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Genotoxic Effect of Tricyclieandidepressant Drug “Clomipramine Hydrochloride’ on Somatic and Germ Cells of Male Mice

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Abstract : Clomipramine hydrochloride is one of the most used tricyclic antidepressant drug in Egypt. This drug contains in its chemical structure on two benzene rings. Benzene is considered to be toxic and clastogenic agent. So, the present study was designed to assess the genotoxic effect of Clomipramine hydrochloride on somatic and germ cells in mice. Three dose levels 0.195 (Low), 0.26 (Medium), and 0.65 (High) mg/kg.b.wt. were used. Seven groups of male mice were utilized in this work. The first group was employed as a control. In the remaining six groups, each of the above doses was orally administrated for two groups, one of them was treated for 5 days and the other group was given the same dose for 30 days. At the end of experiments, the animals were sacrificed for cytogenetic and sperm examination as well as histopathological investigations by using hematoxylin and eosin stains (H and E stains) and electron microscope. Concerning the sperm studies, these studies were confined to 5 days treatment with different dose levels. Moreover, the ultrastructural investigation by electron microscope was restricted to 30 days treatment with drug doses. The results of the dose dependent effect of Clomipramine showed that the treatment with three different doses induced increases of frequencies of chromosome aberrations in bone marrow and spermatocyte cells as compared to control. In addition, mitotic and meiotic activities of somatic and germ cells were declined. The treatments with medium or high doses were more effective for inducing significant increases of chromosome aberrations and significant decreases of cell divisions than treatment with low dose. The effect of high dose was more pronounced for causing such genetic deleterious in respect to effect of medium dose. Moreover, the results of the time dependent effect of Clomipramine observed that the treatment with different dose levels for 30 days led to significant increases of genetic aberrations than treatment for 5 days. Sperm examinations revealed that the treatment with Clomipramine at different dose levels caused significant increase of sperm shape abnormalities and significant decrease in sperm count as compared to control. The adverse effects on sperm shape and count were more obviousness by using the treatments with medium or high doses than those found in treatment with low dose. The group of mice treated with high dose had the highest rate of sperm shape abnormalities and the lowest proportion of sperm count as compared to mice received medium dose. In histopathological investigation, hematoxylin and eosin stains showed that, the using of low dose of Clomipramine for 5 or 30 days caused a little pathological changes in liver tissue. However, using medium and high doses for 5 or 30 days induced severe damages than that observed in mice treated with low dose. The treatment with high dose for 30 days gave the worst results of pathological changes in hepatic cells. Moreover, ultrastructure examination revealed, the mice treated with low dose of Clomipramine had little differences in liver histological architecture as compared to control group. These differences were confined to cytoplasmic inclusions. Whereas, prominent pathological changes in nuclei as well as dilated of rough Endoplasmic Reticulum (rER) were observed in mice treated with medium or high doses of Clomipramine drug. In conclusion, the present study adds evidence that treatments with medium or high doses of Clomipramine have genotoxic effects on somatic and germ cells of mice, as unwanted side effects. However, the using of low dose (especially for short time, 5 days) can be utilized as a therapeutic dose, where it caused relatively similar proportions of genetic, sperm, and histopathological changes as those found in normal control.

Keywords : clomipramine, mice, chromosome aberrations, sperm abnormalities, histopathology
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