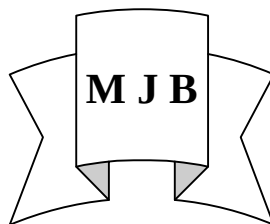


Histological Changes in Liver Associated with Administration of Hydroxyurea in Male Albino Mice

Maysaa Adil Hadi ,Nadia Hamid AL-Taii, *Hussein Naji Abd-Alla
 Dept. of Biology/College of Science - University of Babylon
 *College of Medicine/ Babylon University



Abstract

Hydroxyurea (HU) have been used for treatment of a variety of tumors . It becomes standard therapy for chronic myelogenous leukemia , polycythemia and sickle cell disease . Numerous studies have been published about their side effects but less studies has dealt with HU effect in histological structure of liver , therefore these experiments were designed to study the effect of HU on hepatic tissue .We concluded that HU had negative side effect in the liver.

الخلاصة

استخدم عقار الهيدروكسي يوريا لمعالجة مختلف الاورام واصبح العلاج الاساسي لمرضى ابيضاض الدم النخاعي المزمن واحمرار الدم ومرض فقر الدم المنجلي . اجريت العديد من الدراسات السابقة حول تأثيرات العقار الجانبية لكن الدراسات قليلة حول تأثيره في التركيب النسيجي للكبد لذلك تم اجراء هذه الدراسة لمعرفة تأثير الهيدروكسي يوريا على النسيج الكبدي . نستنتج من هذه الدراسة ان للعقار تأثير جانبي سلبي في نسيج الكبد .

Introduction

Hydroxyurea (HU) was first synthesized in the 1860s. After that it was found to be active against a variety of tumors. It is an antineoplastic drug that reduces the synthesis of deoxyribonucleic acid (DNA) [1] by inhibiting ribonucleotide reductase [2 , 3]. Therefore HU used for inhibition of human immunodeficiency virus (HIV) replication [4] . Hydroxyurea has become standard therapy for chronic myelogenous leukemia, polycythemia, and other myeloproliferative disorders [5] such as essential thrombocythemia [6] . Also it is used for treatment of sickle cell disease [3 , 7 , 8 , 9]. Hydroxyurea is readily absorbed after oral administration, reaches peak blood level in 2-4 hr, and is excreted in the urine with a

half-life of less than 8 hr. It enters cells by passive diffusion and is distributed throughout body fluid [4] . The hepatocytes are the main target of the cytotoxic drugs. The liver is the most active organ in metabolizing foreign compound as HU and generate metabolites nitric oxide (NO) throughout three hours after the injection [10] . Nitric oxide not only more reactive but also more cytotoxic than parent compound [11].

Materials and Methods

Adult albino male mice *Mus musculus* were used throughout the experiment . All mice were given water and pellet *ad libitum* . They divided into two groups, each group consisted of 5 animals and treated as following :-

- 1- The first group of mice were injected intraperitoneal (i.p) with 1 ml of Phosphate Buffer Saline and considered as a control group.
- 2- The second group were injected intraperitoneal with 1 ml of hydroxyurea (Samadroxyurea) which manufactured by the state company for drugs industry and medical appliance Samarra – Iraq was diluted with Phosphate Buffer Saline to prepare, the dosage used in this experiments was (1.02g/kg) [10].

Body weight was taken before and after the experiments then the animals killed by spinal dislocation after 24 hours. The liver was removed , weighted , fixed for 24 hours in formalin 10% solution, processed and the paraffin sections (5 micron thickness) were prepared and stained with Hematoxylin & Eosin (HE) method [12] for light microscopical study.

The liver / body weight ratio was calculated as follow:-

$$\text{Liver/ body weight ratio} = \frac{\text{liver weight(gram)}}{\text{body weight(gram)}} \times 100$$

Analysis of variance (ANOVA) was used for statistical analysis of data and standard error was calculated [13].

Results and Discussion

First: Body and Liver Weight:-

This study indicated no significant differences in body weight and liver/ body weight ratio (Figure -1- and figure-2- respectively) in hydroxyurea treated group as compared with control group.

