Paroxetine Pharmacokinetics and Its Adverse Effects in Korean Healthy Volunteers; Relation to Metoprolol Metabolic Ratio

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It is well known that paroxetine is a substrate of CYP2D6 which metibolic activity shows wide variation in a population and is well correlated with metoprolol MR. We evaluated the paroxetine pharmacokinetics in 16 healthy Korean subjects(EM;15, PM;1) who showed various metoprolol MR(range L 0.057-13.83), and assessed their relationship. Blood samples were drawn serially upto 240hrs after single 40mg dose of paroxetine and side effects were observed throughtout the study period. Plasma paroxetine concentrations were measured by HPLC and pharmacokinetic parameters were estimated using noncompartmental analysisy.

Mean value of oral clearance(Cl/F) was 2.30±1.78 L/kg/hr in EM groupand 0.15 L/kg/hr in one PM, and it was well correlated with metoprolol MR($r=0.64$, $p<0.05$). Mean value of AUC was 548.10±585.05 ng/ml/hr in EM group and 4554.05 ng/ml/hr in PM, and it showed best correlation with metoprolol MR($r=0.974$, $p<0.001$). Mean value of volume of distribution(Vd/F) was 41.78±25.89 L/kg in EM and 14.88 L/kg in PM.

All subjects complained various side effects. The duration of greater metoprolol MR subjects was longer than that of lower MR subjects. The duration of side effects was well correlated with metoprolol MR($r=0.60$, $p<0.05$) and AUC($r=0.60$, $p<0/05$) of paroxetine.

These results suggested the possibility that metoprolol MR could be used for predictive index of the phamacokinetics and even the clinical effects of paroxetine which showed debrisoquine-sparteine-metoprolol type genetic polymorphism.