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The effect of meropenem on the liver of albino mice

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Abstract

Meropenem is a carbapenem antibiotic with broad-spectrum activity against many pathogens associated with complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI) and bacterial meningitis as well as nosocomial pneumonia. The present study looked at the effect of meropenem on liver tissue in mice, taking into account dose and duration of exposure. Nine matured male albino mice were divided into two groups. Group one (G1): served as a control group, receiving 0.1 normal saline intravenously every day. Group two (G2): received 0.1 of 100 mg/kg/day meropenem intravenously for 14 days. Animals were weighed before and after treatment, and they were sacrificed by cervical dislocation following either inhalation. After the end of treatment, liver samples were collected, weighted, and processed for histological examination. The findings revealed liver injuries that involved hepatocytes necrosis, degeneration, blood vessels congestion ,increased the number of cells with divided nuclei, expansion of sinusoid space, pyknotic nuclei, atrophy of nuclei and cytoplasmic vacuolation, aggregation of erythrocytes. We conclude that meropenem have a negative impact on liver function.

Keyword: Meropenem, Liver changes, Weight changes, Behavior changes, Albino mice.

Introduction

Meropenem is an intravenous carbapenem antibiotic used to treat a wide aminotransferase raises and can cause clinically visible cholestatic liver injury in rare causes (Cheunga et al.,2021; Moon et al., 1997) .

The meropenem molecular formula is C17H25N3O5S, and it is chemical structure is shown in figure (1). Meropenem has a molecular weight of 383.5 (Sundaram and Björnsson, 2017). This drug is a white to light yellow powder that is given intravenously every 8 hours at a dose of 0.5 to 1 gram, with dose adjustments for renal impairment (Moon et al., 1997). Meropenem is sold as a generic and under the brand name Merrem in 500 mg or 1 gram lyophilized powder for injectable vials. Diarrhea, nausea, and vomiting, as well as skin rash and pruritus, are the most prevalent side effects (Linden, 2007).

Meropenem is well tolerated in a wide range of adult and pediatric patient populations, with good central nervous system and gastrointestinal tolerance (pubchem, 2022). This drug was recently classified as category D (low likelihood of hepatotoxicity) in a review of drugs with potential hepatotoxicity, with only two published cases of liver impairment linked with meropenem and no known drug rechallenge (rxlist, 2021), meropenem appears to be broadly distributed in tissues and is cleared by both excretion and metabolism (Tattersall et al., 2018).

Animals studies revealed that oral administration had no effect on systemic absorption . humans studies on an oral product have not been carried out., it can be administered intravenously (IV) or intramuscularly (IM) (Sundaram and Björnsson, 2017).

Meropenem was found to be broadly distributed in most organs in animal experiments, with the largest amount observed in the kidney, blood, and urine (Harrison et al.,1989). Yoshida et al. (1993) investigated the penetration of meropenem into the skin of rats with third-degree burns. They discovered that meropenem permeated burned skin better than normal skin, implying that meropenem could be a beneficial drug in the treatment of burn wound infections in human. Tattersal et al. (2018) found that meropenem can cause serious liver damage and that early detection of drug-induced liver damage is critical.

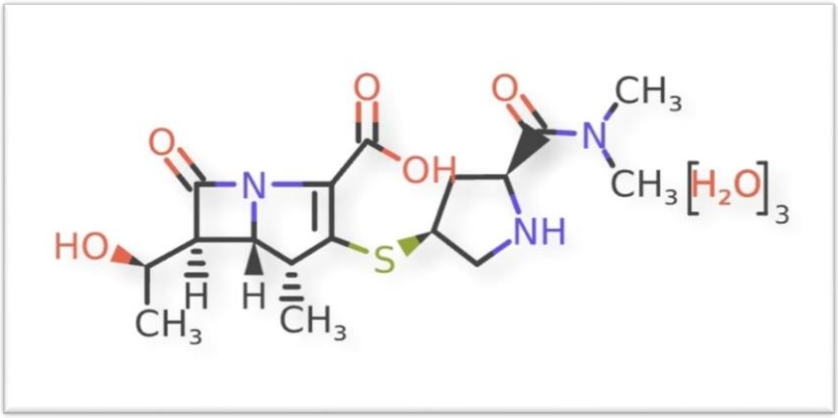

Figure (1) The chemical structure of meropenem (Moon et al., 1997)

Materials and Methods

Experimental animals: Nine , 6-week- old male albino mice with a mean body weight of 26.83±0.40 g were purchased from the national center for drug control and research in Baghdad and housed under standardized environmental conditions of constant temperature, moisture, and a 12-hr.light / 12-hr. dark cycle, without stress factors. Mice were given laboratory food and water.

