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Abstract

Paracetamol is widely used without prescription as an over the counter (OTC) drug. Many studies reported that it causes renal toxicity unlike ACE inhibitors like Captopril that can have renal protective effects. Since many patients may take Paracetamol and Captopril concomitantly, the aim of this study is to evaluate the renal protective effect of Captopril on Paracetamol-induced nephrotoxicity.

The present study was conducted in two phases. Phase (1): high dose Paracetamol: Animals were divided into 4 groups of 6 rats each. Group 1 (control group), Group 2 (Paracetamol 3000 mg/kg group) and Group 3 (Captopril 20 mg/kg group) were pretreated orally with 0.9 % normal saline consecutively for 7 days; Group 4 (Captopril + Paracetamol group) was pretreated with Captopril 20 mg/kg consecutively for 7 days. After 24 hours (on day 8), group 1 administered 0.9 % normal saline, whereas group 2 (paracetamol) and group 4 (Captopril + Paracetamol) administered single oral dose of Paracetamol 3000 mg/kg; group 3 administered captopril 20 mg/kg. Rats were then sacrificed and the kidneys were dissected for histopathological studies. Phase (2): low dose paracetamol: Rats were divided into 4 groups of 6 rats each. Group 1: was treated orally with 0.9% normal saline, Group 2: received paracetamol (300 mg/kg), Group 3: administered captopril (20 mg/

kg) and Group 4: administered both captopril (20 mg/kg) and paracetamol (300 mg/kg) for 10 days consecutively. The animals were then sacrificed and the kidneys were dissected for histopathological studies.

Paracetamol in both high and low doses produced nephrotoxic effects while Captopril showed marked protection against damage induced by Paracetamol on the kidney.

Keywords: Captopril, Histology, Kidney, Nephrotoxicity, Paracetamol, Rat.

Introduction

Paracetamol is used as an analgesic and an antipyretic drug; so it is one of the most commonly used over the counter (OTC) drugs especially by the youth. It is a rapid, reversible, noncompetitive cyclooxygenase inhibitor (Ucheya & Igweh 2006; Hussain et al., 2009; Majeed et al., 2013). Paracetamol can cause dose-related hepatic and renal injury and it exerts acute and chronic nephrotoxic effects (Majeed et al., 2013; Ibrahim & Osman, 2017). Though it is considered safe at therapeutic doses, the intake of large quantities of paracetamol leads to the generation of highly reactive metabolites that react with glutathione and proteins' sulfhydryl groups resulting in cellular dysfunction and hepatic and renal toxicity (Blantz, 1996). It is reported that hepatically-derived Paracetamol metabolites are partially responsible for Paracetamol renal effects (Trumper et al., 1996) and Paracetamol-induced renal failure results in hepatotoxicity in most cases (Mazer & Perrone, 2008).

Paracetamol causes both acute and chronic nephrotoxicity. Acute toxicity after ingestion of large doses produces proximal tubule damage and necrosis. While chronic ingestion of low doses can produce renal dysfunction and damage (Mohamed et al., 2003). However; it is reported that renal failure after paracetamol overdose is usually transient and rarely requires dialysis (Loh & Ponampalam, 2006).

Angiotensin converting enzyme (ACE) inhibitors are frequently used in the pharmacological management of congestive heart failure and hypertension (Habior, 1992). ACE inhibitors are also used in the management of patients with diabetic and non-diabetic nephropathies (Anton et al., 2001). However, other studies reported that ACE inhibitors can cause functional renal insufficiency (Mansour et al., 1999) and acute renal failure (ARF) as reported

by Singh et al. (2003). Nonetheless, Captopril is the prototype oral angiotensin converting enzyme inhibitor that can prevent nephrotoxicity (Mansour et al., 1999).

Captopril, the first orally active ACE inhibitor, has a therapeutic use according to the knowledge of its mechanism of action and efficacy. Captopril contains active sulfhydryl group and shares characteristics with cysteine which is the main substrate of the most important antioxidant, glutathione (Habior 1992). Captopril has the ability to enhance total glutathione, glutathione peroxidase and glutathione reductase activities in various mouse tissues (Elena et al., 2000). However, Ackeman, (2008) reported that captopril decreased the activity of both glutathione peroxidase and glutathione reductase.

