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ORIGINAL RESEARCH

Protective effect of dapagliflozin on colistin-induced renal toxicity

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Abstract

Objectives: Multiple-drug resistance to Gram-negative bacteria has increased significantly in recent years. Colistin is increasingly used as a last line of defense against these bacteria. However, colistin has been associated with nephrotoxicity in experimental animals. This study explores the protective effect of dapagliflozin in a rodent model of nephrotoxicity.

Material Method: The present study includes a total of 24 male rats, of which 16 were given a single 20 mg/kg dose of colistin (Colimycin 150 mg/mL) intravenously to induce renal toxicity. The remaining eight rats were given no drugs in order to serve as the control, Group A. The 16 rats treated with colistin were then divided into two groups. Rats in Group B received 0.9% NaCl saline solution at a dose of 30 mL/kg/day intraperitoneally (i.p.) and 10 mg/kg/day dapagliflozin (Forziga 10 mg) via oral gavage. Those in Group C received 0.9% NaCl saline solution at an i.p. dose of 30 mL/kg/day. Both saline and dapagliflozin were administered as described over the course of ten days. The animals were euthanized and blood samples were taken by cardiac puncture for further analysis. Their kidneys were removed for histopathological and biochemical examination.

Results: Levels of creatinine, BUN, KIM-1, and MDA were significantly increased in the 16-rat (Groups B and C) treatment group, in comparison to the control group; however, these biomarkers were significantly normalized in Group B, which had received dapagliflozin in addition to saline. The GSH levels of Group C showed significant decline when compared to those of the control group, and were significantly normalized in Group B. Histologically, in Group 2, we observed severe tubular dilatation and tubular epithelial cell injury in comparison to the control group. These severe anatomical changes were decreased in Group B.

Conclusion: Apart from its positive effect on glucose regulation, which is the usual purpose of dapagliflozin, we observed that in colistin-induced nephrotoxicity, it decreases oxidative stress by inhibiting SGLT-2, and has restorative effects in terms of histopathology and biochemistry. These findings offer hope that the use of dapagliflozin may be protective for contrast nephropathy, which causes renal tubule damage through oxidative mechanisms. Future studies will further clarify the mechanistic action of colistin and dapagliflozin, and may support the hypothesis that dapagliflozin can be used as an adjunctive therapy in all nephrotoxic conditions.

Keywords

Nephrotoxicity; Colistin; Dapagliflozin; Histopathology

1. Introduction

Colistin is a cyclic-structured antibiotic that has rarely been used until recent years, due to its dose-dependent nephrotoxicity side effects [1]. Multiple antibiotic resistance has begun to occur in patients admitted to intensive care, and in this context, the usage of colistin has increased, playing an important role in patients' clinical recoveries and survival.

Colistin affects the proximal tubule and increases the permeability of the membrane, resulting in increased passage of water and electrolytes. This causes an increase in the blood creatinine parameter, glucosuria, proteinuria, and hematuria; acute tubular necrosis consequently occurs by cytotoxic effect [2]. Nephrotoxicity due to colistin [3] is reversible. Generally, kidney laboratory values return to normal levels within one month [4]. Restrictions in the application of dose-dependent

nephrotoxic colistin have revealed the need for a nephroprotective drug for use in conjunction with colistin. The nephrotoxic mechanism of colistin has yet to be elucidated. This situation has increased the number of studies on the availability of drugs to reduce or halt colistin nephrotoxicity.

The SGLT-2 inhibitor dapagliflozin is used for treating diabetes mellitus (DM). It received FDA approval in January, 2014 [5]. The inhibition of SGLT2 serves to regulate glucose concentration independently from insulin by augmenting renal glucose excretion. Plasma glucose concentration increases comparably with renal glucose filtration. Thus, by increasing glucosuria with dapagliflozin, insulin deficiency and thus hyperglycemia are compensated for [5].

Reactive oxygen species released due to oxidative stress are thought to be the main cause of drug-dependent renal tubular damage. One study shows that hyperfiltration, tubular oxidative stress, and oxygen consumption in a diabetic kidney are diminished by SGLT2 inhibition, which alleviates kidney damage [6]. In this study, we investigated the corrective effect of dapagliflozin on the impaired values of colistin-induced nephrotoxicity, evaluating its appropriateness as a nephroprotective agent.