Study Design: Albino mice were divided into two groups based on the following :

Group 1: control group; contains three mice received standardized lab food and water without treatment.

Group 2 : treatment group; contains six mice received 0.1 ml of meropenem at a concentration of 100 mg / kg injected into the caudal vein for 14 days. Before and after treatment, all of the animals were weighted. At day 15, mice were weighted and euthanized; and their livers were carefully removed, weighted and fixed in 10% buffered formaldehyde solution for histological examination.

Statistical Analysis: To examine the impact of meropenem on research parameters, the Statistical Analysis System (SPSS) program was used. In this study, the least significant difference (LSD) test was utilized to make a significant comparison between means. When P values ≤ 0.05, differences between treatments were considered statistically significant.

Results and Discussion

Behavior changes: The treated animals exhibited lethargy and introversion, as well as increased food and water consumption, leading in little weight gain. Swelling and redness were observed in the injection area in the tail.

Liver Morphology: After treatment, the treated group's liver showed pallor at the edges and blood vessel congestion, whereas the control group's liver was dark red in color, with a smooth surface and firm consistency (Figure 2).

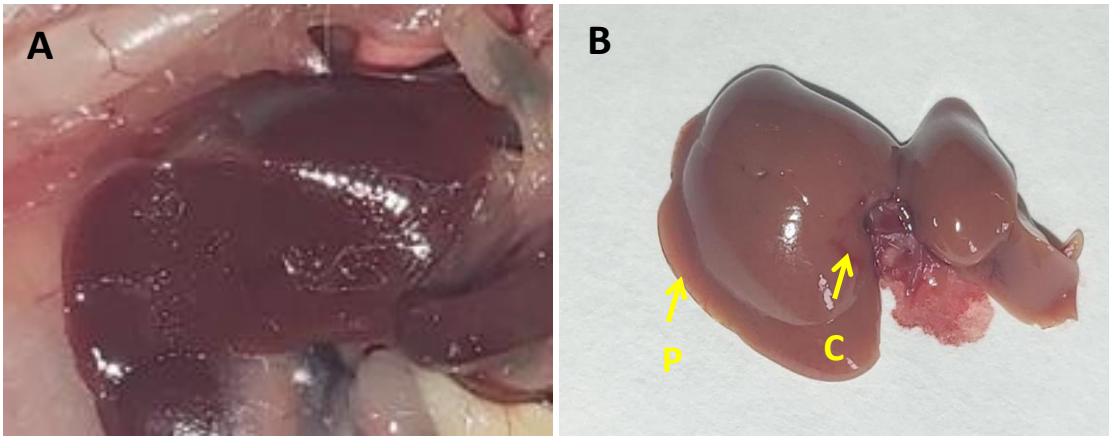

Figure (2) Liver morphology (A) in control group (B) After intravenous injection of 100 mg/kg meropenem in mice for 14 days. The treatment revealed pallor liver edges and blood vessel congestion.

Weight changes: The average body weight of treated animals was statistically significant decrease (P≤0.05) after 14 days of exposure when compared to the control group (Figure 3; Table 1).

When compared to the control group (1.49 ± 0.14), the average weight of the liver in the treated group is not significant (1.36 ± 0.09).

