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Case Report

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Effect of Lisinopril Treatment on Genotoxicity of L-Asparaginase (ASNase) in Bone Marrow Stem Cells for Aculte Lymphoblstic Leukemia (ALL)

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Abstract

Background: *Lisinopril is a drug used to lower blood pressure by blocking the angiotensin-converting enzyme (ACE). It measures the response of myeloid inflammation to bone marrow stem cells. L-asparaginase is a chemotherapeutic agent used to treat acute lymphoblastic leukemia (ALL) by increasing the genotoxicity of bone marrow stem cells. The purpose of this study was to find out the effect of Lisinopril on the genotoxicity of L-asparaginase (ASNase) in bone marrow cells.*

Materials and Methods: *60 Syrian hamster males' are divided into three groups. The first group was treated with Lisinopril 10 mg / kg / day for 14 days. The second group was injected with L-asparaginase 3000 IU / kg. The third group was treated with Lisinopril for 14 days following the intraperitoneal injection of L-asparaginase (ASNase) at the end of day 13. Genotoxicity was assessed by calculating the micronucleus (MN) percentage and the mitotic index (MI).*

Results and Discussions: *ASNase significantly increased genotoxicity by increasing% MN and lowering MI. When lisinopril was taken at 10 mg / kg / day, no significant effect was observed. However, a significant decrease in genotoxic effects was observed when mice received Lisinopril injected with 3000 IU / kg ASNase compared with the group treated with ASNase only. This result is shown by reducing% MN and increasing MI.*
Conclusion: The use of Lisinopril in the treatment of high blood pressure and its cancer treatment agent, L-asparaginase, was found to lower its genotoxicity in bone marrow cells.

Keywords: Lisinopril, L-asparaginase, Angiotensin-Converting Enzyme, Genotoxicity, Stem Cells, Bone Marrow, Mitotic Index and Mononucleosis.

Introduction

Lisinopril is one of the drugs used to treat high blood pressure. It is an angiotensin-converting enzymes (ACE) inhibitor. Lisinopril works by preventing the conversion of angiotensin I (ANG I) into angiotensin II (ANG II) which is considered a powerful vasoconstrictor. It stimulates aldosterone production thus reducing sodium release in the gut. Lisinopril lowers hypotension by decreasing the absorption of sodium and potassium by the kidneys [1-2]. ACE inhibitors usually target stem cells. They correct the inflammatory response of myeloid cells and myeloid precursor in their final location [3]. In tissue culture, ANG II causes cell cycle arrest that leads to cellular hypertrophy [4]. This may be that ANGII causes DNA damage caused by a significant increase in DNA strand breaks [5].

Numerous studies have been linked to high blood pressure and cancer and have found a high rate of cancer deaths in patients with high blood pressure and a link between an increased risk of kidney cancer and high blood pressure [6-8].

Complex reorganization of DNA patterns and mitotic defects are factors associated with multiple carcinomas and DNA double-strand break, which poses a significant risk of genomic instability [9-11]. In the present study Micronuclei (MN) and Mitotic Index (MI) were used as indicators of DNA instability and mitotic abnormalities. MN is a biological marker commonly used to identify DNA damage to radiation and chemical reactions [12]. Micronuclei are tiny nuclear bodies containing DNA that have

been separated from the main nucleus [13]. They are produced in acentric fragments, left untreated following DNA damage, or on dormant chromosomes during mitosis. MN nuclear envelopes are fragile compared to those of the main nucleus, leading to increased chances of tearing and DNA release into the cytosol [14, 15].

On the other hand, MI (the percentage of cell division in metaphase) provides a good signal for optimal cell proliferation and a description of the solid state of cell division and its relation to cancer progression, which can worsen the condition and spread to others body parts [16].

L-asparaginase is an enzyme that can make asparagine into aspartic acid and ammonia. It is used to treat lymphoblastic leukemia, as these cells use asparagine for survival and this enzyme lowers them leading to an increase in genotoxic effects [17]. Tumor cells cannot synthesize these amino acids; therefore, tumor cells are killed by L-asparagine deficiency. Deterioration of L-asparagine causes cell cycle arrest in the G1 stage and increases apoptosis, all leading to cell death [18]. As a result, bone marrow compression is caused by inhibition of normal stem cell secretion caused by L-asparaginase [19]. L-asparaginase also induces micronucleus formation in normal cell lines and tumor and causes genotoxic effects and DNA breaks. According to the above, the use of L-asparaginase increases genotoxicity by creating micronuclei and cell division. The aim of the present study was to investigate the effect of lisinopril on the genotoxicity produced by L-asparaginase in normal bone marrow cells.

