Pharmacokinetics of bambuterol during oral administration to asthmatic children

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Aims To investigate dose proportionality, dosing frequency, and ethnic aspects of the pharmacokinetics of bambuterol in asthmatic children, and to discuss the relationship with previous observations in adults.

Methods Forty-eight children in four different studies completed two double-blind bambuterol treatments each (daily doses of bambuterol hydrochloride): 12 preschool (5 mg $\times$ 2 *vs* 10 mg) and 12 school (10 mg *vs* 20 mg) Caucasians, 12 preschool (2.5 mg *vs* 5 mg), and 12 school (10 mg *vs* 20 mg) Orientals. Peak plasma concentrations and dosing interval area under curve (AUC) of bambuterol and the active metabolite terbutaline were assessed at steady state. Treatment differences were analysed statistically within each study. Differences between the studies and the relation to steady-state AUC in adults were described.

Results Dose proportionality was seen for terbutaline but not for bambuterol. Twice-daily dosing ($2 \times \text{AUC}(0,12 \text{ h})$) could not be shown to differ from once-daily dosing ($\text{AUC}(0,24 \text{ h})$) in the preschool Caucasians. Mean AUC of terbutaline was 128 and 242 $\text{nmol l}^{-1} \text{ h}$ in the preschool Caucasians (5 mg/12 h; 10 mg/24 h), 213 and 406 $\text{nmol l}^{-1} \text{ h}$ in the Caucasian school children (10 mg; 20 mg), 87.4 and 202 $\text{nmol l}^{-1} \text{ h}$ in the Oriental preschool children (2.5 mg; 5 mg), and 356 and 640 $\text{nmol l}^{-1} \text{ h}$ in the Oriental school children (10 mg; 20 mg). Oriental school children had higher plasma concentrations of bambuterol and terbutaline than Caucasian school children. The strict ethnical implication of the difference could not be elucidated, because demographic data were not perfectly matched. Terbutaline AUC was only moderately increased in the Caucasian school children compared with Caucasian adults. The increase was more pronounced in Oriental children and in some preschool Caucasians. The highest concentration of terbutaline, 58 nmol l^{-1} , was seen in an Oriental school child after a 20 mg dose.

Conclusions Caucasian school children can be given bambuterol hydrochloride very much as Caucasian adults, 10 or 20 mg once daily, but Oriental preschool and school children plus preschool Caucasians should be given lower doses.

Keywords: asthmatic children, bambuterol, pharmacokinetics, terbutaline

Introduction

Bambuterol is the bisdimethylcarbamate of the β_2 -adrenoceptor stimulant terbutaline. Bambuterol, which is adre-

nergically inactive, is converted to terbutaline via oxidation and hydrolysis, preferably via plasma cholinesterase [1, 2].

Oral administration of bambuterol to patients with asthma prolongs the bronchodilating effect produced by terbutaline [3, 4]. The clinical efficacy of once-daily bambuterol appears to be equivalent to that of twice-daily sustained-release terbutaline [5]. The basal pharmacokinetics of bambuterol and generated terbutaline in healthy subjects

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Table 1 Patients and regimens.

Ethnic origin	Age group	Number of patients (boys/girls)	Bambuterol hydrochloride (mg day ⁻¹)	Variable	Demographics			
					Mean	Min	Median	Max
Caucasian	Pre-school ¹	8/4	5 × 2 ² , 10	Age (years)	4.8	3	5	6
				Weight (kg)	20.5	15	20	25
	School ³	9/3	10, 20	Age (years)	9.8	7	10	13
				Weight (kg)	33.1	26	34	45
Oriental	Pre-school ¹	8/4	2.5, 5	Age (years)	3.5	2	3	5
				Weight (kg)	15.3	11	14	25
	School ³	10/2	10, 20	Age (years)	7.7	6	7	10
				Weight (kg)	23.6	16	21	44

¹Pre-school children were given bambuterol solution. ²Administered twice daily. ³School children were given bambuterol tablets.

have been investigated by Nyberg *et al.* [6]; total clearance of bambuterol administered intravenously was 1.25 l min⁻¹, 10% of which was of renal origin. The absorption of bambuterol and subsequent generation of terbutaline were slow and prolonged. Hence, the plasma concentration *vs* time profile of terbutaline was rather flat after oral administration of bambuterol, a clinical pharmacokinetic rationale for dosing bambuterol once daily.