2. Materials and methods

2.1 Animal care and experiments

Twenty-four male Sprague Dawley rats each weighing between 200 and 220 g were selected. Rats were nourished ad libitum and housed in sets in steel cages having a temperature-controlled environment (22 ± 2 °C) with 12-h light/dark cycles. All experimental studies described here were approved by the Animal Ethics Committee, and were conducted according to the Guidelines for the Care and Use of Laboratory Animals, as approved by the National Institutes of Health (USA).

2.2 Experimental protocol

Of the 24 male rats were included in the study, 16 were given a single 20 mg/kg dose of colistin (Colimycin 150 mg/mL) to induce renal toxicity. The remaining eight rats were given no drugs and comprise the control (**Group A**). Next, the 16 rats treated with colistin were separated into two groups:

Group B: Rats given 0.9% NaCl isotonic intraperitoneally (i.p.) at a 30 mL/kg/day dose, and a 10 mg/kg/day dose of dapagliflozin (Forziga 10 mg) via oral gavage.

Group C: Rats given only 0.9% NaCl isotonic given i.p. at a dose of 30 mL/kg/day.

Both Group B and Group C received saline and dapagliflozin for 10 days. The animals were then euthanized and blood samples were obtained by cardiac puncture for further analysis. Their kidneys were also removed for histopathological and biochemical assessment.

2.3 Histopathological examination of kidney

In the histological and immunohistochemical portion of the study, ketamine (80 mg/kg, Alfamine®, Alfasan International B.V., Netherlands) and xylazine (10 mg/kg, Alfazyne®, Alfasan International B.V., Netherlands) i.p. sedoanalgesia was perfused with 200 mL of 4% formaldehyde in 0.1 M phosphate buffered saline (PBS). Kidney sections (4 μm) were obtained after fixing with formalin and stained with hematoxylin and eosin. All sections were photographed with the Olympus BX51 microscope and Olympus C-5050 digital camera.

The morphological study was performed with a computerized image analysis system (Image Pro Express 1.4.5, Media Cybernetics, Inc. USA), by an observer blinded to the study group, on 10 microscopic fields per section, at 20× magnification. Tubular injury score was previously described [7]. In summary, tubular damage was determined through observations of tubular vacuolation and tubular epithelial necrosis, and was scored by grading the percentage of affected tubules counted under 400 magnification. Injured tubules score were considered as standard under 400 magnification expressed in tubular numbers per field. Ranking grading in each area was calculated as follows:

Injury score (%) = (numbers of injured tubules/number of whole tubules) 100.

A number of 10 or more areas in the cortex per slide were randomly selected.

2.4 Measurement of kidney injury molecule-1 (KIM-1), BUN and creatinine levels

For all animals, blood levels of urea and creatinine were measured using the Olympus AO5800 auto analyzer with enzymatic method. The biomarker for human kidney damage, Kidney Injury Molecule-1 (KIM-1), augmented by injury in the proximal tubule, was measured using ELISA.

2.5 Measurement of tissue lipid peroxidation (MDA)

Lipid peroxidation was determined in tissue samples by measuring malondialdehyde (MDA) levels, which is defined as the marker of oxidative stress, and can be measured using a thiobarbituric acid reactive substances (TBARS) assay [8]. Briefly, trichloroacetic acid and TBARS reagent were added to the tissue samples, then mixed and incubated at 100 °C for 60 min. After cooling on ice, the samples were centrifuged at 3000 rpm for 20 minutes, and the absorbance of the supernatant was read at 535 nm. MDA levels were calculated from the standard calibration curve using tetraethoxypropane and expressed as nmol/gr protein.

2.6 Measurement of tissue protein levels

Total protein concentration in kidney samples was determined by Bradford's method using bovine serum albumin as usual [9].