Materials and methods

Laboratory animals

Sixty Syrian hamster males' mice were purchased from a private laboratory that supplied laboratory animals for research purposes in Damascus, Syria. They were housed under a light / dark cycle of 12h at a temperature of 24 ± 1 ° C with free food and reverse-osmosis water. Mice were divided into five groups (12 mice per group).
All mice in both groups were killed 14 days later and bone marrow transplants were performed. The bone marrow was removed from the bones by wishing using phosphate buffer saline.

Mice used in the study were divided into the following groups and mice were housed for 14 days without treatment.
1- Control group
2- Group I: Wrong control group
Mice in this group provided drinking water containing 0.1% of alcohol without further treatment for 14 days [20]. Alcohol increases the dissolution of Lisinoprol in water and this concentration has no effect on stem cell function (20).
3- Group II: Lisinopril
Mice were treated with Lisinopril using 10 mg tablets, manufactured by AstraZeneca, UK. Tablets dissolved in 0.1% ethanol water as reported by Rafael-Fortney et al . [20]. Water bottles are changed three times a week. Mice were measured and the amount of water used was recorded to calculate the average dose of Lisinopril, which was found to be 10 mg / kg / day; a dose with an active dose similar to that previously reported [20].
4. Group III: L-asparaginase
A container containing 10000 IU L-asparaginase (Fehlandtstr, Germany). Untreated mice were incubated for 14 days and injected intraperitoneally with L-asparaginase 3000 IU / kg at the end of day 13 [21].
5. Group IV: Treatment of Lisinopril and L-asparaginase
Mice treated with Lisinopril at 10mg / kg / day for 14 days and at the end of day 13 were injected intraperitoneally with 3000 IU / kg ASNase.
C. Genotoxicity assay:
To determine the percentage of MI and MN, five slides of bone marrow cells were repaired and 12000 cells were tested per mouse.
1- Mitotic index assay:
Percentage of MI was calculated according to the method of Allen et al, 1977 [22]. The percentage of cell division in metaphase is calculated using the following calculation.

$$\text{Mitotic Index (\%)} = \left[\frac{\text{Number of metaphase cells}}{\text{Total number of cells counted}}\right] \times 100$$

Micronucleus Test

Bone marrow was extracted using inactive plasma, as previously described by Schmid, 1975 [23]. Percentage of MN is calculated as follows:

$$\text{Micronucleus Index (\%)} = \left[\frac{\text{Number of micronuclei}}{\text{Total number of cells counted}}\right] \times 100$$

Mathematical Analysis

The mathematical package of version 24 social science (SPSS 24) was used to analyze the data. Continuous variables are presented as a standard deviation and different variables are presented as numbers and percentages. An independent Chi-square was used to examine the significance of the relationship between the different variants. One-way ANOVA has been used is to examine the significant differences between schools and variables. The $p < 0.05$ values were considered significant.

Results and Discussion

The total number of cells tested in each test group was 12000 (12x1000cells). MI and MN school numbers and their percentages are given in Table 1. There are no significant values of MI ($p = 0.09$) and MN ($p = 0.07$) and their percentages are reflected in both controls.

Table 1: Shows Reliability and Validity Coefficients of the Four Scales

	Scale	Items	Reliability	Validity
1	Organizational Behavior	8	0.66	0.81
2	Organizational Trust	6	0.88	0.94
3	Organizational Commitment	10	0.74	0.81
4	Job Motivation	9	0.89	0.94

[a]No Significant difference when compared with control group ($p<0.05$)
[b]Significant difference when compared with control group ($p<0.05$)
[c]Significant difference when compared with group injected ASNase ($p<0.05$)

When mice were treated with Lisinopril of 10 mg/kg/day for 14 days, an insignificant decrease in the percentage of MN (p=0.057) and an insignificant increase in the percentage of MI (p=0.06) were obtained when compared to the control groups. Perversely, a significant increase in the percentage of MN (p=0.007) and a significant decrease in MI (p=0.009) were observed when mice were injected with ASNase 3000 IU/kg at the end of the 13th day. However, when mice treated with Lisinopril for 14 -days and injected with ASNase at the end of the 13th day a significant decrease in MN (p=0.03) and a significant increase in MI (p=0.01) were seen as compared with group given ASNase alone.

