSA (21), gender, GFR (22), arrhythmia diagnosis, and digoxin comedication. The significance was tested using a log-likelihood ratio test for differences in objective function between hierarchical models. Finally, covariate specific population-PK parameters were calculated on the basis of individual covariate sets of study subjects and the derived final population pharmacostatistic model.

This model was subsequently used to perform simulations (TRIAL SIMULATOR, Pharsight, Mountain View, California). A covariate model with a joint distribution between age and weight was developed with an age-adjusted variance covariance matrix of the study population to account for the nonlinearity of the correlation between age and weight. The concentration response relation was best described by a logistic regression model,  $P = e^x / (1 + e^x)$ , where  $P$  is the probability of arrhythmia suppression (response) and  $x$  the drug effect ( $-2.4 + 10.1 \cdot \text{sotalol conc.}^{1.9}$ ). In a meta-design, 1,000 patients received 1, 2, 3, 4, 5, 6, 7, or 8 mg/kg/day with a dosing interval of 8 h for four days. In 20 replicates, sotalol trough concentrations at steady state were simulated. Sensitivity analyses were performed for the covariance, the drug, and the response model. As a posterior predictive check, simulated sotalol oral clearances of the simulated patients were compared with the measured sotalol

oral clearances in the studied patient population. A dosing schedule for effective sotalol pharmacotherapy was proposed on the basis of the simulated sotalol trough concentrations at steady state and the exposure-response relationship derived from the COES study.

**Statistical analysis.** Pharmacodynamic parameters of pediatric patients were analyzed using analysis of variance (ANOVA) with post hoc analysis of Tukey's honestly significant difference test and least significant difference test to account for differences of these tests concerning power and control of the experiment-wise type I error (23). Possible age dependency was carried out using linear and non-linear least-square regression techniques using a Spearman's rank correlation coefficient. A p value below 0.05 was considered significant. Analyses were performed using SPSS 9.0 (SPSS Inc., Chicago, Illinois).

## RESULTS

**Demographics and baseline characteristics.** Results are reported as mean values  $\pm$  SD unless stated otherwise. Seventy-six patients were subcategorized into neonates (1 to 28 days, n = 12), infants and toddlers (29 days to 23 months, n = 33), children (2 to 12 years, n = 26), and adolescents (13 to 17 years, n = 5) and included in the population-PK analysis to delineate a dosing schedule. Thirteen premature infants were included in the study. None of the patients had congenital heart disease. A subset of 15 patients (the COES study; 6 neonates, 3 infants, 5 children, 1 adolescent) participated in a study to show the relationship between sotalol plasma concentrations and conversion into sinus rhythm (Table 1). Pharmacokinetic/pharmacodynamic analyses for age-related changes of the QT intervals were performed in 32 age- and gender-matched patients (9 neonates, 8 infants, 12 children, and 3 adolescents). All subsets of patients showed comparable baseline demographic data. None of the patients had abnormal serum electrolytes of potassium, sodium, calcium, or

magnesium and remained within the reference range at any time of the study. Mean sotalol dosages were  $3.6 \pm 1.8$  mg/kg/day with a range from 1 to 9.9 mg/kg/day.

**Relation between sotalol plasma concentrations and antiarrhythmic efficacy.** There were 15 patients (7 female, 8 male) who met the inclusion criteria for this part of the study (Table 1). In one child, sotalol had to be reduced from 8 to 5 mg/kg/day because of QT<sub>cB</sub> prolongation above 470 ms. The 24-h ECG recordings obtained after conversion into sinus rhythm showed three patients with some rare events of supraventricular extrasystole and ventricular extrasystole. One patient showed a short period of sinus tachycardia and two patients showed a 2-min period of SVT. In all patients, sotalol therapy was continued up to six months. Arrhythmia recurrence was noticed in three patients after two months of medication. No proarrhythmic effects such as torsade de pointes tachycardia or bradycardia were noted. Plasma concentration-response relations of sotalol trough level conversions of each patient are shown in Figure 1. The line shows the probability of patients converting into sinus rhythm (response) at trough sotalol concentrations according to an 8-h dosing schedule. Effective minimal sotalol concentrations ranged from 0.21 to 1.05  $\mu$ g/ml. The corresponding maximal plasma concentrations ranged from 0.29 to 2.1  $\mu$ g/ml. The concentration predicted for a 50% probability to convert into sinus rhythm was 0.4  $\mu$ g/ml sotalol and for a more than 95% probability was 1.0  $\mu$ g/ml.

