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FULL PAPER

Cytogenetics Influences of Domperidone on Male Mice *Mus Musculus*

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Abstract:

Domperidone is drug has opposing effects to dopamine and has different pharmaceutical benefits, like vomiting trigger zone inhibition , relaxation of smooth muscle and stimulating lactation. This study aimed to estimate toxicity of domperidone by using mitotic index and micronucleus tests. These tests were served as indicators to investigate Domperidone cytotoxicity and genotoxicity in male mice. In this research we can concluded that domperidone inhibits cell growth, reduce cell viability and has no potential genotoxic effect. Domperidone caused anoticeable decrease in mitotic index and no strong effect on micronuclei.

Keywords
Domperidone, Mitotic index test, Micronucleus test

Introduction

Domperidone is drug that has opposing effects to dopamine has various pharmaceutical effects , like vomiting trigger zone inhibition, smooth muscles relaxation and lactation stimulation(Zhao *et. al*., 2020). The action mechanism of domperidone is that domperidone acts as a gastrointestinal emptying adjunct and peristaltic stimulant. Domperidone gastroprokinetic properties back to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and lowering pressure of esophageal sphincter. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier (Murugaiyan,2017). This medication was chosen for study its genetic influences because of its wide use around the world and its multiple uses. The other aim of study was many countries restricted using this medication and added a warning and other ban it due to an increasing in risk of various serious cardiac effects.(EMA, 2013 ; Health Canada, 2015; Administration FDA, 2004). So, we ran this study to test the cytotoxic and genotoxic effect of dompridone in mice male For further confirmation of its safety on the other side there are studies proposed that domperidone has antitumor activity (Shakya *et. el*., 2023) . The micronucleus assay (MN) has become one of the most important and widespread tests to estimate genotoxic effects of different physical and chemical factors, including DNA damage caused by ionizing radiation(Sommer *et. el*. ,2020). Because of its weight of evidence, invivo testing technique propel more alertness in the domain of genotoxicity. (Alexander 2021)defined micronuclei as tiny membrane restricted compartments with DNA content surrounded by a nuclear membrane split up from the primary nucleus. Micronuclei associated with genomic rearrangements, chromosomal instability, and mutation. micronuclear DNA serves as a complex genome rearrangements source and promoting asignalling enzeme in human that controls cytosolic DNA immunue sensing (cyclic GMP–AMP synthase ; cGAS)-mediated that may contribute to cancer dissemination. Cumulation of MN can served as a bioindicator of genotoxic stress and chromosomal instability in human and non-human pattern. The MN test has become commonly used to estimate chromosomal aberrations induction, which is one of major endpoints of mutageneses. There is no doubt that this test is more essential in risk assessing than other tests such as invitro assay to mammalian chromosomal aberrations . At the present, as yet animal studies are serious for assessment of physical and chemicals factors safety (Vanparys *et. el*., 1985). Percentage of cells in mitosis at any phase defined as mitotic index supply a

measure of cell ability of cells to split and division rate of the cell. It is used to determine growth sites within a tissue and which cell type are spliting of cells (Richard, 1983).

Domperidone's effective dose for the individual should be as low as feasible (commonly 30 mg/day). If necessary,Physician can increase daily oral dose to Maximum limit to 40mg.The treatment duration for vomiting and sever nausea treatment should not last more than a week.(domperidone Datasheet ,2023). Danger of sudden cardiac death and arrhythmias increases with Dosages greater than 30 mg/kg daily in patients domperidone users (Health Canada ,2012) . Domperidone occasionaly utilized as a galactogogue to increases milk production.(Yvonne *et. el.*, 2012) and it is utilized to motivate lactation in transgender and adoptive women.(Jeremy *et. el.*,2023)

Materials

In this investigation fourty male *mus musculus* strain mice age 6-10 weeks average body weight 25-30 gm were used in this study. Mice were housed in aseperate metal cages and they maintained optimum environmental and nutritional conditions during the experiment period and for seven days prior.

Methods

The study was performed on 40 male. Animals were maintained under temperature (25 C°) and 12\12h light\dark for two weeks befor conducting the tests. The experimental animals were divide into two large groups consist of 20 healthy mice males ; one of them used in micronuclei assay and the other to determine mitotic index.Each group divided into four subgroups, administrated orally each group consists of five mice the first group received a dose 0, the second group received 30 mg/kg the third group received 60 mg/ kg and the last group administered with dose 120 mg/ kg. The micronucleus assay was conducted by killing animals after 18 hr. after dosing, the test was conducted according to the protocol followed by (Schmid , 1975). In mitotic index test animals were killed after 24 hr. from dosing, and injected with cholchecin before 2 hr. from killing. cholchecin was prepared at a concentration of 0.05 and then injected into each animal, the test conducted according to(Brusick,1980)

Dose preparation

Domperidone tablets were crushed into powder and suspended in corn oil. Mice dosed with 0,30,60,and 120 mg/kg. The domperidone suspension prepared freshly and directly administrated. The dose calculated as mentioned in (Pandy, 2020).

