ONLINE MODE

M.Sc. SEMESTER III ONLINE EXAMINATION, 2020
TOXICOLOGY
Paper – MTX DCE302

PAPER TITLE : PRE-CLINICAL TOXICOLOGY FOR DRUG DEVELOPMENT

Time : Two Hours *Maximum Marks : 37*

Attempt all questions. All parts of a question must be attempted in continuation. Start answer of a fresh question on a new page. Cite examples and draw labeled diagrams wherever necessary

Question No. 1: **[07x1=07]**
Briefly answer the following

a) MABEL
b) Therapeutic Index
c) MRSD
d) F2 generation
e) DRF
f) NOEL and NOAEL
g) MTD

Question No. 2:

Answer any THREE of the following: **[05x3=15]**

a) What is the role of GLP in toxicology studies?
b) What ethical principles are applied in the use of animals in toxicology?
c) Describe a scheme for clinical examination of animals.
d) Discuss use of rabbits in toxicity studies.
e) Describe single dose toxicity study requirements according toNew Drugs & Clinical Trial Rules (2019).

Question No. 2:

Answer any THREE of the following: **[05x3=15]**

a) Exploratory toxicity screening was done in the mouse, rat and dog for a test compound. All species had similar tolerability to dose based on a surface area (mg/m^2) conversion. Bioavailability assessment was done in the mouse, rat, dog and monkey and the data shows rat > mouse = dog >> monkey. In vitro metabolism was done in liver microsomes from the mouse, rat, dog, monkey and human. The data show that all preclinical species produced similar major metabolites to humans, but the dog had one identified major metabolite that was approximately 30% higher than the other species. Discuss selection of species for GLP Toxicology studies.
b) The NOAEL of a new retinoid, Etretinate, was found to be 50 mg/kg/day in rats and 2 mg/kg/day in dogs. Considering the rat-to-human conversion factor is 0.162

and dog-to-human conversion factor as 0.541, calculate the Maximum Recommended Starting Dose (MRSD) in 60 kg man using safety factor of 1/10.

c) A significant increase in induced mutant frequency was observed after 4-hour exposure with metabolic activation at the highest evaluable concentration tested at 40 microgram/ml of lofexidine HCl. Lofexedine is being developed as an antidepressant drug that could be administered for many months to years in the treatment of the disease. As the toxicologist responsible for the decision making, what toxicology studies will you plan in view of the above findings?

d) Aminoglycosides are a group of antibiotics which are administered once daily at high doses and have been known to produce nephrotoxicity and ototoxicity. A new aminoglycoside molecule plazomicin is being developed and as an expert in toxicology, what tests will you recommend to evaluate nephrotoxicity and ototoxicity of the drug?

e) In rats, plasma ALT and AST levels were elevated approximately 2 fold elevated when 10mg/kg dose of atorvastatin, a lipid lowering agent was added to the diet but no changes occurred in CPK and LDH. In chronic toxicity study in rats (2 weeks to 52 weeks), the target organs affected by atorvastatin was liver and hepatocellular atypia was observed at the dose of 70mg/kg dose at week 26. What safety precaution must be observed when prescribing atorvastatin in humans? The usual dose of atorvastatin is 20-40 mg/day for a 60 kg man.

It should be noted that 40 minutes extra time will be provided to scan your answer sheets, build a PDF and uploaded it.

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