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Pharmacokinetic Properties and Tolerability of Single-Dose Terbutaline in Patients with Severe Asthma Treated in the Pediatric Intensive Care Unit

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ABSTRACT

Background: Asthmatic children requiring treatment in the pediatric intensive care unit (PICU) receive aggressive drug therapy that may include IV administration of β_2-receptor agonists to prevent progression to life-threatening respiratory failure. The only pharmacologic agent in this class currently available for parenteral use in the United States is terbutaline. Study of IV dosing of terbutaline in the pediatric population has been limited.

Objective: The aim of this study was to determine the pharmacokinetic (PK) properties and tolerability of single-dose terbutaline in pediatric patients across a broad age range who were admitted to the PICU and were receiving maximal conventional asthma drug therapy.

Methods: This study was conducted at the PICU at Rainbow Babies and Children's Hospital (Cleveland, Ohio). Patients aged 6 months to 16 years with severe exacerbation of reactive airways disease and who were undergoing maximal conventional therapy and had an arterial catheter were enrolled. Patients were arbitrarily assigned to receive a single IV infusion of 1 of 3 doses of terbutaline (10, 20, or 30 μg/kg), infused over 5 minutes. Blood samples were obtained for the determination of plasma terbutaline concentrations just before terbutaline was administered (baseline), immediately on completion of the IV infusion, and at 10, 20, and 40 minutes and 1, 2, 4, 8, 16, 32, 48, and 72 hours after the 5-minute infusion. PK properties (elimination half-life [$t_{1/2}$], mean residence time [MRT], apparent steady-state volume of distribution [Vd_{ss}], and total body clearance [Cl]) were determined and adverse effects were recorded.

Results: The determination of terbutaline PK properties was possible in 50 of 56 enrolled patients (31 boys, 19 girls; mean [SD] age, 6.5 [4.5] years). The PK properties of terbutaline were linear over the dose range studied and, with the

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exception of the expected dose-dependent increases in peak terbutaline plasma concentration and area under the terbutaline plasma concentration–time curve, no statistically significant differences were observed in PK relative to dose. Therefore, we pooled the data for all subsequent analyses. Statistically significant correlations with patient age were observed with $t_{1/2}$ ($r = 0.4$, $P < 0.006$), MRT ($r = 0.4$, $P < 0.002$), and Vd_{ss} ($r = 0.33$, $P < 0.02$), but not Cl ($r = -0.03$, P = NS). Single-dose terbutaline administration was generally well tolerated.

Conclusions: Single-dose IV terbutaline was well tolerated in this study. In maximally treated asthmatic patients in the PICU, terbutaline elimination may be more rapid than in nonacutely ill children. These PK data suggest that if the drug is to be administered intravenously, the continuous IV infusion method, including loading doses for any subsequent dose escalations, may be the most appropriate. The influence of age and safety of long-term, continuous terbutaline IV infusion requires further study. (*Curr Ther Res Clin Exp.* 2004;65:98–109)

Key words: asthma, children, intensive care, pharmacokinetics, terbutaline.

INTRODUCTION

Asthma is one of the most common diseases of childhood, affecting ~5.3% of children and resulting in ~200,000 hospital admissions of children each year in the United States. In severely affected asthmatic patients, acute decompensation may lead to significant morbidity and mortality.[1,2] Mortality in asthmatic children ranged from 1.8% to 3.8% per 1 million children in 1990–1991 and 1995–1996, respectively, falling slightly to 3.3% per 1 million children in 1997–1998.[1] The goal in the treatment of pediatric patients with severe asthma is to reverse the airway obstruction, thereby preventing the progression to respiratory failure.[3,4]

Initial treatment for a severe exacerbation of childhood asthma commonly consists of oxygen, aerosolized and/or subcutaneous adrenergic agents, aminophylline, and systemic corticosteroids. If this therapy fails to improve the acute asthmatic symptoms and progression to life-threatening respiratory failure is impending, some authors have reported benefit from the addition of IV β-agonists.[5] The use of relatively selective β_2-agonists offers the benefits of less stimulation of the β_1-receptors and therefore less potential for unwanted adverse effects (AEs). The only pharmacologic agent in this class currently available for parenteral use in the United States is terbutaline.

According to a MEDLINE search for English-language articles (key terms: *asthma, terbutaline, pharmacokinetics, beta-agonists,* and *intensive care*; years: 1966–2003), study of IV dosing of terbutaline in the pediatric population has been limited. Hultquist et al[6] assessed the pharmacokinetic (PK) properties of IV terbutaline in 7 patients aged 8 to 12 years, and Fuglsang et al[7] reported on

10 patients aged 7 to 15 years. Both of these studies were limited by the relatively narrow age range of the patients studied and by the fact that none of these patients were being concurrently treated with other medications for severe status asthmaticus. Furthermore, the basis for terbutaline bolus dosing recommendations is dubious and appears to be extrapolated from accepted dosing of epinephrine subcutaneously and albuterol intravenously.[8,9]

In this study, we describe the PK properties of terbutaline in pediatric patients who are concurrently receiving maximal conventional asthma medication therapy to determine whether any age-related or dose-dependent differences exist in terbutaline disposition.

PATIENTS AND METHODS

This study was conducted at the pediatric intensive care unit (PICU) at Rainbow Babies and Children's Hospital (Cleveland, Ohio). All patients admitted over a 5-year period who were aged 6 months to 16 years, had severe exacerbation of reactive airways disease, who were undergoing maximal conventional therapy, and who had an arterial catheter were candidates for the study. *Maximal conventional therapy* was defined as oxygen therapy to maintain blood oxygen saturation >95%, maximal-dose albuterol inhalation therapy at intervals of <1 hour (eg, q1h or continuously), an aerosolized anticholinergic agent (eg, ipratropium, atropine), IV corticosteroids, and IV aminophylline (at the discretion of the treating physician) to a target serum concentration of 15 to 20 mg/L. Patients were excluded if they had a history of cardiac arrhythmia or if they had received terbutaline within 72 hours of the initiation of the study.

This study was approved by the Institutional Review Board for Human Subject Investigation of the University Hospitals of Cleveland. Written informed consent for study participation was obtained from each child's parent/legal guardian.

Terbutaline Administration and Sample Collection

Each patient was given a single IV infusion of terbutaline over 5 minutes through an indwelling peripheral catheter. Based on the broad IV terbutaline dose recommendations in the literature, combined with our own experience (unpublished observations), we elected to assess terbutaline PK properties and tolerability over a 3-fold dose range (10, 20, and 30 μg/kg). Patients were enrolled in 1 of 4 arbitrary age groupings in an attempt to ensure adequate age distribution across the 3 doses studied. By study design, the first 5 patients enrolled into each of the 4 age groups received the 10-μg/kg dose. In the absence of any serious terbutaline-associated AEs, the next 5 patients in each age group received the 20-μg/kg dose before the dose was increased to 30 μg/kg in subsequent groups. This dose-escalation strategy was implemented to permit early detection of any terbutaline dose-dependent AEs that would preclude dose escalation to the next-higher dose for a specific age. Blood samples (1–2 mL) for the determination of plasma terbutaline concentrations were ob-

tained just prior to terbutaline administration (baseline), immediately on completion of the IV infusion, and at 10, 20, and 40 minutes and 1, 2, 4, 8, 16, 32, 48, and 72 hours after completion of the infusion. Blood samples were obtained from a blood vessel contralateral to that used for terbutaline administration. All terbutaline infusions and blood sampling for PK analysis were performed by a pediatric research nurse or study investigator.

During the study period, all patients were monitored continuously according to the following local PICU standard for severe asthma: (1) heart rate; (2) electrocardiography with event recording; (3) respiratory rate; (4) arterial catheterization for blood pressure recording; and (5) pulse oximetry. All patient-management issues were managed at the discretion of the PICU attending physician and management team. If at any time during the 72-hour study period, the PICU management team opted to use additional terbutaline doses, the patient exited the study. The PK data collected from patients exiting the study before completion were analyzed if their involvement had lasted a minimum of 2 hours. Data on AEs were included for analysis if the patient completed the 2-hour postdose data collection. Terbutaline AEs were identified and recorded by the patient management team in conjunction with a study investigator.

