Effect of MDR1 genetic polymorphism on the disposition of digoxin: population pharmacokinetic approach

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Since both genetic and environmental factors influence on the disposition of a drug, we analyzed the population pharmacokinetics of digoxin in relation to MDR1 genotypes as well as pathophysiologic variables using NONMEM. Total 337 digoxin concentrations obtained from 205 Korean adult patients were fitted to the presence or absence of the MDR1 mutant alleles (C3435T and G2677T.A) interacted to the co-variables such as age, sex, body weight, Scr and co-medication of known Pgp inhibitors or inducers, etc. The best model selected from multiple nonlinear fitting of concentration data to one compartmental pharmacokinetic model is as follows: Cl = 9.93 (L/h) *[1+0.006*(Clcr-100)]*0.86Pgp inhibitor*(0.873C/T3435 or 0.773T/T3435 or 0.848G/(T,A) or (T,A)/(T,A) 2677). Vd= 9.41(L/kg) *[1+(0.005*(Clcr-100)].

The coefficient varialtion (CV) of Cl was estimated to 35.3 % and that of Vd was 1.1%. The residual CV was 20.3 %.

These results suggest that both C3435T and G2677(A,T) mutant alleles of MDR1 are significant factors in determining the digoxin disposition, which is interacted by the pathophysiological covaribles such as body weight and Clcr. The population tool to predict the personalized dosages from both genetic and environmental information in a given individual patient.

Key words: MDR1 variants, environmental factors, population pharmacokinetics, digoxin disposition