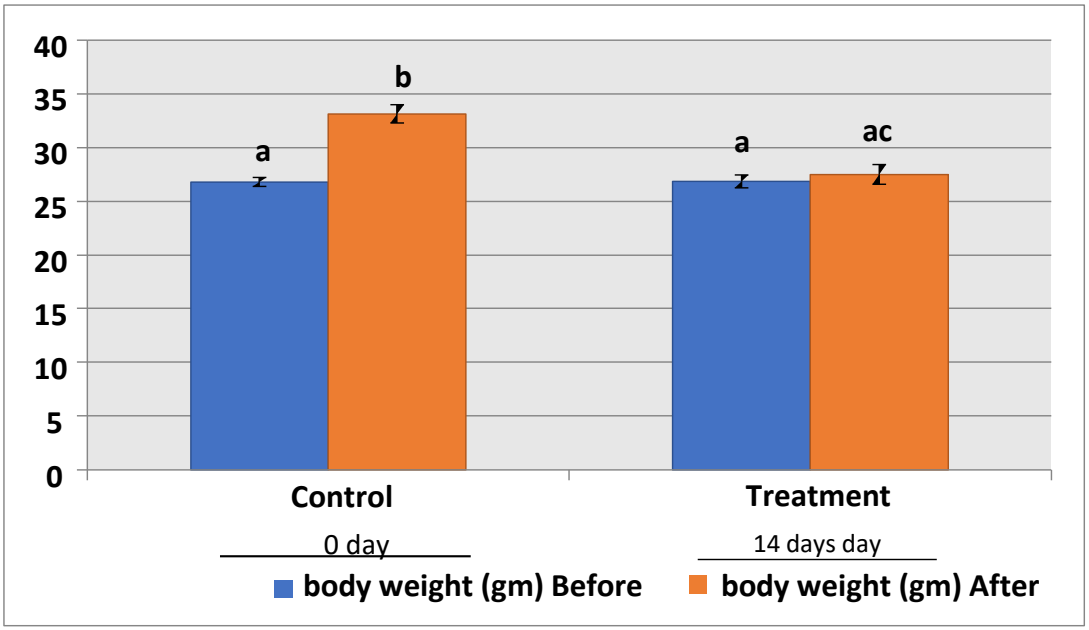

Table (1): showed alteration in the mean Body weight of animals after 14 days of injection with 100 mg/kg meropenem

Treatment	Mean body weight (gm)
Control	33.13 ± 0.84a
100 mg/kg meropenem	27.49 ± 0.93c

Data represent the mean ± standard error (SE). different small letter means significant difference at P ≤ 0.05.

Histological changes: The liver in the control was dark red in color, with a smooth surface and a firm consistency. This group's sections showed healthy hepatic lobules with normal hepatocytes and sinusoids (Figure 4). After 14 days, microscopic examination of treated group liver sections revealed severe congestion of blood vessels in the portal area and central veins, an increase in the number of cells with divided nuclei, hepatocytes degeneration and necrosis with pyknotic and atrophy of nuclei, infiltration of mononuclear inflammatory cells, cytoplasmic vacuolation, and sinusoid space expansion (Figure 5 to 7).

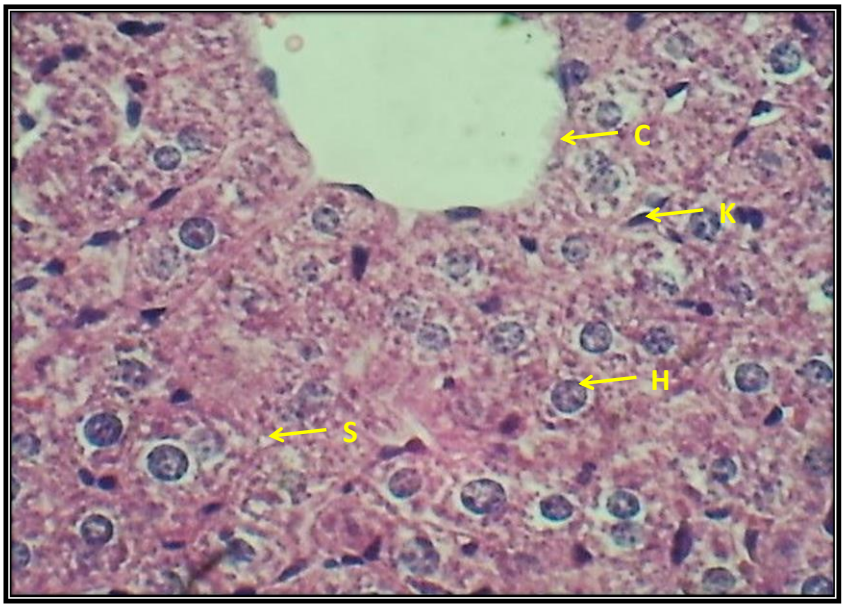

Figure (4) Cross section of the liver from the control group showed normal histology of hepatocytes (H) , hepatic sinusoid (S), central vein (C), and kupffer cells (K). Stained with Hematoxyline – Eosin 40X.

