Physiological and gene expressional alternation in obesity animal model for ADME/PK characterization

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Rosiglitazone is an anti-diabetic drug in the thiazolidinedione class of drugs as a peroxisome proliferator-activated receptor-γ agonist [1,2]. Rosiglitazone is known to be metabolized by CYP2C8 or CYP2C9 and biotransformed into N-desmethyl rosiglitazone (N-Dm-RSG) and p-hydroxy rosiglitazone (p-OH-RSG) [3]. Several animal models of type II diabetes mellitus have been used for the development of anti-diabetic agents, and ob/ob mouse is one of the typical models of type II diabetes with leptin-deficiency. This study was for the pharmacokinetic profiling of rosiglitazone and its metabolites, N-desmethyl rosiglitazone (N-Dm-RSG) and hydroxy rosiglitazone (OH-RSG) in an animal model of diabetes using ob/ob mice.

Male ob/ob (B6.V-Lepob/J) and control (C57/B6) mice were used for the pharmacokinetic study of rosiglitazone and its metabolites N-Dm-RSG and p-OH-RSG. Rosiglitazone (5 mg/kg dose) were administered by intravenous or oral administration and the blood were obtained at the time points from blank to 24 hr. Samples were analyzed by LC/MS/MS system with AB Sciex 4000 QTRAP and Agilent 1200 series HPLC system. Physiological characteristics were significantly different between control and ob/ob mice such as body weight and glucose levels. Pharmacokinetic profiles of rosiglitazone (RSG) and its metabolites, N-desmethyl rosiglitazone (N-Dm-RSG) and hydroxy rosiglitazone (OH-RSG) were plotted after 5 mg/kg dose by intravenous and oral administration in C57/B6 and ob/ob mice (Fig. 1). Area under the plasma concentration–time curve (AUC) levels were 50.8 ± 13.7 mg·hr/ml for control and 66.6 ± 11.8 mg·hr/ml for ob/ob mice, the maximum plasma concentrations (C max ) were 12.9 ± 1.7 mg/ml for control and 14.8 ± 1.9 mg/ml for ob/ob mice, and the time to maximum plasma concentration (T max ) were 0.42 ± 0.13 hr for control and 0.55 ± 0.27 hr for ob/ob mice. AUC values were not significantly different (50.8 ± 13.7 mg·hr/ml for control and 66.6 ± 11.8 mg·hr/ml for ob/ob mice). Pharmacokinetics of N-desmethyl rosiglitazone (N-Dm-RSG) in ob/ob mice was different from that in control C57/B6 mice. AUC levels of ob/ob mice were higher than that of the control C57/B6 mice after oral administration (5.4 ± 0.91 mg·hr/ml for control and

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9.1 ± 1.4 mg·hr/ml for ob/ob mice). Profiles of hydroxy rosiglitazone (OH-RSG) were not significantly different between ob/ob and control C57/B6 mice. The AUC values were 4.9 ± 1.8 mg·hr/ml for control and 3.7 ± 0.96 mg·hr/ml for ob/ob mice. This study is the first pharmacokinetic profiling of rosiglitazone and its metabolites in ob/ob mice as diabetic animal model.

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