شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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and Geological Sciences

COMPARATIVE CYTOLOGICAL, CYTOGENETICAL AND MOLECULAR STUDIES ON THE EFFECT OF TAMIFLU AND ADAMINE ON MALE ALBINO MICE.

**A THESIS SUBMITTED FOR
THE AWARD OF THE Ph.D. DEGREE FOR TEACHER PREPARATION IN SCIENCE (ZOOLOGY)**

BY

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ABSTRACT

Tamiflu and Adamine are anti-viral drugs and clinically used for the treatment of influenza. Hence, the present study was carried out to evaluate and compare the probable impacts of two of the anti-viral drugs on bone marrow chromosomes and liver of adult male albino mice from the cytogenetical, histological and ultrastructural points of view.

In order to achieve these intended goals, the experimental design was carried out in the following manner: one hundred fifty adult male albino mice were used in the present study. They were allocated into ten equal groups. The first group served as control group and each animal was orally treated with saline solution (0.9 % NaCl), and the second, third and fourth groups were treated orally with 16 mg/kg b.wt. of Tamiflu daily for five, ten and fifteen days, respectively. While, each animal from the fifth, sixth and seventh groups received orally 20 mg/kg b.wt. of Adamine daily for five, ten and fifteen days, respectively. The animals of eighth, ninth and tenth groups were treated orally with 16 mg/kg b.wt. of Tamiflu in addition to 20 mg/kg b.wt. of Adamine daily for five, ten and fifteen days, respectively.

ABSTRACT

Treatment of male albino mice with Tamiflu and Adamine separately and simultaneously induced bone marrow structural chromosomal aberrations. These aberrations were constituted of centromeric attenuation, deletions, fragments and ring chromosomes, end to end association and centric fusion exhibiting a statistically highly significant increase ($P < 0.001$) after treatment with both drugs simultaneously for ten and fifteen days, while all aberrations were exhibiting a statistically significant increase ($P < 0.05$) after treatment with Tamiflu for five days in comparable with the control group. The results of the total structural chromosomal aberrations were significantly time- dependent manner.

The results of this study in all treated groups recorded decrease in the mitotic index of bone marrow cells after administration of Tamiflu and Adamine separately and simultaneously for five, ten and fifteen days in comparable with control group, the decrease of mitotic index was time-dependent.

Micronucleus assay results showed that Tamiflu and Adamine treatment induced genotoxicity in bone marrow cells, and the number of micronucleated polychromatic erythrocytes (MnPCEs) was gradually increased significantly ($p < 0.05$) by the increase of time in all treated groups when compared to the

control one. Also, cytotoxicity test showed that the ratio of polychromatic erythrocytes/normochromatic erythrocytes was decreased significantly ($p < 0.05$) after fifteen days of treatment with Adamine and Adamine concurrently with Tamiflu when compared to the control one.

The current results of comet assay indicated that treatment with Tamiflu and Adamine separately or together significantly ($p < 0.001$) increased DNA damage in the liver cells. This effect was time dependent as compared with control group.

Results of quantitative real time reverse transcriptase polymerase chain reaction **(**qRT-PCR**)** analysis showed that, treatment with Tamiflu decreased the gene expression of BAX gene in liver after five and ten days, while the treatment with Adamine increased the gene expression of BAX in liver in comparison with control one. There was an increase in BCL-2 gene expression in hepatocytes of all treated groups except treatment with Adamine for five days.

Histological examination of liver of treated mice with Tamiflu and Adamine included enlargement and congestion of central and hepatic veins in addition to erosion of their endothelial lining cells, cytoplasmic vacuolation of

hepatocytes, pyknosis of their nuclei and dilatation of blood sinusoid.

The electron microscopical investigation of the hepatocytes of treated mice illustrated cytoplasmic vacuolation, mitochondrial swelling, fragmented rough endoplasmic reticulum, the nuclei of some hepatocytes had irregular envelope and condensed heterochromatin, dilated microvilli in sinusoid, in addition to the appearance of active Küpffer cells with many lysosomes and filopodia in their membrane.

Key words: Tamiflu, Adamine, Chromosomes, Comet assay, Histology, Liver, Micronucleus, qRT-PCR, Ultrastructure.

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