The chemical and physical changes of DNA lead to DNA damages, which affect its infrastructure and lead to losing its function. Distinct forms of DNA damages can be produced by a variety of exogenous and endogenous factors including free radicals, radiation, chemicals, and topological changes [24]. Reactive oxygen species (ROS) have been reported to directly induce other forms of DNA damage through oxidizing nucleoside as well [25]. Chemotherapy drugs also increase ROS levels, which contribute to genotoxicity [26]. Genotoxicity and cytotoxicity can be produced by MN induction [27]. Therefore, MN assay is widely used to study the clastogenic and aneugenic potentials of chemicals and other agents that cause DNA damage, as it gives a good image of the genotoxicity that occurs [28]. Accordingly, MN assay is employed as a very suitable test to measure genotoxic potential in human peripheral blood lymphocytes [29]. This assay is considered a specific measurement of genotoxicity for many mutagens and carcinogens as well. It is worth noting, however, that MN formation is associated with the defects and losses of genetic material and can be used together with MI to enhance the results obtained, especially when studying genotoxicity in blood cells [30].

Solvent containing 0.1% ethanol water did not show any effect on the MN and MI formation rate as clearly shown in Table 1. The absence of any genotoxic effect of this concentration of alcohol is consistent with the results reported by Rafael-Fortney et al. [20].

Lisinopril insignificantly decreased genotoxicity through decreasing MN and increasing MI compared with the control group, as shown in Table 1. The changes in these values of MN and MI are worthy considering because the mice appeared in a normal condition as if they were not treated with any substance. This insignificant reduction in genotoxicity could be attributed to that Lisinopril scavenges free radicals that have the ability to cause great damage to the DNA [24].

L-Asparaginase induced highly significant genotoxicity via increasing MN and decreasing MI, as noted in Table 1. L-Asparaginase is known to induce DNA damage and abnormality in the cell cycle, which is manifested by cell cycle arrest and DNA breaks. Moreover, L-Asparaginase can induce micronucleus formation in normal cells and increase DNA breaks [17]. These DNA damages degrade the level of l-asparagine in the cell membrane leading to depletion of its concentration followed by protein dysfunction and cells death [31]. It is worth mentioning that the process of converting asparagine into aspartic acid and ammonia by L- asparaginase is accompanied by an increase in oxidation levels and a decrease in the reduction state [32]. This oxidation state may increase ROS level and induce DNA damage [25-26].

When mice treated with Lisinopril for 14 -days and injected intraperitoneally with ASNase at end of the 13th day, a significant reduction in genotoxicity of L- asparaginase was observed, as given in Table 1. Significant decrease of MN and increase of MI can clearly be noticed when compared with the group that received L- asparaginase alone. This reduction in genotoxicity may be due to the capability of Lisinopril to inhibit Angiotensin converting enzyme (ACE). It is well documented that ACE can increase DNA degradation and affects its stability; this is why ANGI is converted to ANGII, which induces DNA damage caused by an increase in DNA breaks [5].

Furthermore, Lisinopril decreases mitotic errors, which are hallmarks of most carcinoma and DNA double strand breaks. Usually, high blood pressure is caused by an increase in the ANGII. Lisinopril inhibits ANGII production and protects bone marrow stem cells. On the other hand, ACE inhibition can protect myeloid precursor cells from ANGII high concentration which may justify the good relationship between kidney cancer and hypertension [7-8]. This may also suggest that reducing blood pressure by Lisinopril could lessen the possibility of having cancer.

Conclusion

Lisinopril can reduce genotoxicity induced by L- asparaginase in bone marrow stem cells. This effect may imply that using Lisinopril to reduce high blood pressure in patients with acute lymphoblastic leukemia who are receiving treatment with L-Asparaginase can

compromise the effectiveness of their cancer therapy.

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