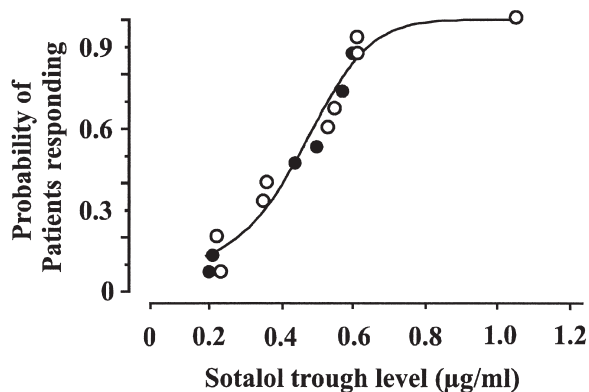
**Influence of age on sotalol's QT interval prolongation.** First, the patients' QT-RR intervals under sotalol therapy were plotted as presented in Figure 2A. The individual QT-RR interval of a 50-day-old infant and an 8-year-old child with 22 and 36 QT-RR intervals, respectively, are marked. Then the heart-rate-corrected QT intervals as increase above baseline were plotted versus their respective sotalol concentrations (Fig. 2B) to detect PD differences. The QT<sub>c</sub> interval showed a steeper increase in neonates compared with the older patients. Statistical calculations of the indi-

**Table 1.** Demographic Characteristics of Pediatric Patients

Group	n	Gender (F/M)	Age (yrs)	Height (cm)	Body Weight (kg)	BSA (m <sup>2</sup> )	GFR (ml/min/1.73m <sup>2</sup> )	Arrhythmia (SVT/VES)	Digoxin (n)
Total (ALL)	76	27/49	3.51 (4.53)	88 (37)	16.0 (17.1)	0.60 (0.44)	101 (58)	74/2	16
COES									
Neonates	6	1/5	0.05 (0.01)	51 (2)	3.6 (0.4)	0.23 (0.02)	52 (17)	6/0	0
Infants and toddlers	3	2/1	0.46 (0.28)	64 (16)	5.6 (3.1)	0.31 (0.13)	84 (37)	3/0	0
Children	5	3/2	7.17 (3.42)	124 (24)	27.4 (12.4)	0.96 (0.31)	176 (28)	5/0	0
Adolescents	1	1/0	13.01	142	39	1.09	166	1/0	0
Total COES	15	7/8	3.80 (1.20)	84 (40)	13.7 (13.8)	0.55 (0.41)	107 (63)	15/0	0
ALL minus COES									
Neonates	6	2/4	0.05 (0.02)	49 (10)	3.2 (0.7)	0.21 (0.04)	39 (21)	6/0	1
Infants and toddlers	30	8/22	0.61 (0.47)	66 (10)	6.9 (2.3)	0.35 (0.09)	76 (29)	30/0	12
Children	21	9/12	6.70 (3.20)	118 (24)	26.7 (15.6)	0.92 (0.34)	132 (45)	19/2	4
Adolescents	4	1/3	14.5 (2.2)	168 (17)	57.4 (22.7)	1.62 (0.40)	165 (30)	4/0	0
Total ALL minus COES	61	20/41	3.54 (4.54)	89 (37)	16.6 (17.9)	0.62 (0.45)	99 (50)	59/2	16

Data reported as mean (SD).

ALL = 76 plasma concentration profiles of pediatric patients; BSA = body surface area; COES = patients for the sotalol concentration effect relationship; GFR = glomerular filtration rate; SVT = supraventricular tachycardia; VES = ventricular ectopic tachycardia.



**Figure 1.** Probability of arrhythmia suppression in the 15 children with supraventricular tachycardia (COES study patients) versus sotalol trough concentration under steady-state conditions and an 8-h dosing interval. Filled circles = 6 neonates (<28 days).

