Non-Linear Mixed Effects PK/PD Modelling of Acute Autoinhibitory Feedback Effects of Escitalopram on Extracellular Serotonin (5-HT) Levels in Rat Brain

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Introduction

Escitalopram (ESC) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) with antidepressant as well as anxiolytic activity (Sánchez et al., 2004; Thase, 2006). SSRIIs selectively block neuronal 5-HT reuptake, which results in increased neurotransmitter concentrations at the synaptic and somatodendritic level. The release of 5-HT from the neurons is negatively regulated by 5-HT autoceptors (Bundgaard et al., 2006). The model is schematically illustrated in Fig. 2. The acute 5-HT response, \( R \), was described by

\[
\frac{dR}{dt} = k_R R - k_R M
\]

(3)

The residual variability was 18% for the PK and 30% of the PD model. The bootstrap analysis (n=200) confirmed the high precision for the PK model, while for the PD, the %RSE were higher than estimated by NONMEM, especially for \( k_R \), IV\(f_{\text{esc}} \), and IV\(f_{\text{rec}} \) (>100%). The 95% predictive performance plots (n=200, shown below) were made from the final model with covariance estimates added for \( R_0 \), \( f_{\text{esc}} \), and \( f_{\text{rec}} \).

Results continued

The bootstrap analysis (n=200) confirmed the high precision for the PK model, while for the PD, the %RSE were higher than estimated by NONMEM, especially for \( k_R \), IV\(f_{\text{esc}} \), and IV\(f_{\text{rec}} \) (>100%). The 95% predictive performance plots (n=200, shown below) were made from the final model with covariance estimates added for \( R_0 \), \( f_{\text{esc}} \), and \( f_{\text{rec}} \).

In conclusion, the NLME autoinhibitory feedback model was successfully implemented. Predictive performance appeared adequate and variability estimates were low (PK) to moderate (PD). Considerably higher variability was seen for IV\(f \) of the in vivo potency (IC\(f_{\text{rec}} \)) and also \( k_R \) and \( R_0 \) from the bootstrap analysis. The model may serve as a tool to compare the PK/PD behaviour of different SSRIs after acute administration.

References