Official Journal Issued by Faculty of Veterinary Medicine

Benha Veterinary Medical Journal

Journal homepage: https://bvmj.journals.ekb.eg/

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Original Paper

Gentamicin potentiate tigecycline induced cardiotoxicity in rats: the cardiac susceptibility to oxidative stress

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ARTICLE INFO

Keywords

Tigecycline
Gentamicin
Apoptosis
Cardiotoxicity
Oxidative stress

Received 15/08/2022
Accepted 02/09/2022
Available On-Line 09/10/2022

ABSTRACT

Tigecycline (TIG) toxicity is a threat to health because of the mortality risk attributed to its overdose. Large doses result in fatal cardiomyopathy and acute cardiotoxicity. Gentamicin (GEN) is an aminoglycoside antibacterial agent that affects kidney function, causing nephrotoxicity. Six groups of rats (n=5) were used. Control (DW), TIG 7 (TIG 7 mg/kg IP), TIG14 (TIG 14 mg/kg IP), gentamicin (GEN), TIG 7+ GEN, and TIG 14+ GEN groups. Cardiac catalase (CAT) activity, glutathione (GSH), and malondialdehyde (MDA) levels in the heart, as well as histopathological changes were recorded. Myocardium from TIG 14+ GEN group exhibited typical changes for myocardial apoptosis and degeneration, as well as an increase in interleukin-6 (IL-6) and annexin-V levels, were recorded specially in the TIG 14+ GEN group. GEN, in addition to its nephrotoxicity, increases TIG-induced cardiotoxicity. GEN may increase the cardiotoxicity of high dose TIG. Particularly large doses of GEN have a negative impact on the cardiac oxidative stress caused by TIG.

1. INTRODUCTION

Tigecycline (TIG) is a glycylcycline antimicrobial agent utilized in treatment of intraabdominal infectious diseases, hospital-acquired pneumonia, diabetic foot infections, skin disease, and infectious disease caused by multidrug-resistant bacteria (Prasad et al. 2012). Even so, preliminary research showed that tigecycline is a new category of anti-cancer drugs. Furthermore, latest evidence has shown that TIG successfully kills leukemia, renal, and hepatic cancerous cells and significantly improves chemotherapy agents in vitro and in vivo at diagnostically achievable levels (Wang et al. 2017).

Even with its anti-cancer properties, increased blood accumulation of tetracyclines can cause life-threatening adverse reactions like liver and renal damage (Sauer et al. 2022). Numerous types of research on tigecycline-induced coagulopathy were also published (Sabanis et al. 2015; McMahan and Moenster, 2017). This procedure leads to major coagulation substance utilization, followed by pathophysiological coagulation, which therefore damages the vascular endothelial barrier and helps to microthrombosis and microhemorrhage (Rajendran et al. 2013). Such pathophysiologic processes that contribute to various system organ ischemia and ischemia-reperfusion injury are linked to an increased risk of cardiovascular risk (Wu et al. 2018).

Moreover its anti-cancer effects, TIG has been shown in multiple studies to hinder mitochondrial production of proteins (Jhas et al. 2013).

There is additionally substantiation that TIG inhibits the manufacturing of enzyme complexes, giving rise to mitochondrial toxic effects; consequently, TIG-induced acute metabolic acidosis is uncommon (Vandecasteele et al. 2018).

Gentamicin (GEN), an aminoglycoside antimicrobial drug, is efficient against deadly infections caused by gram-negative bacteria including both people and animals (Famurewa et al. 2020). Despite the complications associated, it is a potent aminoglycoside antibiotic often used to battle varieties of bacteria that have developed resistance to many antimicrobials (Rosenberg et al. 2020).

Utilizing multiple antimicrobials during the same time is risky if the prescription drugs are responsive to the microorganism or the mixture causes toxicity (Acar, 2000). As a result, the medical consequences of these prescription drugs cannot be ignored (Zolfagharzadeh et al. 2014). Accidental use of these substances may lead to throughout oxidative stress and a wide range of abnormalities such as nephrotoxicity (Edelstein et al., 2018), hepatic illnesses (Rosa et al. 2018), and cardiovascular illnesses (Brunetti et al., 2019), and malignancies (Jing et al. 2014).

The purpose of this study attempts to show the optimistic effects of sequence of administration of TIG / GEN combination and analyze the association between the high dose of TIG and GEN to investigate the apoptosis role in cardiotoxicity.

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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).

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 in Egypt. Rats were acclimatized for 2 weeks, temperature 25°C. Rats were given commercial diet and free access to water. Ethics Committee of the Faculty of Veterinary Medicine, Benha University approved the study (BUFVTM 06-02-21).

