Poster

[P26-4] P26-4: Central nervous system drugs (3)

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[P26-4-2] Clinical evaluation of lithium with tubular reabsorption mechanisms and urinary pH based on hospital pharmacometrics

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Background

Lithium carbonate has been used for the treatment of bipolar disorder over the years. Its effective blood concentration range is narrow and quickly reaches clinical toxic levels. Approximately 80 percent of lithium filtrated at glomerular are taking tubular reabsorption. The form of lithium in urine changes by pH; the concentrations of the ionic form increase under acidic condition. Therefore, the amount of the tubular reabsorption of lithium (LiTR) is also affected by urinary pH. However, dosing strategy for individual patients that considers a process of LiTR has not been reported. We have evaluated a population pharmacokinetic (popPK) analysis with LiTR model.

Methods

Routine clinical data including 389 blood lithium concentrations measured by atomic absorption spectrometry were collected from 214 patients. The PK of lithium was described with a one-compartment distribution model with first-order absorption and elimination, and a nonlinear mixed effects model was used to analyze the popPK models. Renal function (RF) was calculated using the Cockcroft &Gault formula and standardized to total body weight of 70kg and creatinine clearance (CLCr) of 6 L/h/70kg. LiTR model was composed of a compartment representing renal with a transition clearance between compartments (Q) influenced by CLCr. Lithium carbonate presents in two forms in patients (MID; Li^{+}+$LiCO_3^{-}$, ION; $2Li^{+}$+CO_3^{2-}), so we evaluated an influence of the fraction ION and MID on clearance (CL). The fraction was calculated using Henderson–Hasselbalch equation incorporating urinary pH.

Results

CL was explained by two sources in the final PK model. The first one was non-renal CL/F; 0.435 L/h. And the other was renal CL/F including the fraction of lithium forms influenced by urinary pH; RF x (0.617 x ION + 0.657 x MOL) L/h. The contribution of MID to CL was slightly larger than that of ION. Q decreased by about 90% exponentially if CLCr was reduced by 1.0 L/h.

Conclusions

As a result, hospital pharmacometrics based on physiological mechanism was performed, CL was influenced by the tubular reabsorption, urinary pH is a meaningful index on the lithium treatment, suggesting that lithium blood concentration could be predicted by urinary pH.