Background of the Study:

Paracetamol is exceedingly used by patients and it is considered as an over the counter drug (OTC). Many studies reported that it can cause renal toxicity. On the other hand, ACE inhibitors like captopril might have renal protective effects; since many patients may take paracetamol & captopril concomitantly, thus, the goal of the present study is to evaluate the renal protective effect of captopril on paracetamol-induced nephrotoxicity.

Materials and Methods

Animals

In the present work, Male Wistar rats weighing 200 - 250 g were used. Rats were kept and maintained under laboratory conditions with 12 h light/dark cycles in the Faculty of Pharmacy, Northern Border University, KSA, and were given free access to food (standard pellet diet) and water ad libitum. The animals were randomly divided into 4 groups (n=6) for each experiment.

Drugs

Captopril (Capoten®) tablets (E. R. Squibb & Sons Limited, United Kingdom) and Paracetamol (Panadol ®) tablets (500 mg) (GlaxoSmithKline (GSK) Company, United Kingdom) were purchased from the local drugstores in the Kingdom of Saudi Arabia.

Methods

Experimental protocol

High dose Paracetamol (3000 mg/kg) experiment.

Animals were divided into 4 groups (n = 6). Group 1 (control group), Group 2 (Paracetamol group) and Group 3 (Captopril group) were pretreated orally with 0.9% normal saline consecutively for 7 days; Group 4 (Captopril + Paracetamol group) was pretreated with Captopril 20 mg/kg consecutively for 7 days. After 24 hours (on day 8); group 1 was given 0.9% normal saline whereas group 2 (paracetamol) and group 4 (Captopril + Paracetamol) were given a single oral dose of paracetamol 3000 mg/kg; group 3 was given captopril 20 mg/kg. Rats were then sacrificed and the kidneys were dissected for histopathological studies, after 48 hours of hepatic injury induction.

Low dose Paracetamol (300 mg/kg) experiment.

Rats were divided into 4 groups of 6 rats each. Group (1): was treated orally with 0.9% NS, Group (2): received paracetamol 300 mg/kg, Group (3): administered captopril 20 mg/kg and Group (4): administered Cap 20 mg/kg plus P 300 mg/kg for 10 days consecutively. The animals were then sacrificed and the kidneys were removed for histopathological studies.

Histological study

The kidney tissue was dissected out and fixed in 10% neutral formalin solution. The tissue was processed and embedded in paraffin wax and sectioned at a thickness of 5 microns similar to the standard procedure. The tissue was then deparaffined with xylol, and histological observations were performed, using H-E technique (Bancroft & Stevens, 1990). The slides were examined using light microscope (X400).

Results

Effects of high dose Paracetamol and Captopril on Rat kidney:

Kidney sections from the normal control rats (G1) showed normal renal corpuscle, glomerular capillaries, proximal tubules and distal tubules (Fig.1). The administration of high dose of Paracetamol (3000 mg/kg) caused many histopathological lesions to the renal tissue with the presence of atrophy of

the glomerular capillaries of some corpuscles, the dilation and atrophy of the lining epithelium of distal tubules and the presence of homogenous or tubular hyaline casts (Fig.2); The proximal tubules had normal appearance as indicated in Figure 2. Sections of rat kidneys from the group that received captopril 20 mg/kg (G3) exhibited well organized tubular epithelium with normal kidney structures which are even better than the control group (Fig.3). Renal sections from rats that received a high dose of paracetamol (3000 mg/kg) plus captopril (20 mg/kg) (G4) showed preservation of normal structure of renal corpuscle, glomeruli and both proximal and distal tubules (Fig. 4).

