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Gentamicin and tigecycline combined treatment potentiates liver injury in rats

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ABSTRACT

In most diseases, concurrent exposure to antibacterial is essential. The purpose of this research is to determine how co-administration of the antibiotics gentamicin (an aminoglycoside) and tigecycline (a tetracycline) affects the liver of rats. Rats received distilled water, tigecycline 7 (TIG 7), tigecycline 14 (TIG14), gentamicin (GEN), tigecycline 7 + gentamicin, and tigecycline 14 + gentamicin groups. After 10 days, TIG and/or GEN caused tissue damage that is seen in considerable biochemical changes in assays of liver functions. Also, a significant elevation of AST, ALT, ALP, cholesterol, and a significant decrease in albumin after TIG or GEN treatment when compared to control groups were observed. A considerable increase in these parameters was observed following TIG and GEN combination. Besides this, there were noticeable pathological alterations in the tissues of the liver. In addition, after TIG and GEN treatment, there is a considerable overexpression of PCNA in the tissues of the liver. As a result, TIG and GEN therapy administered together caused more evident liver damage than either therapy administered individually. According to the findings overall, using TIG and GEN simultaneously in clinical practice is concerning, so it should be done with caution to prevent synergistic negative results.

1. INTRODUCTION

The liver is the most responsible organ for the detoxification and removal of toxic chemicals, xenobiotics, and different medications (Abdou et al. 2020; Soliman et al. 2022a,b). Because of this, even at therapeutic levels, any drug might have an adverse effect on the liver (Osterreicher and Trauner, 2012). Consequently, one of the most frequent reasons for post-marketing cautions and drug withdrawals is hepatotoxicity (Shehu et al. 2017).

Gram-negative bacterial infections are treated with aminoglycoside antibiotics, which are extremely powerful and have a broad spectrum of activity (Becker and Cooper, 2013; Ali et al. 2020). The most significant member of the aminoglycoside family, gentamicin (GEN), is frequently used in human clinics to treat life-threatening Gram-negative infections (Bijleveld et al. 2016). Despite their positive effects, there is substantial evidence that GEN may have a hepatotoxic adverse effect, which could limit their clinical use in the future (Khaksari et al. 2021). According to these suggested processes, oxidative stress and inflammation are two of the main factors contributing to the hepatotoxicity caused by GEN therapy (Arjinajarn et al. 2017).

Tigecycline (TIG) is a 1st generation glycylcycline antibiotic, especially against multidrug-resistant bacteria and has a broad-spectrum action (Cui et al. 2019; Elgazzar et al. 2022). TIG is a parenteral, bacteriostatic glycylcycline antibiotic. TIG's primary mode of action is similar to that of other tetracyclines in that it inhibits the translation of bacterial proteins by reversibly binding to a region of helical structure on the 30S subunit of bacterial ribosomes (Yaghoubi et al. 2022). Additionally, it effectively overcomes Acinetobacter baumannii (Liu et al. 2018). The majority of patients in intensive care units have complex medical conditions, several common diseases, immunosuppression, regularly invasive procedures, and need broad-spectrum antibacterial medications (Cui et al. 2019). It has an extremely long half-life in humans and is primarily eliminated unmodified in the bile (27–42 h). TIG effectively and extensively penetrates tissues and fluids, including the lungs, skin, liver, heart, bone, and kidneys, to reach therapeutic concentrations (Yaghoubi et al. 2022).

Tigecycline when used in combination with aminoglycosides rather than alone, it may have a synergistic effect that slows the development of tigecycline resistance. In clinical practice, such a combination might be a successful alternative for treating respiratory infections (Ni et al. 2021). It might be difficult for clinicians to manage serious infections like pneumonia and bacteremia. Numerous in vitro researches have examined the synergistic effects of aminoglycosides and tetracyclines against Enterobacteriaceae (Ni et al. 2021). Doxycycline and amikacin combinations showed beneficial synergistic effects against E. coli isolates (Lai et al. 2016).

The goal of this research was to show the optimistic effects of the sequence of administration of TIG / GEN combination and analyze the association between the high dose of TIG and GEN to investigate the role of apoptosis in the hepatic toxicity.

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2. MATERIAL AND METHODS

2.1. Drugs

TIG (Tygacil®, 50 mg/ml, Pfizer Inc, Cairo, Egypt), GEN (Garamicin®, 80 mg/ml, Memphis, Cairo) were purchased commercially.

2.2. Experimental animals

Thirty Wister albino male rats weighing 160-200 g were obtained from the Laboratory Animal Center, Faculty of Veterinary Medicine, Benha University Egypt. Rats were acclimatized for 2 weeks, at temperature of 25°C. Rats were given a commercial diet and free access to water. Ethics Committee of the Faculty of Veterinary Medicine, Benha University approved the study (BUFVTM 04-02-21).