If at any time during the study period >25% of the patients receiving a given terbutaline dose experienced significant arrhythmias, severe hypotension (>20% decrease in blood pressure), or the onset of intractable emesis or headache, the dose-escalation scheme was discontinued in that age group. The expectation of this study was that any significant AEs should occur within the first few minutes to 1 hour after completion of dosing, when the drug concentration was maximal. To characterize patient tolerability of the terbutaline dose, we defined a terbutaline-induced AE as a >20% increase in heart rate or >20% decrease in systolic or diastolic blood pressure from baseline for 2 consecutive measurements within 1 hour of terbutaline dosing.

Determination of Plasma Terbutaline Concentrations and Pharmacokinetic Profile

Plasma terbutaline concentrations were determined by a modification of the method of Edholm et al[10] using liquid chromatography with electrochemical detection. For the solid-phase extractions, an ASPEC XL System (Gilson Inc., Middleton, Wisconsin) was used. Fifty microliters of 2-μg/mL metaproterenol sulfate (internal standard) in water was added to 500-μL plasma samples and standards. The samples were loaded onto previously conditioned (acetonitrile → water), silica-bonded, phase-extraction cartridges (1 mL/100 mg; Bond Elut, Varian, Inc., Palo Alto, California) and were then eluted with 2 × 1 mL of methanol and dried under nitrogen at 30°C in a Turbovap LV-Evaporator (Zymark Corporation, Hopkinton, Massachusetts). The samples were reconstituted in Millipore water (150 μL; Millipore Corporation, Billerica, Massachusetts) and injected onto an LC-400 liquid chromatograph (Bioanalytical Systems, Inc. [BAS], West Lafayette, Indiana) equipped with a BAS LC-4B amperiometric de-

tector (applied potential = +0.900 V), a dual-carbon glassy electrode, and a $Ag/AgCl_2$ reference electrode. The guard column (4 mm × 4 cm) packed with 300 silica particles (Vydac Adsorbent, Vydac Hesperia, San Diego, California) was inserted before the analytic column, an Alltima C_{18} 5-μ 150-mm × 4.6-mm column (Alltech Associates Inc., Deerfield, Illinois). Separation was carried out at 24°C. The mobile phases (flow rate = 0.8 mL/min) comprised an acetonitrile (24%)–potassium phosphate buffer (pH 6.0, 0.067 m) (76%) to which 4% sodium dodecyl sulfate was added (0.7% of final mobile phase volume) to enhance separation of the peaks. Elution times for metaproterenol and terbutaline were 11.6 minutes and 16.7 minutes, respectively. The lower limit of quantitation was 0.5 ng/mL and linear over the range of 0.5 to 200 ng/mL. The within-run precision and accuracy for plasma standards were 1.95% and 2.46%, respectively (mean coefficient of variation), and the between-run precision and accuracy averaged 7.24% and 5.74%, respectively. Plasma terbutaline concentrations were determined in our pediatric pharmacology laboratory.

Pharmacokinetic Analysis

The PK parameter estimates for terbutaline were determined by standard noncompartmental methods[11] using Kinetica version 4.1 (InnaPhase Corporation, Champs-sur-Marne, France). For each patient, plasma terbutaline concentrations were plotted against time on a semilogarithmic scale. The peak terbutaline plasma concentration (C_{max}), time to peak concentration (T_{max}), and minimum plasma terbutaline concentration were determined directly from the plasma concentration–time curve. The area under the terbutaline plasma concentration–time curve (AUC) was obtained using the linear trapezoidal rule up to the final measured concentration and extrapolated to infinity using beta. The elimination half-life ($t_{1/2}$) was determined from the postdistributive terminal portion of the plasma concentration–time curve. Total body clearance (Cl) was determined using the formula dose/AUC from time zero to infinity. The apparent steady-state volume of distribution (Vd_{ss}) was determined using the following equation:

$$Vd_{ss} = ([dose][AUMC])/AUC^2 - ([dose][T]/[AUC][2]),$$

where AUMC is the area under the first moment of the concentration–time curve and T is the infusion duration. Mean residence time (MRT) was calculated as AUMC/AUC.

