Negative effect of therapeutic, double and overdoses of cefixime on the liver and kidneys of male albino rats

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Abstract

This study was designed to investigate the negative effect of double and excessive doses on the treatment of cefixime on male rats. 20 animals were selected with weights ranging from 190-200 mg and were in good health. These animals underwent good ventilation and appropriate laboratory conditions. The animals were divided into four groups, the first group was drawn with distilled water and the control group was returned, the remaining three groups were dosed using cefixime as a therapeutic dose, double dose, and overdose, respectively. After the 21-day dose, the results showed that tissue damage occurred in the liver tissue and significantly increased its enzymes in dosing groups with cefixime. Also, tissue damage in the kidneys with a significant decrease in the level of urea and a significant increase in the creatinine level of cefixime doses compared with the control group.

Key word: Cefixime, Liver Enzyme AST, ALT, Urea, Creatinine

How to cite this article: Shaker SH, Razooqi QA, Shaban RK (2020): Negative effect of therapeutic, double and overdose of cefixime on the liver and kidneys of male albino rats, Ann Trop Med & Public Health; 23(S13B): SP231389. DOI: http://doi.org/10.36295/ASRO.2020.231389

1- Introduction:

Cefixime is widely used in treating infections in children, and it can commonly cause minor gastrointestinal adverse effects. However, hepatotoxicity and acute renal failure are among the rarely reported serious adverse drug reactions of cefixime and other cephalosporins. Cefixime is a third-generation cephalosporin that is indicated for the treatment of infections caused by various pathogens, especially gram-negative bacteria. It is generally a well-tolerated and safe antibiotic. Its common adverse effects are gastrointestinal disturbances such as abdominal pain and indigestion (3%), diarrhea (16%), flatulence (4%), loose stool, and nausea (6%–7%) [1]. Cefixime is a third generation semi-synthetic orally active cephalosporin and is well stable to inactivation by beta-lactamase enzyme. It is effective against different human ailments including drug resistant enteric fever. Cefixime is a bactericidal drug causing its action by inhibiting synthesis of the bacterial cell wall [2]. Cefixime is an antibiotic useful for the treatment of a number of bacterial infections. This includes middle ear infections, endocarditis, meningitis, pneumonia, bone and joint infections, intra-abdominal infections,
skin infections, urinary tract infections, gonorrhea, and pelvic inflammatory disease. It is also sometimes used before surgery and following a bite wound to try to prevent infection. Cefixime can be given by injection into a vein or into a muscle and orally tablet form. [3] It is on the WHO Model List of Essential Medicines, the most effective and safe medicines needed in a health system.[4].

The half life of a drug is a derived parameter that changes as a function of both clearance and volume of distribution. The apparent volume of distribution of a drug is a function of the volume of tissues in which drug distributes, partition coefficient of drug between tissues and circulatory blood, the blood flow to the tissues and binding of drugs to the plasma and tissue proteins. The total body clearance depends upon blood flow to the organ, fraction of unbound drug in blood and maximal ability of the organ to remove the drug. Most of these factors are under environmental and genetic control . [5,6] . Clinical studies are generally underpowered to identify trends in hepatotoxicity, while studies undertaken to assess hepatic signals are often complicated by numerous variables. With few prospective population-based studies, case histories and registries of spontaneous reports of adverse drug reactions are actually the main source of toxicity data.[7].

2- Material and Methods
2-1- Animals:
In this study, 20 adult male rats weighing (180-200) grams were used. The animals were raised in a room under standard conditions for ventilation, temperature (25 ± 2 °C), humidity (60-70%) and light / dark condition (12/12). The animals were supplied with water and fed a standard commercial feed.

2-2- The design of experiment:
The experiment was designed as rats were randomly distributed into four groups.

Group 1: Dosing each animal 1 ml of distilled water and served as control.

Group 2: Doses of animals with cefixime (Therapeutic dose) (30 mg/kg b. wt.)

Group 3: Doses of animals with cefixime (Double dose) (60 mg/kg b. wt.)

Group 4: Doses of animals with cefixime (Overdose) (120 mg/kg b. wt.)

Cefixime was orally Dosage once daily for 21 consecutive days.

The dose of cefixime treatment was determined based on the dose given to human [8].

2-3- Preparation of Blood
At the end of the experiment rats were fasted for 24 hours. Blood samples were collected directly using cardiac catheterization in the tubes free of any anticoagulant agent to separate the serum into the experimental samples for biochemical analysis, including urea, creatinine and liver enzymes.

2-4- Histopathological

Liver and kidney tissue samples were fixed in formalin 10% 24 hours ago, dehydration by ethyl alcohol in increasing concentrations (70%, 80%, 95%, 100% and 100%), cleansed with xylene and then combined with paraffin. Upon analysis, all embedded paraffin tissue was divided at (5µm) stained with hematoxylin and eosin. These samples were examined under a 40X magnification optical microscope.

3-Results
3-1- Physiological standards:

It is noted from the table that the treatment of male rats with Cefixime with therapeutic, double and overdose resulted in significant reduction events. (P≤0.05) In urea level and significant increase. (P≤0.05) liver enzymes AST, ALT, compared with the group of healthy animals (control group). the creatinine no statistically significant differences (P≥0.05). were observed in the therapeutic and double dose group, but a significant increase (P≤0.05). in its concentration was observed in the cefixime overdose group compared with the control group.

