Effects of Orotic Acid-Induced Non-alcoholic Fatty Liver on the Pharmacokinetics of Metoprolol and Its O-desmethyl Metabolite in Rats
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Purpose
In 1% orotic acid (OA) containing diet-induced non-alcoholic fatty liver disease (NAFLD) rats, significant decrease (by 31.4%) in dextromethorphan O-demethylase activity, which represents activity of rat CYP2D isoforms, was observed. As metoprolol is metabolized by CYP2D subfamily both in humans and rats, possible changes in the pharmacokinetics of metoprolol and its metabolite, O-desmethyl metoprolol (O-DMM), were examined in OA diet-induced NAFLD rats.

Methods
The pharmacokinetics of metoprolol and O-DMM were evaluated after intravenous administration of 1 mg/kg metoprolol to NAFLD rats and controls.

Results
The total area under the plasma concentration – time curve (AUC) of metoprolol in NAFLD rats after its intravenous administration was significantly greater than that in controls due to their slower non-renal clearance (CLNR). This was due to decreased hepatic metabolic clearance of metoprolol as a result of reduced hepatic blood flow and microcirculation in fatty liver. On the contrary to the preliminary study results of decreased CYP2D activity in NAFLD rats, comparable in vitro hepatic intrinsic clearance (CLint) values for the disappearance of metoprolol and formation of O-DMM were observed in control and NAFLD rats. Although the hepatic metabolic clearance of metoprolol in NAFLD rats was significantly slower than in controls, no significant change in plasma concentrations of O-DMM and AUC_{O-DMM}/AUC_{metoprolol} ratios was observed in NAFLD rats. These results suggest slowed elimination of O-DMM in NAFLD rats.

Conclusion
The study results suggest that caution is required regarding pharmacotherapy in NAFLD patients even in early stage. In cases where the drugs have intermediate to high hepatic extraction ratio, possible reduction in their perfusion-limited hepatic metabolism may result increase in their plasma concentrations.