Transit Compartment Model Useful for Describing Absorption of Quetiapine XR and IR

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Objectives:
Quetiapine fumarate is an atypical antipsychotic that has demonstrated efficacy in patients with schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder. Quetiapine is available in two different formulations: XR (extended release) and IR (immediate release). Quetiapine XR exhibits a slower absorption compared with quetiapine IR, with generally lower C_{max} and longer t_{max}. The objective of this work was to develop a population PK model for both these quetiapine formulations in order to facilitate simulations of quetiapine PK across formulations, regimens, and the clinical dose range.

Methods:
The population PK model was developed based on data from a randomized, double-blind, crossover study in healthy volunteers (n=58, ClinicalTrials.gov Identifier NCT00702676) with the aim to study the sedation profile following administration of quetiapine XR and IR. The details of the study have been reported elsewhere [1]. In order to simultaneously describe the quetiapine PK profiles obtained with both formulations, a population PK model utilizing transit compartments [2] was applied to data using NONMEM VI.

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[…]
; transit rate constant
KTR     = (NB+1)/MTT

; log transform of 2nd Stirling approximation
LNFA    = 0.5*LOG(2*3.14159*NB)+NB*LOG(NB)-NB+LOG(1 +
1/(12*NB))

$DES

MYT = T -(DAY-1)*24

IF (MYT.LT.0.001) THEN
INPU    = 0
ELSE
INPU    = EXP(LOG(BIO*PODO)+LOG(KTR)+NB*LOG(KTR*MYT)-
KTR*MYT-LNFA)
ENDIF

K       = CL/V
K12     = Q/V
K21     = Q/VP

DADT(1) = INPU - K*A(1) - K12*A(1) + K21*A(2)
DADT(2) = K12*A(1) - K21*A(2)
[…]
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Figure 1. Sample NONMEM code for implementing the transit compartment model (published on nmusers mailing list by Sebastien Bihorel 27 Aug 2008)

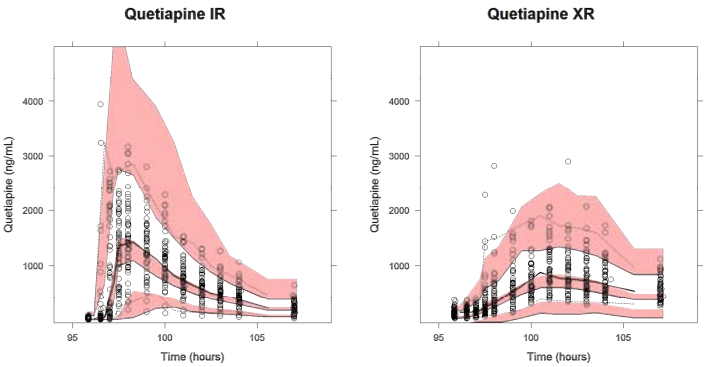

Figure 2. Visual predictive check of plasma concentration of QTP versus time. Symbols represent the observations and the lines represent the median, 2.5th and 97.5th percentile of the observations. The shaded areas represent the 95 % confidence intervals for the simulated prediction median and 2.5th and 97.5th percentiles

Results:
A two-compartment model with transit compartment absorption feeding directly into the central compartment was successfully fitted to data. Separate estimates of mean transit time (MTT) and number of transit compartments (NB) were obtained for the different formulations. MTT for XR and IR was estimated to be 4.65 h and 1.14 h, respectively. Other structural model population parameters were the same regardless of formulation. CL/F for quetiapine was estimated to be 96.8 L/h and V_{ss} to be 515 L/h. Interindividual variability (IIV) in bioavailability was similar (40%-45%) for both formulations. The IIV in MTT was 45% for the IR formulation and 23% for the XR formulation. As opposed to the original noncompartmental analysis, it could be shown in this study that quetiapine XR gave similar exposure in terms of AUC as quetiapine IR. This was because a single value of CL/F was valid for both of the formulations.

References:
[1] Datto C., et al. Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. Clin Ther. 2009;31:492-502.
[2] Savic R., et al. Evaluation of a transit compartment model versus a lag time model for describing drug absorption delay. PAGE 13 (2004) Abstract 513 [www.page-meeting.org/?abstract=513].

Conclusions:
The transit compartment model was able to describe absorption characteristics of both quetiapine XR and IR. The exposure in terms of AUC as well as the variability in bioavailability was similar following administration of either quetiapine XR or IR, thus providing further support for the bioequivalence of the two formulations.

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