Table shows the concentration of liver enzymes, urea and creatinine

<table>
<thead>
<tr>
<th>Standards Groups</th>
<th>ALT (mIU/ml)</th>
<th>AST (mIU/ml)</th>
<th>Creatinine (mg/dl)</th>
<th>Urea (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>46±3</td>
<td>140±2</td>
<td>0.38±0.3</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>Therapeutic cefixime group</td>
<td>56±1</td>
<td>170±2</td>
<td>0.34±0.2</td>
<td>36±3</td>
</tr>
<tr>
<td>Double dose cefixime group</td>
<td>69±2</td>
<td>257±2</td>
<td>0.38±0.3</td>
<td>33±1</td>
</tr>
<tr>
<td>Overdose cefixime group</td>
<td>78±2</td>
<td>246±3</td>
<td>0.47±0.2</td>
<td>34±2</td>
</tr>
</tbody>
</table>

- The values represent the arithmetic mean of the standard error.
- Vertically different letters mean there is a significant difference at the level of significance (P ≤ 0.05).
- Number of animals 4 in each group.
3-2- Histological results of liver and kidney tissue:

Image (1) The liver section of the control group illustrates the central vein (CV) and hepatocytes (HC) arranged around it in the form of hepatic cords and the possibility of observation of hematopoiesis (S) H & E 400X.
Image (2) The liver section Cefixime therapeutic group demonstrates central vein (CV) and fatty degeneration in hepatocytes (FD) H & E 400X.

Image (3) The liver section Double dose Cefixime group demonstrates the thickness of the central vein wall (TW) and hepatic cell degeneration (HC) and central vein congestion (CON) and indistinguishable liver boundaries H & E 400x.

Image (4) Liver segment Cefixime overdose group shows the dissociation of the central vein lining.
(DES) and hepatic cell degeneration (HC) and necrosis of some cells (N) and indistinguishable hepatocytes H & E 400X.

Image (5) segment kidney control group illustrates the renal glomerulus (G), proximal twisted tubules (PCT) and distal (DCT) H&E 400X.

Image (6) The kidney section of the Cefixime therapeutic group demonstrates hemorrhage within the kidney tissue (H) as glomerulus can be observed naturally (G) and urinary tubules (UT) H & E 400X.
Image (7) segment kidney the double Cefixime group clip shows hemorrhage within the kidney tissue (H) and histological necrosis (N) H & E 400X.

Image (8) segment kidney Cefixime group overdose shows the breakdown of renal glomerular walls (GW) and necrosis of urinary tubule cells (N) H & E 400X.
4- Discussion:

Notes from the table that the treatment of male rats with Cefixime with therapeutic, double and overdose resulted in significant reduction events ($P \leq 0.05$). In urea level compared with the control group. This result was not consistent with the results of Ahmed [10] who used Cefotaxime in albino rats, where he observed a significant increase in the level of urea. It is believed cause of reduced urea concentration is largely confined to advanced liver disease [11]. This reflects the central role that the liver plays in urea production via the urea cycle. Some antibiotics are considered a common cause of drug induced liver injury [12].

He also pointed [13] out that the reason for the low concentration of urea is due to advanced liver disease (cirrhosis, liver failure). It was also observed from the table that there was a significant increase in the level of creatinine only in the overdose group cefixime compared with the control group. This result is consistent with both Ahmed [10] and [14].

Creatinine and urea levels in the blood are common biochemical, which are the criteria used to determine kidney function. Creatinine uses the plasma level to determine the glomerular filtration rate during urea, and is used to determine the renal toxicological properties of antibiotics [15]. In this study, impaired renal function in cefixime overdoses increased significantly in plasma creatinine, compared with the rest of the groups. It is an indicator of the toxicity of the kidneys that causes a decrease in the
glomerular filtration rate which leads to creatinine build-up in the blood[16]. It is noted from the above table that the dose of animals with cefixime resulted in a significant increase in the concentration of liver enzymes ALT and AST compared with the control group. These results were consistent with both [10] and [20] Khaled [17].

It is well-known that cefixime is widely used as a third generation cephalosporin antibiotic that has a broad spectrum of bactericidal activity [18]. However, an increasing number of evidence indicates that it has risk of elevation of the liver enzyme, cholestatic abnormalities and liver injury as adverse effect [19, 20]. The increase in liver enzymes may be from rat doses with cefixime due to damage to the liver tissue and thus increase levels of AST and ALT enzymes in the blood serum. [21].

The liver section Cefixime therapeutic group demonstrates central vein (CV) and fatty degeneration in hepatocytes (FD) and The liver section Double dose Cefixime group demonstrates the thickness of the central vein wall (TW) and hepatic cell degeneration (HC) and central vein congestion (CON) and indistinguishable liver boundaries as for Liver segment Cefixime overdose group shows the dissociation of the central vein lining (DES) and hepatic cell degeneration (HC) and necrosis of some cells (N). These results are consistent with [22]. Also noted from the histological sections of the kidneys of rats treated with cefixime bleeding is shown inside the kidney tissue (H) with histological necrosis (N), renal glomerular walls break down (GW) and necrosis of urinary tubule cells (N). These results are consistent with [21,22].

5- Conclusions:

The current study found that, for a long time, therapeutic, double and excessive doses of cefixime treatment had a negative and histological effect on the liver and kidney tissues.

References:


