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Study of the Effect of Plavix on Micronuclei in Albino Mice

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Abstract: ***The advanced basic science of toxicogenomics is a branch of toxicogenetics, aimed at self-engaging acoustic factor activation of advanced components of customized systems. The PCES micronuclei test provides a rapid and accurate way to detect the genotoxicity of chemical compounds that cause a clastogenic or anogenic effect, and it is also of statistically significant value because it can register a much larger number of cells compared to the metaphase chromosome analysis test. Except that he is The other cannot detect microscopic lesions in the cells' DNA. Adopting the technique of estimating micronuclei in exfoliated epithelial cells in prior monitoring of the occurrence of tumors Cancer and treatment response monitoring programmes. 2 Adopting micronuclei technology in expanded programs to screen chronic disease groups for toxicological agents Genetic.***

Keyword: Plavix, Toxicogenomics, Toxicogenetics, Cytogenetic Markers.

1. INTRODUCTION

The advanced basic science of toxicogenomics is a branch of toxicogenetics, aimed at self-engaging acoustic factor activation of advanced components of customized systems.

Toxicity and genotoxicity effectively depend on interactions with DNA and/or digestive systems that determine the function of the genomic genome such as the spindle apparatus or topoisomerase enzymes (Morrissi et al., 2005).

The co-toxicity of chemical agents is an essential characteristic of the electrophilic potential for bonding with the nucleophilic positioning of nucleophilic nucleophiles in macromolecules such as DNA, so their toxicity is enhanced by advanced cell science (Meng et al., 2004)

Objectives of the Study
Investigating the efficacy of the antibiotic Plavix using cytogenetic markers

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2. RELATED WORKS

Genotoxic Tests

Ex vivo and in vivo assays intended to identify substances that produce direct or indirect genotoxic harm via a variety of pathways are referred to as genotoxic tests (ICH, 2008). The danger of DNA damage could be determined and stabilized thanks to these tests. Gene mutations, chromosomal damage, recombination, and the multi-step process of malignancy—a complicated process in which genetic alterations are only one component—all contribute to the stability of DNA damage. Compounds that are positive in tests that detect types of damage have the potential to be carcinogenic and/or mutagenic in humans. Suspicion that a compound may cause inherited effects has been considered similar to the same compound that causes cancer. In addition, the results of such tests may be valuable for interpreting cancer studies (ICH, 1997).

Genetic Toxicology

It is one of the branches of toxicology. It identifies and analyzes the action of factors that cause toxicity to genetic components in living systems. The primary goal of toxicogenetics is to reveal and understand the characteristics of a relatively small group of factors that are highly specific to nucleic acids and result in serious effects on genetic elements at sub-toxic concentrations. Agents that cause genetic changes at subtoxic exposure levels, resulting in organisms with altered genetic characteristics, are called genotoxic. Genetically toxic substances have chemical or physical properties that facilitate interference with nucleic acids (Bryan Et Al., 2000).

Genotoxic Agents

Continuous efforts have been made to identify genotoxic agents in order to evaluate the impact of environmental and occupational exposure on health, and to define the effects of exposure through extensive studies. To identify harmful cases and investigate high-exposure population groups (Maluf and Erdtmann, 2000). It has been shown that many chemical compounds released into the environment as waste from various industries or chemical compounds and minerals used as raw materials in various industrial products and pesticides used in agriculture have negative effects on public health, and their relationship to the emergence of various diseases and the appearance of birth defects, their effects on genetic material and their relationship to cancerous tumors has become Well known (Al-Bayati et al., 1990; Armstrong et al., 1994). It has been observed that physiological levels of zinc induce programmed death in prostate cancer cells. Zinc contributes to facilitating the formation of holes associated with Bax, which establishes the emergence of mitochondrial apoptosis (Peifeng et al., 2008).

Exposure Effects to Genotoxic Agents

Chemical contaminants that are carcinogenic and mutagenic are found in nature in large quantities (COM/06/S3-December, 2006). Because of their connections to social norms, dietary habits, and employment, these pollutants have two major effects on people:

1. Impact on hematologic cells
2. Impact on sperm cells

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While its effects on somatic cells are directly linked to the emergence of malignancies, which are regarded as significant human diseases, its effects on germ cells lead to genetic abnormalities (Sugimura et al., 1976). One of the primary causes of cancer is the environment (Doll and Peto, 1981; Mange and Mange, 1999).

Genotoxic Tests

Genotoxic tests can be defined as ex vivo and in vivo tests designed to detect compounds that cause direct or indirect genotoxic damage through various mechanisms (ICH, 2008). These tests made it possible to identify and stabilize the risk of DNA damage. The fixation of DNA damage occurs in the form of gene mutations, and on a larger level, chromosomal damage.
Recombination is the multi-step process of metastasis, which is a complex process in which genetic changes play only one part. Compounds that are positive in tests that detect types of damage have the potential to be carcinogenic and/or mutagenic in humans. Suspicion that a compound may cause inherited effects has been considered similar to the same compound that causes cancer. In addition, the results of such tests may be valuable for interpreting cancer studies (ICH, 1997).

Measurement of MN Frequency

The frequency of micronuclei is generally reported as the total number of micronuclei or the number of micronucleated cells (MNCs) per 1000 dinuclear cells and as a percentage. The general average value of 6.5% of the frequency for the minor kernels can be considered as the basis for the main population. 75% of the database is under 12% frequency and 95% is under 26.8% frequency. The interquartile range that defines most frequently occurring values is below 3% and 12%. The average minimum recurrence rate is higher in females than in males (7% vs. 6.3%) and in individuals aged 40 years or older compared to individuals aged less than 40 years (7% vs. 5.9%) (Bonassi et al., 2001). In a review it prepared of published research on genetic toxicity screening using groups of pesticide sprayers, which included MN, CA and Comet, P32post labeled DNA adducts, COM considered the clear increases in these markers and their clear relationship to exposure to be indicative of ingestion and exposure to DNA-damaging chemicals. COM also listed the findings. It serves as an indicator of increased risk of mutagenic potential as well as potential carcinogenic potential. However, it is not possible to confirm or quantify the risk due to the poor quality of many studies and repeated public findings (COM/06/S3-December 2006). There is evidence of an increase in the frequency of micronuclei with increasing age in both males and females, which appears to be apparent in all age groups (Hagmar et al., 1998; Fenech, 1998; Titenko-Holland et al., 1997; Crott et al., 2001). (Violante, 2003; Wang et al., 2004; Bonassi et al., 2005; Fenech et al., 2005). The effects are due in part to numerical changes in chromosomes. There is sufficient evidence to draw conclusions about whether age-related effects of micronuclei also occur in peripheral blood mononuclear lymphocytes (Bolognesi, 1999; Kirsch-Volders and Fenech, 2000). These findings support the high frequency of micronuclei in peripheral blood lymphocytes in females, approximately 20-40%, which are mostly found between 30-59 years of age (Fenech and Rinaldi, 1994; Raddalck et al., 1995; Bolognesi, 1999). (Bonassi et al., 2001; Violante., 2003; Fenech et al., 2005). The effect of smoking on the frequency of CBMNs in peripheral blood lymphocytes appears to be associated only with high levels of smoking (more than 30 cigarettes per day). It is possible that it is covered by nutrition in