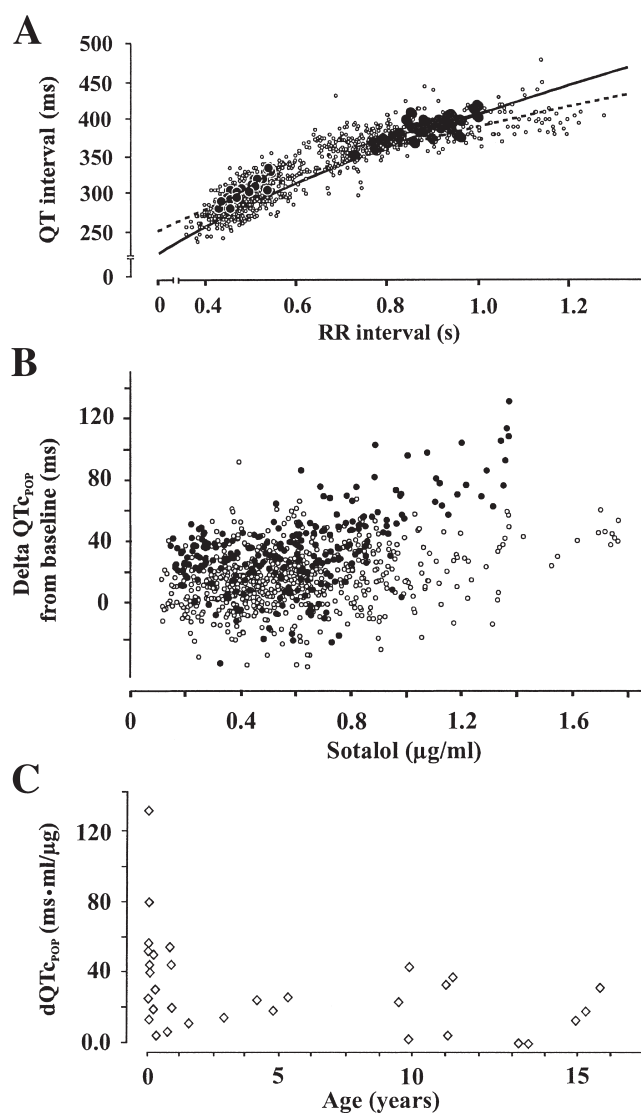
vidual sotalol-normalized increase in QTc interval (dQTc) indicated a 160% to 280% higher sensitivity in the neonates compared with infants, children, and adolescents ( $r = 0.51$ ,  $p < 0.003$ ) (Figs. 2C and 3). Sotalol concentrations in the individual patients ranged between 0.21 and 2.05  $\mu\text{g/ml}$ . There was no evidence of a systematic bias in the dependency between the concentration range, age, or dQTc slopes.

**Development of the dosing schedule.** The final population pharmacostatistic model for sotalol with parameter point estimates and their variability is summarized in Table 2. Sotalol pharmacokinetics were best described by a one-compartment base model with first-order input and elimination. Body weight, height, and BSA were identified as the most relevant predictors for oral clearance and volume of distribution. Owing to their high collinearity, inclusion of more than one of these size covariates in the model did not further improve predictability. Inclusion of age for the prediction of sotalol clearance in patients younger than one year prevented overprediction of clearance in this age group (Fig. 4). All other covariates were not significant predictors for sotalol pharmacokinetics once size and age were included.

