EFFECT OF COMBINATION TREATMENT OF AZELNIDIPINE ON ANTIOXIDATIVE ACTIVITY OF OLMESALTAN IN HUMAN VASCULAR ENDOTHELIAL CELLS

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[Purpose] Angiotensin II (AII) type 1 receptor blocker (ARB) and calcium channel blocker (CCB) are frequently used in the therapy of chronic kidney disease (CKD), because these antihypertensive agents exhibit the superior protective effects against organs such as kidney and cardiovascular tissues, via the antioxidative properties. However, the mechanism of antioxidant effect in combination with ARB and CCB is not fully elucidated. The aim of this study is to examine whether the combination of olmesartan (OLM) and azelnidipine (AZL) enhance the antioxidative activity, and to elucidate this mechanism using human umbilical vein endothelial cells (HUVECs).

[Methods] The effects of OLM, AZL or both on the oxidative stresses induced by uremic toxins, i.e., lipopolysaccharide, AII, indoxyl sulfate, and oxidized-human serum albumin were examined. Intracellular ROS generation was detected by the fluorescent probe CM-H2DCFDA.

[Results and Discussion] All uremic toxins increased ROS generation in HUVECs. The combination treatment with OLM and AZL more strongly decreased these ROS generation than either alone. Moreover these ROS productions were also suppressed by inhibitors, such as NADPH oxidase inhibitor, PKC inhibitor, and PI3K inhibitor. [Conclusions] We found that the combination of OLM and AZL was more effective antioxidative treatment in CKD, and the inhibition of the NADPH oxidase activity via PKC or PI3K might be involved in this processes.

PHARMACOKINETICS AND LIMITED SAMPLING STRATEGIES OF MOSAPRIDE IN RATS

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[Purpose] The objectives of this study were to characterize the pharmacokinetics of mosapride as well as develop limited sampling strategies (LSSs) for the estimation of mosapride area under the curve (AUC) in the rat.

[Methods] Rats received mosapride (1, 5, 10, 15 mg/kg) intravenously in the dose-linearity control groups. For the enzyme inhibition and induction groups, 5 mg/kg mosapride were administration to the rats after pretreatment with ketoconazole and dexamethasone, respectively. The plasma concentrations of mosapride were followed for 360 min, and the kinetics parameters were estimated by compartmental analysis. Multiple regression analysis was used to determine the LSSs. The AUC was the dependent variable and the timed concentrations were the independent variables.

[Results and Discussion] The disposition of mosapride in rats displayed two-compartmental characteristics. The kinetic parameters were linear in the dose range studied. In the ketoconazole treatment group, the AUC and the terminal half-life of mosapride increased about 4- and 2-fold, respectively. However, in the dexamethasone-pretreated rats the AUC and the terminal half-life of mosapride remained unchanged. A total of 38 rats’ profiles were randomly split into two groups. One group (N=28) was assigned as the index group and used to establish the limited sampling strategy. The other-validation group (N=10) was used to validate the developed LSSs. The AUC was the dependent variable and the timed concentrations were the independent variables.

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[Conclusions] The pharmacokinetics of mosapride in rats following bolus administration was linear. The systemic exposure of mosapride in rats, in terms of AUC, can be precisely predicted using LSSs with one to four concentrations.