Statistical analysis

All data of this study were presesnted as mean ± standard deviation (SD). The program used to assess statistical analysis was SPSS 20.0. $P < 0.05$ was identified as significant statistically symbolled * , and $P < 0.01$ symbolled ** represented significant at $P < 0.01$.

Results

In this research , the cytotoxic and genotoxic effects of domperidone have been identified by using micronuclei(MN) and mitotic Index(MI). Table (1) Explain the differences between negative control and other groups . This table shows no significant differences between negative control and 30 mg/kg (3.10 ± 0.756). Significant differences when the dose increased to 60 mg/kg at $p < 0.05$ (6.10 ± 0.831) and 120 mg/kg at $p < 0.01$(7.70 ± 0.644).

Table (1): Mean differences of the values of Mitotic index in bone marrow cells of white mice in the 0 , 30, 60, 120 mg/kg groups

Groups	Mean ± Std Error
Negative control	9.85 ± 0.437
Domperidone 30 mg/kg	3.10 ± 0.756
Domperidone 60 mg/kg	6.10 ± 0.831*
Domperidone 120 mg/kg	7.70 ± 0.644 **

(paired- samples t-test) *Significant at p < 0.05, ** significant at p < 0.01

Table (2) explain differences in micronucleated poly chromatic erythrocytes and micronuclei. The occurance of MNPCE found in dose 30, 60, and 120 mg/kg in treated mice male and its numbers were close from ngative control values.

Table (2): Mean differences of the values of Micronuclei in cells of bone marrow of white mice in negative , 30, 60, 120 mg/kg groups

Groups	PCE analysed	Mean ± Std Error
Negative control	20000	3.00 ± 0.316
Domperidone 30 mg/kg	20000	0.4 ± 0.748
Domperidone 60 mg/kg	20000	1.60 ± 0.748
Domperidone 120 mg/kg	20000	2.20 ± 0.916

(paired- samples t-test) *Significant at p < 0.05, ** significant at p < 0.01

Discussion

Results of this research indicate that domperidone inhibited growth of cells and reduced viability of cells these data show its cytotoxic effects on these cells., which consistent with (Shakya *et. el*.2023) who conducated astudy on Domperidone antitumor activity in breast cancer cells and demonstrated that domperidone downregulated the expression of cyclins and CDKs, mitochondrial apoptotic pathway activation , increasing of mitochondrial superoxide generation, causing inhibition in STAT3 and mentioned that there is no study reporting the cytotoxic effect of

domperidone on cancer cells and his team research is the first on the anticancer activity of domperidone in human TNBC BT-549 and CAL-51 cells. . These findings raise an intriguing possibility: targeting DRD2 with domperidone could potentially be an effective strategy for treating TNBC cells . (Yuan *et. el*. 2024) reported that domperidone caused reducing in growth and viability of cells in a time-dose-dependent manner and there are pointers that domperidone may have anti-cancer property, also mentioned that domperidone inhibited significantly proliferation of Esophageal squamous cell carcinoma (ESCC) in vivo and in vitro. ,these finding consistent with our study.

According to(Vanparys *et. el*., 1982) domperidone did not cause mitotic arrest and chromosomal damage invitro in human lymphocytes and invivo in bone marrow and germ cells of mice. In agreement with prior results all of these research indicated negative finding for domperidone genotoxic effect as (Vanparys *et. el*., 1985) noted that in their research , so that it can be concluded that domperidone has no ability to induce gene mutations or chromosome abberations. (Murugaiyan, 2017) mentioned that domperidone and excipients compatibility shows no chemical or physical interaction between drug and excipients. A research has shown that patients with schizophrenic treated with dopamine receptor antagonists such as domperidone have lower incidents of cancers (Dalton *et el.*, 2005) because these medications cause interference with cell cycles subsequently inhibited cells growth and viability, so we think that more studies are needed to ensure the effectiveness of this drug in treating cancer in future.

Conclusions

Domberidone inhibited cell growth, reduce cell viability cause decreasing in mitotic index with increase the dose, no strong effect on micronuclei incidence and has no potential genotoxic effect . It should be keeping in mind that domperidone poses adanger and need to more research and studies.

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