2.3. Experimental design

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

2.4. Sampling

Rats were euthanized 24 hours after the trial ended, and blood samples were taken from Retro-bulbar venous plexus. Sera were then separated at 2000 xg for 10 minutes and kept at -20°C for further biochemical tests. A portion of heart was selected for the histological evaluation and fixed in 10% neutral-buffered formalin. While another portion was transferred in isotonic saline for flowcytometry measurements of annexin-v and interleukin-6, another portion was maintained at -80°C for oxidative damage assessment (IL-6).

2.5. Preparation of tissue homogenates for oxidative cascade analysis

Heart (one g) was homogenized using a 5 ml buffer solution containing 50mM potassium phosphate and 1mM EDTA (PH 7.5) and triton-x. The resulting homogenate was centrifuged in a cooling centrifuge for 20 minutes at 4000 rpm, and it was then frozen at -80°C for storage. Following that, the oxidative status was assessed by measuring the levels of MDA, CAT, and GSH. All procedures were carried out in accordance with the manufacturer's instructions (Bio-diagnostics Company, Egypt).

2.7. Histopathological examination

After proper fixation, the cardiac specimens were gradually dehydrated in ethyl alcohol of increasing strength and cleaned in xylene. All specimens were then paraffinized, sectioned into 5 m slices, and histologically inspected after staining with hematoxylin and eosin (H&E).

2.8. AnnexinV-FITC and interleukin-6 (IL-6) assay

Apoptosis and inflammatory cytokines quantification kits (Biorbyt Ltd, Cambridge, United Kingdom) were used. The manufacturer's method was used to assess the levels of apoptosis and inflammatory response using a single-cell suspension from heart tissue as previously described by Pathak and Khandelwal (2009). The analysis was performed using a flow cytometer.

2.9. Statistical analysis

One Way ANOVA using SPSS (Version 21; SPSS Inc., Chicago, USA) was used to do multiple comparisons between treatment groups. P-values were adjusted for multiple comparisons using Duncan's method for post hoc comparisons. All values are explicated as mean and 95% confidence interval. The significant differences were recognized at P a value below 5%. Principal component analysis (PCA) was also used to compare all designed groups.

3. RESULTS

3.1. Effect of TIG and GEN combination on oxidative state of heart tissue

Our findings indicated that the combined application of TIG and GEN therapy caused a noticeable alteration in the oxidative status of the heart cells. Figure (1) showed that when TIG and GEN were administered together, MDA levels significantly elevated in comparison to the control, TIG 14, and GEN groups. The co-administration of TIG and GEN might significantly lower GSH concentration levels associated with a noticeable decline in CAT activity in heart tissue. The changes in the antioxidant components of the heart caused by the combination therapy of TIG and GEN were dose dependent. As can be seen, combination of GEN with a greater dose of TIG (14 mg/Kg) resulted in serious damage.

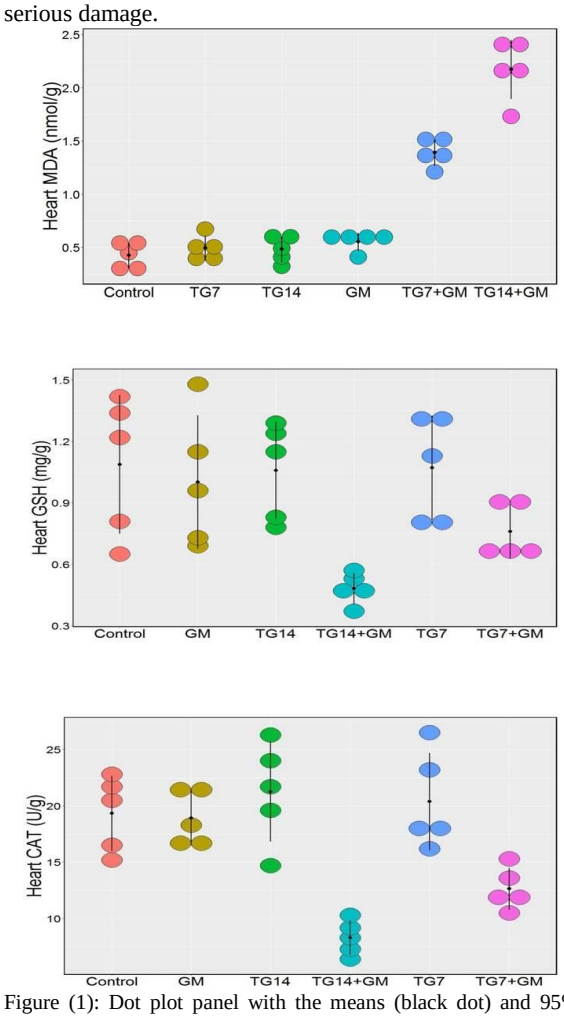

Figure (1): Dot plot panel with the means (black dot) and 95% confidence interval (the stretching out black lines from the means) of the MDA (A), GSH (B), CAT (C), in the control, TIG7, TIG14, GM, TIG7+GEN, and TIG14+GEN.