Suggested differences in dose between asthmatic children and adults are based on differences in magnitude of steady-state plasma concentrations of terbutaline in relation to Caucasian adults. The four studies presented in this paper aimed at investigating dose proportionality, dosing frequency, and ethnic aspects of the pharmacokinetics of bambuterol in asthmatic children. The recommended maintenance oral doses of bambuterol hydrochloride (hereafter only denoted 'bambuterol') for Caucasian adults are 10 mg or 20 mg once daily. Bambuterol 10 mg or 20 mg constituted starting points for the pharmacokinetic survey of bambuterol in children. Based on the results in school children, regimens of reduced doses were investigated in preschool children. Unpublished data on file indicate that Chinese adults are more exposed to terbutaline than Caucasian adults. Therefore, the pharmacokinetics of bambuterol were investigated separately in Caucasian and Oriental children.

With this knowledge available, it should be possible to consider the clinical pharmacokinetic implications for regular treatment of children compared with Caucasian adults.

Methods

Studies

Data from four studies with asthmatic Caucasian and Oriental preschool and school children were compiled. All studies were performed in accordance with the declaration

of Helsinki and approved by local Ethics Committees in Sweden, The Philippines, and Thailand. Parents gave informed consent before their children were enrolled.

Patients and procedures

Twelve Oriental (Philippine) preschool children, 12 Oriental (Thai) school children, 12 Caucasian (Swedish) preschool children, and 12 Caucasian (Swedish) school children each completed two regimens of oral racemic bambuterol. Studies were performed sequentially, first in school children then in preschool children. Caucasian and Oriental children were not perfectly matched regarding age. All studies were double-blind, placebo-controlled, randomised, and crossover. Pre-school children (defined as children below 7 years of age) were given an oral solution of bambuterol and school children were given bambuterol tablets (Bambec[®], AstraZeneca Pharmaceuticals Productions, Sweden). Demographics and treatments for evaluated patients are shown in Table 1.

Bambuterol could be dosed up to 20 mg once daily in Caucasian school children and up to 10 mg once daily in Oriental school children (*c.f.* Results). These doses, divided by two, were set as upper limits in preschool children. Thus, 10 mg and 5 mg once daily were the highest doses tested in Caucasian and Oriental preschool children, respectively. Dose proportionality was addressed in the Oriental preschool children by testing the still lower bambuterol dose of 2.5 mg. Unpublished data on file suggest that bambuterol 5 mg once daily would be insufficient in Caucasian preschool children and was therefore not studied. However, 5 mg × 2 was tested in that group as a way to still maintain sufficiently high plasma levels of terbutaline if *C*_{max} after 10 mg × 1 would appear too high.

Each of the two regimens lasted for 1 week in Caucasian children and Oriental school children, 2 weeks

in Oriental preschool children. There was no wash-out between regimens. Patients were instructed to eat standardized meals before drug intake and to abstain from any food and beverage up to 2 h after dosing. The compliance with these prandial restrictions was only monitored on the last day of each regimen. Pre-school Caucasian children were administered 10 mg once daily and 5 mg twice daily; blinding was maintained by giving active drug in the morning and placebo in the evening during the once-daily regimen. The other three groups were administered bambuterol exclusively in the morning after breakfast.

Concomitant administration of steroids or sodium cromoglycate was allowed, provided dosages were kept constant for 3 weeks prior to and throughout the study. Fenoterol was allowed as rescue medication. Other oral bronchodilators were to be avoided as from the day before the first dose up to the end of the study. From a pharmacokinetic point of view, violations to these drug restrictions were negligible.