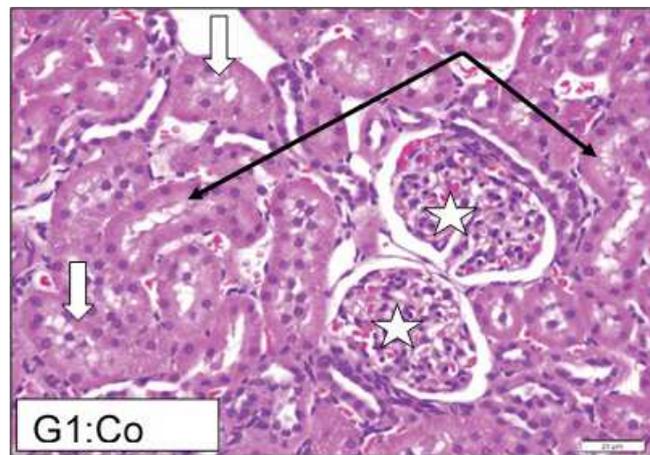


Figure 1: Normal control group: renal section from a control rat showing normal renal corpuscle and glomerular capillaries (star), proximal tubules (white arrows) and distal tubules (black arrows). (H-E, X400).

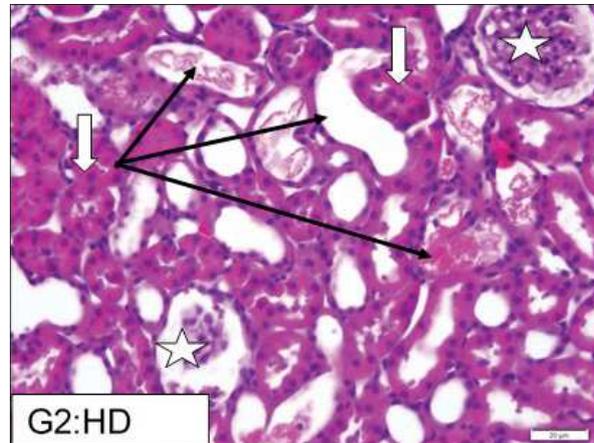


Figure 2: Paracetamol 3000 mg/kg group: kidney section from a rat that administered a high dose Paracetamol 3000 mg/kg (G2) demonstrating atrophy of glomerular capillaries of some corpuscles (star), marked dilation and atrophy of lining epithelium of distal tubules and presence of homogenous or tubular hyaline casts (black arrows) but with normal appearance of proximal tubules (white arrows). (H-E, X 400).

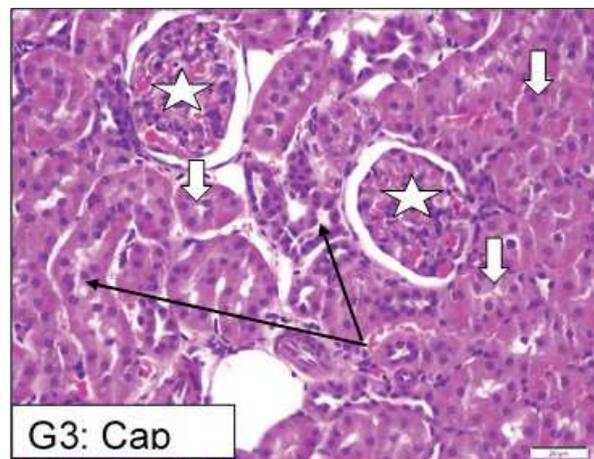


Figure 3: Captopril 20 mg/kg group: renal section from a rat that received Captopril 20 mg/kg (G3) showing normal kidney structure which is even better than the control group, tubular epithelium is well organized (black and white arrows) and the glomeruli appear normal (stars). (H-E, X 400).