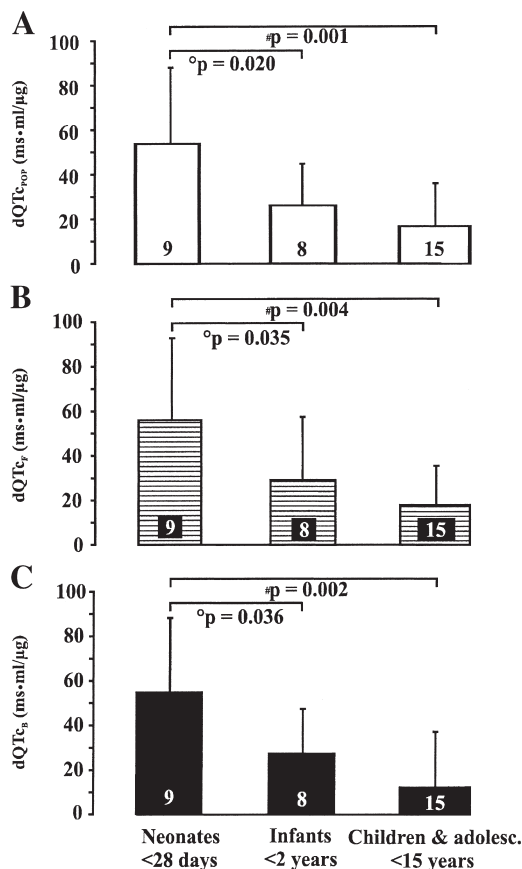
Sotalol concentrations were simulated based on simulated oral clearances. The distribution of the simulated oral clearances was similar compared with the measured clearances (mean  $\pm$  SD:  $2.66 \pm 1.76$  ml/min and  $2.47 \pm 1.89$  ml/min, respectively) (Fig. 4). Simulated sotalol trough concentrations were sorted according to age group and daily dose (Fig. 5A). Analyses of the replicates showed an intra- and inter-day variability lower than 3%. Figure 5B illustrates the patient fraction with arrhythmia suppression according to the simulation. The range of daily doses is necessary for achieving a 50% probability (start dose) and more than 95% probability to respond to sotalol therapy in nearly all patients (target dose). For safety reasons, the daily dose was limited assuming that nearly all patients (upper limit of the box-plot analysis) do not exceed a trough level of 1  $\mu\text{g/ml}$ . To avoid putting children at risk with an adult dosing

schedule (every 12 h), an 8-h dosing interval was chosen. This ensured a similar degree of fluctuation between trough and maximal sotalol concentrations in children compared with adults (1.1 in adults; 0.8 in the pediatric population).

Table 3 shows a delineated optimized and an estimated clinically useful dosing schedule. To demonstrate its usefulness we classified retrospectively the effective dosages of patients according to these dosing ranges. Seventy-five percent of neonates ( $n = 12$ ) had effective dosages between 2 and 4 mg/kg/day and 8% below this range. A total of 58% of infants younger 6 months ( $n = 19$ ), 64% of infants between 6 months and 2 years ( $n = 14$ ), and 70% of children between 2 and 6 years ( $n = 10$ ) had effective dosages between 3 and 6 mg/kg/day: 21%, 29%, and 20%,

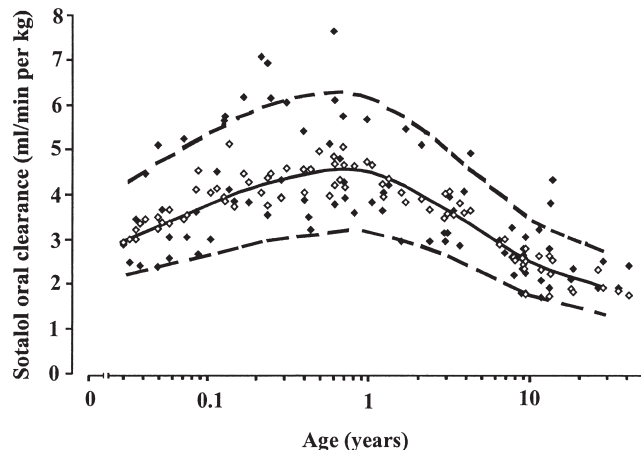


**Figure 2.** (A) QT-RR (open circles) intervals of patients under sotalol (1 to 9.9 mg/kg/day) therapy. Filled circles = a 50-day-old infant (4.1 mg/kg/day); large filled circles = 8-year-old child (2.9 mg/kg/day). Solid line = fit of baseline neonate/infant QT-RR data dotted line: a fit of baseline children/adolescent data. (B) Differences of QTc<sub>POP</sub> intervals from baseline in neonates (filled circles) and all other pediatric patients (open circles) versus sotalol concentration. (C) Sensitivity of the QTc interval prolongation towards sotalol (dQTc<sub>POP</sub>).



