Voriconazole dosing in children under 2 years

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Background. There are no dosing guidelines for voriconazole in children aged <2y, despite worldwide use in this population.

Methods. Using the Pmetrics population modeling package for R, we fitted our clinically validated voriconazole population model[1] to data from children <2y old who received IV and oral voriconazole from 2005–2016 at our hospital. After confirming satisfactory prediction of measured voriconazole concentrations, we simulated cohorts of 1000 children each with differing IV and oral dosing regimens. For each regimen, we calculated the probabilities of trough concentrations outside and within the target range of 1.0 – 5.5 mg/L or 12-h adult oral/IV AUC after 2 loading and 5 maintenance doses every 12h.

Results. There were 38 children with mean (range) age 1y (1w to 2y), weighing 8.3 (3.7–14.7) kg. Initial predictions were poor due to inter-occasion variability; thus, we separated subjects into occasions based on observed changes in dose-adjusted trough concentrations >100%. There were 78 occasions, with 2.2 (1-8) observations per occasion. The mean Bayesian posterior prediction bias and RMSE were -0.005 and 1 .2 mg/L, with observation-prediction regression intercept and slope of 0.2 and 0.93, R^2 0.77. Inter-occasion CV% in individual PK parameters ranged from 13% (bioavailability) to 67% (rate of absorption). There were no apparent age-parameter relationships.

Simulated Regimens		Trough (mg/L)			12-h AUC (mg*h/L)		
Load/maintenance (mg/kg)	Route	<1	1 – 5.5	>5.5	<14	14-34	>34
11/10	IV	57%	32%	11%	24%	40%	35%
9.3	IV	61%	31%	8%	31%	35%	34%
9*/8*	IV	63%	29%	8%	36%	37%	27%
8/7	IV	67%	27%	7%	43%	34%	23%
14/13	Oral	62%	27%	11%	38%	34%	29%
11/10	Oral	68%	24%	9%	51%	28%	21%
9.7	Oral	76%	24%	0%	46%	34%	20%
10/9*	Oral	69%	23%	8%	56%	27%	17%
9/8	Oral	72%	21%	7%	60%	24%	15%

*Approved European doses for ages 2-12y.

Conclusions. This is the largest evaluation of voriconazole PK in children <2y. Initial vori dosing in these children can likely be the same as the approved European dosing for children 2-12y, based more on AUC, but due to large variability in

achieved concentrations, TDM should be performed.

Reference:

1. Neely M, Margol A, Fu X, et al. Achieving target voriconazole concentrations more accurately in children and adolescents. Antimicrob Agents Chemother **2015**; 59:3090–3097.

Notes:

Simulation was wrong in initial abstract. I used model 34 (original) but since ages were in years (vs. weeks in young), the weights were too high.

Redid simulation and PTA not good.

Added a PNA Hill function and better match with population.