Background

Memantine is a primary amine with a pKa of 10.27 and a logP of 3.28, used for the treatment of Alzheimer’s disease. About 95% of an oral dose is cleared renally as unchanged drug and renal and total clearance is highly sensitive to change in urinary pH but not urine flow rate. Thus, total clearance decreases from a median of 230 ml/min to 42 ml/min as urine pH is increased from about 5 to about 8 and the fraction of drug unionised in the distal tubule increases by approximately three orders of magnitude.

Aim

To simulate the effect of urine pH on memantine pharmacokinetics (PK) with a mechanistic kidney model.

Methods

A novel mechanistic kidney model (Mech KiM) was developed as a component of the Simcyp population based simulator (V12.1), accounting for glomerular filtration, passive secretion and reabsorption, active tubular uptake and secretion by known transporters, and renal drug metabolism (Figure 1).

Physiology – The development of Mech KiM required extensive collation of physiological data from literature. These data included nephron dimensions, the number of nephrons per individual, the number of proximal tubule cells per gram of kidney (PTCPKG), the volume of the cortex, medulla and renal blood vessels, tubular urine flow rates, the extent of blood bypass within the kidney and the pH of urine, blood and intracellular spaces.

Trial design – The pharmacokinetics of memantine after 10mg oral doses of its HCl salt were simulated under conditions of acidic (pH 5.0) and alkaline (pH 8.0) urine using the full PBPK model and Mech KiM in Simcyp V12.1. Ten trials were simulated under both conditions with a virtual population of 12 healthy male subjects matched for the age range (22-31y) in the in vivo study reported by Freudenthaler et al. (1998)1. In this study memantine was dosed to steady-state and urine pH was changed for the last dosing interval. It was not possible to recreate this regimen exactly in Simcyp. Therefore, a loading dose was applied in simulations in order to achieve memantine concentrations similar to those observed in vivo at the beginning of the final dosing interval.

Glomerular filtration – Excretion of memantine by glomerular filtration was defined by the product of glomerular filtration rate (GFR) and the free fraction of the drug in blood. Passive diffusion – Passive diffusion clearance of unbound, unionised drug was described by a CLdiff value of 50µl/min/million cells. This value was assumed to apply to diffusion across both the apical and basolateral membranes of the renal cells in all segments distal to the glomerulus. It was determined by sensitivity analysis with respect to the urinary recovery of memantine after dosage under normal urine pH conditions. The value is consistent with the nearly complete oral bioavailability of memantine.

Active secretion – Memantine is a substrate of the uptake transporter OCT2, present on the basolateral membrane of proximal tubule cells2. An intrinsic uptake clearance by OCT2 of 4.7µl/min/million cells was assigned based on scaling of the available in vitro data (Figure 2). In the absence of any data on the apical transport of memantine, it was assumed that this is mediated by apical efflux transporters such as MATEs at the same clearance rate as defined for basolateral uptake by OCT2 and that the efficiency of transport is not affected by changes in tubular fluid pH.

Results

The model recovered plasma drug concentration – time profiles under both extremes of urinary pH. The predicted increase in median AUC (all individuals; last dosing interval) on going from acidic to alkaline conditions was 17.5%, compared to the observed value of 17.9% (Figure 3).

Under alkaline conditions Mech KiM recovered the amount of memantine excreted unchanged by the kidneys during the last dosing interval accurately. However, the recovery under acidic urine conditions was lower than the observed amount (Figure 4). The predicted increase in the urinary recovery of unchanged memantine under acidic relative to alkaline conditions was 5.3 fold, compared to the observed increase of 7.1 fold (Figure 4).

Conclusions

These findings form a basis for further calibration and verification of Mech KiM with respect to defining the process of passive tubular reabsorption and factors that modulate it for a wider series of drugs.

References