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APPLICATION NUMBER
19-865/S-010

Pharmacology Review(s)

Pharmacometrics Review (ADDENDUM)

NDA:	**19-865**
Volume:	**1 – 11 volumes**
Compound:	**Betapace (Sotalol)**
Submission Date:	**19 Oct 1999 / 22 May 2000**
Sponsor;	**Berlex Laboratories, Inc.**
Pharmacometrics Reviewer:	**Joga Gobburu**

The dosing scheme based on body size (allometric weight model) and age (Emax – type model) involves a nonlinear function (refer to the original review). Upon discussions with Dr. Raymond Lipicky, a simplified body size (linear BSA model) formula (with age described by an Emax – type model) is derived here. Within practical limits, this simplified model performs similar to the earlier model.

The pharmacokinetics of sotalol in pediatrics is, now, described using a two compartment model with the following covariate models:

$CL = CL_{pop} \cdot BSA \cdot Age/(Age+Age50)$
$Vc = V_{pop} \cdot BSA$
$Q = Q_{pop} \cdot BSA$
$Vt = Vt_{pop} \cdot BSA$

Where, CL = systemic clearance, V = volume of distribution of the central compartment, Q = inter-compartmental clearance, Vt = volume of distribution of the peripheral compartment and the subscript 'pop' signifies the mean population value.

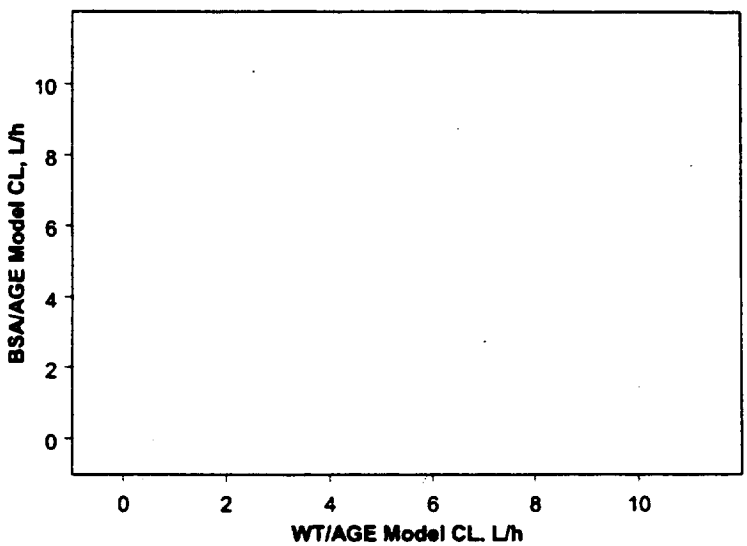
Also, the residual error model did not require the additive error part of the previous combined proportional and additive error model. This is so because the standard deviation of the additive error was estimated to be 0.004 ug/L (which was deemed too low) and exclusion of the additive error component did not affect the estimation of the other parameters and the objective function value. All other features of the model were similar to the previous models.

Table A1. Summary pharmacokinetic parameters of sotalol in pediatrics for the BSA/AGE model.

Parameter	CL $L/h/m^2$	Vc L/m^2	Q $L/h/m^2$	Vt L/m^2	KA h^{-1}	Tlag h	Age50 Years
Mean	5.05	33.6	1.32	12.9	1.13	0.257	0.0377
SE (%)	3.9	7.6	22.6	20.7	13.9	11.8	30
Inter-individual Variability (% CV)	21	25	0c	101	42	44	
SE (%)	30.6	27.7	0.0c	94.9	44.3	57.9	
Residual Error (% CV)	17						
SE (%)	13.1						

The objective function value of the current model is 5961, while that of the previous WT/AGE model was 5951. These two models are not nested models (one cannot eliminate parts of one model to derive the other model) and hence comparison of the goodness-of-fit needs to be done cautiously. The most important PK parameter is the systemic clearance (CL) that determines the steady – state concentrations (sotalol is used chronically). The individual clearance values of the two models seem to be in good agreement, as shown in Figure A1.