Statistical Analysis

PK and statistical analyses were performed by the Section of Pharmacokinetics and BioInformatics at the study site. Estimates of PK parameters and demographic data were examined univariately and graphically to determine distributional characteristics and were described overall and by dose and age group. Interval-level data were described by means, SDs, and ranges, and categoric data were described with frequencies. The percentage change from baseline for

physiologic parameters was calculated for each patient at each time point and examined for indications of AEs as defined earlier.

Analysis of variance was used to test for the main effects of age group and dosing level. The relationship of age as a continuous variable with the PK parameters was analyzed with linear regression, and the results were reported as the percentage of variance in the dependent variable explained by age. The level of significance was set at $P < 0.05$. Statistical analysis was performed using the SAS software version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Fifty-six patients were enrolled in the study. Six patients (10.7%) were excluded from data analysis: 2 patients were withdrawn due to inadequate involvement time in the study, another lost IV access, and a fourth patient was begun on a terbutaline continuous IV infusion by the PICU clinical care team prior to 2 hours postdose. In addition, PK analysis for 2 patients was excluded because the measured terbutaline concentrations at all time points were 5-fold and 25-fold lower than observed in our study population, leading to speculation that errors occurred in the drug dose given. Thus, complete terbutaline PK analysis was possible in 50 patients (31 boys, 19 girls; mean [SD] age, 6.5 [4.5] years). Demographic characteristics for each dose group are shown in **Table I**.

Pharmacokinetic Properties

The overall mean (SD) plasma terbutaline plasma concentration–time curves for the 3 doses administered are shown in **Figure 1**. With the exception of

Table I. Demographic and clinical characteristics of study patients.*

Characteristic	Terbutaline Group, μg/kg			All Patients (N = 50)
	10 (n = 19)	20 (n = 18)	30 (n = 13)	
Age, y				
Mean (SD)	6.1 (5.2)	6.0 (5.0)	7.7 (5.0)	6.5 (4.5)
Range	0.6–16.7	0.5–13.6	1.9–16.0	0.5–16.7
Sex, no. (%)				
Boys	9 (47.4)	13 (72.2)	9 (69.2)	31 (62.0)
Girls	10 (52.6)	5 (27.8)	4 (30.8)	19 (38.0)
Body weight, kg				
Mean (SD)	21.2 (14.0)	27.0 (20.0)	37.0 (27.5)	27.4 (21.0)
Range	4.7–56.5	6.8–61.0	11.3–90.0	4.7–90.0
Body surface area, m^2				
Mean (SD)	0.83 (0.4)	0.93 (0.5)	1.17 (0.6)	0.96 (0.5)
Range	0.27–1.61	0.35–1.70	0.53–2.10	0.27–2.10

*No significant between-group differences were found.

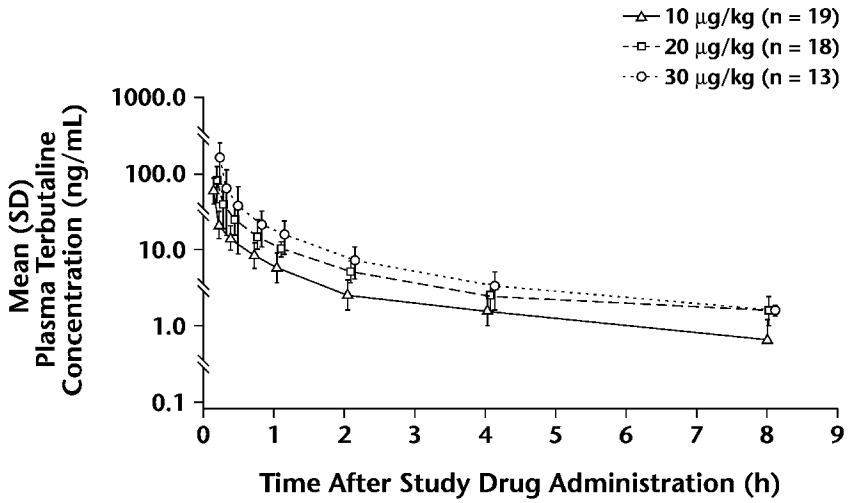

Figure 1. Plasma terbutaline concentration–time curves after 3 IV bolus doses administered over 5 minutes in 50 acutely ill pediatric patients.

expected dose-dependent increases in terbutaline C_{max} and AUC (data not shown), no statistically significant differences were observed in any terbutaline PK parameter estimates relative to dose. Terbutaline disposition was linear across the dose range studied (dose vs AUC: $r^2 = 0.98$). Because terbutaline disposition was linear over the dose range studied and no statistical differences were observed in terbutaline PK parameter estimates (**Table II**), the data were pooled for subsequent analyses.

Table II. Single-dose pharmacokinetic properties of terbutaline in study patients, by age group.* (Values are expressed as mean [SD].)

	Age Group, y				
Parameter	<2 (n = 15)	2–<6 (n = 10)	6–<12 (n = 14)	12–<18 (n = 11)	All Patients (N = 50)
Age, y	1.2 (0.5)	3.7 (1.4)	8.6 (2.1)	13.7 (1.5)	6.5 (4.5)
$t_{1/2}$, h	1.5 (1.2)	1.9 (0.9)	2.1 (1.1)	2.5 (1.1)	1.9 (1.1)
MRT, h	1.5 (1.1)	1.5 (0.5)	2.0 (0.9)	2.5 (1.1)	1.9 (1.0)
Vd_{ss}, L/kg	0.5 (0.4)	0.6 (0.2)	0.8 (0.4)	0.7 (0.3)	0.6 (0.4)
Cl, mL/kg · min	6.3 (3.7)	6.3 (1.2)	7.0 (1.8)	5.0 (1.5)	6.2 (2.4)

$t_{1/2}$ = elimination half-life; MRT = mean residence time; Vd_{ss} = steady-state volume of distribution; Cl = total body clearance.

*Statistically significant correlations with patient age were observed with $t_{1/2}$ ($r = 0.4$, $P < 0.006$), MRT ($r = 0.4$, $P < 0.002$), and Vd_{ss} ($r = 0.33$, $P < 0.02$), but not Cl ($r = -0.03$, P = NS).

The terbutaline PK parameter estimates subdivided into 4 age groups are shown in Table II. Although terbutaline $t_{1/2}$ and MRT appear to increase slightly with age, the differences were not clinically meaningful. Terbutaline Cl exhibited a nonsystematic variability with age, and terbutaline Vd_{ss} did not change significantly. Linear regression methods were used to examine the relationship between important terbutaline PK parameter estimates and age more closely. A statistically significant correlation in terbutaline $t_{1/2}$ ($r = 0.4$, $P < 0.006$), MRT ($r = 0.4$, $P < 0.002$), and Vd_{ss} ($r = 0.33$, $P < 0.02$), but not Cl ($r = -0.03$, $P =$ NS) was observed with patient age (**Figure 2**). However, significant correlations for $t_{1/2}$, MRT, and Vd_{ss} (as evidenced by the scatter around the regression line) accounted for ≤16% of the total variability (ie, $t_{1/2}$ $r^2 = 0.16$; MRT $r^2 = 0.16$; and Vd_{ss} $r^2 = 0.11$), suggesting that their clinical/pharmacologic significance is limited. Further analysis to determine whether these plots would be best described by a curvilinear relationship resulted in poor data fits (data not shown).

