EFFECTS OF GINKGO BILOBA EXTRACT ON PHARMACOKINETICS AND PHARMACODYNAMICS OF TOLBUTAMIDE AND MIDAZOLAM IN HEALTHY VOLUNTEERS

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The aim of this study was to clarify the influences of single and long-term administration of Ginkgo biloba extract (GBE) on pharmacokinetics of tolbutamide and midazolam, respectively, as a selective in vivo probe substrate of cytochrome P450 (CYP) 2C9 and 3A4 activity, in healthy volunteers. In addition, the effect of GBE on hypoglycemia of tolbutamide was determined. After an overnight fasting, tolbutamide (125 mg) and midazolam (8 mg) were orally administered to 10 male healthy volunteers before and after repeated (360 mg/day, 28 days) or single (120 mg) administration of GBE, and they received 75g glucose 1 hr after the dosing of tolbutamide. In the long-term administration, plasma concentrations of each drug and blood level of glucose were measured up to 24 hr after the oral administration of drugs. Area under the concentration curve (AUC) for tolbutamide after repeated GBE intake was significantly (16%) lower than that before the GBE intake. Repeated GBE intake tended to reduce the hypoglycemic effect of tolbutamide although the effect was not statistically significant. On the other hand, AUC for midazolam was significantly (25%) increased by the repeated GBE intake and the oral clearance of the drug was significantly (26%) decreased. The effect of single GBE intake on the pharmacokinetics of tolbutamide and midazolam is also now under investigation. In conclusion, these results suggest that the long-term administration of GBE could increase CYP2C9 activity and decrease CYP3A4 activity so that pharmacokinetics for the substrates of these enzymes might be altered.