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smokers (Fenech, 1993; Di Giorgio et al., 1994; Duffaud et al., 1997; Kirsch-Volders and Fenech, 2000; Bonassi et al., 2005). There is also evidence of an age-related increase in chromosomal abnormalities with the exception of gaps (Bolognesi et al., 1997a). It has been shown that the parameters of the modes of action and the criteria for identifying and counting micronuclei in peripheral blood lymphocytes have the greatest influence on the frequency of micronuclei followed by exposure to genotoxic agents and then the effects of other factors (such as age, sex, etc.) (Fenech et al., 2003; Fenech et al., 2005). One of the first practical findings that physical and chemical variables can significantly alter the genetic material in cells with genuine nuclei was the detection of chromosomal damage that can result from exposure to ionizing radiation or carcinogenic substances (Evans, 1977). Data indicate that chromosomal anomalies are directly caused by damage at the easily observable DNA level, despite the fact that our knowledge of chromosome structure is still insufficient. For instance, unrepaired double-strand breaks in DNA can cause chromosomal breakdowns, and repair failures in single-strand breaks in DNA can cause chromosomal rearrangements (Savage, 1993). DNA. (Savage, 1993) Chromosome loss and chromosomal segregation error (non-disjunction) have also been considered to be important events in cancer and aging and are likely the result of spindle or centromere insufficiency or as a result of reduced condensation of chromosome structure before metaphase (Evans, 1997; Guttenbach, 1994). Micronuclei are expressed in cells that have completed nuclear division, so they are realistically recorded at the binucleate stage of the cell cycle (Heddle, 1973; Fenech and Morley, 1985). Nucleoplasmic bridges between nuclei (NPTs) are sometimes observed in the binucleate cell. These are likely to be dicentromere chromosomes, in which the two centromeres are drawn to opposite poles of the cell, and the DNA in the resulting bridge is covered by a nuclear envelope. Therefore, nucleoplasmic bridges in dinuclear cells provide an additional and complementary measure of chromosomal rearrangement, which can be recorded together with micronucleus counting (Fenech, 2000). Cells divide at different rates in vivo and outside in vitro, depending on physiological conditions, genetics, and micronutrients. Therefore, many methods were proposed based on Stathmokinetic and Flowcytometric trends and DNA labeling, but the method that gained the most preference due to its simplicity and lack of uncertainty resulting from its effect on the basic level of genetic damage is the estimation of the micronucleus by inactivation of cytoplasmic division (Cytokinesis-block micronucleus assay) (Fenech and Morley, 1985a; Fenech and Morley, 1985b; Fenech and Morley, 1986). According to CBMN estimate, cells that have finished one nuclear division are stopped utilizing Cytochalasin-B (Cyt-B) in order to prepare for cytoplasmic division; these cells can be easily identified by looking double-nucleated. During cytoplasmic division, the microfilament ring that constricts the cytoplasm between daughter nuclei is formed by actin polymerization, and Cyt-B is an inhibitor of this process (Carter, 1967). intracellular (Carter, 1967) In actuality, it is feasible to gather all dividing cells using Cyt-B, irrespective of their compatibility level and the proportion of dividing cells, and then record MNi in binucleated cells only. This makes it possible to compare chromosomal damage logically between cell groups, even though their cleavage kinetics may differ. Originally developed for use with cultured human lymphocytes (Fenech and Morley, 1985a; Fenech and Morley, 1985b), this technique is currently used to other types of lymphocytes, including bone marrow cells and solid malignancies (Masunaga et al., 1991; Odagiri et al., 1994). Additionally, recent

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Advancements Have Made the Following Possible:

A. MNi consisting of complete chromosomes can be distinguished from MNi consisting of cytoplasmic fragments (Degrassi and Tanzarella, 1988; Hanappani and Perry, 1988; Farooqi et al., 1993; Hando et al., 1994; Parry et al. , 1995; Elhajouji et al., 1995).
B. Conversion of shear repair sites into MNi in one cell division. (Fenech and Neville, 1992)
C. Using molecular probes to identify nondisjunction events in binucleate cells (Zijno et al., 1994; Elhajouji et al., 1994; Schuler et al., 1997).
D. Containing apoptotic and necrotic cells within an estimate. CBMN (Kirsch-volders et al., 1999; Fenech et al., 1999)

It is assumed that micronucleus estimation can be used as an alternative to analyzing metaphyseal chromosomes to test the genetic toxicity of new chemicals. The current trend of mutation research has been harnessed to this topic (Kirsch-Volders et al., 1997). The current working methods and data for testing micronuclei outside the living body (in vitro) were reviewed at the International Workshop - Washington on working methods for genotoxicity testing, which took place in (Kirsch-Volders et al., 2000) 1999.

