2013-14

Rajnibhai V. Patel
PharmInnova Award
Best M. Pharm Thesis

WINNER

Runner-Up

Mr. Lokesh Yadav

Research Guide

Dr. G B Jena

Subject:
Pharmacology

Thesis Title :
Influence of 3-Aminobenzamide, a Poly (ADP-Ribose) Polymerase Inhibitor on Genotoxicity & Cytotoxicity: A Study with Selected Mutagens in Mice

College:
NIPER, SAS Nagar, Punjab

Rapid process to identify drugs which are toxic for genes

Outcome of Research:

During drug development process, every new chemical entity has to be screened for its toxic effects on genes and cells. This research has proposed a novel and effective approach for rapid identification of genotoxins (toxic agents for the genes) in the drug development process. The investigators claimed that genotoxicity of the compounds can be enhanced by pretreatment of the compound with a chemical moiety (3-AB, a PARP inhibitor). The concept can be used in preclinical studies of weak genotoxins to yield safer compounds for clinical use. With further validation this approach can be used to detect DNA damaging potential of pollutants/short-lived metabolites, which produce conflicting results in different testing models.

Thesis Title: Influence of 3-Aminobenzamide, a Poly (ADP-Ribose) polymerase inhibitor on genotoxicity and cytotoxicity: Study with selected mutagens in mice

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ABSTRACT

Genotoxicity testing of new chemical entities is an integral part for the preclinical drug development process. Improvement in the detection limit and sensitivity of genotoxicity assays is required, as the standard test battery concept fails to detect some carcinogens (non-genotoxic) and weak genotoxins. Genetic toxicologists are continuously making efforts for the improvement in the detectable limits, sensitivity and scoring methodology. The ultimate aim of improving the sensitivity is to detect the marginal genotoxins, which are not easily detectable with acute doses in preclinical studies due to physiological self-defence system i.e., DNA repair processes. But in chronic exposures these marginal genotoxins overweighs the physiological defence system and produce DNA damaging effects. One of the key defence systems involved is the DNA repair system (including Poly (ADP-Ribose) Polymerase: PARP) and several reports highlighted that end-point of genotoxicity assays is influenced by DNA repair mechanisms. Thus, with the inhibition of PARP (chemically by 3-Aminobenzamide, a prototype PARP inhibitor: 3-AB), the physiological defence system can be compromised. To prove the present hypothesis, 3-AB (30 mg/kg), was used to evaluate the DNA damaging potential of zidovudine (AZT, 400 mg/kg), doxorubicin (DOX, 5 mg/kg) and cyclophosphamide (CP, 50 mg/kg) and sucrose (SUC, 3 gm/kg as negative control) in Swiss female mice. The endpoints of evaluation include micronucleus assay, comet assay, chromosome aberration assay and immunohistochemistry of PARP-1 as well as phosphorylated histone H2AX (γ-H2AX), along with cytotoxicity assessment by DNA fragmentation assay, TUNEL assay and histology. Results of the present study clearly demonstrate that the genotoxicity and cytotoxicity (apoptosis) has been significantly increased in the combinations (3-AB+AZT, 3-AB+DOX and 3-AB+CP) in comparison to the respective controls (AZT, DOX and CP). There was no increase in the genotoxicity per se with SUC, 3-AB and 3-AB+SUC in comparison to saline control. The correlation analysis suggests that all the genotoxicity assay parameters are well correlated with each other. Present study clearly indicates that, in the presence of 3-AB the genotoxicity signals of weak genotoxin can be successfully detected. With an increased sensitivity, compounds that are marginal or weak genotoxins can be successfully screened. Further, cytotoxicity for many target organs can be enhanced in pathological conditions by the intervention of PARP inhibitor, as it leads to apoptotic cytotoxicity of the cells responsible for the disease