METABOLISM OF IBUPROFEN IN CHIMERIC MICE WITH HUMANIZED LIVER

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[Purpose] Ibuprofen (IBP), which is a widely used nonsteroidal anti-inflammatory drug (NSAID), is a 2-arylpropionic acid derivative. Remarkable species and strain differences in the metabolic pathways of IBP have been reported. In humans, a major metabolite of IBP is acyl glucuronide, whereas in rats the main metabolite is 2'-hydroxy IBP. In this study, we examined whether chimeric mice with human hepatocytes (human-chimeric mice), which have more than 70% human hepatocytes in their liver, are useful for the prediction of human metabolism of IBP.

[Methods] IBP was orally administered to human-chimeric mice and Slc:Wistar/ST rats, and 24 hour urine was collected. The urine samples were subjected to solid phase extraction, and IBP and its metabolites were quantitated by means of LC/MS/MS.

[Results and Discussion] In Slc:Wistar/ST rats, the main metabolite of IBP was hydroxy-IBP and no unchanged IBP was detected in urine. The glucuronide and the taurine-conjugate of hydroxy-IBP were observed. In human-chimeric mice, the glucuronide of IBP was detected as the main metabolite. IBP and the taurine conjugate of IBP were also formed. The metabolic profile of IBP in human-chimeric mice was similar to reported data in humans.

[Conclusion] Human-chimeric mice showed human-type metabolism of IBP.

EVALUATION OF A DRUG’S METABOLIC STABILITY AND STRUCTURE ANALYSIS OF ITS METABOLITES BY MULTIPLE REACTION MONITORING

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[Purpose] In drug candidate screening, metabolic stability evaluation of a drug and structure analysis of the drug’s metabolites are conducted. The purpose of the former is to select metabolically stable compounds and the purpose of the latter is to design drugs by determining dominantly metabolized portions of drug candidate compounds. Hence, it is desirable to have the metabolic stability of a candidate compound and the structures of its metabolites analyzed through a single measurement. In this study, we tried to obtain structural information on metabolites while intending to acquire metabolic stability data at the same time.

[Methods] In vitro metabolism of Imipramine and Atorvastatin were performed using Rat liver microsomes. The MRM method was constructed as follows: First, in order to evaluate metabolic stability, MRM transitions were constructed, measuring the unchanged compounds and internal standard. Next, another MRM transition was constructed by taking the mass shift value based on the measured response of predicted phase I metabolites, and adding this to the m/z value of the three fragment ions originating from the unchanged compounds. Finally, these MRM transitions were combined. Metabolite samples were analyzed by LC/MS/MS using the MRM method, including the above-mentioned MRM transitions. The percent remaining of the unchanged compounds was calculated, and the structures of their metabolites were analyzed after searching for the metabolites.

[Results, Discussion and Conclusions] The percent remaining for both Imipramine and Atorvastatin was calculated. Both structural information and quantitative changes of the metabolites were obtained. The results suggested that MRM is useful in evaluating drug candidates and their metabolites both quantitatively and qualitatively during the screening.