ASSOCIATION OF RISPERIDONE METABOLISM WITH DEBRISOQUINE HYDROXYLATION

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Risperidone, a new antipsychotic drug, is known to form an active metabolite 9-OH risperidone. We examined the possible association of the 9-hydroxylation of risperidone with CYP2D6 activity during phase I clinical study in korean subjects.
Method: Single blind cross-over study for the tolerance of single oral dose and sequential drug interaction studies in metabolism were performed in 12 healthy volunteers with predetermined debrisoquine phenotypes. They took single oral doses of 1and/or 2 mg of risperidone. Plasma levels of risperidone and 9-OH risperidone were determined upto 72 hrs after dose by radioimmunoassay. The 6 EMs among the volunteers were subjected for the quinidine(600 mg/day) risperidone(2 mg) interaction study.
Results: The dose-limiting adverse effect of risperidone was orthostatic hypotension. The plasma $t_{1/2}$ of risperidone in 1PM(14.8 hr) was quite longer than those observed in the EMs(2.1 to 7.8 hr). There were significant correlations between metabolic ratio of metoprolol(MR) and the $t_{1/2}$ of risperidone, and between MR and log(risperidone AUC/9-OH risperidone AUC) in the subjects (r=0.79 and 0.93, respectively). The co-administration of quinidine resulted in prolongation of risperidone half-life and reduced AUC of 9-OH risperidone. However the 9-hydroxylation pathway was not completely abolished by quinidine.