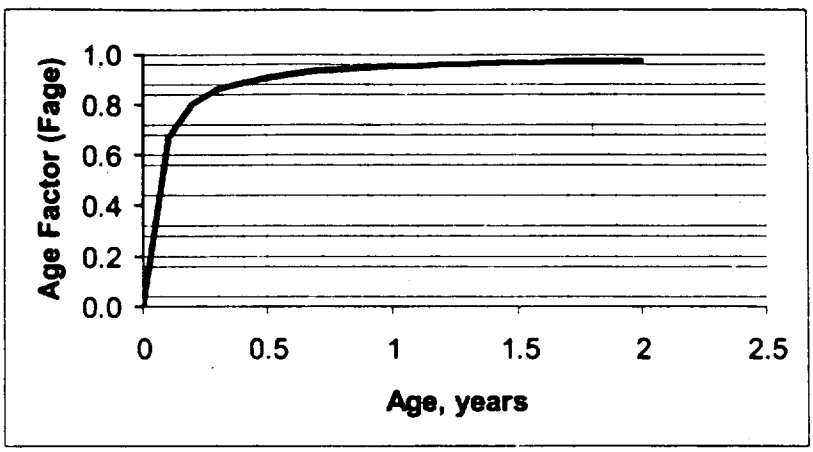
Figure A1. Individual systemic clearance of sotalol as predicted by the previous WT/AGE model and the current BSA/AGE model. The solid line indicates the line of identity and the filled circles indicate the individual (posthoc) clearance values predicted by the BSA/AGE model.



The advantage of the BSA/AGE model is that it allows an easier determination of the starting dose in the pediatric patients, while preserving the accuracy. Although BSA is derived from body weight and height using a formula (nonlinear in nature) that requires a calculator, prescribers usually have a nomogram readily available at their disposal.

A starting dose of 30 mg/m^2 adjusted for age according to Figure A2 is recommended.

Figure A2. Age factor that should be multiplied to the dose for determining the starting dose in pediatrics. The factor reaches a value of 1 by about 2 year. The slope of the curve is steeper for the neonates and infants. Since the influence is most in the lower range of the age axis, a graph with logarithmic age axis is also provided.



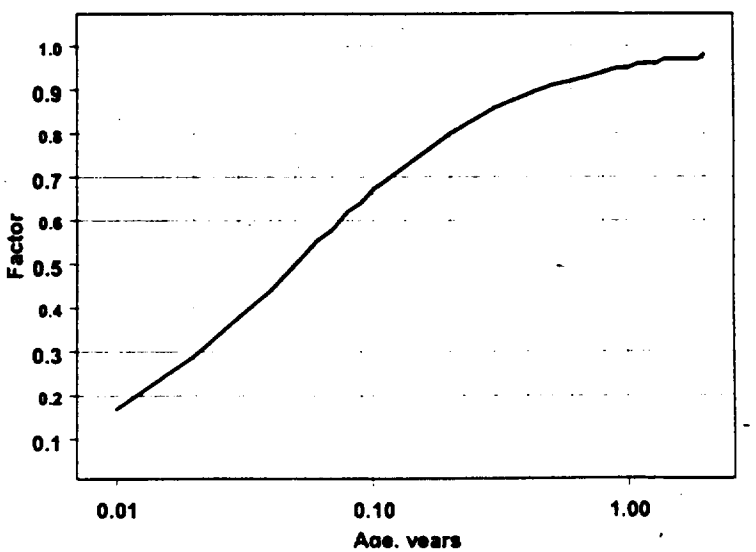


Figure A2. Simulated sotalol concentrations after the last dose (30 mg/m2 tid) at steady – state using the BSA/AGE and BSA models. The aim is to give a dose to a pediatric patient so as to achieve similar concentrations to that of 80 mg bid dose to an adult. Expected concentrations when the starting dose is not adjusted for age ("Not adjusted for age") in a neonate (age = 0.011 yr, BSA=0.17), when adjusted for age ("Adjusted for age in a neonate") and in a school – going child (age = 12.2 yr, BSA=1.23). Also shown are the simulated concentrations in an adult (BSA=1.73, age = 50 years, '•') after 80 mg bid starting dose, using the BSA/AGE model. The original NDA (adults) indicates that the average steady – state minimum and maximum concentrations after 80 mg bid are 317±63.7 ug/L and 868±137 ug/L (page 7 of original clinical review). The simulated concentrations agree with the previously observed concentrations. The concentrations produced by a 30 mg/m^2 dosing after adjustment for age (if necessary) in the neonate and the school – going child are similar to those in the adult. Their terminal half – life of the neonate (about 30 h) is different from that of the older patients (about 10 h). For this reason, concentrations persist for longer duration before elimination in the neonates and infants.

