Esmolol Population Pharmacokinetics in Critically-ill, Pediatric Patients

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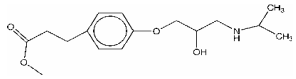
BACKGROUND

INTRODUCTION

Esmolol Chemical Structure:



Basic Pharmacology

- β_1-selective antagonist
- very short duration of action
- administered for beta blockade of short duration

Adult Clinical Pharmacology

- Rapid control of ventricular rate in atrial fibrillation/flutter
- Noncompensatory sinus tachycardia
- Initial loading dose of 500 µg/kg
- Maintenance infusion of 50 - 200 µg/kg/min
- Ester linkage hydrolyzed rapidly by erythrocyte esterases
  - free acid metabolite and methanol
- No CYP dependent metabolism
- $t_{1/2}\alpha \sim 2$ min; $t_{1/2}\beta \sim 9$ min
- Apparent Vd ~ 2 L/kg
- Clearance 128-250 ml/kg/min
- Free acid metabolite
  - 1/1500th the activity of esmolol; $t_{1/2}\beta \sim 3.7$ h; excreted in the urine

Assumptions for Dosing Pediatric Population

- No data to suggest that red cell esterase activity in children is different
- Studies in children suggest a more rapid clearance or terminal elimination of drug relative to adults

Pediatric Trials with Esmolol

- **ETHIC**:Infants and Children Undergoing Treatment of Hypertension in After Surgical Repair of Coarctation of the Aorta
- **ESCAPE**: Pediatric Patients with Supraventricular Tachycardia
- Neither study designed for pop-PK
- Clinical settings different (OR vs Cath Lab) as well as clinical conduct
- ETHIC patients anesthetized

Demographic Characteristics

	ETHIC	ESCAPE	COMBINED
Age	30 newborns: ≤28 days 41 infants: >28 d to <1y 72 child: ≥1y to 6y	14 child: ≥ 2 to 11y 13 adol:12-16yr	30 newborns 41 infants 97 child/adolesc
Weight(kg)	newborns: 3.6 (0.4) infants: 5.8 (1.9) child: 34.3 (20)	48.9 (23.6)	23.2 (22)
Race	hispanic: 25 (17%) black: 9 (6%) white: 107 (75%) other: 2 (2%)	non-Hispanic white: 30 (88%) non-Hispanic black: 4 (12%)	
Gender	♀: 50 (35%) ♂: 93 (65%)	♀: 11 (41%) ♂: 16 (59%)	♀: 61 (36%) ♂: 109 (64%)

Pediatric Trials with Esmolol

	ETHIC	ESCAPE
Number	107	22
Dose (bolus)	125, 250, or 500 µg/kg	1000 µg/kg push
Dose (infusion)µg/kg/min	125, 250, 500	15-min infusion at 300
PK sampling	0, 5, 10, and 15 min after the start of CIVI	0, 5, 10, and 15 min after load and 3, 6, 9, 12, 15 and 20 min after CIVI
Initial PK Analysis	Empirical pop. model $C(t) = Css * (1 - e^{-et})$	NCA 2CPM (WINSAAM)
Vd (mL/kg)	ND	283 (145); [131– 732]
$t_{1/2}\beta$ (min)	4.8	6.9 [5.2-10.9]
Clearance (mL/kg/min)	Infants: 281 (267,296) Children: 126 (83, 169)	119 (51); [25-237]

OBJECTIVES

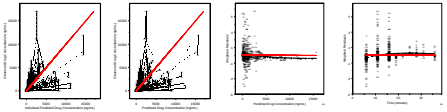
1. To describe esmolol pharmacokinetics in pediatric patients via population-PK modeling
2. To identify covariate, demographic and clinical factors that are important predictors of variability in esmolol PK parameters

DESIGN / METHODS

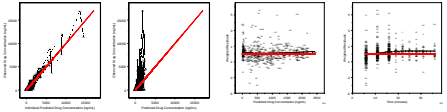
- Combined data set contained 552 observations and included 4 dosing regimens (loading doses of 125, 250, 500 and 1000 µg /kg over 10 - 20 seconds and maintenance infusions of 125, 250, 300 and 500 µg /kg/min over 15 min)
- PK database was analyzed using nonlinear mixed-effects modeling with the NONMEM software, Version V, Level 1.1 (FO and FOCE Methods)
- The underlying structural model was a two compartment open model with two consecutive zero-order staged infusions as input

RESULTS

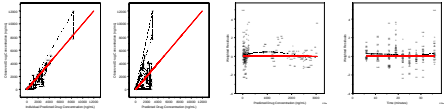
Base Model, Combined Dataset



Final Model, Combined Dataset



Final Model, Escape Dataset Only



Relevant Model Runs

Model Description	MOFV	ΔOFV
Base: 2 CPM	-7951.3	NA
2CPM; fixed allometric on CL	-7275.5	-675.8
2CPM; fixed allometric on CL and V	-7321.2	-630.1
2CPM; fixed allometric on CL; CL~RACE	-7275.1	-0.4
2CPM; fixed allometric on CL; CL~SEX	-7274.2	-1.1
2 CPM; fixed allometric on CL; CL~AGE	-7265.4	-10.1

RESULTS (continued)

Final Model

Parameter		Estimate	%RSE
CL (L/hr)	θ_{CL}	10.2	14.3
	$\theta_{CL\sim AGE}$	0.1	60.4
V (L)	θ_V	9.96	15.3
Q (L/hr)	θ_Q	0.78	56.8
V2 (L)	θ_{V2}	7.84	19.9
Inter-individual Variance			
	ω^2_{CL}	4.54	49.6
	ω^2_V	0.42	136.9
	ω^2_Q	1.57	319.7
	ω^2_{V2}	1.81	219.9
Residual Variance			
	σ^2_{Add}	290.0	82.1
	σ^2_{Prop}	0.59	30.8

- 3 subjects were influential to model prediction
- Mixture models improved prediction and residual error but were not meaningful from the standpoint of individual patient guidance

CONCLUSIONS

- The pediatric population PK model provided a robust description of esmolol PK across a wide range of ages (0.01 – 16.7 years) and body weights (2.6 – 114.1 kg).
- While 3 patients were found to influence model outcomes, there were no compelling reasons to remove them from the analysis. Model predictions were consistent with a linear, time-independent system.
- Newborns and infants appear to clear esmolol faster than children greater than 1 year of age. Clearance in children greater than 1 year of age is similar to that observed in adults.

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