2.3. Experimental design

Six equal groups of rats were formed (5 rats each). 1st (Vehicle Control) received distilled water. 2nd (TIG7); 3rd (TIG 14 mg/kg IP: Vergidis et al. 2015) and fourth Group; GEN treated rats were injected GEN (80 mg/kg/day, IP; Soliman et al. 2007). The 5th group (GEN + TIG7) rats received GEN (80 mg/kg/day, IP) + TIG 7 mg/kg IP: and the 6th group (TIG 14 + GEN) received GEN (80 mg/kg/day, IP) + TIG 14 mg/kg IP. Both drugs were given as a single daily dose for ten days

2.4. Sampling:

Rats were euthanized 24 h after the end of the experiment; two blood samples were collected from ocular veins; first on EDTA for hematological study and second for obtaining serum for biochemical analysis. Hepatic samples were collected for histopathological and immunohistochemical examination.

2.5. Serum biochemical analysis:

The biochemical markers were aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (ALP), cholesterol, and albumin. The previous biochemical tests were evaluated in accordance with data protocol provided by using commercial kits purchased from Bio Diagnostic Company, Giza, Egypt.

2.6. Histopathological and immunohistochemical examination

For histopathology, the liver tissue from each rat was rapidly fixed in 10% neutral-buffered formalin. The specimens were gradually dehydrated, embedded in paraffin, cut into 5-µm sections, and stained with hematoxylin and eosin (H&E) according to the method described by Bancroft and Gamble (2008). Then light microscopy was used to examine liver tissue sections (Leica, Germany). The immunohistochemical study was performed using proliferating cell nuclear antigen (PCNA) according to Wang et al. (1997).

2.7. Statistical analysis:

Statistical analysis was carried out utilizing SPSS (Version 20; SPSS Inc., Chicago, USA).The considerable variations through groups were estimated by one-way ANOVA using the Duncan test as a post hoc. All values are explicated as mean ± SE, with significance considered at $P \leq 0.05$.

3. RESULTS

3.1. Effect of TIG and GEN combination on biochemical parameters

Concerning the biochemical parameters results, rats administrated GEN showed significant elevation of AST, ALT, ALP, and cholesterol, and a significant decline in albumin when compared to control groups. A considerable increase in these parameters was observed following TIG and/or GEN administration and these results were recorded in Figure 1.

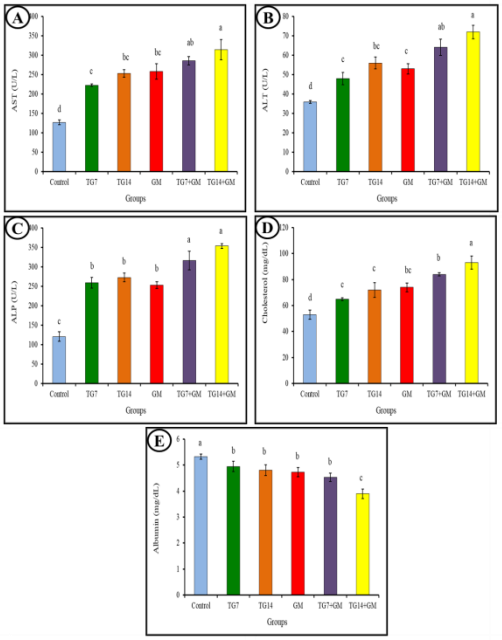

Figure (1): Effect of TIG and/or GEN on liver biomarkers including, ALT, AST, ALP, albumin, and cholesterol.

3.2. Histopathological changes in liver

Liver sections of the control group demonstrated normal architecture of portal area homing portal vein, hepatic artery, and bile duct (Fig 2A). TIG 7 appeared with necrosed areas surrounding the central vein and hepatic cords observed with slight disorganization. Degenerated endothelium of hepatic sinusoids (Fig 2B). TIG14-treated group revealed a congested portal vein and infiltrated inflammatory cells surrounding portal area (Fig 2C). GM-treated group exhibited obvious infiltration of inflammatory cells surrounding portal area, necrotic areas and sub-endothelial edema (Fig 2D). TIG7+GM (Fig 2E) and TIG14+GM (Fig 2F) showed severe degenerative changes along hepatic tissue with complete loss of its normal architecture. Most hepatocytes in a congested portal vein were apoptotic, with degenerated sinusoids and desquamated endothelium.