**Figure 3.** Mean ± SD QT interval prolongation normalized for sotalol concentrations. (A) dQT<sub>cPOp</sub>; (B) dQT<sub>cPp</sub>; (C) dQT<sub>cB</sub> in neonates (<28 days), infants (<2 years), and children and adolescents (<15 years). p values according to ANOVA with Tukey's honestly significant difference test (#) and least significance difference test (\*).

respectively, below this range. Ninety-five percent of children older than 6 years (n = 21) were effectively treated in the range between 2 and 4 mg/kg/day; none of the patients were below this range. In summary, between 78% and 95% of patients were effectively treated according to this retrospective analysis of the patients' effective dosages.



**Figure 4.** Measured (closed diamonds) and model predicted oral sotalol clearance based on body weight (open diamonds). Median (solid line) and the 10th and 90th percentile (dashed line) of 1,000 simulated data sets.

**Adverse events.** Of 76 patients, three had heart rate-corrected QT<sub>cB</sub> intervals exceeding 470 ms with subsequent dose reduction.

### DISCUSSION

The results of the study provide an age-specific, practical, and safe dosing regimen based on body weight and age for sotalol in pediatric patients with SVT. This could contribute to a more rapid and safer antiarrhythmic drug treatment for children and may prevent hemodynamic instability with subsequent long lasting hospitalizations of patients. This dosing regimen is based on the 50% and 95% probability to convert patients into sinus rhythm. Using dose simulations, three clinically useful age categories were delineated, from 2 mg/kg/day up to 6 mg/kg/day, with an 8-h dosing interval. The study results raised concern about a safe use of the drug in neonates. The QT interval was on average twice as long in neonates under sotalol compared with older children.

This is the first report on the therapeutic range of sotalol in SVT in the pediatric population. In pediatric patients with SVT, the minimal effective sotalol plasma concentra-

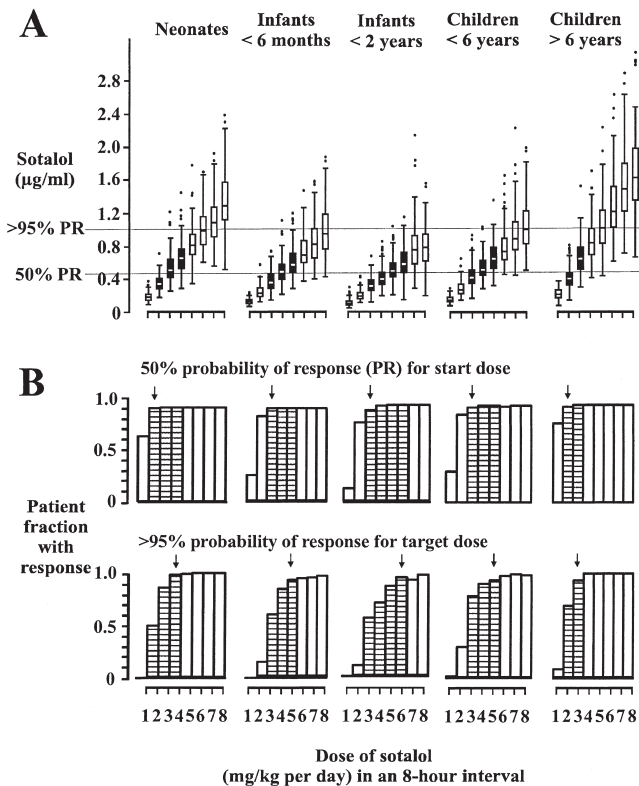
**Table 2.** Final Population Pharmacokinetic Model\*