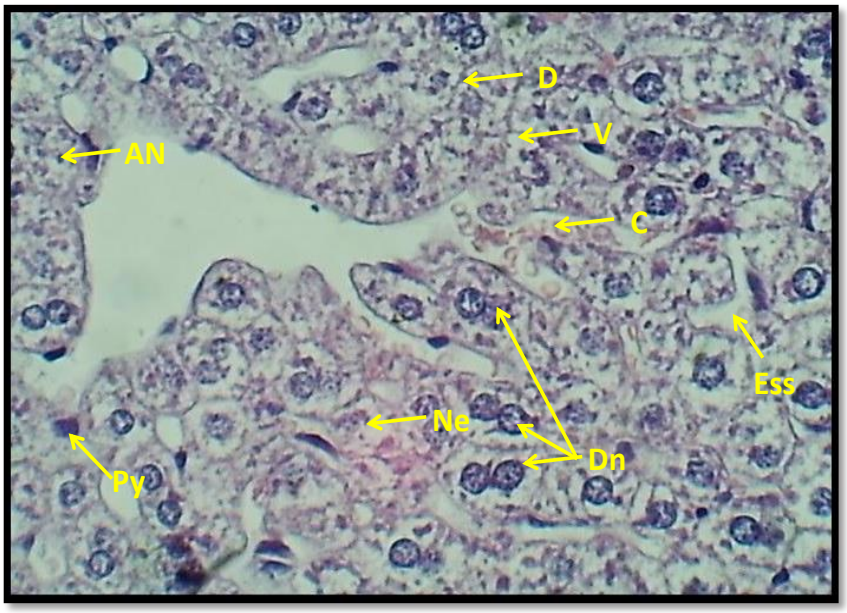

Figure (5) section of the liver from the treated group after 14 days of injection showed injuries involved hepatocytes necrosis (Ne); degeneration (D); blood vessels congestion (c); increased the number of cells with divided nuclei (Dn); expansion of sinusoid space (Ess); pyknotic nuclei (Py); atrophy of nuclei (AN) and cytoplasmic vacuolation (V). Sections stained with Hematoxyline – Eosin 40X.

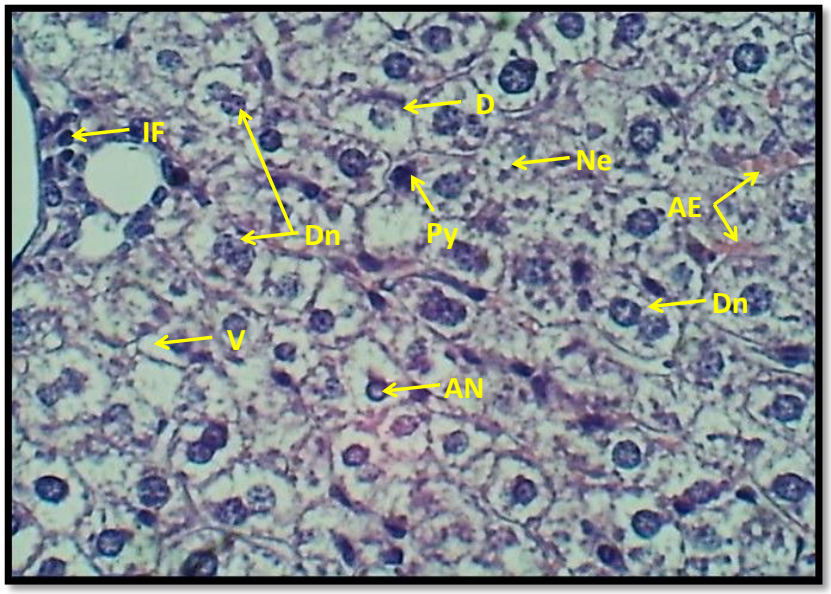

Figure (6) Cross section of the liver from treated group showed injuries involved hepatocytes necrosis (Ne); degeneration (D); increased the number of cells with divided nuclei (Dn); infiltration of mononuclear inflammatory cells (IF); pyknotic nuclei (Py); aggregation of erythrocytes (AE); atrophy of nuclei (AN) and cytoplasmic vacuolation (V). All sections stained with Hematoxyline – Eosin 40X.