3.3. Effect of TIG and GEN combination on PCNA protein expression level

Hepatocytes immunoreactivity of PCNA was represented by nuclear and/or cytoplasmic brown staining. Control group emphasized negative reactivity to PCNA antibody (Fig 3A). TIG 7 (Fig 3B), TIG 14 (Fig 3c), and GEN-treated group (Fig 3D) showed marked moderate nuclear PCNA reaction. TIG 7 + GEN (Fig 3E) and TIG 14 + GEN-treated groups (Fig 3F) showed markedly increased PCNA expression.

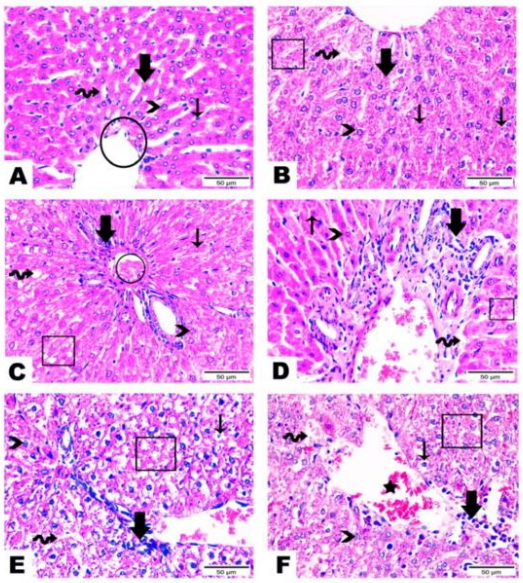

Figure (2): Photomicrographs presented the pathological variations in liver tissues among examined groups as follows: (A) Liver sections of Negative Control Group displayed area of central vein with typical lining endothelium (circle) and emerged from it, organized hepatic cords (thick arrow) encircled polygonal hepatocytes with great circular central light vesicular nucleus (arrowhead). The cords split up by hepatic sinusoids (wave arrow) with its Kupffer cells lining (thin arrow). (B) Liver section of TIG7 treated group demonstrated necrosed areas surrounding central vein (cube). Slight disorganization (thick arrow) of hepatic cords was observed. Hepatocytes marked mostly in alight vesicular form (arrowhead) except a few detected in apoptotic appearance (thin arrows). Notice degenerated endothelium of hepatic sinusoids (wave arrow). (C) Liver section of TIG14-treated group revealed congested portal vein (circle) and infiltrated inflammatory cells surrounding portal area (thick arrow). Hepatic cords are labeled with high vacuolations (cube) and encircled by dilated hepatic sinusoids (wave arrow). Hepatocytes appeared in normal (arrowhead) as well as karyolitic form (thin arrow). (D) GM-treated group exhibited obvious infiltration of inflammatory cells surrounding portal area (thick arrow), necrotic areas (cube), and sub-endothelial edema (wave arrow). Hepatocytes posed light vesicular form (arrowhead) as well as apoptotic one (thin arrow). TIG7+GM & TIG14+GM (E & F) showed severe degenerative changes along hepatic tissue with complete loss of its normal architecture (cubes). Congested portal vein (star) as well as aggregated inflammatory cells (thick arrows) posed allocation of portal area. Light vesicular appearance of few hepatocytes (arrowheads) while apoptotic shape in most hepatocytes (thin arrows). Notice degenerated sinusoids with desquamated endothelium (wave arrows). (H&E staining, & Scale Bar= 50µm).

4. DISCUSSION

It is known that gentamicin might cause hepatotoxicity (Ali et al. 2020; Khaksari et al. 2021; Bulboacă et al. 2022). For the current experimental animals, a variety of blood chemical parameters, including the enzymes used to assess organ functioning, were estimated. The blood levels of ALT, AST, and ALP significantly increased in the current study. Various enzymes' levels are extremely sensitive to the health or diseases of these organs (Tietz, 1996). The findings of the current study are consistent with those of previous studies (Khaksari et al. 2021; Bulboacă et al. 2022).

Additionally, it was discovered that the rise in serum ALP levels was associated with cholestasis-related liver cell injury and elevated biliary pressure (Clemens et al. 2019). It's interesting to note that one of the main causes of GEN-related liver damage has been documented to be excessive formation of reactive oxygen radicals (ROS) (Mohamadi Yarijani et al. 2019). Notably, there is a definite connection between the generation of ROS and inflammation, which has been noted in a variety of illnesses, including hepatic problems (Dandekar et al. 2015).