2.7 Determination of tissue glutathione (GSH) levels

The content in tissue samples of GSH, the indicator of cellular defense component of cells, was measured spectrophotometrically according to Ellman's method [10]. In this method, thiols interact with 5, 5'-dithiobis- (2-nitrobenzoic acid) (DTNB) and form a colored anion with maximum peak at 412 nm. GSH

TABLE 1. The biochemical, oxidative parametres on blood samples of rats

	Normal Group	Colistin and Saline Group	Colistin and Dapagliflozin group
MDA (nmol/g tissue)	78.2 ± 6.05	139.6 ± 9.1 **	98.09 ± 10.7 ##
BUN (mg/dL)	53.16 ± 2.23	80.5 ± 5.82 **	40.3 ± 1.14 ##
Creatinine (mg/dL)	0.49 ± 0.009	0.89 ± 0.09 **	0.47 ± 0.01 ##
GSH (nmol/g tissue)	11.5 ± 1.06	4.9 ± 1.05 *	7.1 ± .95 #
KIM-1 (pg/mL)	41.06 ± 6.7	315.8 ± 21.9 **	155.09 ± 19.1 ##

** $P < 0.05$, Colistin + Saline compared with A, ** $P < 0.0001$, Colistin + Saline compared with A, # $P < 0.01$, Colistin + Dapagliflozin compared with B, ## $P < 0.0001$, Colistin + Dapagliflozin compared with B.*

levels were calculated from the standard calibration curve and denoted as nmol/μgr protein.

2.8 Statistics

SPSS version 15.0 was used for data analyses. Parametric variables groups were compared by Student's *t*-test and analysis of variance (ANOVA). Non-parametric variables were associated by Mann-Whitney U test. Results were given as mean ± standard error of mean (SEM). $P < 0.05$ was accepted as statistically significant; moreover, $P < 0.001$ was accepted to be highly significant.

3. Results

3.1 Evaluation of the plasma Cr, BUN and KIM-1 levels

Plasma Cr levels increased significantly in Group B (colistin + saline) compared to Group A (control) ($P < 0.0001$), and the Group B (colistin + dapagliflozin) creatinine levels changed significantly ($P < 0.0001$). In parallel, the BUN levels increased ($P < 0.0001$) in Group B, compared to Group A. The treatment with dapagliflozin attenuated kidney levels ($P < 0.0001$), compared to the Group B (Table 1). The activities of KIM-1increased in Group B compared with Group A ($P < 0.0001$), and in Group B, declined after administration of dapagliflozin, compared to those of Group C ($P < 0.0001$). The treatment with dapagliflozin restored all these activities, compared to Group B (Table 1).

3.2 Lipid peroxidation product in the renal tissues

İn Group B, the MDA levels increased in renal tissues ($P < 0.0001$), compared to group A. The treatment with dapagliflozin attenuated the lipid peroxidation in renal tissue, compared to Group C ($P < 0.0001$) (Table 1).

3.3 Antioxidant parameters in the renal tissues

The activities of GSH in renal tissues declined in Group B compared to A ($P < 0.01$), and GSH was augmented after administration of dapagliflozin in Group B, with comparison to that of Group C ($P < 0.05$). The treatment with dapagliflozin restored all these activities in Group B, compared to Group C (Table 1).

3.4 Analysis of the renal histology

Histological analysis of kidney samples of Group C rats treated with sterile saline showed normal renal cortex and glomeruli (Fig. 1a, Table 2). However, the kidneys of Group C rats showed severe tubular damage and tubular dilatations and epithelial cell vacuolizations (Fig. 1b). The dapagliflozin treatment received by Group B appears to produce a total nephroprotective effect with regard to the colistin-induced renal injuries (Fig. 1c, Table 2).

4. Discussion

A polypeptide antibiotic used since the 1950s, colistin was discontinued in the 1970s when it was found to be nephrotoxic, but was reintroduced into clinical practice in the 2000s due to an increase in Gram-negative pathogens [11].

Kidney damage is the biggest factor restricting treatment in the clinical use of colistin. Dose adjustment should be done very carefully in patients with chronic renal failure or in those receiving multiple medications [12]. The increase in the usage of colistin as an alternative in patients with multiple antibiotic resistance [13] has highlighted the need for a drug with antioxidant effects that will ameliorate the kidney damage caused by the aforementioned drug.

