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Effects of Drugs on Serum Biochemical Profile and Renal Failure in Humans and Experimental Rats: A Preliminary Report

Nabaa Kamal Al shafei[1*] and Abdelfattah Nour[2]
[1]*Departmernt of Biochemistry, Bahri University, Faculty of Veterinary Medicine, Bahri University, Sudan*
[2]*Department of Basic Medical Sciences, School of Veterinary Medicine, Purdue University, USA*
*Corresponding author's Email: nabaak@yahoo.com

ABSTRACT

Antibiotics and cancer treatment drugs have been associated with renal failure. In developing countries, antibiotics are often obtained without prescription and this misuse increases the risk of renal failure, especially for patients which have been taking gentamicin for a long-term. For example, taking the aminoglycoside antibiotic, particularly in diabetics, without close medical supervision has been suggested to the cause kidney damage and renal failure in many patients. The objectives of this preliminary study were to investigate the association of antibiotics and renal failure in Hemodialysis (HD) patients in Egypt; and to document the changes in biochemical profiles and histopathology of the kidneys when nephrotoxicity is induced by the antibiotic gentamicin (GM) and the cancer therapeutic agent Cisplatin (Cis). Serum biochemical profiles of HD patients and rats with induced renal failure were compared. Fifty HD patients and six normal people were employed in the study. Sixty experimental rats were divided into three groups: Control, gentamicin-induced renal failure group, and cisplatin-induced renal failure group. The survey of HD patients revealed that 6% of the renal failure is antibiotics related. GM and Cis caused kidney damage and renal failure in rats. The levels of blood serum urea, creatinine, and potassium significantly increased in drug-induced renal failure rats. Serum sodium decreased in GM rats with renal failure and in HD patients compared to the control groups. The histopathological changes in renal tissues in Cis and GM induced renal failure appeared in early stage of renal dysfunction. More studies are needed to determine the correlations between biochemical markers and histopathological changes that may be used as an early warning system for assessing earlier drugs-induced stress to the kidneys before renal failure progresses.

Key words: Gentamicin, Csplatin, Drug-Induced renal failure, Hemodialysis, Serum biochemical profile

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INTRODUCTION

The accumulation of solutes in the blood and tissues is mainly due to inability of the failing kidneys to filter the blood plasma and remove the wastes of metabolism and the unwanted substances. Retained solutes are generally called uremic toxins when they contribute to the deterioration of the physiological and biochemical functions of the kidneys as the renal failure progresses. Therefore, kidney failure or dysfunction causes accumulation of toxins in the body, which result in health complications because of the effects on the blood, the brain, and the heart. These adverse health effects make renal failure a very serious and fatal disease if it is neglected. Several factors, including drugs such as antibiotics, are implicated as causes of renal failure in patients (Heleigh, 2012). The major causes of renal disease in such patients include drug toxicity and glomerulonephritis (Adu and Tse, 2001). The administration of drugs can lead to the deterioration of the renal function. For example, taking aminoglycoside antibiotics, particularly in diabetics, without close medical supervision has been suggested as the cause of renal failure. Moreover, non-steroidal anti-inflammatory drugs (NSAIDs) are considered a major cause of chronic renal failure. Accordingly, it is recommended that such drugs should be avoided or used under strict medical supervision. Perhaps the most widely used drug in the aminoglycosides category is Gentamicin (GM). Apart from their beneficial effects, aminoglycosides induce nephrotoxicity in 10-20% of therapeutic cases. The nephrotoxicity is characterized by tubular necrosis and other structural damage and cell death results in decreased in glomerular filtration (Martínez et al., 2007). In most developing countries, antibiotics are often obtained directly from the pharmacy without prescriptions. On the other hand, Cisplatin (Cis) (cis diamminedichloroplatinum, cis-DDP), a platinum-based drug that has been commonly used in the chemical treatment of various cancers (David et al., 2010), has been implicated as a cause renal failure. Cancer is spreading in developing countries at an alarming rate. It is important to note that irrespective of the insulting agent, the changes that occur as a result renal failure include changes in the serum biochemistry profile, and histopathological characteristics of the failing

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kidney (Stordal and Davey, 2007). The objectives of this work was to investigate the association of antibiotics and renal failure in Hemodialysis (HD) patients in Egypt and to document the changes in biochemical profiles and histopathology of the kidneys when nephrotoxicity is induced by antibiotics (gentamicin) and cancer therapeutic agent (Cisplatin).

MATERIAL AND METHODS

Experimental animals

Sixty white male albino rats between the ages of 50-60 days and with mean weight of 190 g were used in this investigation of the present study. Animals were obtained from laboratory animal research Center, faculty of veterinary medicine, Benha University, Benha, Egypt. Rats were housed in hygienic metal cages in the laboratory animal housing facility of the faculty of veterinary medicine of Benha University, Benha, Egypt. Clean and free drinking water and food were supplied ad libitum. Also, the animals in their cages were kept at constant experimental conditions in terms of temperature, humidity, and air pressure, and are provided with optimal nutritional conditions throughout the period of the experiment. Experimental rats were kept two weeks for acclimatization before the beginning of the experiment.

Drugs induced nephrotoxicity

The experimental induction of renal toxicity in male rats was carried out using cis and GM. Experimental rats were randomly assigned to one of three equal groups (20 rats each), placed in individual cages as follows:

Group (1): Normal non-treated rats, served as control group; Group (2): Animals were injected with Cis solution intra-peritoneally (IP), once at a dose of 6mg/kg body weight as described by Bagnis et al. (2001) for induction of renal failure (Cis injected group); Group (3): Animals were injected daily with IP injections of GM at a dose of 80 mg/kg of body weight for eight days as outlined by Abdel-Gayoum et al. (1994) for induction of renal failure (GM injected Group).

Blood samples

In day nine of the experiment, I ml blood sample from each rat was collected from the orbital sinus in clean test tubes. Care was taken not to inflict undue stress on the rats, or contaminate the samples. Benha University's Protocol for humane handling of animals was strictly followed. Blood samples were allowed to coagulate at room temperature for 30 minutes, and then centrifuged at 3000 revolutions per minute for ten minutes. The clean serum from each sample were aspirated carefully by a pasture pipette, and transferred into a dry, sterile, and labeled glass vials. The sera were then kept in a deep freezer at -20^{o}C until biochemical analysis of the samples was performed. Four animals from each of the three groups were humanely euthanized and dissected at 48 hours intervals till the end of experiment, following the institutionally approved procedures for humane handling of experimental animals. Serum urea was determined by using the urease- modified Berthelot enzymatic reaction following the procedure of Patton and Crouch (1977). Serum creatinine was determined by using Jaffe Colorimetric end point method according to the method of Houort (1985). Serum sodium was determined colorimetrically according to the method of Trinder (1951). Serum potassium was determined colorimetrically using the turbid metric method according to the procedure described by Terri and Sesin (1958).

Tissue samples

At the 7th day of the experiment and immediately after the rats were euthanized and dissected, the two kidneys were isolated, washed with saline and blotted between filter papers. A half from each of the two kidneys was preserved in 10% neutral formalin in separate labeled jars for histopathological examinations. Samples were dehydrated through ascending grades of ethanol, cleared in xylene, embedded in paraffin wax, and sectioned at 4 - 5 µ thick. The sections were stained with hematoxylin and eosin, for general histopathological examination as described by Bancroft and Stevens (1977) Crossman stain was used following the procedures outlined by Gray (1954).

Survey data analysis of HD patients

Ninety nine (n=99) chronic HD patients at Benha University hospital, Egypt (Artificial kidney Unit) were identified, fifty patients (n=50) were randomly selected for the study. Six normal people were used as control. The data for this study included survey data of the 50 randomly selected chronic HD patients. The main method of data collection for this study was structured mainly as a closed-ended questionnaire. The questionnaire was made flexible enough so it could be used for patients with different educational backgrounds, and from different economic strata. In an effort not to put the patients under stress while there were going through their regular hemodialysis session, the average interview time was planned not to exceed half an hour. After carefully explaining the goals of the study to each patient, consent was obtained from each patient before the interview. The study was also approved by the hospital board of Benha

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University, Benha, Egypt, that made sure that the study would adhere to the guidelines that govern the ethical use of human subjects in research.

Biochemical profile of serum samples from HD patients

From each of the fifty HD patient, a blood sample for serum separation were drawn during the dialysis in clean test tube from the arterial end of the vascular access of the internal arterio-venous fistula. Samples were also obtained from each of the six normal controls. Blood samples were collected in 3 ml tubes and processed as described earlier for experimental rats. Laboratory assays were performed, using the procedures outlined. On each serum sample, blood urea (Ur), creatinine (Cr), sodium (Na), and potassium (K) were determined.

Statistical analysis

Data were expressed as means ± standard error of the mean, and were compared using the F-test analysis of variance (ANOVA) following the method described by Snedecor and Cochran (1969). Survey data was calculated as percentages and reported in the table 3.

RESULTS

Serum biochemical profiles of HD patients and rats with induced renal failure were compared. The results of the serum biochemical profiles of the experimental animals and HD patients are presented in table 1 and table 2, respectfully. The summarized survey data of HD patients is presented in Table 3. Figure 1 shows the normal histology of the rats' kidneys. Figure 2 and Figure 3 depict the histopathological changes that occurred in the kidneys following the GM and Cis injections, respectively. Comparisons were made at the 7th day post injections to illustrate the drug-induced renal damage.

Table 1. Comparison between serum biochemical profiles in experimental rats

Serum Parameters	Control group (mg\dl)	Cis group in day nine (mg/dl)	GM group in day nine (mg/dl)
Urea	41.06 ±3.76^{b}	47.91 ± 16.05^{c}	422.30 ±75.24^{a}
Creatinine	1.06 ±0.32^{c}	1.32 ± 0.10^{b}	3.34 ±0.25^{b}
Sodium	143.95 ± 1.02^{a}	143.98 ± 3.16 ^{a}	115.32 ±8.47 ^{b}
Potassium	5.89 ± 0.46^{,b}	4.71 ± 0.30 ^{b}	8.52 ±0.26 ^{a}

Data are presented as mean ± standard error. Means values with different superscripts in the same row are significantly different (P<0.05)

Table 2. Comparison between serum biochemical profiles in control and HD patients, Benha University Hospital, Benha, Egypt (2011)

Serum Parameter	Control (mg\dl)	HD Patients (mg/dl)
Urea	20.5 ±4.45 ^{a}	83.67 ±21.67 ^{b}
Creatinine	0.74 ±0.15 ^{a}	5.08 ±1.69 ^{b}
Sodium	120 ±24.09 ^{a}	71.67 ±16.65 ^{b}
Potassium	3.91 ±0.8 ^{a}	7.46 ±2.42 ^{b}

Data are presented as mean ± standard error. Means values with different superscripts in the same row are significantly different (P<0.05)

Table 3. Frequency of the cause of renal disease in HD patients, Benha University Hospital, Benha, Egypt, 2011.