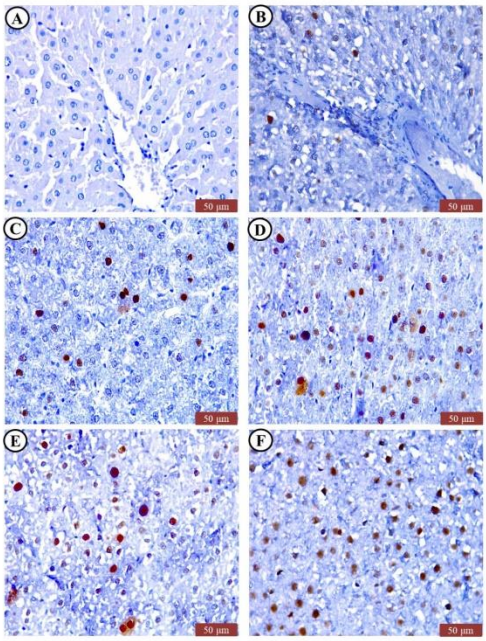

Figure (3): Photomicrographs displayed PCNA antibody reactivity in hepatic tissue sections from different studied groups. (A): Control group presented negative reactivity to PCNA antibody. (B&C): TG 7 and TG 14-treated group exposed little reactivity to PCNA. D) GM treated group exposed moderate nuclear PCNA reaction. (E & F): TG 7 + GM and TG 14 + GM-treated groups emphasized strong nuclear PCNA expression. (PCNA, 400x Magnification, Scale bar = 50µm).

Furthermore, GEN toxicity increases the blood levels of AST, ALT, and ALP, which are typically regarded as sensitive measures of liver function, and damages and/or increases permeability of cell membranes (Khan et al. 2011). ALP, a marker of the endoplasmic reticulum, is widely used to assess the integrity of the plasma membrane while AST is present in both the cytoplasm and mitochondria. The increased level of these enzymes in the serum revealed that the liver of the rat had been damaged by oxidative stress and GEN. Rats treated with gentamicin have higher serum levels of these enzymes (Rashid and Khan, 2017). A substantial increase in the blood levels of ALT and AST in rats given tetracycline (Shabana et al. 2012). Oxytetracycline raised serum AST, ALT, and ALP activity and caused hepatotoxicity in rats (Jayanthi and Subash, 2010; Elshopakey and Elazab).

Oxidative stress based on excessive free radical production may be responsible for the hepatic damage caused by oxytetracycline, as seen by elevated serum levels of the liver injury indicators AST, ALT, ALP, cholesterol, and decreased serum total protein levels (Abdel-Daim and Ghazy, 2015).

The group receiving GEN treatment has considerably higher total cholesterol levels. Similar results were

mentioned by Shahidullah et al. (2016). The results of the calculated serum cholesterol level are similar to those of Abu-Spetan et al., (2001) who demonstrated that GEN treatment produces a significant elevation in the cholesterol level. This finding can also be compared with the study of Akter et al., (2013) who stated that mice treated with GEN showed a significant increase in blood TC level. Additionally, there was a considerable increase in cholesterol levels in the serum of rats given doxycycline (Shabana et al. 2012).

The present study stated that a significant decrease in albumin after TIG or GEN treatment when compared to control groups. GEN lowered the levels of Albumin in the serum of rats (Aboubakr and Abdelazem, 2016). Furthermore, rats given doxycycline had considerably lower levels of albumin (Shabana et al. 2012).

Tigecycline is mostly metabolised in the liver, where it is also released in bile together with its metabolites. The liver contributes significantly to coagulation by producing clotting factors (Heinz and Braspenning, 2015). One patient in case reports showed elevated transaminase and total bilirubin levels after receiving tigecycline despite not having a liver disease (Sabanis et al. 2015). However, Sun et al. (2017) found that 33 of 59 patients had an elevated ALT or total bilirubin level.

On the other hand, there was no significant hepatotoxicity of therapeutic doses of oxytetracycline and GEN to carp (Kondera et al. 2020).

Our histological analysis of liver sections collected from rats treated with TIG and GEN either alone or concurrently revealed the observed hepatic dysfunction. Histopathological investigation indicated liver lesions in both the TIG and GEN treated groups, with the combination group showed the most severe lesions. Similar results were reported by Ali et al. (2020) and Elshopakey and Elazab (2021).

Hepatocytes immunoreactivity of PCNA was represented by nuclear and/or cytoplasmic brown staining. Control group emphasized negative reactivity to PCNA antibody. TIG 7, TIG 14 GEN-treated group marked moderate nuclear PCNA reaction. TIG 7 + GEN and TIG 14 + GEN-treated groups markedly increased PCNA expression. PCNA was detected in the nucleus of cells and was involved directly in DNA replication. According to some researchers, PCNA can also cause apoptosis in cells exposed to oxidative stress (Hidaka et al. 2005).

5. CONCLUSION

The concurrent TIG and GEN treatment elicited additional extensive hepatic, injury than their individual treatment. Based on this study, prescribing TIG with GEN should be done with greater attention and rigorous precautions to avoid their potential side effects.

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