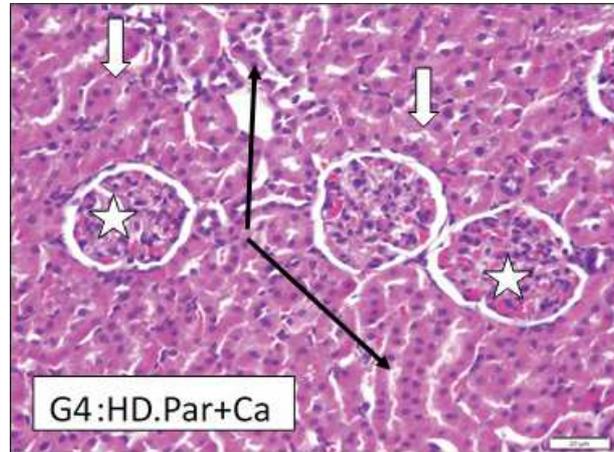


Figure 4: Paracetamol 3000 mg/kg + captopril 20 mg/kg group: kidney sections from a rat that received high dose paracetamol (3000 mg/kg) plus Captopril (20 mg/kg) (G4): showing the preservation of normal structure of renal corpuscle and glomeruli (white stars), both proximal (white arrows) and distal tubules (black arrows). (H-E, X 400).

Effects of low dose Paracetamol and Captopril on Rat kidney:

Renal sections from normal control rats that administered normal saline (G1) showed normal renal corpuscles and tubules (Fig. 5). The histopathological examination of the renal cortex of kidneys from rats pre-treated with Paracetamol (300 mg/kg) for 10 days (G2) showed disorganized dilated tubules and the rest showing lining epithelium of dark stained degenerated nuclei and deformed renal corpuscles of decreased cellularity (Fig.6). Kidney sections of a rat pre-treated with captopril (20 mg/kg) for 10 days (G3) show renal corpuscles and tubules have normal, if not better, appearance than the control (Fig. 7). Renal sections from rats pre-treated with captopril 20 mg/kg and paracetamol 300 mg/kg concomitantly for 10 days (G 4) showed marked protection from paracetamol-induced damaging effect. Similar to Group 3, both renal corpuscles and tubules also had improved appearances when compared to the control group (Fig.8).

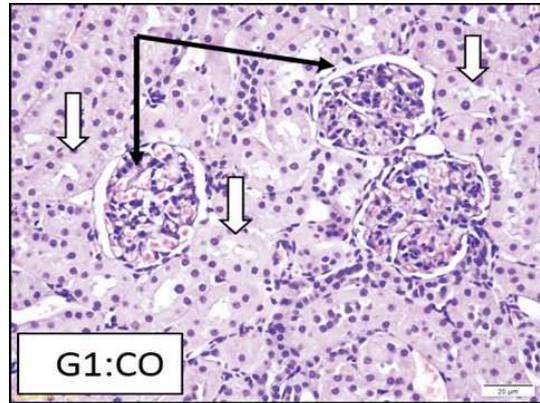


Figure 5: Normal control group: renal sections from normal control rat administered normal saline (G1) showing normal renal corpuscles (black arrows) and tubules (white arrows). (H-E, X 400).

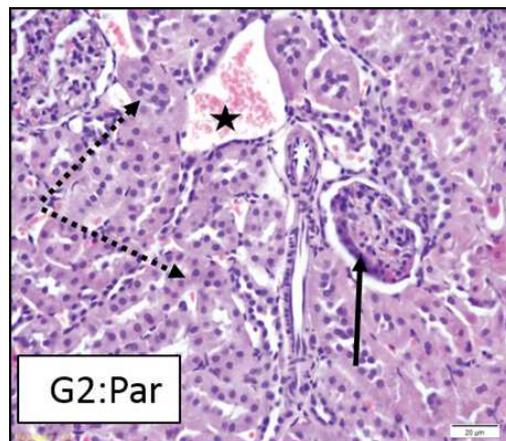
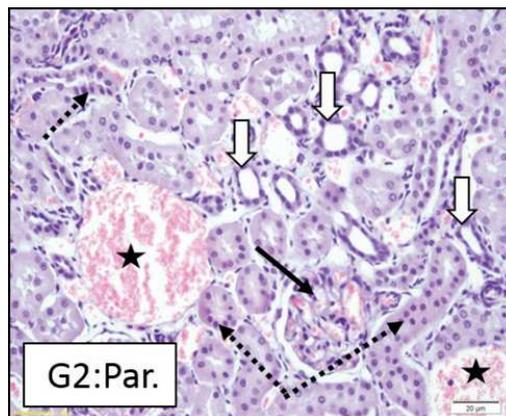


Figure 6: Paracetamol 300 mg/kg group: section of the renal cortex from rats pre-treated with Paracetamol 300 mg/kg for 10 days (G2) showing disorganized dilated tubules (white arrows) the rest having lining epithelium of dark stained degenerated nuclei (dotted arrows) and deformed renal corpuscles with decreased cellularity (black arrow). (H-E, X 400).