In this study, acute tubular necrosis is created by administering a single dose of 20 mg/kg colistin intraperitoneally to rats; this damage is proved histopathologically shortly thereafter. An increase in MDA levels and a significant decrease in antioxidant (GSH) levels is observed in renal cells followed by the application of the drug. Although the nephrotoxic mechanism of colistin is not fully known, these findings demonstrate that damage may be caused by oxidative stress.

According to current guidelines, the diagnosis of acute kidney failure is based on a dynamic increase in serum creatinine, yet this increase may be affected by non-renal factors and may occur late after kidney damage. Kidney damage molecule 1 (KIM-1, also known as TIM-1) is a proximal tubule-specific transmembrane protein that rises markedly in the proximal tubule after injury [14]. Studies using KIM-1 as a marker of acute renal failure, as well as of chronic kidney failure, are ongoing [15].

The present study finds that KIM-1 levels climb in response to colistin-induced tubular damage. Moreover, an increase in

TABLE 2. Percentages of the renal injury

	Normal Group	Colistin and Saline Group	Colistin and Dapagliflozin group
Tubuler epithelial cell injury percent	3.3 ± 0.8	31.9 ± 5.7 *	12.5 ± 6.6 #
Tubular dilatation percent	1.9 ± 1.1	15.2 ± 3.4 *	8.03 ± 2.4 #

** $P < 0.0001$, Colistin and Saline Group compared with normal group # $P < 0.001$, Colistin and Dapagliflozin group compared with Colistin and Saline Group.*

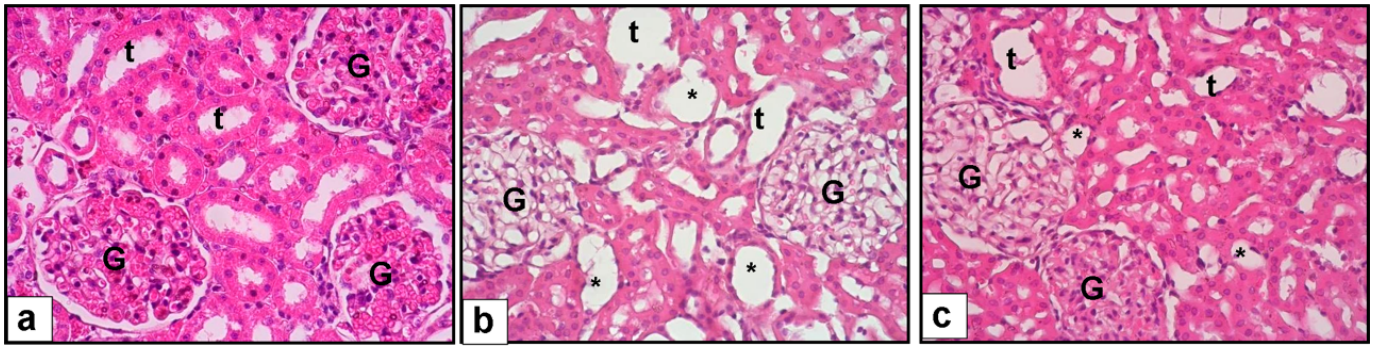

FIGURE 1. Kidney histolopathology H&E (× 40). a: Control group, normal glomerul (G) and tubul (t), b: Colistin and Saline given group, tubuler dilatation and tubuler epithelial cell injury (*), c: Colistin and Dapagliflozin group, decreased tubuler dilatation and tubuler epithelial cell injury (*).

KIM-1 value secondary to colistin nephrotoxicity, and a reduction in KIM-1 values attended the addition of dapagliflozin to the treatment protocol. These results indicate that dapagliflozin stabilizes membrane proteins and also demonstrate that KIM-1 can be used as an acute renal failure marker.