Second :- Histopathological study:-

A:- Hydroxyurea group :-

Some parts of hepatic lobules had normal architecture such as normal size of

hepatocytes and normal nucleus (figure 3) . Another hepatic lobules had some histological changes which we can summarized as follow:-

- 1- Cloudy swelling and intracellular odema which reflect failure of membrane ion pumps because of lack of cellular ATP allowing the cell to accumulate fluid [14] .The earliest light microscopic evidence of cellular injury is loss of normal staining intensity of the cytoplasm owing to swelling of membrane – bound organelle , swelling of endoplasmic reticulum and mitochondria and described as cloudy swelling [15] as seen in figure (4). This may be due to the effect of HU in vasodilation which results from the HU – derived nitric oxide [3, 11].
- 2- Necrosis :- Small areas of necrosis was seen in figure (5) which results from exposure to HU . Necrosis was light eosinophilic [15].
- 3- Vascular congestion (figure 4 A&6A,B) and infiltration of inflammatory cells (figure 6C).The focal accumulation of inflammatory cells usually seen in relation to the site of necrotic hepatocytes .This inflammatory cells migrate by chemotactic agents from tissue debris. [15].

The hepatocytes with their high degree of metabolic activity are disturbed by many substances and demonstrate the histological and cellular responses known such as cloudy swelling , necrosis and fatty change [15].

All previous histological changes may be due to *in vivo* formation of nitric oxide (NO) after three hours of administration of hydroxyurea and then exhibits its

biological effects [3 , 8, 10, 11]. These previous studies revealed that there was ability of liver tissue to convert HU to NO and provided in sight into the metabolism of this drug. The liver is one organ that is clearly influenced by NO as inflammatory mediator [2 , 17 ,18] which plays an important role in endothelium- derived relaxation and inflammation [12].

B. control group:- Normal architecture of liver was seen (Figure :7) which is similar to those described by [19].

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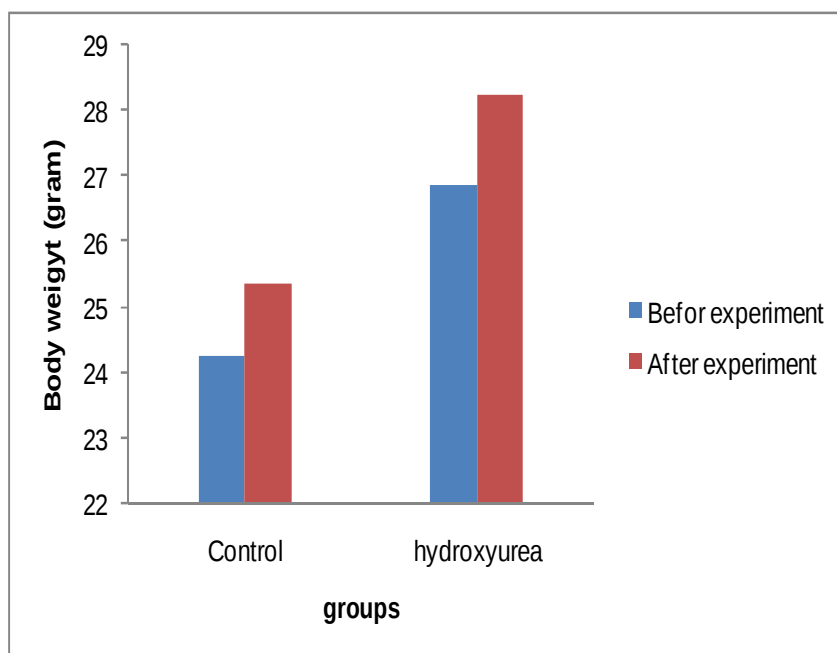