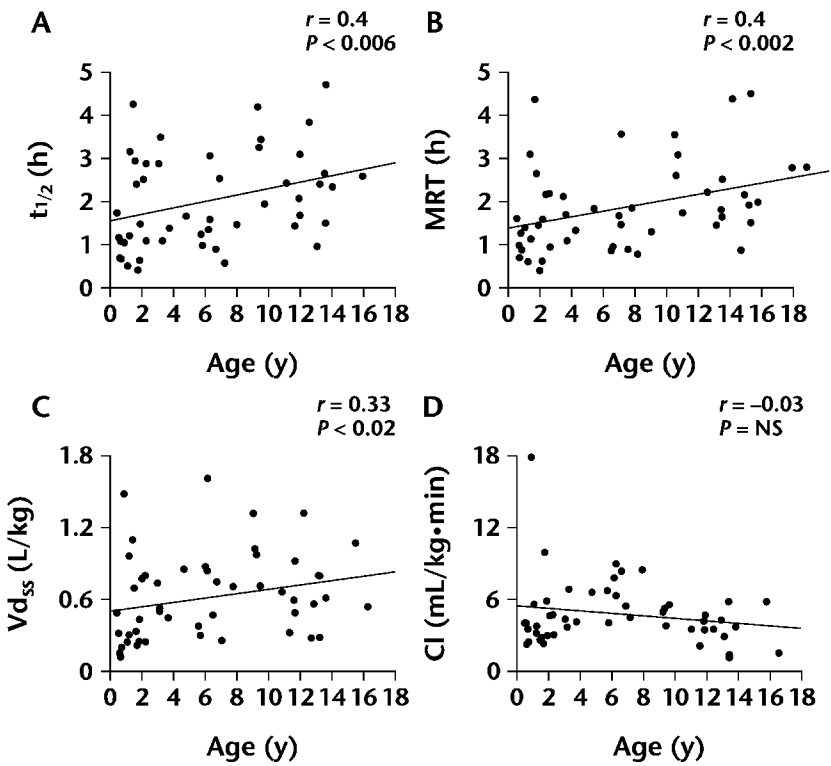

Figure 2. Relationships between terbutaline pharmacokinetic parameter estimates (elimination half-life [$t_{1/2}$; A], mean residence time [MRT; B], volume of distribution in the steady state [Vd_{ss}; C], and total body clearance [Cl; D]) and patients' age.

Patient Tolerability

Fifty-five patients were included in the tolerability analysis. Overall, the single-dose terbutaline was generally well tolerated by the study patients. Six patients (10.9%) experienced probable terbutaline-associated AEs, as evidenced by important changes in vital signs on ≥2 consecutive measurements over the first hour of the study. Two patients (3.6%) experienced an increase in heart rate >20% from baseline; 1 patient (1.8%), a decrease in systolic blood pressure >20% from baseline; and 3 patients (5.5%), a decrease in diastolic blood pressure >20% from baseline. Only 1 patient (1.8%) received therapy (IV fluid bolus), for possible drug-induced hypotension.

DISCUSSION

A number of effective drugs are available for the treatment of asthma in children.[1] Most of the advances in our understanding of available asthma medications have focused on optimal ambulatory-based therapies. Appreciation of the importance of chronic inhaled corticosteroid (ICS) therapy, the availability of more potent ICS formulations, long-acting β_2 agonists, and a better understanding of the utility of leukotriene modifiers have all markedly reduced the number of serious acute asthmatic events necessitating visits to the pediatric emergency department or hospitalization.[1] Nevertheless, acute asthma attacks in select patients will progress to status asthmaticus requiring prompt and aggressive therapy. In all instances, administration of a prompt-acting β_2-agonist aerosol and aggressive corticosteroid therapy remain the first-line therapy for acute reversal of bronchoconstriction.[1,12,13] Unfortunately, some of these patients may not respond optimally to these well-defined strategies and may benefit from the additional IV administration of a β_2 receptor agonist.

The IV administration of terbutaline to children with status asthmaticus responding poorly to maximal conventional therapy may avoid the patient's continued deterioration to respiratory failure.[4] This approach to supplemental β_2-agonist therapy has been controversial, as many clinicians believe one can achieve maximal β_2-receptor stimulation via the aerosolized route, whereas others counter that severely constricted airways may limit the amount of aerosolized albuterol that actually reaches the small airways, the target area of most importance.[4] This latter belief is supported by the differences in aerosolized airway drug penetration characteristics observed in patients with varying degrees of asthma compared with healthy controls.[14] Also, patient response to IV terbutaline may be less than optimal, as no terbutaline-based PK dose data exist for children across a broad age range or for children in acute status asthmaticus receiving maximal conventional asthma drug therapy.

Limited terbutaline PK data following IV administration in pediatric patients are available.[6,7] Fuglsang et al[7] described terbutaline PK in 13 children aged 7 to 15 years. Terbutaline PK data were available in 10 of these children.