The Human Micronucleus Project (HUmn)

HUmn is an international collaborative project that currently includes more than 30 laboratories around the world, and aims to improve and encourage the application and understanding of lymphocyte CBMN quantification as an ex vivo measure of chromosomal breaks and chromosome losses in members of the human population (Fenech et al., 1999). One of the most important areas of focus in the HUmn project is the important differences in working methods in preparing the estimation and recording of micronuclei to reduce their confounding effects. This will enable better estimation of the occurrence of genetic toxicity events, thus increasing the realism of comparing rates of DNA damage between individuals and populations, and identifying exposure events that induce an increase in MN (Bonassi et al., 2001). There is a growing effort worldwide to determine the influence of environmental, genetic, and lifestyle factors on the stability of the gene pool in human populations. Measurement of micronuclei in peripheral blood lymphocytes and, to a lesser extent, epithelial cells, erythrocytes and fibroblasts is one of the techniques adopted by large numbers of laboratories. Micronuclei consist of chromosomal fragments or complete chromosomes that are not contained in the main daughter nuclei during nuclear division, so MN provides a measure of both chromosome breakage and loss. It has been shown to be at least as sensitive a proxy for chromosomal damage as classical metaphyseal analysis (Fenech, 1993; Di Giorgio et al., 1994; Fenech and Rinaldi, 1994; Raddlack et al., 1995; Gaziev, 1996; Duffaud et al. al., 1997; MacGregor, 1997). The main benefit of estimating micronuclei is the ease of registration and the statistical power obtained from registering larger numbers of cells, compared to what is applied in the analysis of metaphase chromosomes. When using chinetochore and centromere identification methods, it is possible to differentiate between micronuclei resulting from chromosomal breaks and micronuclei resulting from chromosomal malsegregation (Gaziev, 1996; MacGregor et al., 1997; Fenech et al., 1997b).

An important step in the development of micronuclei estimation is the recording of micronuclei in cells that have completed a single nuclear division, which allows micronuclei to form (Fenech, 1993; Duffaud et al., 1997).

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Micronucleus Assay Test

First proposed by Countryman and Heddle in 1976, the use of micronuclei (MNi) as a chromosomal damage indicator in peripheral blood lymphocytes (PBL) evolved with the introduction of the cytoplasmic mitotic arrest method (Fenech and Morley, 1985a, b). This method made it possible to record micronuclei only in nuclear division-completed cells. Consequently, the previously described identification technique has gained widespread application in assessing the existence and degree of chromosomal damage in human populations exposed to genetically harmful elements in a variety of occupational demographics, the environment, or lifestyle choices. Evaluations were also conducted on subpopulations within the main population that were thought to be at risk because of their genetic makeup or because they had specific disorders. According to Fenech (1993), Ban et al. (1993), Benner et al. (1994)a, Tucker and Preston (1996), Duffaud et al. (1997), and Hagmar et al. (1998), this biomarker needs to be useful as a predictor of deviant health outcomes. Heddle (1973) and Schmid (1975) presented a less complicated alternative technique for independently assessing chromosomal damage in vivo. This method involved detecting micronuclei, which hematologists also refer to as Howell-Jolly bodies, in dividing cell populations such bone marrow and red blood cells in the blood. surrounding. It is currently among the top in vivo cytogenetic evaluations created for toxicogenomics. even in cases when it isn't the technology used for other cellular populations both within and outside the body. Since then, techniques for measuring micronuclei in cell types that have their nuclei outside of the body have been developed (Fenech et al., 1999). Among labs engaged in environmental mutagenesis, micronuclei testing has gained more and more attention. Studies based on this life indicator are being published at a rapid pace (Surralles and Natarajan, 1997; Fenech et al., 1999).