Venous blood (10 ml) was drawn from an indwelling catheter during the last 24 h of each regimen: before, and 3 and 6 h after dosing in the Caucasian preschool children; before, and 1, 3, 6, and 12 h after dosing in Oriental preschool children; before, and 1, 3, 6, 12, and 24 h after dosing in Caucasian and Oriental school children. Blood was collected into sodium-heparinized Venoject® sampling tubes. An esterase inhibitor (D2456, a bambuterol analogue [7]) was added to a concentration of $10 \mu\text{mol l}^{-1}$, the tubes were immediately centrifuged, and the plasma was stored at -20°C until measurement of bambuterol and terbutaline.

Urine was collected 1–6 h or 3–6 h after the last morning dose of each regimen. Portions of 10 ml were frozen and saved at -20°C until measurement of bambuterol (not in Oriental preschool children) and terbutaline.

Clinical laboratory assessments and drug analyses

Standard clinical laboratory values were checked before randomization and at follow-up visits. Reported and observed adverse events were recorded.

Plasma cholinesterase activity (nmol butyryl thiocholine hydrolysed per min by $5 \mu\text{l}$ blood) was tested before and during treatment of the Caucasian school children [8].

Bambuterol was analysed by gas chromatography-mass spectrometry as described previously [7]. At 1 nmol l^{-1} in plasma and 8 nmol l^{-1} in urine, lower limits of quantification, the within-day coefficient of variation (CV) was about 4% and 5%, respectively. The plasma concentration of bambuterol was not analysed in the samples taken at 12 h and 24 h in the Caucasian school children.

Terbutaline was analysed using coupled-column high performance liquid chromatography with electrochemical detection according to a modification of a previously described method [9]. At 8 nmol l^{-1} in plasma, the CV was 2.1% within a day and 3.6% between days. The applied lower limit of quantification was 4 nmol l^{-1} . The same method was used for terbutaline in urine. The assay calibration curve was then extended up to 5000 nmol l^{-1} to allow for measurement of the higher concentrations in urine. At 80 nmol l^{-1} , the lower limit of quantification, within-day variation was 3.7% in the urine analysis.

Symbols and calculations

T10, T20	bambuterol tablet 10 and 20 mg, respectively
S2.5, S5, S10	bambuterol solution 2.5, 5 and 10 mg, respectively
C	plasma concentration
t	time
C_{max} , C_{min}	maximum and minimum plasma concentration, respectively
t_{max}	the time when C_{max} occurred
$\text{AUC}(t_1, t_2)$	area under the plasma concentration time curve between t_1 and t_2 , calculated using the trapezoidal rule, linear/linear up to C_{max} and then log/linear (if a plasma concentration was estimated to zero the linear/linear trapezoidal rule was always applied)
CL_R	renal clearance, amount excreted in urine divided by $\text{AUC}(1,6 \text{ h})$ or (preschool Caucasians only) $\text{AUC}(3,6 \text{ h})$
s.d.	standard deviation

If not measured, the plasma concentration at the end of a dosing interval was equalled to the 0 h value (end of the second last dosing interval) or the 24 h value (preschool Caucasians after 5 mg twice daily). Plasma concentrations below the limit of quantification were used when detectable, and otherwise set to half the limit of quantification or an estimated value, e.g. using interpolation between measurable concentrations. If all plasma concentrations in a patient were below the limit of quantification, the value in that patient was set to half the limit of quantification at mean t_{max} for the group and the other values were set to zero.

