Population PK of midazolam from preterm neonates to adults: a maturation model

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Background & Aim

In this analysis we aimed to develop a maturation model for the CYP3A4/5 enzyme activity using midazolam clearance as in vivo probe for preterm neonates from 26 weeks gestational age (GA) onwards to adults.

Methods

Pharmacokinetic data after IV midazolam administration were obtained from 6 previously reported studies (Table 1). Population PK modeling was performed with a two compartment model using NONMEM v6.2. In a systematic covariate analysis, the influence of postnatal age, gestational age, postmenstrual age, body weight (BW) and PELOD score (organ failure) was investigated.

Results

Upon inclusion of preterm neonate datasets, BW proved a significant covariate for clearance. The influence of BW was best described using an allometric equation (Equation 1) with a BW-dependent maturational exponent (BWME). BWME gradually changed from 0.91 in preterm neonates to 0.50 in adults, with Coeff1 of 0.88 (7.6%) and exp2 of – 0.128 (30.8%) (Table 2). BW was also linearly correlated with V1, and in an allometric equation with V2 with an exponent of 0.78. Clearance was reduced by 93% in ICU patients. A 5.8 fold increase in V2 was estimated in patients after major craniofacial surgery.


Visual diagnostics plots of each dataset of final model. Observed concentrations versus predicted concentrations by the model (PRED) for midazolam. Below: the overall diagnostics of the combined data.

Conclusion & Perspectives

A maturation model for midazolam clearance from preterm neonates to adults has been developed for both ICU as well as non-ICU treatment patients, showing that CYP3A4/5 activity matures in (preterm) neonates up to 5-10 kg of body weight. Thereafter, maturation slows down resulting in minimal increase between 10 and 81 kg of body weight.

Table 1. Overview of the datasets used to develop the midazolam PK model.

Table 2. Population parameter estimates of the PK model in children (Figure 1).

Table 3. Legend for Figures 2 and 3.

Legend for Figures 2 and 3.

Figure 2. (1-4)

Figure 3. (5-10)