Parameter	Model	Estimate (%CV)	IIV† (%CV)
CL/F‡ [l/h]	$\theta_1 \cdot (\text{weight}[\text{kg}]/7.3)^{\theta_2}$	$\theta_1$ 2.08 (6.5)	25.9
	For age <1 yr: $\theta_1 \cdot (\text{weight}[\text{kg}]/7.3)^{\theta_2} \cdot (\text{age}[\text{yr}]/0.76)^{\theta_3}$	$\theta_2$ 0.580 (14.4)	
		$\theta_3$ 0.248 (22.3)	
Vd/F§ [l]	$\theta_4 + \theta_5 \cdot (\text{weight}[\text{kg}] - 7.3)$	$\theta_4$ 15.8 (5.4)	27.0
		$\theta_5$ 1.51 (10.7)	
$k_{a  }$ [h <sup>-1</sup> ]	$\theta_6 + (\text{CL}/\text{Vd})$	$\theta_6$ 0.895 (9.5)	89.7
$t_{lag}¶$ [h]		$\theta_7$ 0.445 (18.0)	93.1
Residual error	Proportional: CV 8.8%; additive: SD# 24.8 ng/ml		

\*The parameters describe a one-compartment pharmacokinetic model with first-order input and elimination, and lag-time. This model can be described by the following expression for the concentration, C, versus time, t:

$$C = \frac{F \cdot \text{Dose} \cdot k_a}{Vd \cdot (k_a - \frac{CL}{Vd})} \cdot \left( e^{-\frac{CL}{Vd} \cdot (t-t_{lag})} - e^{-k_a \cdot (t-t_{lag})} \right)$$

†Interindividual variability. ‡Oral clearance. §Volume of distribution corrected for bioavailability. ||First-order absorption rate constant. ¶Lag time: time difference between drug administration and modeled first appearance of sotalol in plasma. #Standard deviation.



**Figure 5.** Black box plots and hatched bars indicate recommended dosing range. (A) Simulated sotalol trough concentrations (125 patients per group and dose level) for pediatric patients with supraventricular tachycardia. Lines indicate 50% and more than 95% efficacy. (B) Patient fraction with 50% and more than 95% probability of arrhythmia suppression. Arrows indicate start and target doses.

tions ranged from 0.21 to 1.05 µg/ml. None of these children has had a history of previous resistance to beta-receptor blockers.

Sotalol concentrations, however, and antiarrhythmic response were investigated in depth in an older study published by Wang et al. (13) in 11 adults with ventricular tachyarrhythmia with a mean age of 55 years and a high frequency of ventricular arrhythmias. Eight of these patients had previously been resistant to beta-blocker receptor therapy. Their effective sotalol trough levels ranged from 0.34 to 3.44 µg/ml. Thus, although the effective concentration range seems higher in adults compared with children, a comparison between both population groups is limited by the etiology of arrhythmia, underlying heart disease, and previous resistance to beta-receptor blocking therapy. This was an open uncontrolled study, and spontaneous remission of tachycardia might bias the results. The natural cause of the disease, however, has been sparingly investigated, but spontaneous remission is quite unlikely in the short term (4), supporting the reliability of the results.

In the present study, sotalol had a greater QT-prolonging effect in neonates than in non-neonates. In older children, QT prolongation approximated adult values. Serum electrolytes were not different in these patients, and a stereoselective disposition of sotalol cannot be assumed (24). Al-

though this confirms previous investigations (6), the present results extend our knowledge. Whereas Saul et al. (6) attributed the age-dependent differences of QT prolongation to the maturation of the kidneys, we provide evidence that the maturation of myocardial potassium channels, in part may explain these longer QT prolongations in young children. This is of importance because there is a common mechanism of drug-induced QT prolongation (12), meaning that not only sotalol but also other cardiac or noncardiac drugs with the same mechanism of action might behave similarly in neonates. Hence, the results might explain conflicting data concerning QT interval prolongation in the pediatric population reported from other drugs, such as cisapride (25,26), or it might be helpful in predicting such effects for future applications of drugs (12).