Figure-1-Changes in body weight in treated groups

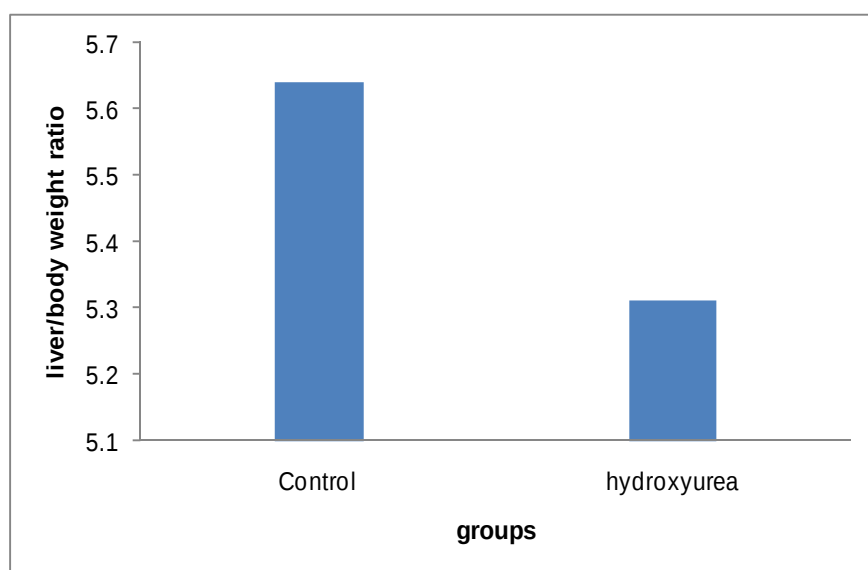


Figure-2-Changes in in liver/ body weight ratio in treated groups

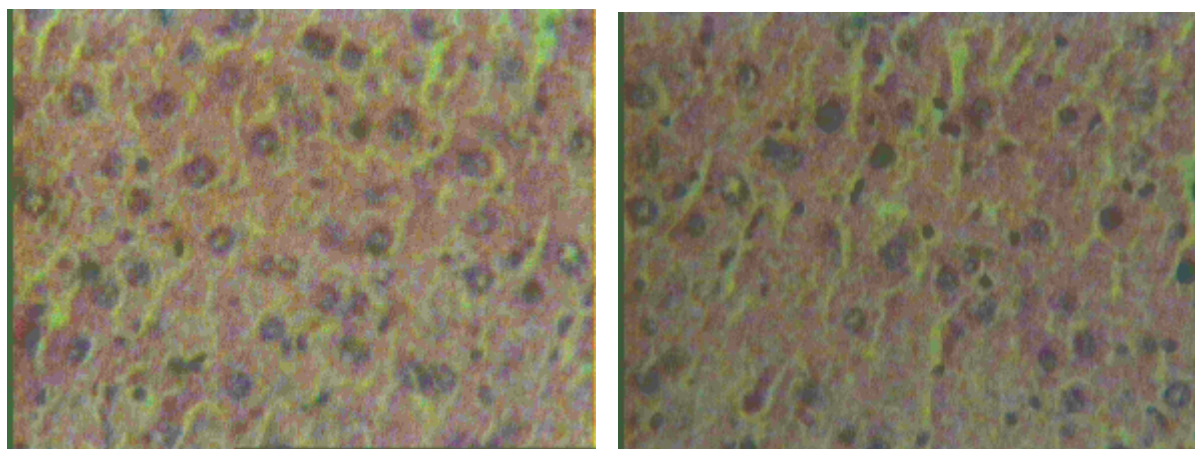
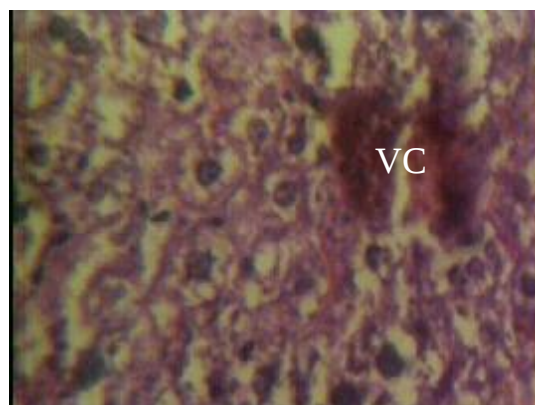
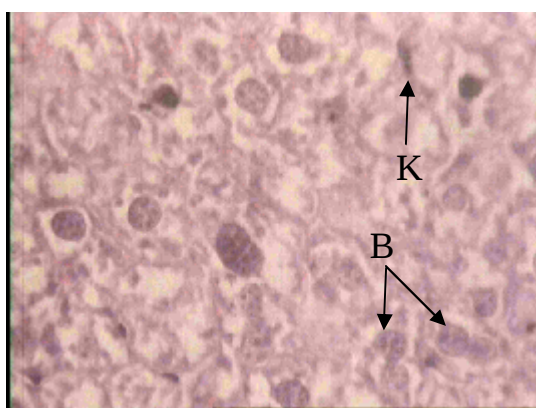


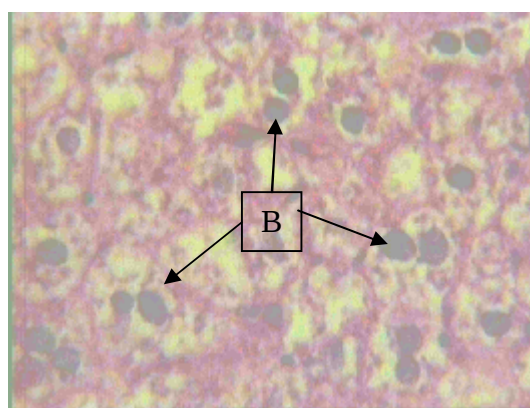
Fig -3- Hepatic tissue of mice treated with hydroxyurea show normal hepatocytes & normal hepatic architecture (HE: 600X).