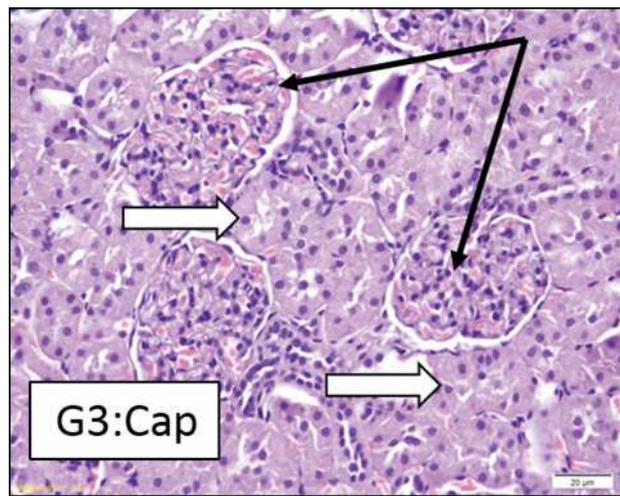


Figure 7: Captopril 20 mg/kg group: kidney section from a rat pre-treated with Captopril 20 mg/kg for 10 days (G3) showing both renal corpuscles (black arrows) and tubules (white arrows) with normal appearance which is even more improved than the control. (H-E, X 400).

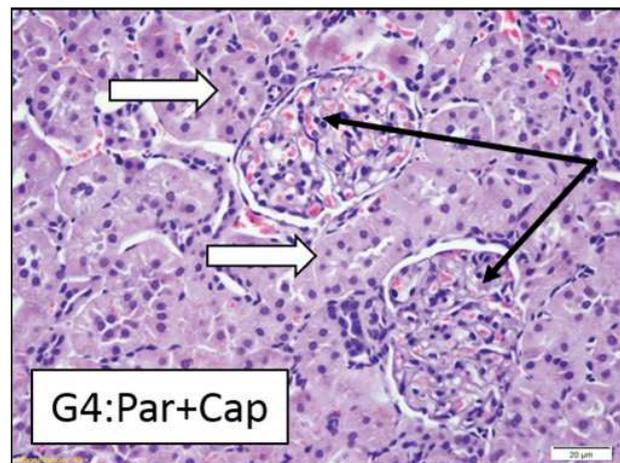


Figure 8: Captopril 20 mg/kg + Paracetamol 300 mg/kg group: renal section from a rat pre-treated with Captopril 20 mg/kg and Paracetamol 300 mg/

kg concomitantly for 10 days (G4) showing significant protection from Paracetamol induced damaging effect. Both renal corpuscles (black arrows) and tubules (white arrows) exhibited normal appearances which are even more improved than those of the control. (H-E, X 400).

Discussion

Paracetamol, known also as acetaminophen, is a pain reliever and a fever reducer that is used to treat many conditions such as headaches, muscle aches, arthritis, backaches, toothache, and colds. However; in overdose it can cause acute renal failure with the possibility of leading to chronic renal failure following its chronic use (Corina et al., 2004). Paracetamol toxicity is mediated in the liver and kidneys by cytochrome P450 enzymes and by the activity of its reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which is detoxified by intracellular glutathione (GSH). This metabolite reacts with GSH and sulfhydryl groups causing cellular dysfunction and hepatic & renal toxicity (Blantz, 1996).

Since Captopril contains active sulfhydryl group and shares structural features with cysteine, which is the main substrate for GSH. Anton et al. (2001) stated that captopril (angiotensin converting enzyme inhibitor) has a protective role against paracetamol-induced nephrotoxicity.

