QUANTITATIVE DETECTION OF REACTIVE METABOLITES USING FLUORESCENCE-TAGGED GLUTATHIONE
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Reactive metabolites (RM) have been often reported to be involved in expression mechanisms of drug-induced toxicities. In particular, the occurrence of idiosyncratic drug toxicity (IDT) is a great concern for clinical drug development and the most frequent cause of post-marketing attrition and withdrawals. It has therefore become important to minimize the formation of reactive metabolites to avoid the potential toxicity and overall attrition. Recently, an outstanding system for quantitative detection of RM using dansylated GSH (dGSH) as a trapping agent was reported by BMS's group. We have customized the methodology and then optimized further for accurate quantification of RM.

**Methods:** Fluorescence (FL) intensity of dGSH was measured in mixtures of 0.1% v/v aqueous HCOOH-MeCN at various content of MeCN (5% step, from 0 to 100%). Known problematic compounds (100 µM) associated with RM formation were incubated for 30 min at 37ºC in the pooled human liver microsomal system in the presence of dGSH (1 mM). The aliquots of incubation mixtures were analyzed by FL-HPLC.

**Results:** FL intensity of dGSH increased with the content of MeCN and needs to be corrected. We found that FL intensity was almost in proportion to MeCN content in a range of 30% to 70%, and it enabled us to quantify adducts using a calibration curve in combination with a linear FL correction in the range. Using the customized methodology, RM-dGSH formation from troglitazone, diclofenac and indomethacin were quantified to be 21.9 ± 0.41, 3.76 ± 0.56 and 0.179 ± 0.021 pmol/min/mg protein, respectively.


POPULATION PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF A GROWTH HORMONE RECEPTOR ANTAGONIST, PEGVISOMANT, IN JAPANESE AND WESTERN ACROMEGALY PATIENTS
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Pegvisomant is a new growth hormone receptor antagonist used for the treatment of acromegaly. In the current dose regimen, dose adjustments are recommended based on individual serum IGF-I levels in order to maintain the serum IGF-I concentration within the age-adjusted physiological normal range. A PPK/PD model for pegvisomant was established, based on the pooled data obtained from the Japanese and Western acromegaly patients (n=169). We reported in the 20th JSSX that the PPK of pegvisomant was best described by a model that incorporates saturable elimination. The objective of this study was to estimate the baseline (E₀), ratio of maximal decrease in IGF-I concentration (Emax) and concentration of pegvisomant corresponding to 50% of the maximal effect (IC₅₀) of pegvisomant after subcutaneous doses and to determine demographics and clinical covariates that affect pegvisomant PD. Population analysis were performed using NONMEM software (version V, level 1.1). The PK profiles of pegvisomant were described with a 1-compartment infusion model. Covariates assessed were race, sex, age, body weight, ALT, AST, alkaline phosphatase, baseline IGF-I, baseline GH and concomitant medications. The final model could accurately describe the relationships between pegvisomant concentrations and IGF-I inhibition. Baseline GH significantly affected IC₅₀ and E₀, indicating that pegvisomant IC₅₀ and E₀ increased with baseline GH. No significant relationship was found between race and pegvisomant PD parameters. These results suggest possibility of use of the same dosage and administration in Japan as in the EU and in the US.