Statistical analysis

C_{max} , AUC, and CL_R of bambuterol and generated terbutaline were calculated individually. Mean treatment differences within each study were investigated using analysis of variance (ANOVA). C_{max} , C_{min} , AUC, and

Figure 1 Mean plasma concentrations and s.d. in Caucasian pre-school (upper panels) and school children (lower panels). Pre-school children were administered bambuterol 5 mg (dotted-dashed lines) twice daily and 10 mg (dashed lines) once daily, school children bambuterol 10 mg (dashed lines) and 20 mg (continuous lines) once daily.

amount excreted in urine were assumed to be proportional to dose and the variations of these measured quantities were assumed to be proportional to their magnitudes. Therefore, multiplicative ANOVA models were applied; treatment differences of log transformed data were analysed. Dose proportionality, high *vs* low dose, was tested using data from Oriental preschool and school children and Caucasian school children, one group (study) at a time with observed CL_R , dose-normalized C_{max} , and AUC, using factors patient, period, and treatment. Once-*vs* twice-daily dosing was tested using data from the preschool Caucasians (5 mg $\times$ 2 *vs* 10 mg) with observed

C_{max} , CL_R , and AUC adapted to twice daily dosing ($2 \times AUC(0,12 \text{ h})$ after 5 mg $\times$ 2 *vs* $AUC(0,24 \text{ h})$ after 10 mg), using factors patient, period, and dosing frequency. Pharmacokinetic differences between the four studies presented in this paper (Caucasian *vs* Oriental children, preschool *vs* school children) and the relation to steady-state AUC in adults [6] were described. Classic 95% confidence limits were calculated for antilogged geometric mean ratios. Formal power calculations were not performed.

The relationship between dosing interval AUCs in steady state of terbutaline and bambuterol (systemic

Figure 2 Mean plasma concentrations and s.d. in Oriental pre-school (upper panels) and school children (lower panels). Pre-school children were administered bambuterol 2.5 mg (dotted lines) and 5 mg (dotted-dashed lines) once daily, school children bambuterol 10 mg (dashed lines) and 20 mg (continuous lines) once daily.

capacity to generate and eliminate terbutaline in relation to systemic exposure to administered bambuterol) was described with a potency function (Equation 1).

$$AUC_{\text{terbutaline}} = B \times AUC_{\text{bambuterol}}^A \quad (1)$$

A linear mixed effect model analysis was performed using log transformed data. The parameters A and ln B were assumed to be normally distributed random variables within the group of investigated children and the observational error in terbutaline AUCs was assumed to be log-normally distributed. The observational error in

bambuterol AUC was not regarded. Data points based on estimated values of the independent variable, AUC of bambuterol, were excluded.

Results

Pharmacokinetics of bambuterol and terbutaline

C_{max} and AUC of bambuterol and generated terbutaline are described in Tables 2 and 3 and outcome of the statistical analysis in Table 4. Note that plasma was not sampled at 1 h from preschool Caucasians and therefore

Parameter	Ethnic origin	Age group	Dose (mg day ⁻¹)	n	Mean	Min	Max
$C_{\max}$ (nmol l ⁻¹)	Caucasian	Pre-school ¹	5 × 2	12	4.5	1.5	11.7
		Pre-school ¹	10	12	5.8	1.3	13.2
		School	10	12	10.6	1.5	24.7
		School	20	12	21.9	9.7	42.4
	Oriental	Pre-school	2.5	12	1.6	0.5	2.6
		Pre-school	5	12	4.7	1.2	8.3
		School	10	12	13.6	6.6	32.6
		School	20	12	54.1	20.6	110.0
AUC ² (nmol l ⁻¹ h)	Caucasian	Pre-school	5 × 2	12	36.3	12.6	82.1
		Pre-school	10	12	63.4	14.2	127.6
		School	10	12	57.7	25.3	107.8
		School	20	12	175.6	91.6	278.9
	Oriental	Pre-school	2.5	12	10.6	0.7	31.4
		Pre-school	5	12	39.6	7.6	80.7
		School	10	12	97.9	52.2	182.1
		School	20	12	328.3	155.4	522.0

¹First post-dosing assessment was done after 3 h. ²AUC during 12 h for twice-daily dosing.

Table 2 Bambuterol, peak plasma concentration and AUC.