Saul et al. (8) did not detect PD age-dependent differences in QT interval prolongation. In the present study, sotalol had a greater QT prolonging effect in neonates than in non-neonates. This might be a matter of sample size because PD data show high intersubject variability. An increase in sample size, especially in neonates, from 6 of 22 patients (8) to 9 of 32 patients (our investigation) and a rich PK/PD dataset of the individual patients revealed a higher sensitivity of QT interval prolongation of very young children toward sotalol in the present study. Sotalol is neither metabolized nor bound to plasma proteins; the main elimination route is passive glomerular filtration (24). A stereoselective disposition with relatively higher d-sotalol concentrations in neonates is unlikely, because stereoselective analysis of sotalol plasma concentrations had not supported this possibility. Sotalol leads the list of antiarrhythmic drugs with dose-dependent increases of torsade de pointes tachycardia (11). Given the higher sensitivity for sotalol-induced QT prolongation in neonates, we recommend that sotalol be used only with careful QTc monitoring, especially in this age group. Sotalol's incidence of torsade de pointes tachycardia in the pediatric population has not been reported, but a systematic research for the safety of sotalol therapy in neonates should be performed. The robustness of the QT data analysis is supported by nearly identical results comparing the population-derived mode with Bazett's and Fridericia's correction modes for all patients. The

**Table 3.** Age-Specific Dose Regime for Sotalol in Children With Supraventricular Tachycardia

Group	8-h Dosing Interval	
	Optimized Dose of Sotalol According to the Trial Simulation (Start/Target) (mg/kg/day)	Recommended Clinically Useful Dose of Sotalol (Start/Target) (mg/kg/day)
Neonates	2/4	2/4
Infants <6 months	3/5	3/6
Infants <2 yrs	3/6	3/6
Children <6 yrs	3/5	3/6
Children >6 yrs	2/3	2/4

population-derived mode has not yet been validated, but it should demonstrate the coherence of the QT-RR relationship across a broad age range in the pediatric population.

The adequacy and reproducibility of population pharmacokinetics is underlined by the fact that size and age were identified as the only predictors of sotalol pharmacokinetics in pediatric patients, in agreement with a previously reported study (14). Glomerular filtration rate did not further improve the final model, most likely because of the absence of subjects with pathophysiologically impaired renal function. Body weight and BSA were similarly good predictors of oral sotalol clearance. For children with low BSA or low body weight, age as an additional covariate improved the model further, accounting for the postnatal maturation of the kidneys. In the context of previous investigations (6,8), some points concerning the depicted covariates of age and body weight as a basis for the development of the dosing schedule have to be mentioned. According to the exclusively renally eliminated sotalol, oral sotalol clearance and GFR are strongly related (6,27). Body weight and BSA were also strongly related to the GFR in this population. The Food and Drug Administration dosing recommendations derived a dosing schedule and a calculation formula based on BSA with an additional factor for children below a BSA of 0.33 m<sup>2</sup> taken from a nomogram. For simplicity, practicability, and in accordance with other commonly used antiarrhythmic drugs in children (10), we chose body weight as a basis for the development of the dosing schedule and added age as a second covariate. Both of these covariates are easily and reliably accessible with a minimum chance of calculation errors at bedside.

A limitation of the developed dosing schedule is that only subjects with normal renal function were part of the patient population. Because patients with renal failure were not investigated in this study, this aspect needs further investigation. Sotalol should therefore be used with caution and with plasma concentration monitoring as a guide in patients with renal disease.

In conclusion, in our clinical drug investigation we learned about the precise quantitative relation between drug exposure and response and how this relates to the patients' covariates. Only this quantification enabled us to simulate a clinical trial, to predict the drug response, and, finally, to delineate a dosing regimen. This research should provide a safer and more rapid antiarrhythmic pharmacologic treatment in children with SVT. Having established effective sotalol trough levels, the delineated dosing guideline can be easily switched to an individually guided therapy on the basis of sotalol trough levels. Better knowledge about effective drug levels may also aid in the decision-making regarding when to discontinue sotalol and try other antiarrhythmic drugs.

#### Acknowledgments

We are indebted to Edmund V. Capparelli, PharmD (San Diego, California), and Jean-Philippe Couderc, PhD

(Rochester, New York), for helpful comments and for critically reviewing the manuscript. We thank Phasia Uebeler and Marta Petermann (now deceased) (Department of Experimental and Clinical Pharmacology, Hamburg, Germany) for excellent technical assistance.

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