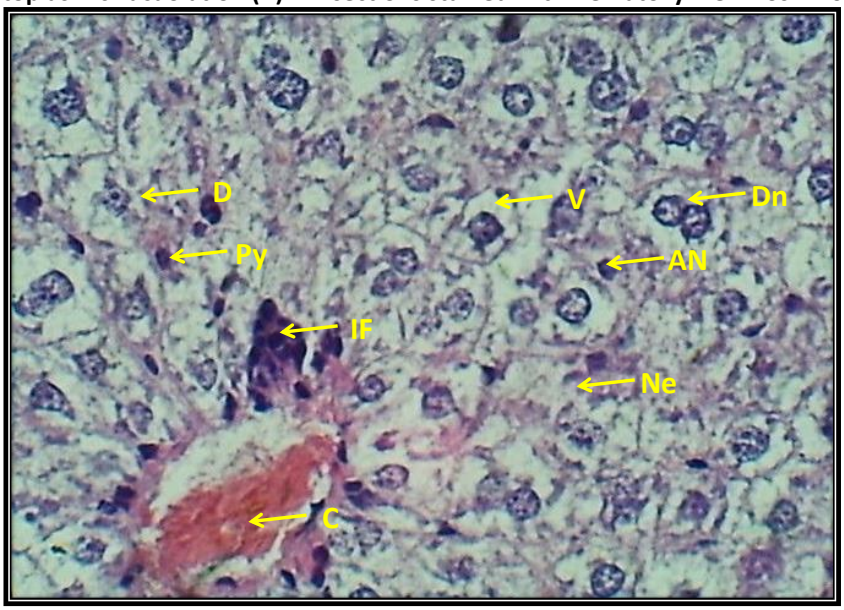

Figure (7) Cross section of the liver from the treated group showed hepatocytes necrosis (Ne); degeneration (D); blood vessels congestion (C); increased the number of cells with divided nuclei (Dn); infiltration of mononuclear inflammatory cells (IF); pyknotic nuclei (Py); atrophy of nuclei (AN) and cytoplasmic vacuolation (V). Sections stained with Hematoxyline – Eosin 40X.

A recent study on mice revealed several changes at various levels. This study showed behavior changes such as lethargy, introversion and increased food and water consumption, which could be due to the drug's side effects of headache , nausea and dizziness This was linked to post-injection inflammation in mice, as well as swelling and redness in the injection site . An allergic reaction to the drug is a Less prevalent cause (Mayoclinic, 2022).

Near the liver's margin, changes in liver morphology have been associated with a certain amount of pallor. This liver pallor may be brought on by

hemorrhage, edema, anemia, pathological dilatation, or the diffusion of CO_2 from Hb. Blood vessel congestion was also observed, which could be caused due to this drug. Meropenem is one of the Idiosyncratic drug-induced liver injury (iDILI). According to Ye et al. (2018), the mechanism of iDILI involves activation of both the innate and adaptive immune system.

In the present study, mice exposed to meropenem had considerably lower mean body weight. This decrease in body weight could be attributed to the exposed- reduced mice's food consumption or to the liver damage [14]. As a previous study by Mohamad et al. on mice treated with duprost that showed appetite and weight loss, as well as aggressive behavior (Mohamed et al., 2017).

The liver is a prominent target organ for chemicals and drugs because it is engaged in xenobiotics metabolism . As a result, hepatotoxicity is an important endpoint in the evaluation of xenobiotics effect. Clinical chemistry and histopathological evaluations are commonly used methods for detecting organ-specific effects related to chemical exposure (Mayoclinic, 2022). Hepatocyte degeneration stems, which leads to hepatocyte death by apoptosis and necrosis (Ye et al., 2018).This clarifies the causes of the tissue alterations that occur in the current study.

The most important and prevalent outcomes of drug induced liver injury include necrosis, inflammatory response, and apoptosis (Kleiner, 2018). Apoptosis is the body's control over programmed cell death and regular cell turnover Renehan et al., 2001).It is caused by chemicals, and drugs exposure. According to this study, meropenem cause direct DNA damage. In a previous study, histological findings of the effects of duprost drug on the liver revealed that the liver showed hepatotoxicity as evidence by the formation of granulomatous lesions in the liver parenchyma, inflammatory cells in dilated sinusoids, as well as inflammatory cells aggregation close to the blood vessels wall (Mohamed et al., 2017). The alterations in the liver architecture in response to meropenem could be due to its toxic effects, which are principally caused by the formation of reactive oxygen (ROS) that cause damage to the various membrane components of the cell. Previous research has shown that paracetamol causes mild focal hepatitis in the lobules and portal areas (Roomi et al.,2008; Ibrahim et al., 2011) as well as necrosis in rats (Ibrahim et al., 2011) and hemorrhagic, necrosis in humans, with pyknosis and eosinophilic cytoplasm (Boyd and Bereckzky,1996; Clark et al.,1974)

Conclusion

In conclusion, these findings show that meropenem has a negative impact on liver structure and function.

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