

A population PK/PD model for bispectral index of the fast acting anesthetic AZD3043 in healthy volunteers

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Objectives:

To describe the population pharmacokinetics (PK) of the sedative and anesthetic compound AZD3043 and its pharmacological effect assessed by the bispectral index (BIS) in healthy volunteers.

Methods:

- Data from two clinical studies in 125 healthy volunteers
- AZD3043 was administered as:
 - 30-min infusions (1-81 mg/kg/h)
 - 1-min infusions (60-360 mg/kg/h)
 - 1-min infusion (48 to 240 mg/kg/h) immediately followed by a 30-min infusion (10 to 40 mg/kg/h).
- Arterial plasma concentrations of AZD3043 measured up to 150 minutes after the start of infusion,
- BIS recorded until the subject was regarded as awake after sedation or anesthesia.
- Population pharmacokinetic/pharmacodynamic analysis performed using NONMEM 7 (ICON, Hanover, MD, USA) and PsN. Goodness of fit was assessed using objective function values, standard errors, graphics and visual predictive checks.

Results:

A 3-compartment model, with a lag-time for the drug to appear at the site of sampling, described the PK of AZD3043. The clearance (CL) and volume of distribution (V) parameters were allometrically scaled with body weight. CL was high, 2.1 L/min, suggesting elimination occurred not only in the liver as the CL was higher than liver blood flow. Plasma esterase activity did not, however, influence CL. Peripheral V's were low, but increased with increasing dose. V_{ss} (sum of all V's) ranged from 12 L in the lowest dose group to 35 L in the highest dose group. A sigmoid E_{max} model was used to describe the relationship between arterial concentrations and BIS. EC_{50} was estimated to 54 $\mu\text{mol/L}$. Between-subject variability in EC_{50} was 35%, suggesting that individual titration to the desired effect may be needed. An effect compartment model, with a half-life of k_{e0} estimated to 1 min, was used to describe the delay in effects in relation to the concentrations. A two-compartment effect-site model [1] did not improve the fit, suggesting rapid and/or limited distribution within the brain.

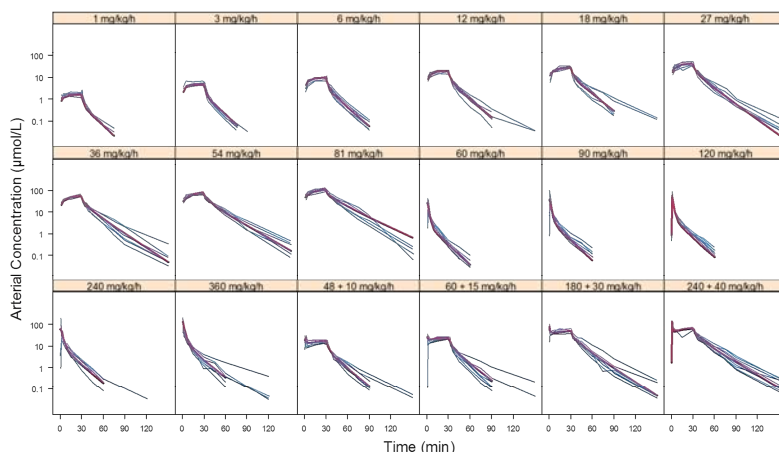


Figure 1: Observed (blue) and model predicted (red) arterial plasma concentrations of AZD3043 vs. time.

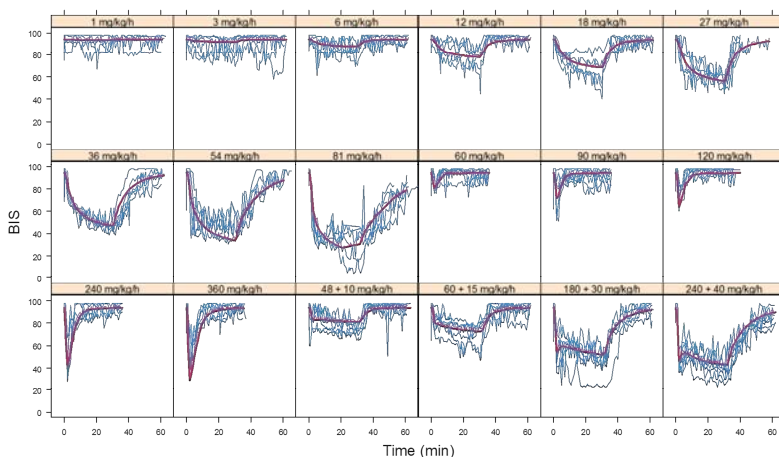


Figure 2: Observed (blue) and model predicted (red) BIS vs. time.

Conclusions:

- AZD3043 was rapidly metabolized and distributed.
- The extent of distribution was low but dose dependent.
- The short half-life and rapid equilibration with the effect site was reflected in a fast onset and offset of effects on BIS.

References:

[1] Björnsson MA, Norberg Å, Kalman S, Karlsson MO, Simonsson USH. A two-compartment effect site model describes the bispectral index after different rates of propofol infusion. *J Pharmacokinet Pharmacodyn* (2010); 37:243-255