In the present study, the administration of a high dose of paracetamol (3000 mg/kg) caused nephrotoxicity manifested by atrophy of glomerular capillaries of some corpuscles, marked dilation and atrophy of the lining epithelium of distal tubules and by the presence of homogenous or tubular hyaline casts. The histopathological examination of the renal cortex of rats that were pre-treated with the lower dose of paracetamol (300 mg/kg) consecutively for 10 days showed dilated and disorganized tubules, deformed renal corpuscles with decreased cellularity and with lining epithelium that has dark stained degenerated nuclei.

The nephrotoxicity of Paracetamol observed in this work is similar to that of other studies which reported that the pathophysiology of renal toxicity in paracetamol poisoning can be attributed to cytochrome P-450 mixed function oxidase isoenzymes present in the kidney. Other mechanisms also focused on the role of prostaglandin synthetase and N- deacetylase enzymes (Mazer &

Perrone 2008) in renal toxicity. Paracetamol-induced significant elevations in the serum concentrations of urea and creatinine ($p < 0.05$) that caused disturbance of kidney functions as reported by Ibrahim & Al-Shaikh (2016).

It is reported that in most cases paracetamol-induced renal failure becomes evident after hepatotoxicity, (Loh & Ponampalam 2006; Mazer & Perrone 2008). Renal failure due to acute tubular necrosis occurs in 25 % of patients with severe hepatic damage (Majeed et al., 2013). It is also suggested that the hepatically derived paracetamol metabolites are partially responsible for paracetamol renal effects (Trumper et al., 1996). Also the present findings agree with other reports which indicated that paracetamol exerts acute and chronic nephrotoxic effects. Acute toxicity after ingestion of large doses of paracetamol (10 – 15 g) is characterized by necrosis and damage to the proximal tubule; while chronic ingestion of much lower doses (500 – 1000 mg) produced renal damage, resulting in analgesic nephropathy (Mohamed et al., 2003). These histopathological changes may be attributed to renal inflammation that is related to the elevated concentrations of TNF- α and IL-12 and the decrease in IL-10 levels all of which are consequences of paracetamol administration (Ibrahim & Al-Shaikh, 2016).

However, the present results are in contrast with those reported in other studies that stated that the administration of paracetamol doesn't lead to the development of chronic analgesic nephropathy as these epidemiologic studies failed to demonstrate a significant correlation between paracetamol use and chronic renal disease or classic analgesic nephropathy (Blantz, 1996).

In the present investigation, the results indicated that the groups that administered captopril revealed normal kidney structure with well-organized tubular epithelium. Interestingly, the renal cortex sections from rats pre-treated with captopril and paracetamol 300 mg/kg concomitantly for 10 days showed significant protection from paracetamol induced damaging effects as both renal corpuscles and tubules were normal with improved appearances. Similarly, a high single dose of paracetamol (3000 mg/kg) administered by rats pre-treated with captopril showed preservation of normal structure of renal corpuscle and glomeruli.

ACE inhibitors are widely used for treatment of congestive heart failure,

hypertension an, diabetic and non-diabetic nephropathies (Anton et al., 2001). Captopril, which is one of the ACE inhibitors,(Mesbah et al., 2012), contains sulphhydryl group that acts as a scavenger of oxygen-derived free radicals which is not present in other ACE inhibitors (Ercument et al., 2000).

It is reported that ACE inhibitors usually improve renal blood flow (RBF) and sodium excretion rates in congestive heart failure and reduces the rate of progressive renal injury in chronic renal disease, but their use can also be associated with acute renal failure (Anton et al., 2001).

Ali (2012) has reported that captopril has a defensive effect against 5-Fluorouracil-induced damage to kidney & liver. He stated that this defensive effect of captopril lies on its free radical scavenging and antioxidant effects which are sulphhydryl dependent. This mechanism may explain the protective effect of captopril against paracetamol-induced nephrotoxicity that is presented in this work.

Conclusion

From the aforementioned results, the present study found that Paracetamol with both high and low doses produced nephrotoxic effects. The administration of Captopril with Paracetamol led to protective effect against Paracetamol-induced nephrotoxicity.

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