DEVELOPMENT OF CATEGORY APPROACH MODEL TO PREDICT CHEMICAL HEMATOTOXICITY
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[Purpose] It becomes very difficult to assess the hazard of general chemicals by animal tests, because of animal protection movement, time and costs. In this study, we developed the category approach model for the hematotoxicity in the repeated dose toxicity endpoints by identifying molecular level mechanism including initiating events.

[Methods] The toxicological findings were organized from reports of repeated-dose test on rats. The mechanism information of hematotoxicity was collected from published references. We focused on the chemicals showed the hemolysis with methemoglobin (Met-Hb) formation at first, and collected the chemicals group showing same mechanism, which is the basis of the prediction by category approach. The validation of the category approach model was performed.

[Results & Discussion] The hemolysis accompanying Met-Hb mechanistic model was developed based on 3 individual mechanisms, such as initiating by hydroxylamine, benzoquinone imine or chlorophenol derivatives. This mechanistic model was successfully validated using two substances which are contained in the group of the hemolysis accompanying Met-Hb formation.

[Conclusions] The validation of the category approach model for the hemolysis with MetHb formation successfully achieved. And it would lead to predict the potential toxicities of untested chemicals due to same mechanism.

SEARCH OF FACTORS AFFECTING PHARMACOKINETIC BEHAVIOR INDUCED BY MULTI-DRUG REGIMENT OF PSYCHOTROPIC DRUGS. –ROLE OF CYTOCHROME P-450 AND MATE1–
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[Purpose] Triazolam (TZ) and diazepam (DZ) are commonly prescribed for the treatment of psychotic disorders, but are known as the abuse of drugs. Intoxication associated with overdose of multiple psychotropic drugs containing TZ and DZ has been frequently reported. The first purpose is to search the factors affecting pharmacokinetic behavior induced by overdose of TZ and DZ.

[Methods] The levels of TZ, DZ and their metabolites in each tissue were determined by LC-ESI-MS/MS, after TZ in combination with DZ was administered to mice. The interaction with TZ and DZ was examined using human recombinant CYP3A4 and CYP2C19, or liver microsome of human and mouse. Further, the affinities of TZ, DZ and their metabolites for MATE 1 and P-glycoprotein were measured using hMATE1- expressing Xenopus laevis Oocytes and Caco-2 cells.

[Results and Discussion] The levels of TZ and DZ in each tissue of mice treated with the combination of TZ and DZ were increased. The transport of TZ, DZ and their metabolites into the brain was increased and the elimination of them from each tissue was delayed. When the activity of DZ for CYP2C19 was saturable, CYP3A4 was mainly involved in the oxidation of DZ. Therefore, the oxidation of TZ was inhibited in liver microsome of human and mouse. On the other hand, TZ, DZ and their metabolites had the low affinities for P-gp, whereas they were the moderate substrates for MATE1. Accumulation of TZ, DZ and their metabolites in each tissue was observed, suggesting that MATE1 may not play an important role in the renal tubular secretion of them.