Parameter	Ethnic origin	Age group	Dose (mg day ⁻¹)	n	Mean	Min	Max
$C_{\max}$ (nmol l ⁻¹)	Caucasian	Pre-school ¹	5 × 2	12	13.4	9.6	18.4
		Pre-school ¹	10	12	14.8	7.8	22.4
		School	10	11 ²	13.8	5.5	19.9
		School	20	12	23.3	9.0	33.3
	Oriental	Pre-school	2.5	12	6.4	4.5	9.4
		Pre-school	5	12	11.5	8.0	21.0
		School	10	12	21.2	13.4	35.2
		School	20	12	37.7	21.4	58.0
AUC ³ (nmol l ⁻¹ h)	Caucasian	Pre-school	5 × 2	12	128.6	84.5	187.1
		Pre-school	10	12	242.4	95.9	334.3
		School	10	11 ²	212.8	112.1	353.9
		School	20	12	405.9	174.7	578.6
	Oriental	Pre-school	2.5	12	89.1	43.4	175.4
		Pre-school	5	12	205.5	107.2	416.7
		School	10	12	356.0	262.6	570.7
		School	20	12	639.6	337.8	981.7

¹First post-dosing assessment was done after 3 h. ²Analytical interference with salbutamol in one patient. ³AUC during 12 h for twice-daily dosing.

Table 3 Terbutaline, peak plasma concentration and AUC.

their $C_{\max}$ values, especially for bambuterol (c.f. below), should not be compared on an equal basis with the other children's values, from whom samples were collected at 1 h.

Peak plasma bambuterol was observed on average 1–3 h (always <6 h) after dosing. Where a comparison was possible, steady-state $C_{\max}$ of bambuterol in the Oriental children and AUC of bambuterol in all groups were not proportional to the administered dose. Twice the AUC(0,12 h) after S5 was not statistically significantly

different from AUC(0,24 h) after S10 in the preschool Caucasians, showing that dividing the dose did not alter the daily exposure to bambuterol. $C_{\max}$ and AUC were higher in the Oriental than in the Caucasian school children (Figures 1 and 2), especially after T20. Renal clearance of bambuterol had poor predictive value for the exposure to bambuterol (Figure 3).

Peak plasma concentration of generated terbutaline was observed on average 3–4 h (always <12 h) after oral dosing with bambuterol. Steady-state $C_{\max}$ and AUC of

Figure 3 Dose-normalised AUC *vs* renal clearance of bambuterol in Caucasian pre-school and school children (open circles) and Oriental school children (filled circles) during oral administration of bambuterol.

terbutaline were proportional to the administered dose, except for a small reduction of $C_{\max}$ with dose in the Caucasian school children. Twice the AUC(0,12 h) after S5 was not statistically significantly different from AUC(0,24 h) after S10 in the preschool Caucasians, showing that, also for terbutaline, dividing the dose did not alter the daily exposure. Figure 4 indicates that the steady-state relationship between terbutaline and bambuterol AUCs was ethnically independent and nonlinear. The typical values of A and B (Equation 1) were 0.534 and 27.4, respectively. The 95% CI of A (0.480–0.588) did not include 1, supporting the visual indication of a nonlinear relationship.

Figure 4 AUC of terbutaline *vs* AUC of bambuterol in Caucasian (open circles) and Oriental (filled circles) children during oral administration of bambuterol. The continuous line represents the outcome of a linear mixed effect model analysis of the relationship between $\ln$ AUC of terbutaline and $\ln$ AUC of bambuterol (c.f. text).

$C_{\max}/C_{\min}$ of terbutaline was 2.7 and 2.2 in Caucasian school children after T10 and T20, 2.4 in the Oriental school children after T10 and T20, 2.6 and 1.6 in the Caucasian preschool children after S10 and S5 $\times$ 2, and 2.3 in the preschool Oriental children after S5 (plasma terbutaline was often below the limit of quantification at the end of the dosing interval after S2.5).

