Evaluation and application of drug-induced toxicity using experimental animals

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Regarding the in vivo drug-induced toxicity, the production of reactive metabolite (s) is considered to be an initiation reaction for both intrinsic- and idiosyncratic-type of toxicity. GSH content in kidney, heart and muscle is much lower than in liver, lung and spleen in normal rodents. GSH levels in the kidneys and muscles decrease rapidly by drug administration and recover slowly. A series of animal models that have established and utilized for drug-induced toxicity by reducing the scavenge ability by administering GSH synthase inhibitor L-buthionine-(S, R)-sulfoximine (BSO) to experimental animals will be introduced. (1) BSO was administered to normal mice for 7 days, an acute kidney injury model was established, and this model was able to detect the renal damage of the drug with high sensitivity. (2) A mouse model of rhabdomyolysis was established using a combination of a new quinolone antibiotic and a statin and a combination of a fibrate and a statin. This required the use of BSO, and became a test system that could assess the risk of drug-interaction with statins. (3) In the liver injury model in mice, the involvement of immune/inflammation-related factors is clear, but in rats it is unclear and liver damage is unlikely to occur. Therefore, in rats, combined use of BSO is necessary to induce liver injury. (4) GSH-conjugation of acyl glucuronide metabolites was inhibited by BSO, indicating that acyl glucuronide metabolites were involved in vivo in renal injury. Although there are still unclear about idiosyncratic drug-induced organ damage in humans, information from in vivo animal models will be useful for future research.
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