Background and Aims

Temozolomide (TMO) is a 6-mercaptopurine nucleoside analogue. It is used in the treatment of several hematological tumors and solid tumors. Its elimination is mainly via the kidneys, mainly via glomerular filtration. The renal clearance of TMO results from two processes: an active renal transport and an active renal excretion. The latter is the major component of the renal elimination of TMO. The aim of this study was to evaluate the efficacy and safety of TMO in healthy volunteers in order to extrapolate the results to the patient population.

Materials and Methods

Study design

The study was a randomized, open-label, single-blinded, two-treatment parallel-group study. The study was conducted at the Department of Clinical Pharmacy and Pharmacology of the University of Louvain, Brussels, Belgium. In total, 8 male healthy volunteers received a single dose of 2 g of TMO as IV infusion over 40 minutes. Plasma samples were collected from 0 to 10 h and were analyzed for TMO concentrations.

Population pharmacokinetic modelling of total and unbound temozolomide in the plasma of healthy volunteers after intravenous administration

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Methods

The PopPK model of total and unbound plasma concentrations were fitted using a non-parametric approach with Phoenix (version 6.1.3). One- and two-compartmental PK models were tested for total TMO plasma concentrations. Two-compartmental PK models were chosen for the data analysis in order to derive the TMO unbound concentrations. The basis of the Bayesian information criterion (BIC), goodness-of-fit plots, normalized prediction error (npde) plots and visual predictive check (VPC) were used to determine the final model selection.

Results

The probability of achieving a target of 8 mg/L based on PTA was 81.4% for the 2 g/8 h dosing option and 99.8% for the 2 g/12 h dosing option. The probability of reaching a target of 8 mg/L during 40% of the time was 50.8% for the 2 g/8 h dosing option and 79.3% for the 2 g/12 h dosing option.

Discussion and Conclusions

TMO shows a b-compartmental pharmacokinetics.

TMO protein binding is high but saturable, with unbound concentrations ranging from 3.6 to 20% of total concentrations within the limits of the total concentrations observed.

PTA is low for conventional dosing, arguing for the use of more frequent administrations and discussions with health authorities.

Current licensed dosage regimen is suboptimal for MCA.

TMO is a mitotic inhibitor and the model was used to evaluate the PK of unbound TMO in target patients' populations.

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