Reactive oxygen species (ROS) are known to be one of the main causes of drug-induced nephrotoxicity [16–18]. ROS creates cell damage via several mechanisms, such as peroxidation of membrane lipids, proteins, and DNA. In a study conducted with antioxidant molecules such as vitamin E, astaxanthin, garlic, and ascorbic acid, an improvement in kidney parameters was observed by reversing oxidative stress [19–21]. Similarly, in the current study, a statistically significant reduction in BUN, MDA, and creatinine levels, as well as in histopathological indicators, was observed in the group treated with dapagliflozin, and an elevation of GSH was noted. In an in vitro study by Poornima, a DPPH (1,1 diphenyl -2-picrylhydrazyl) assay was made, and the author noted that in a high dose of dapagliflozin, oxidative stress diminishes due to increasing nitric oxide and inhibiting ROS activity [22]. Dapagliflozin SGLT2 inhibitors show potent antioxidant properties along with its established antidiabetic activity [23]. The results of the current study suggest that dapagliflozin prevents damage caused by oxidative attack by increasing antioxidant mechanisms and reducing lipid peroxidation in tubular damage induced via colistin.

Another study shows the role of GSH activity in apoptosis and nephrotoxicity triggered by colistin [21]. In this study by Chang *et al.* on kidney ischemia-reperfusion injury in mice, dapagliflozin, an SGLT2 inhibitor, was shown to improve kidney function and reduce apoptotic cell death in mouse kidneys damaged by ischemic reperfusion [24].

In the present study, we observe that dapagliflozin has a preventive effect on the increase of antioxidant parameters and lipid peroxidation triggered by colistin, and note its ameliorating effect on kidney damage in the treatment of colistin toxicity. These effects are thought to occur by increasing radical scavengers' ability to protect the cellular membrane and prevent oxidative attack.

Plenty of energy is needed to reabsorb electrolytes and organic solvents from the proximal tubule [25]. However, the proximal tubule creates a high amount of oxygen consumption by the kidney. This makes the proximal tubule more susceptible to hypoxia and type-2 diabetes disease [26, 27]. Anita T. *et al.* showed that in diabetic rats, basal oxygen consumption of the proximal tubule increased significantly in comparison to that of healthy animals [6]. In a study conducted by O'Neill *et al.*, it was reported that oxygen consumption was almost two times higher in diabetic rats than in healthy controls, and SGLT-2 inhibition synchronously decreased GFR and increased sodium and glucose reabsorption [28]. In a study in which Mosenzon *et al.* investigated kidney diseases in patients with type-2 diabetes, dapagliflozin was found to prevent and reduce the progression of kidney failure in patients with type-2 diabetes, with and without atherosclerotic cardiovascular disease, compared to placebo [13]. These outcomes suggest that SGLT-2 inhibitors are nephroprotective, and therefore may play a role in nephrotoxic drug use. These studies are consistent with our results, which demonstrate that dapagliflozin improves kidney function by lowering KIM-1 levels. Ghlissi *et al.* used vitamin E and C to combat colistin nephrotoxicity [19, 21], and similarly to our histopathological study, both statistic and visual improvements were observed in renal tubular brush border loss, vacuolization, and desquamation of epithelial cells. These effects of vitamins E and C, which have antioxidant properties, support the prevention or correction of damage due to oxidative stress, and suggest that dapagliflozin also prevents oxidative damage by reducing it.

In the study of the prevention of nephrotoxicity in the model of ischemic reperfusion injury performed by Chang *et al.*

[24], only groups treated with saline and dapagliflozin were compared; the study reported a histopathological improvement only in the group given dapagliflozin. In the present study, where we induced colistin nephrotoxicity, dapagliflozin improved histopathological findings and supported our hypotheses about antioxidant activity.

5. Conclusions

Apart from its success in blood glucose regulation, which is the main current application of dapagliflozin, we observed that, in colistin-induced nephrotoxicity, oxidative stress decreases by inhibition of SGLT-2, and can by restored in histopathological and biochemical terms. Future studies will further clarify the mechanisms of action of colistin and dapagliflozin, and may support the hypothesis that dapagliflozin can be used as an adjunctive therapy in all nephrotoxic conditions.

AUTHOR CONTRIBUTIONS

Ejder Saylav Bora and Oytun Erbas designed the study. Mumin Alper Erdoğan, Ayfer Meral and Zeynep Karakaya collected the data. Oytun Erbaş and Mumin Alper Erdoğan analyzed the data. Ejder Saylav Bora analyzed the results and prepared the drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ege Uniersity Animal Experiments Ethic Committee of Ege University Faculty of Medicine (Number: 2019/224). No Informed Constent used because it's an experimental study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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