Impact of Lopinavir Limit of Quantification (LOQ)-Censored Data Replacement on Population Pharmacokinetic (PK) Plasma and Saliva Modeling in HIV-Infected Children

#1082

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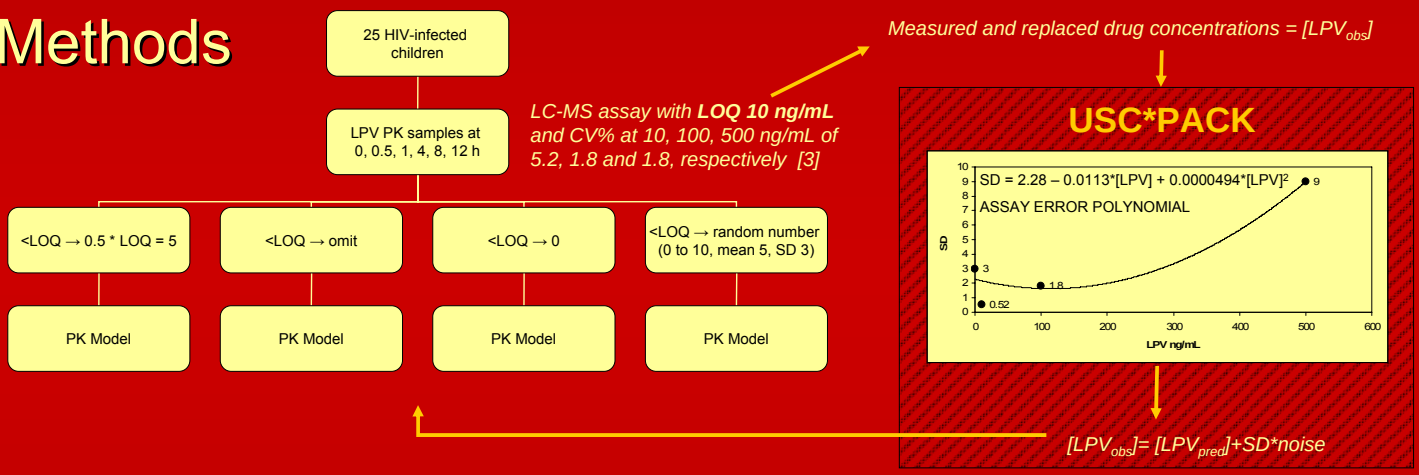
Introduction

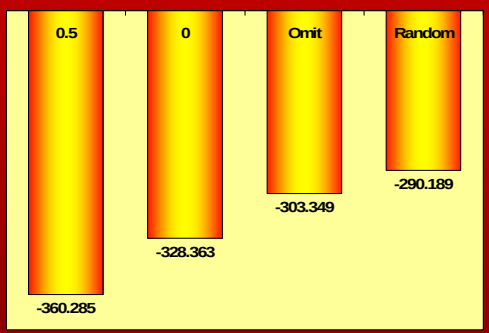
- Low measured drug concentrations are usually censored on the basis of a limit of quantification (LOQ)
- There is no standard definition of LOQ; typically it is chosen during assay development/validation on the basis of percent coefficients of variation (CV%) that are generally equal to or below 20% [1] and are also below the accepted therapeutic range of drug concentration should one exist
- Censored data present a problem during construction of pharmacokinetic/pharmacodynamic population models by compromising detection of peripheral compartments. Censoring also may confound attempts to quantify adherence or dose optimization.
- Numerous methods have been proposed to replace LOQ-censored drug concentrations. [2]
- We quantified the effect of three common methods plus replacement with random values on a PK model of lopinavir (LPV) in plasma and saliva in HIV-infected children.

Methods



Results

10/173 (5%) plasma and 44/173 (25%) saliva samples <LOQ (15.6% overall)



PK model log-likelihood

	0.5		0		Omit		Random	
	Plasma	Saliva	P	S	P	S	P	S
R-squared	0.967	0.114	0.975	0.067	0.977	0.103	0.981	0.147
Intercept	0.252	0.101	0.135	0.121	0.226	0.135	0.242	0.104
Slope	0.969	0.473	0.980	0.259	0.974	0.434	0.992	0.507

Linear regression of observed vs. predicted LPV concentrations

Method	TLAG	KA	KEL	KCP	VC	KPC	VP
0.5*LOQ	2.07	3.32	0.06	34.06	68.10	1.28	1093.91
0	1.91	2.43	0.06	25.57	60.69	0.53	1055.99
Omit	1.99	2.49	0.21	25.43	60.71	0.59	895.02
Random	1.81	2.47	0.22	21.38	57.68	1.82	951.61

Mean Bayesian posterior PK model parameter estimates

Conclusions

- All four methods resulted in similar parameter estimates and predicted vs. observed LPV concentrations in plasma, less so in saliva.
- The population parameter estimates from the Random method were 2.8 x 10^{30}, 3.8 x 10^{16} and 5.2 x 10^{5} times as likely as the 0.5, 0 and Omit methods, respectively.
- **Since model likelihood is strongly dependent on method of LOQ replacement, LOQ censoring should be abolished in favor of concentration and SD reporting for all concentrations, even 0.**

[1] Guidance for Industry: Bioanalytical Methods Validation for Human Studies. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 1998.

[2] Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001; 28(5):481-504.

[3] Volosov A, Alexander C, Ting L, Soldin SJ. Simple rapid method for quantification of antiretrovirals by liquid chromatography-tandem mass-spectrometry. Clin Biochem. 2002; 35(2):99-103.