The Widespread Use of Micronuclei Estimation is Evident for Two Reasons:

(1) The peripheral blood lymphocyte micronucleus (PBLMN) test provides a true measure of chromosomal breaks and chromosomal losses with less cost and less effort than chromosomal abnormalities.

(2) The recent availability of technology to stop cytoplasmic division has eliminated the confusion resulting from effects on the dynamics of cell division. The effect of different protocols on the frequency of microkernels is one of the main issues that we need to address due to the many modifications of the original protocol in use, but the published literature confirms that the effect of the protocol on the final outcome is sometimes limited and at other times significant (Bonassi et al., 2001).

3. METHODOLOGY

Materials and Methods

Giemsa Stain Solution

Prepare the stock solution by dissolving 2 g of Kamza dye powder in 100 ml of methanol and keeping it in a sealed, opaque bottle and mixing it with a mixing device for 24 hours. Then the dye was filtered with Whatman paper 1, and when dyeing the glass slides, 1 ml of the stock solution was taken. 4 ml of Sorensen's buffer solution was added to it

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Hypotonic Potassium Chloride Solution (Kcl 0.075M)
Dissolve 1.1175gm of KCl in 200ml of distilled water and store at 4°C until use, and use it warm at 37°C.

Bone Marrow Cell Collection in Albino Mice:
After the specified period for each test had passed, the mice were killed by cervical dislocation, the animal was placed on its back in a dissection dish, the skin was opened, the femur bones were extracted and cleaned, the bone marrow was pushed into a centrifuge tube, and the cells were collected and treated according to the type of test. Male gonads were also extracted and treated in experiments to study meiotic chromosomal abnormalities.

Pces in Bone Marrow and Peripheral Blood of Albino Mice:
This Test Was Conducted According to the Method Described by Schmid (1975) As Follows:
After killing the animals, the bone marrow was extracted with PBS and placed in a centrifuge tube. Cells were centrifuged at 1000 rpm for 10 minutes. The clearing was discarded and the cells were drop-dropped onto a drop of fetal bovine serum onto a clean slide. The slides were left to dry in air and then fixed with methanol for five minutes. Slides were stained with May-Gruenwald stain and then with Giemsa. The slides were rinsed with distilled water, left to dry, and then examined for the purpose **of** recording immature red blood cells containing micronuclei. Micronuclei determination test in immature red blood cells in the bone marrow of albino mice: 5 mice were used in this group of experiments.

Study of the Effect of Mitomycin
Mice were treated with intracecal injection, 5 mice were left untreated, and models were taken by killing a group from each treatment and a control group at 18 hours after treatment.

4. RESULTS & DISCUSSION

Effect of the Drug (Mitomycin-C MMC)
Based on the results of previous experiments, it was found that treatment with doses of 2.5, 5 and mg/kg b.wt10. of MMC did not induce death but it significantly reduced the percentage of immature erythrocytes in Treated rat bone marrow.

Effect of Exposure to Plavix Doses
Plavix was tested for chromosome-breaking strength in male albino mice using a quantification test Micronuclei in immature red blood cells in the bone marrow and peripheral blood. When (5) individuals of white mice, the Balb strain, were dosed with an average age of six weeks and an average weight of 25 m, the dose was 18 gm per hour, while two similar groups were left without dose and were considered a control group. The mice were then killed, peripheral blood samples were taken, and bone marrow was extracted to prepare slides and study non-red blood cells Mature for the purpose of calculating the frequency of micronuclei in both the treatment and control groups. The results of the current study showed that exposure to Plavix caused a significant, dose-dependent increase in the