Mean AUC of terbutaline after S10 in the Caucasian preschool children was slightly higher than after T10 in the Caucasian school children showing that some patients in the former group were more exposed to the active

Table 4 Mean ratios and 95% confidence ranges of pharmacokinetic parameters. (Values in bold indicate statistical significance.).

Bioanalyte	Parameter	Studies of Caucasian children		Studies of Oriental children	
		Pre-school children (S5 $\times$ 2)/(S10 $\times$ 1) ¹	School children T20/T10 ²	Pre-school children S5/S2.5 ²	School children T20/T10 ²
Bambuterol	AUC	1.14, 0.85–1.52	1.57, 1.24–1.98	2.41, 1.06–5.49	1.69, 1.23–2.31
	$C_{\max}$	0.77, 0.59–1.01	1.16, 0.78–1.75	1.38, 0.78–2.46	2.08, 1.46–2.95
Terbutaline	AUC	1.11, 0.90–1.37	0.97, 0.84–1.12	1.12, 0.85–1.48	0.88, 0.75–1.04
	$C_{\max}$	0.93, 0.79–1.10	0.85, 0.76–0.96	0.86, 0.66–1.13	0.87, 0.74–1.03
	CL _R	1.03, 0.83–1.28	1.07, 0.90–1.28	1.13, 0.66–1.92	1.00, 0.54–1.85

¹The ratio of AUC was calculated as 2 $\times$ AUC(0,12 h) after bambuterol S5 twice daily divided by AUC(0,24 h) after S10 once daily; the ratio of $C_{\max}$ was dose-normalized. ²Ratios of AUC and $C_{\max}$ were dose-normalized.

moiety than in the latter (Oriental preschool and school children could not be similarly compared because common doses were not administered). $C_{\max}$ and AUC were higher in the Oriental than in the Caucasian school children.

Renal clearance of terbutaline was on average about 70, 90, 40, and 65 ml min^{-1} , in Caucasian preschool and school children and Oriental preschool and school children, respectively, and not dose dependent (Table 4). AUC of terbutaline was related to renal clearance (Figure 5).

Plasma cholinesterase activity in Caucasian school children

Mean basal plasma cholinesterase activity was 16.30 (11.86–19.31) nmol min^{-1} per 5 μl blood. During treatment, plasma cholinesterase activity was inversely correlated to plasma bambuterol. Mean maximum inhibition, 1–3 h after dose, was 63.6% (50.0–80.0) with T10 and 72.1% (49.7–84.4) with T20. At the end of the dosing interval, plasma cholinesterase was still inhibited by, on average, 16.6% and 41.2%, with T10 and T20, respectively.

Adverse events

Adverse events differed marginally in frequency between treatments and were those known to occur with β_2 -

adrenoceptor agonist treatment or were respiratory symptoms associated with the disease under investigation. Intensity was mild or moderate. Two Caucasian school children were hospitalized because of asthma deterioration after T10 and T20, respectively.

Discussion

Dose linearity and systemic exposure

Hydrolysis of bambuterol is to a great extent catalysed by plasma cholinesterase. Bambuterol is a potent inhibitor of plasma cholinesterase in adults [10] and therefore partly inhibits its own metabolism. In the present study, the measurements performed in Caucasian school children showed that plasma cholinesterase was inhibited in children, too, a conceivable reason for the nonlinear pharmacokinetics of bambuterol. Inhibition of hydrolytic enzyme(s) should furthermore have an impact on the capacity to generate terbutaline. The correlation between terbutaline and bambuterol AUC, nonlinear and ethnically independent (Figure 4), suggests that this was so. One could expect that terbutaline AUC would increase less than expected from dose escalation, but in fact dose linearity was seen for terbutaline (Table 4). Apparently, less presystemic generation of terbutaline was systemically compensated for. Oxidized bambuterol is much less stable than bambuterol itself [11]. Spontaneous hydrolysis of such intermediary metabolites may therefore have contributed to the generation of terbutaline. Moreover, in the absence of normal plasma cholinesterase, other esterases are probably able to perform the necessary hydrolytic steps [12].