Four patients were hospitalized "because of an asthma attack of short duration" and 9 were hospitalized because "pulmonary function had deteriorated after their medication was stopped in preparation for a bronchial allergen challenge test." These investigators demonstrated apparent steady-state conditions for plasma terbutaline concentration with administration of a bolus dose over 5 minutes followed by a continuous 2-hour IV infusion. Unfortunately, standard terbutaline PK parameter estimates were not provided and the way in which the data are presented precludes further calculation. Nevertheless, with their dosing strategy[7] each patient appeared to achieve steady-state plateau concentrations and their data suggest that terbutaline Cl was rapid, with a correspondingly short $t_{1/2}$. In contrast to these apparent findings, Hultquist et al[6] described different terbutaline PK characteristics in 7 children (aged 8–12 years) with chronic asthma who had discontinued all terbutaline treatment 7 days before the study. In **Table III**, these terbutaline PK data are compared with single-dose IV terbutaline PK data in healthy adult volunteers.[6,15] These data are different from the terbutaline PK data obtained in our study and the data reported by

Table III. Pharmacokinetic properties of terbutaline as reported in children[6] and adults.[15]

Parameter	Children (n = 7)	Adults (n = 6)
Age, y		
Mean	9.8	37.0
Range	8.0–11.7	23–44
Body weight, kg		
Mean	28.6	64.0
Range	21.5–37.0	53–81
Dose*		
Mean	5.5 (SD, 0.31) μg/kg	0.25 mg
Range	5.0–5.95 μg/kg	–
$t_{1/2}$, h		
Mean (SD)	12.1 (2.4)	13.7 (1.3)
Range	8.8–15.8	–
Cl		
Mean (SD)	3.8 (0.9) mL/kg · min	0.2 (0.03) L/kg · h
Range	2.7–5.4 mL/kg · min	–
Vd, L/kg		
Mean (SD)	1.57 (0.19)	1.8 (0.13)†
Range	1.28–1.83	–
MRT, h		
Mean (SD)	7.3 (0.3)	9.1 (1.7)
Range	4.6–9.6	–

$t_{1/2}$ = elimination half-life; Cl = total body clearance; Vd = volume of distribution; MRT = mean residence time.
*Administered intravenously over 5 minutes.
†Reported as steady-state volume of distribution.

Fuglsang et al.[7] The reasons for this discrepancy are unclear but could be related to disease severity and/or the treatments provided. Hemstreet et al[16] described an increased theophylline Cl in pediatric patients with asthma in the intensive care unit when they were receiving continuous IV isoproterenol hydrochloride compared with when these same children were not receiving isoproterenol and attributed this difference to the isoproterenol-induced increase in hepatic blood flow for this hepatically cleared drug.[17] Considering that all of our patients were severely ill and were receiving maximal adrenergic therapy, it is plausible that the shorter terbutaline $t_{1/2}$ and MRT and the decreased Cl may be reflective of a similar effect, as elsewhere described for isoproterenol.[16,17] Terbutaline is metabolized by the liver, primarily via conjugation reactions that may be influenced by drug- or disease-induced alterations in hepatic blood flow or other yet unrecognized pathophysiologic effects.

The clinical benefit of adjunctive continuous IV terbutaline infusion to aggressive aerosol β_2-agonist therapy requires further clinical assessment. After single-dose administration, the drug was well tolerated in our study patients. However, our data suggest that in maximally treated asthmatic patients in the PICU, terbutaline Cl may be decreased and thus the duration of airway dilatory action may be shortened compared with the duration of action of the drug in less severely ill patients. Our data support continuous IV infusion as the preferred method for IV terbutaline administration (vs intermittent bolus) in critically ill asthmatic patients. Moreover, the variability we observed in terbutaline PK strongly suggests that if dose escalation of a continuous IV terbutaline infusion is to be used based on clinical requirements, all dose escalations should be preceded by a loading dose to ensure rapid attainment of the new steady-state concentration. Such a dosing strategy would also accommodate any potential age- or disease-related effects on terbutaline disposition. The influence of age and safety of long-term continuous terbutaline IV infusion require further study.

CONCLUSIONS

In this study of asthmatic children receiving maximal asthma therapy in the PICU, the terbutaline PK data suggest that if the drug is to be administered intravenously, continuous IV infusion, including loading doses for any subsequent dose escalations, may be the most appropriate method, and that elimination may be more rapid in acutely ill children than in nonacutely ill children. Single-dose IV terbutaline was generally well tolerated.

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