A



B



C

Fig-4- Hepatic tissue of mice treated with hydroxyurea show cloudy swelling and vascular congestion (VC) .

K : kupffer cell, B:binucleated hepatocytes . (HE: 600X)

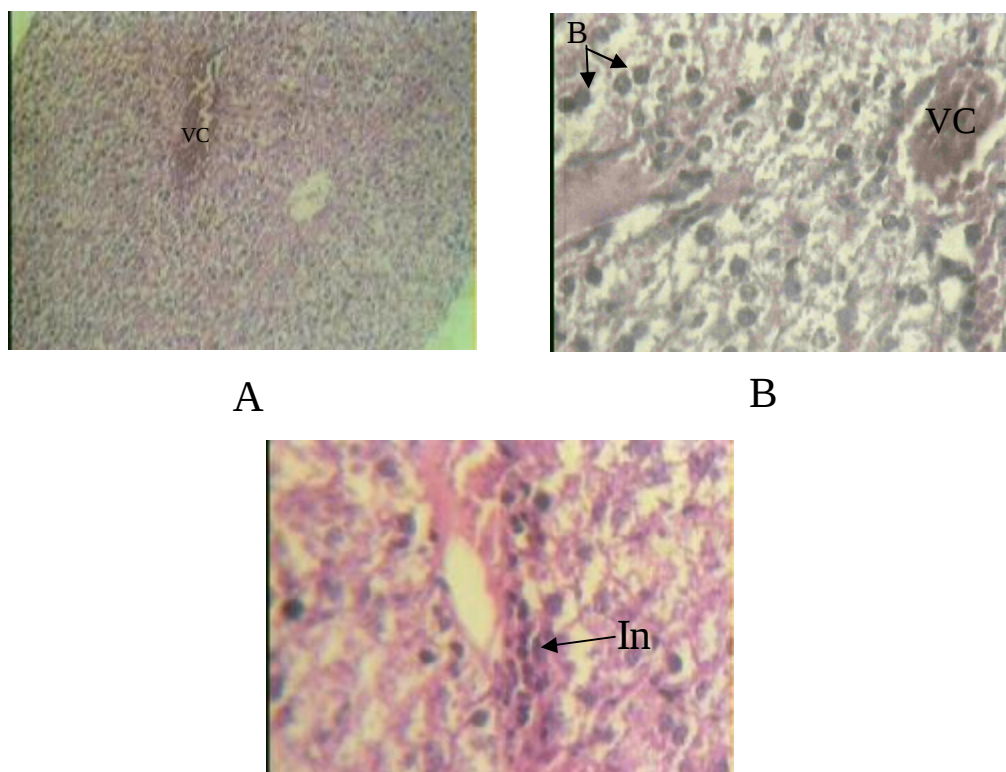


Fig-6- Hepatic tissue of mice treated with HU show vascular congestion (VC), infiltration of inflammatory cells (In) & binucleated hepatocytes (B). (HE: A: 150X, B&C: 600X).

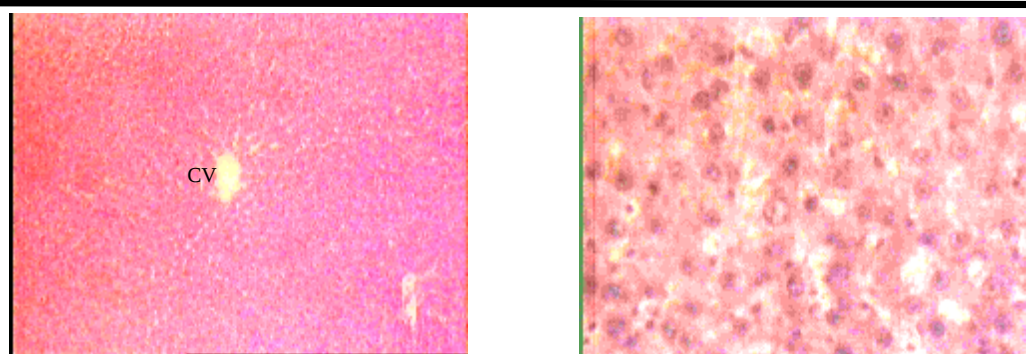


Fig-7- Hepatic tissue of mice treat with pbs (control group showed normal architecture of hepatic lobules & hepatocytes. (HE A: 150X, B: 600X) CV: central vein.