3.2. Effect of TG and GM combination on apoptosis and inflammatory response

The results of the annexin V study revealed a considerable decrease in the proportion of intact cells, as well as a large increase in the fraction of apoptotic cells (early and late) and necrotic cells in animals given both TIG and GEN versus their sole treatments (Figure 2).Within the above-mentioned data frame, co-administration of GEN with a 14 mg/kg TIG (TIG 14+ GEN group) triggered more apoptotic sequels than the other groups.

Additionally, the TIG and GEN combination therapy induced inflammatory reactions, as shown in Figure (3) by an increase in the tissue levels of the inflammatory cytokine (IL-6). The cardiac IL-6 levels were substantially enhanced in TIG 14+ GEN group compared to control, TIG 14, and GEN groups. Despite the promoted inflammatory reaction in a dose of combined therapy, the intensity of the inflammation was markedly increased in TIG 14+ GEN group compared with other treated groups. These data suggest the effect of TIG and GEN combination has happened in a dose dependent pattern.

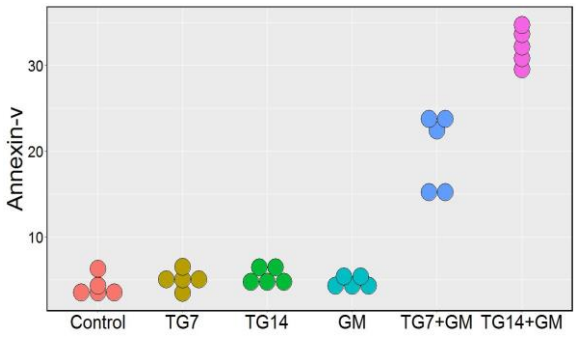

Figure (2): Dot plot panel with the means (black dot) and 95% confidence interval (the stretching out black lines from the means) of the Anexxin-V, in the control, TIG7, TIG14, GEN, TG7+GEN, and TIG14+GEN.

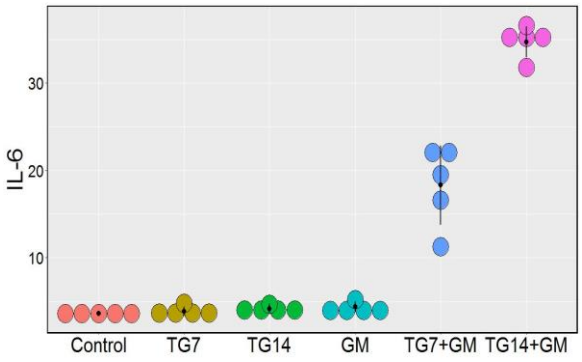

Figure (3): Dot plot panel with the means (black dot) and 95% confidence interval (the stretching out black lines from the means) IL-6, in the control, TIG7, TIG14, GEN, TG7+GEN, and TIG14+GEN.

3.3. Histopathological changes in heart

The examined heart of animals in the normal control group 1 showed myocardium with normal muscle fibers and vesicular nucleus (Figure 4A). In rats treated with TIG7 and TIG 14 alone presented accumulated blood within capillaries and in-between muscle fibers. Notice degenerated muscle fibers (Figure 4B, C). Alongside, GEN-treated group exposed severe inter-muscular extravasation of blood, severe dilatation and congestion of capillaries, and focal degeneration of muscle fibers was noticed (Figure 4D). In prospect cardiac myocyte in (TIG 7 + GEN) AND (TIG 14 + GE) treated group highlighted moderate inter-muscular extravasations of blood, these microscopic lesions do not showed in figure Apoptosis not accompanied by an inflammatory reaction (Figure 4 E, F).

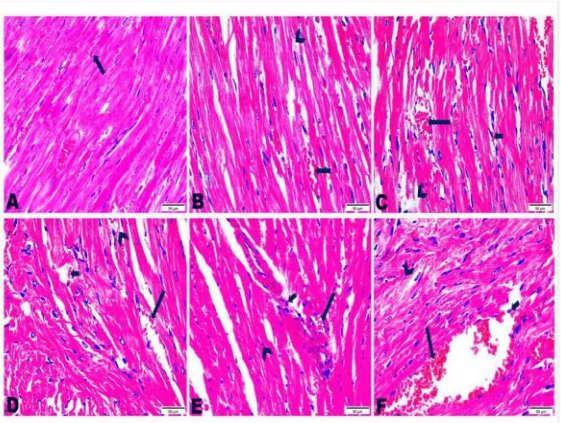

Figure (4): Photomicrographs presented histopathological changes in heart sections between examined groups. (A): Control group. (B): TIG7 (C): TIG14 (D): GEN (E and F): TIG7+GEN and TIG14+GEN, respectively. (H&E stain, x400 magnification, scale bar = 50µm).

