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DECREASED PHENYTOIN BIOAVAILABILITY CAUSED BY COADMINISTRATION OF RHUBARB THROUGH ACTIVATION OF P-gp

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Abstract:

Phenytoin (PHT) is an antiepileptic with narrow therapeutic window. Rhubarb, the rhizome of *Rheum palmatum*, is an important herb in clinical Chinese medicine. This study investigated the effect of rhubarb on the pharmacokinetics of PHT and the underlying mechanisms.

Rats were orally administered with PHT (200 mg/kg) with and without rhubarb decoction (2 g/kg, 4 g/kg and seven doses of 2 g/kg) in a crossover design. Blood samples were withdrawn via cardiopuncture at predetermined time points and serum concentrations of PHT, PHT glucuronide, 4-hydroxy phenytoin (HPPH) and HPPH glucuronide were determined by HPLC method before and after treatment with glucuronidase. LS-180 cell line was used to evaluate the effect of rhubarb on the efflux of PHT mediated by P-gp.

Our results showed that coadministration of single dose and multiple doses of rhubarb significantly decreased the C_{max} and AUC_{0-t} of PHT, PHT glucuronide, HPPH and HPPH glucuronide. Cell line study indicated that rhubarb increased the efflux of PHT.

In conclusion, rhubarb markedly decreased the oral bioavailability of PHT through activation of P-gp. Patients treated with PHT are suggested to avoid concurrent use of rhubarb to ensure the efficacy of PHT.

Keywords: Phenytoin, rhubarb, pharmacokinetics, P-glycoprotein.