Clinical pharmacokinetic aspects of dosing bambuterol to children

The presented four studies were evaluated and described on a steady-state basis. Time to the steady state in adults, as determined by terminal half-lives of bambuterol and generated terbutaline [6], is less than 1 week. The terminal half-life of terbutaline as such is similar in Caucasian children and adults [13,14]. The present studies in children indicated that bambuterol was more rapidly eliminated and so probably had a shorter terminal half-life than terbutaline. Therefore, it is reasonable that steady states for bambuterol and terbutaline were reached after one week and that therefore estimates of $C_{\max}$ and AUC after 1 and 2 weeks can be compared on an equal basis. $C_{\max}/C_{\min}$ of terbutaline is close to 2 in healthy adults during once daily dosing [6]. This ratio was higher in the children, but it was considerably reduced during twice-daily dosing, thus offering a means of creating flatter terbutaline concentration curves.

Mean $C_{\max}$ and AUC of bambuterol and terbutaline

Figure 5 Dose-normalised AUC *vs* renal clearance of terbutaline in Caucasian children (open circles) and Oriental children (filled circles) during oral administration of bambuterol.

were higher in Oriental school children than in the Caucasian school children during T10 and T20, possibly because metabolism of bambuterol and renal clearance (Figure 5) of terbutaline differed between the groups. The treatment difference in $C_{\max}$ of bambuterol was more pronounced in the Oriental school children, indicating that the nonlinearity in the pharmacokinetics of bambuterol operated at a lower concentration level than in the Caucasian school children. The studies in school children were not perfectly matched. Therefore, ethnical implications of the pharmacokinetic differences must not be overemphasized.

It is often recommended that drug dosing to children, compared with adults, should be reduced in proportion to the children's lower weight. This routine dose-adjusting principle in paediatric practice is mainly based on the assumption that clearance of the drug is linearly proportional to body weight. With linear pharmacokinetics, apparent clearance after oral administration (CL_{app}) is calculated as dose divided by AUC. During regular treatment, the dosing interval AUC should therefore be directly proportional to dose and inversely proportional to apparent clearance (Equations 2–4):

$$AUC = \text{Dose} / CL_{app} \quad (2)$$

If we multiply both sides of Equation 2 by body weight (BW):

$$AUC \times BW = \text{Dose} \times BW / CL_{app} \quad (3)$$

$$(AUC \times BW) / \text{Dose} = BW / CL_{app} = \text{Constant} \quad (4)$$

However, this was not the case for terbutaline generated from bambuterol administered to the children, as shown in Figure 6. Instead, the ratio increased with body weight implying that CL_{app} does not increase as fast as body weight. Thus, dosing bambuterol according to body weight cannot be generally recommended in children, particularly not in younger ones.

Plasma AUC of terbutaline was increased by approximately 30% in the Caucasian school children but it was doubled in the Oriental school children after T20 compared with adults given a similar dose [6]. Therefore, Caucasian school children should be given up to 20 mg day⁻¹ at the most, whereas Oriental school children should not be given more than 10 mg day⁻¹. Data on file suggest that 5 mg bambuterol would give insufficient effect in Caucasian preschool children, and the found plasma concentration of terbutaline in Oriental preschool children after 2.5 mg seemed to be too low to be of therapeutic values. Thus, until more information is available, initial target doses in Caucasian and Oriental preschool children should be 10 and 5 mg day⁻¹, respectively.

Figure 6 Body weight and dose-normalised AUC of terbutaline during dosing of bambuterol in Caucasian adults (open diamonds), Caucasian children (open circles), and Oriental children (filled circles) *vs* body weight. Dashed line is median y-value. Adult data on file.

Conclusions

Caucasian school children can be given bambuterol hydrochloride very much as Caucasian adults, 10 or 20 mg once daily, but Oriental preschool and school children plus preschool Caucasians should be given lower doses.

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