4. DISCUSSION

Heart is a remarkably resourceful part of the body, pumping 10 tons of blood per day on mean with 100,000 beats per minute. Its mechanical and electrophysiological capabilities necessitate an effective supply of energy as well as large energy reservoirs. The combination of fatty acid oxidation and mitochondrial oxidative phosphorylation results in relatively effective energy creation in the heart. These procedures produce redox processes in which oxygen plays a crucial role, resulting in the creation of substantial quantities of reactive oxygen species (ROS) (Costa et al., 2012).

Even with this, tetracyclines are known to be successful in lowering inflammation by blocking matrix metalloproteinases (MMPs), a condition that characterizes abdominal aortic aneurysm (Sapadin and Fleischmajer, 2006), preventing excessive angiogenesis, and inhibiting apoptosis. A study by Soory (2008) adds to this by addressing the function of adjunctive tetracyclines medication in the treatment of metabolic disorders and its effectiveness in lowering oxidative stress. The FDA issued a black box warning on the accepted or unapproved use of TIG as it is associated with an increased risk of mortality, and the leading reasons for this higher death rate remain unknown (Yaghoubi et al., 2021).

Oxidative stress, a known risk for coronary artery disease (CAD), potently evidenced the onset of atherosclerosis, and NADPH oxidases have been capable of creating reactive oxygen species (Lüscher, 2015). Furthermore, NADPH oxidases isoforms composed of a multitude of catalytic subunits (Nox1, Nox2, Nox3, Nox4, Nox5, Duox1 and Duox2) are primarily involved in the pathophysiology of atherosclerosis (Taleb et al., 2018; Abougomaa et al. 2020). The unusual formation of reactive oxygen species (ROS) or reactive nitrogen species (RNS), like NO, induced oxidative stress, which provoked the emergence and development of CAD (Tejero et al., 2019). MDA is a lipid peroxidation side product that has been used in cell

membranes as a lipid peroxidation indicator (Oda and Derbalah, 2018).

Clear evidence of previous findings in Ulutaş et al. (2006) studied that gentamicin induces nephrotoxicity in rats; they also proved that gentamicin raise MDA level (Elkomy et al. 2019). MDA levels were found to be significantly higher in cardiac tissues of rats in this research, particularly in TIG and GEN co-administered animals. Enhanced annexin-V levels were recorded in TIG and GEN -treated animals. This investigation indicates that these incidents trigger the apoptotic cascade. GSH is a key component of the cellular antioxidant scheme, which neutralized the harmful damage caused by free radicals produced by oxidative stress (Bayrak et al., 2021). As a result, the decrease in GSH and raise in MDA levels could be attributed to the cardiotoxic mechanism of combined TIG 14+ GEN metabolism, which tends to result in inequity of antioxidant defense and ROS creation. These data corroborate and broaden previous research indicating a link among oxidative stress and TIG-induced cardiotoxicity. It was demonstrated that TIG causes increased ROS creation as well as protein damage measurements (Elgazzar et al., 2022).

Tigecycline raises levels of mitochondrial superoxide, hydrogen peroxide, and (ROS). In tigecycline-treated cells, oxidative damage to DNA, protein, and lipid was observed, which is consistent with oxidative stress (Tan et al., 2017).

Previous research demonstrated the existence of DNA damage and repair processes brought on by TIG and/or GEN therapy (Elgazzar et al., 2022).

Pathological research on rabbits demonstrated that long-term GEN administration causes myocardial muscle cell congestion and necrosis, which would be linked to inadequate systemic circulation (Saleh, 2018). There have been few histopathological studies on the effect of gentamicin on myocardial tissue (Ali et al., 2020)

Observational researches on humans have discovered that elevated concentrations of proinflammatory cytokines in AKI are linked to decreased heart function. Increased circulating tiers of TNF-α and IL6 have indeed been linked to the advancement of heart failure and death (Olsson et al., 2014).

Flow cytometry analysis of annexin V-FITC staining revealed that the TIG 14/ GEN combination risen the apoptotic population numbers, but there were no significant differences between the TIG 14 alone and GEN-treated cells (P>.0.05), so even though Flow cytometry assay was conducted to analyze the number of viable, apoptotic, and necrotic cells in cardiac tissue in different groups (Yasuhara et al., 2003).

According to the Annexin V assay, gentamicin raised the percentage of apoptotic cells ($p< 0.05$) when compared to the control (Jadidian et al., 2015).

5. CONCLUSION

Our results are consistent with the hypothesis that high dose GEN may increase the cardiotoxicity of high dose TIG. Microscopic cardiac lesions induced by TIG metabolites are associated with elevated levels of cardiac biomarkers. Large dose of GEN has a negative impact on the cardiac oxidative stress caused by TIG.

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