A POSSIBLE MECHANISM FOR LIVER TOXICITY INDUCED BY BIRB-796, AN ORAL ACTIVE P38 MITOGEN-ACTIVATED PROTEIN KINASE INHIBITOR

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[Purpose] BIRB-796, a selective inhibitor of p38 mitogen-activated protein kinase, has entered clinical trials for the treatment of autoimmune diseases. Levels of alanine transaminase, a biomarker of hepatic toxicity in clinical pathology, were found to be increased in Crohn’s disease patients treated with BIRB-796. The purpose of the present study was to clarify the molecular mechanism(s) of this hepatotoxicity.

[Methods] We performed a toxicogenomic analysis using a highly-sensitive DNA chip, 3D-Gene™ Mouse Oligo chip 24k, and the glutathione-trapping method with mouse and human liver microsomes.

[Results and Discussion] BIRB-796 treatment activated the nuclear factor (erythroid-derived 2)-like 2 signaling pathway, which plays a key role in the response to oxidative stress. A reactive intermediate of BIRB-796 was detected by the glutathione-trapping method using mouse and human liver microsomes. BIRB-796’s hepatotoxicity may be induced by the production of this reactive metabolite in the liver.

[Conclusions] Considering these results, the reactive metabolite found in this study is probably involved in the hepatotoxicity caused by BIRB-796 treatment.

FLUVASTATIN CAUSES SEVERER HEPATIC INJURY AND MYOPATHY IN RATS FED A HIGH-FAT AND HIGH-SUCROSE DIET THAN A STANDARD DIET: ASSOCIATION WITH THE SUPPRESSION OF HEPATIC ORGANIC ANION TRANSPORTING POLYPEPTIDE 2

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[Purpose] We determined whether nutritional status affects statin-induced adverse effects using rats fed a high-fat and high-sucrose (HF) diet or a standard diet (SD diet).

[Methods] To determine whether nutritional status affected the overall hepatic elimination of fluvastatin and caused systemic exposure to fluvastatin to increase, we determined effects of fluvastatin on the expression of drug transporters and drug-metabolizing phase I and II enzymes in the SD or HF diet-fed rats.

[Results and Discussion] Rats that consumed a high-fat and high-sucrose (HF) diet developed hepatic steatosis. Treatment with fluvastatin (8 mg/kg) ameliorated hypertriglyceridemia and hepatic steatosis in rats on a standard (SD) diet, but caused an elevation in levels of plasma aspartate aminotransferase and creatine kinase activities, leg muscle weakness and myositis in those on the HF diet. Oatp1, Mrp3, CYP1A, CYP2C, and UGT2B1 protein levels were moderately decreased and CYP3A and Oatp2 mRNA and protein levels were markedly suppressed by fluvastatin, while Mrp2, Mdr1b, UGT1A1, and UGT1A5 protein levels were not significantly changed.

[Conclusions] These results indicate that nutritional status may influence the adverse effects of fluvastatin, and inhibition of transporter-mediated hepatic uptake in the HF diet-fed group may have resulted in suppression of fluvastatin’s elimination.