일반연제 7

Idintification of the Effect of *SRD5A2* Genotype on Pharmacodynamics of Dutasteride: A PK-PD Modeling Approach

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Dihydrotesterone (DHT) converted by 5 α-reductase from testosterone is thought to be the androgen primarily responsible for the development of Benign Prostatic Hyperplasia. Dutasteride is a potent and specific irreversible competitive inhibitor of 5 α-reductase type 1 and type 2 for control of BPH.

The aim of this study is to evaluate the effect of genetic polymorphism of *SRD5A2* on the pharmacodynamics of dutasteride by PK-PD modeling approach.

We conducted a phase I clinical study of a single oral 0.5 mg dose of dutasteride in 40 healthy Korean male volunteers (active drug for 30 subjects). We also obtain genotype of *SRD5A2* V89L, coding gene of 5 α-reductase type 2 which shows more polymorphic in Asian. Data were analyzed by nonlinear mixed effect modeling using NONMEM. We used a indirect response model to explain the pharmacokinetic-pharmacodynamic characteristics of 5 α-reductase inhibitor. Pharmacokinetics were well explained by two compartment model with first order absorption, absorption lag, and first order elimination. In this lower only one dosage, nonlinear elimination could not be estimated well as previous developed model. Pharmacodynamic model represented that the dutasteride inhibit the formation of DHT by inhibit 5 α-reductase.

Pharmacokinetic parameters were similar to those of other previous studies. (PK parameters: ka=2.79 h^{-1}, Vd=530 l, Cl=10.7 lh^{-1})

Drug concentrations corresponding to 50% suppression of enzyme activity (EC50) were about 3 fold smaller in *SRD5A2* V89L homomutant group(L/L) than wild type group (V/V) in PK-PD model incorporated genotype as covariate to EC50. (EC50: V/V=0.375, L/L=0.102)

These findings suggest dutasteride can be more potently acting in person who have *SRD5A2* V89L mutation. It is consistent with the result of in vitro inhibition study.

A PK/PD mixed effect modeling approach was useful to explain the effect of genetic polymorphism on the pharmacodynamics of dutasteride 5 α-reductase inhibition.