SCIENTIFIC ABSTRATCS

Accelerated Cytotoxicity Mechanism Screening

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By discovering how chemical compounds/xenobiotics cytotoxicity is affected when their metabolic pathways are inhibited or activated, the metabolic pathways that activate versus detoxify chemical compound can be identified. Reactive metabolites contributing to cytotoxicity can also be identified. In this lecture, the pretreatment of inhibitors and activators of xenobiotic metabolizing enzymes as well as other xenobiotic cellular targets in freshly isolated rat hepatocytes for the accelerated cytotoxicity mechanism screening (ACMS) of xenobiotics (a technique used in our laboratory) are discussed. This technique is useful for determining toxicity mechanisms. The inhibitors/ activators have been selected on the basis of their selectivity, modulator effectiveness, and their lack of toxicity. The use of these inhibitors/activators with other cells or subcellular fractions (e.g. mitochondria) for assessing target organ toxicity mechanisms is also reviewed.

Keywords: Cytotoxicity; Enzymes; Xenobiotics

Pharmacokinetic/Pharmacodynamic (PK/PD) Relationship-based Approach to Understand the Variability of Central Neurological Effects of Ethanol

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Pharmacokinetic/pharmacodynamic (PK/PD) relationships describe the quantitative relationships between the drug-induced effects and the concurrent corresponding drug concentrations in an individual. Since a long time, rough qualitative relationships have been described between neurological presentation and plasma ethanol concentration in acute ethanol ingestion. However, to date, precise quantitative PK/PD relationships have not been extensively studied. We studied PK/PD relationships in ethanol poisonings. Plasma concentrations were measured using an enzymatic assay. Coma depth was assessed using the Glasgow Coma Scale (GCS). Non-linear regression was used for modeling PK/PD relationships. The PK/PD relationships were well fitted with the sigmoidal Emax model. A maximal toxic effect (GCS of 3) was associated with a wide range of plasma ethanol concentrations, suggesting the saturation of drug targets at high doses. During the course of poisoning, the relationships between the depth of coma and the corresponding plasma concentrations were of sigmoidal shape. The elevated values of the Hill coefficient showed that a small decrease in plasma concentrations near the EC50 was associated with a dramatic improvement in the level of consciousness. In chronic alcoholic patients, EC50 was higher than in non-tolerant. Analyzing blood concentrations with respect of the delay elapsed since the ingestion may help predicting the time of awakening and thus the evaluation of outcome. In conclusion, PK/PD relationships are helpful in suggesting mechanisms of inter-individual variability of central neurological response to ethanol.

Keywords: Alcoholic Neuropathy; Pharmacokinetics; Pharmacodynamics; Ethanol