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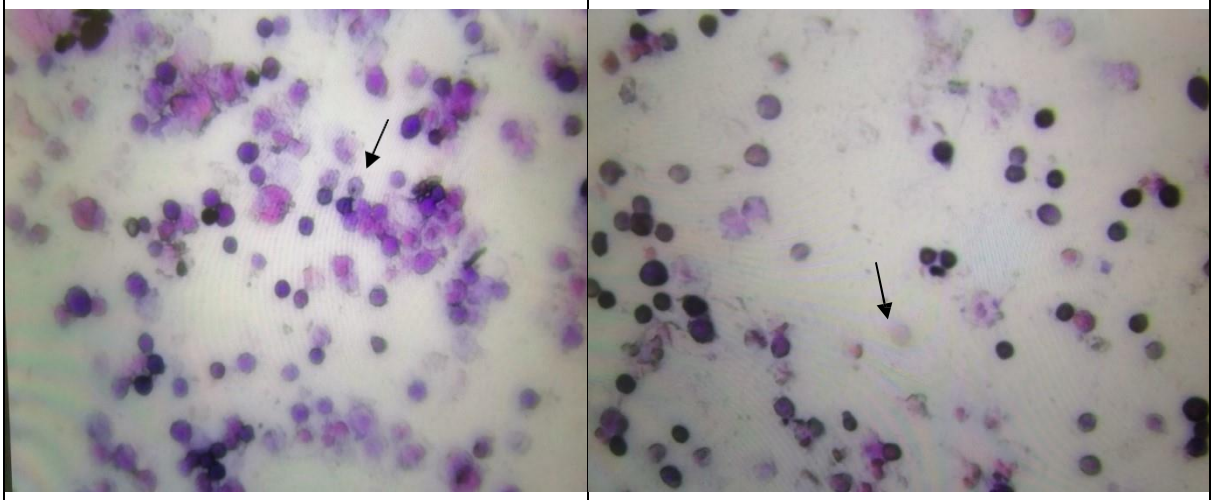
number of immature red blood cells (PCES) containing micronuclei (Figure 1) at a higher rate in the exposed animals than the values of the control group. Table (1) shows the dose-response relationship for For smaller nuclei.

Table (1) Induction of cytogenetic damage in albino mice by exposure to Plavix expressed Average frequency of micronuclei in immature red blood cells of the bone marrow.

Groups	PCEs	MNiPCEs	Mni
	MD ± SE	**MD ± SE**	**MD ± SE**
Negative	6 ± 15.7	6±2.22	6±2.45
Positive MTC	61.0 ± 15.7*	161.6 ± 2.22*	170 ± 2.45*
Treatment	49.4 ± 15.7*	87.6 ± 2.22*	90 ± 2.45*



a- Contain 1 MNiPCEs | b- MNiPCEs Normal

The results of the current study showed that Plavix caused a statistically significant decrease in the percentage of immature red blood cells in bone marrow samples at 18 hours. This leads to the assumption that there is Effect on the rate of red blood cell formation. It also appeared that exposure to Plavix caused a significant, dose-dependent increase in the frequency of cells undergoing apoptosis and cells undergoing necrosis. This is consistent with Bai and Meng (2005) who found that exposure of Wistar rats caused a significant increase in the mRNA levels of the Ps3 and bax genes in a dose-dependent behavior, while the mRNA levels of the 2-1bc gene decreased significantly in the lungs of the exposed animals and that the increase Dose-dependent levels of Ps3 and Bax in the lungs were observed to be associated with decreased levels of 10-2 protein and were obtained. Using the chemokine immunology method. This leads to the conclusion that exposure to Plavix can cause a change in the expression of genes related to programmed death, and I assume that its administration can

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induce programmed death in the lungs of mice, and this is what the current study reached by observing the percentage of cells that undergo the phenomenon Programmed death.

5. CONCLUSION

The PCES micronuclei test provides a rapid and accurate way to detect the genotoxicity of chemical compounds that cause a clastogenic or anogenic effect, and it is also of statistically significant value because it can register a much larger number of cells compared to the metaphase chromosome analysis test. Except that he is The other cannot detect microscopic lesions in the cells' DNA.

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