Poster

[P27-4] P27-4: Cardiovascular drugs (1)

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[P27-4-4] Pharmacokinetics and hypoglycemic effect of cibenzoline in treatment with losartan or metoprolol in rats

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Background

Cibenzoline is well known to cause serious hypoglycemia through the enhancement of insulin secretion, and is often used with cardiovascular agents. Losartan and metoprolol have been reported to improve and decrease the insulin sensitivity, respectively. However, little is known about the interaction in the hypoglycemic effect of cibenzoline in the treatment with losartan or metoprolol. The objectives of this study are to assess in the pharmacokinetics and the hypoglycemic effect of cibenzoline after the treatment of losartan or metoprolol for 14 days in rats.

Methods

Male Wistar rats (9 weeks old) were used. Losartan (10 mg/kg/day) and metoprolol (5 mg/kg/day) were subconsciously treated to rats for 14 days via the osmotic mini pump. Sham operation was performed for the control study. On the 13 days after treatment, rats were fasted overnight, and then received an intravenous injection of cibenzoline (5-20 mg/kg). Blood samples were withdrawn from the formal artery at predose and the designated postdose intervals. Plasma glucose and insulin concentrations were measured by the mutarotase glucose oxidase method and the ELISA method, respectively. Plasma cibenzoline concentrations were determined by the LC-MS/MS method. The effect of losartan or metoprolol on the hypoglycemic effect of cibenzoline was investigated by the analysis of covariance.

Results

The plasma glucose concentration decreased significantly at 45 min after cibenzoline injection. The decreased glucose concentration was sustained dose-dependently. Losartan treatment significantly prolonged the hypoglycemic effect of cibenzoline, however metoprolol treatment did not influence. A rapid secretion and elimination of endogenous insulin in plasma was observed, depending on the dose of cibenzoline. Losartan treatment significantly suppressed the insulin peak level induced by cibenzoline. A two-exponential decline of cibenzoline concentration in plasma was observed. The dose-normalized plasma concentration indicated a nonlinear pharmacokinetics of cibenzoline. However, no obvious differences related to the losartan treatment were observed in the time courses.

Conclusions

Coadministration of cibenzoline and losartan might enhance the hypoglycemic effect of cibenzoline, although the plasma insulin concentration is suppressed. The trough concentration of cibenzoline would not predict the enhancement of hypoglycemic effect by losartan.