Studying The Toxicity Effect of Hydroxyurea on The Spleen of Male Albino Mice

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Abstract

Hydroxyurea (HU) is one of many drugs that used for cancer treatment such as Leukemia, previous studies have shown the side effects of hydroxyurea which occurred during treatment, studying the potential toxicity of this drug on the spleen (one of the major organs of immunity) have not been taken by consideration, therefore the present study designed to reveal the effects of hydroxyurea on the splenic tissue. The present study have shown several histopathological changes in splenic tissue which then effect on the functions of spleen as a result of the potential toxicity of hydroxyurea on spleen.

Introduction

Hydroxyurea (HU) was developed for 50 years ago as an anticancer drug and has been used to treatmen t myeloproliferative syndromes, some types of leukemia, melanoma and ovarian cancer, it might also be used with radiation to control skin cancer (Yves& Jean,1997). The safety profile of hydroxyurea has been characterized in patients with sickle cell disease (Platt, 2008; Kratovil, et.al. 2006), and in some time added into retroviral combination therapy to potentiate human immune deficiency virus (HIV) suppression (Giampiero, et.al. 2002). It rapidly absorbed and then degraded by urease of the intestinal bacteria and distributed throughout the body and concentrate in leukocytes and erythrocytes (Adragna, et.al. 1994). After three hours of injection, hydroxyurea metabolized to nitric oxide (NO) that considered as a cytotoxic and mutagenic compound (Burkitt, and Raafat, 2006).

The possible side effects of hydroxyurea are hair loss, inflammation of mouth, loss of appetite, nausea, diarrhea, fever, dryness and darkening of skin and nail (hyperpigmentation), inflammation of pancreas, liver toxicity, abdominal pain, redness of the face, blood disorders and others (Lanzkron, et.al. 2008; Thiele, et.al. 2000). The main adverse reaction associated with hydroxyurea therapy resulting from growth of rapidly dividing, resulting in neutropenia, anemia, thrombocytopenia and delayed wounds healing (Adriana, 2001). It can also lower the activity of the immune system making person more susceptible to infections (Giampiero, et.al. 2002), therefore the spleen is the organ of the immunity and play and important role in the immune’s defense of the body that may affected by hydroxyurea as observed in the present study.

Materials & methods:-

Two groups of albino mice (21 days old) were used for this experiment, each group consists from 5 animals.

The first group of animals were injected intraperitonial (I.P.) with 1mL of phosphate buffer saline as a control group, while the second group) which was treated
with hydroxyurea that injected intraperitoneal (I.P.), hydroxyurea (samadroxyurea) that used in these experiments manufactured by the state company for drugs industry and medical applications Samarra-Iraq at concentration (1.02 g/kg) in phosphate buffer saline (Jian, et.al.,1997).

The experimental animals of two groups regained their normal body weight compared to the control ones, they were scarified by spinal dislocation after one week of injection.

Then the spleen were removed, weighted and processed for light microscopic study, HX-Eosin stains have been used (Presnell, J. and Schreibman, 1997).

The spleen/body weight ratio was calculated as follow:

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\text{Spleen/Body weight ratio} = \frac{\text{Spleen weight (gram)}}{\text{Body weight (gram)}} \times 100
\]

T-test was used for statistical analysis (Al-Rawi, 2000).

**Results & Discussion:-**

The present study demonstrated there in no significant change in the body weight and in the ratio of spleen/body weight as compared with the control group (Fig.:1 & Fig.2).

The light microscopic study of the control group revealed that the splenic tissue consist of discrete while nodules called white pulp, embedded in a red marix called the red pulp (Fig.:3) (Wheater, et.al. 1987; Leslie, et.al. 2003)

The main histopathological changes resulted in the splenic tissue of mice after treatment with hydroxyurea involved congestion in several area of splenic tissue (Fig.:4 & Fig.:6). Which was the most frequent finding as a result from weaken of blood vessel wall due to accumulation of red blood cells in the vessels (Xue-Jun, et.al. 2008). Also spleen appeared grossly discolored, this finding corresponded to the increased incidences of congestion (Michael, 1996).

The potential toxicity of cancer drug (hydroxyurea) was necrosis (Fig.:5 & Fig.:6) which can recognized by changes in the cell body and in the nucleus, the cellular changes of necrosis are swelling of the cytoplasm which becomes homogeneous and loses its normal reticulated appearance. There is loss of the normal sharp contour and obliteration of the cell boundaries (Fig.:5), the nuclear material are more shrinking (William, 1953).

In (Fig.:7) we can see cell lysis that refer to the breakdown of a cell caused by damage to its plasma membrane which caused by chemical agent as in the present study. The splenic tissue readily undergo hyperplasia after treatment period with hydroxyurea (Fig.:9) which is the meant an increase in the cell number of a part and it gradually merges into the process of neoplasia or tumor formation (Todd, et.al. 1997).

The tumors of spleen are usually due to accumulating or bleeding in the spleen (Andreas, et.al 2008) as seen in (Fig.:8) as a result of mice treatment with hydroxyurea.
Figure (1): Change in the body weights (gm) before & after a period of treatment of mice with hydroxyurea.

Figure (2): Changes in the ratio of spleen/body weight (gram) in the mice treated with hydroxyurea.
Fig. (3): The splenic tissue of mice in the control group. (H. & E.: 40X).
(W): White pulp.
(R): Red pulp.

Fig. (4): The splenic tissue of mice after treatment with hydroxyurea. Shown the congestion (C) & accumulation of RBCs in the blood vessel. (H. & E.: 400X, 600X).
Fig.(5): The necrosis (N) in the splenic tissue of treated mice. Shown the swelling cytoplasm & losses of normal reticulated appearance. (H. & E.: 400X & 600X)

Fig.(6): splenic tissue in treated group of mice. Shown the congestion (C) & necrosis (N). (H. & E.: 400X)

Fig.(7): the splenic tissue of treated mice with hydroxyurea. Shown the lysis of splenic tissue. (H. & E.: 600X)
Fig.(8): Shown the bleeding in spleen after hydroxyurea treatment which caused tumors in spleen. (H. & E.: 400X, 600X)

Fig.(9): Shown the hyperplasia in splenic tissue after hydroxyurea treatment. (H. & E.: 400X)
References