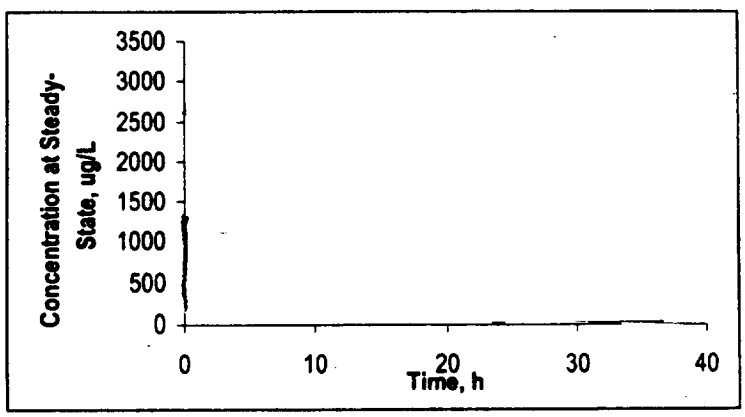


Illustration of determining the starting dose in pediatrics:

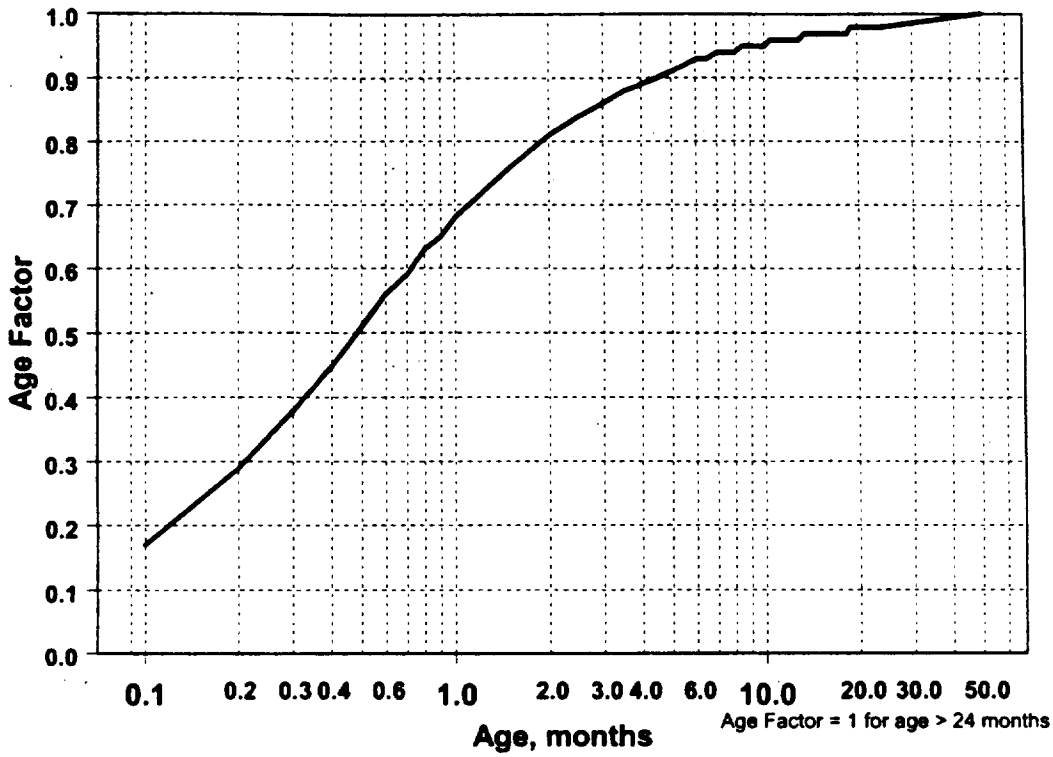
Patient #37000: WT = 2.2 kg, BSA = 0.17 m^2, Age = 0.011 yrs.
The starting dose = 30 mg/m^2 tid· 0.17 m^2 = 5.1 mg · 0.018 (Age factor from Figure A2) = 0.9 mg tid. Since for neonates and infants the drug will be administered as simple syrup, the dosing adjustment is practically feasible.

Patient #14001: WT = 38.5 kg, BSA = 1.23 m^2, Age = 12.21 yrs.
The starting dose = 30 mg/m^2 tid· 1.23 m^2 = 36.9 mg (Factor is 1 for age greater than 2 yr) = 36.9 mg tid. Whether such a dose can be administered given the dose strengths needs some consideration.

The bullet#6 (page 15) of the original clinical pharmacology review should be replaced with the following:

Draft Labeling

The graph below depicts the relationship between the age (in months) of the patient (logarithmic age axis) and the adjustment factor that needs to be multiplied to the starting dose, in patients with age less than 24 months.



/S/ 12/26/00

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RD/FT initialed by Patrick Marroum Ph.D.

Cc list: NDA 19-865, HFD 110, HFD 860 (Mehta, Gobburu), CDER Document room