Causes of renal disease	Frequency
Renal hypertensive disease	18 (36%)
Diabetic nephropathy + renal hypertensive disease	8 (16%)
Uremia, etiology unknown	7 (14%)
Pre-eclampsia	5 (10%)
Rheumatoid arthritis	3 (6%)
Treatment with antibiotics	3 (6%)
Kidney calculi (nephrolithiasis)	2 (4%)
Polycystic Kidney disease	2 (4%)
Diabetic nephropathy	1 (2%)
Severe anemia	1 (2%)
Total	50 (100%)

HD: Hemodialysis patients. Data from all patients were pooled and percentages calculated and displayed in the present table,

From Table 1, when rats are compared at 9th weeks after drug-induced renal failure, it could be observed that urea levels in the serum increased compared with the control. However, the increase is more pronounced in the GM rats. On the other hand, creatinine also increased and this is similar to that observed for urea. Sodium significantly (P<0.05) decreased in the GM group but not in the Cis group. Potassium showed a significant increase in the GM group compared to the control. However, potassium in the Cis group was not statistically different from that of the control group.

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Table 2 presents the data for serum urea, creatinine, sodium and potassium in normal and HD patients. Similar to what observed for drug-induced renal failure in rats, urea and creatinine increased in HD patients compared to the control. Sodium significantly decreased in HD patients, while potassium significantly ($P<0.05$) increased. The trend in the serum biochemical profile observed in GM- induced renal failure is similar to that of HD patients.

Macroscopic and microscopic appearance

Macroscopically, the kidneys of experimental animals were enlarged in size, pale in color, and edematous or soft in consistency. The cut section also was pale in color. Microscopically, the kidney sections obtained from the control groups show a normal histological structure (Figure 1).

The hyaline cast in lumina of renal tubules in shown in figure 2 for kidneys obtained from the rats at seventh day post GM injection. Also shown, is the cell infiltration and vacuolation in their cytoplasm (Figure 2).

Figure 3 shows that at day seven of the Cis group, there was necrotic cellular debris in the lumina in some renal tubules, and others contained albuminous granules. Other tubules showed cloudy swelling.

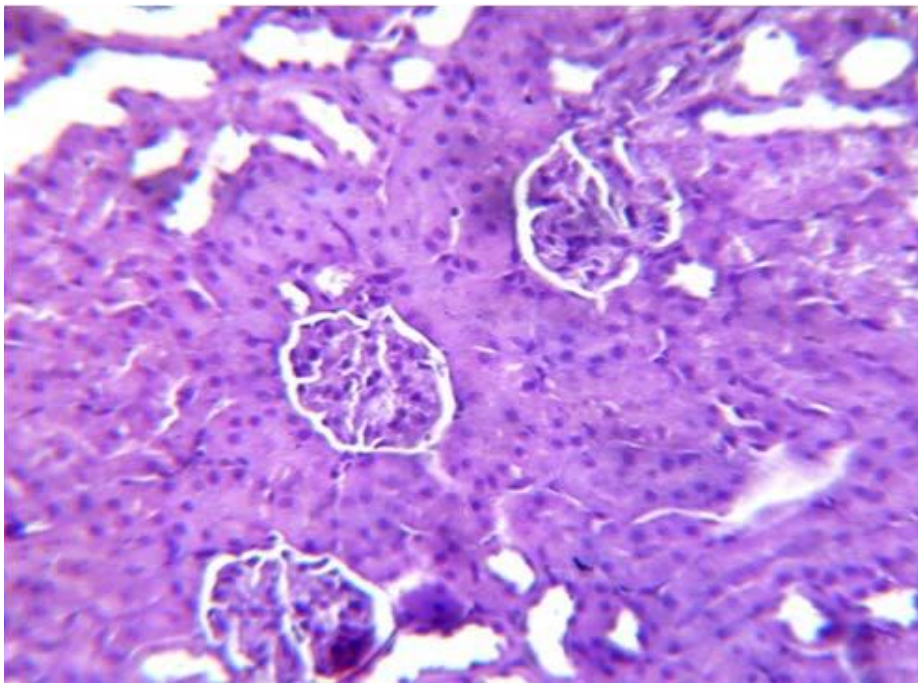

Figure 1. Kidney of normal adult rat (renal cortex) shows normal histological structure with H & E stain under light microscope (100X)

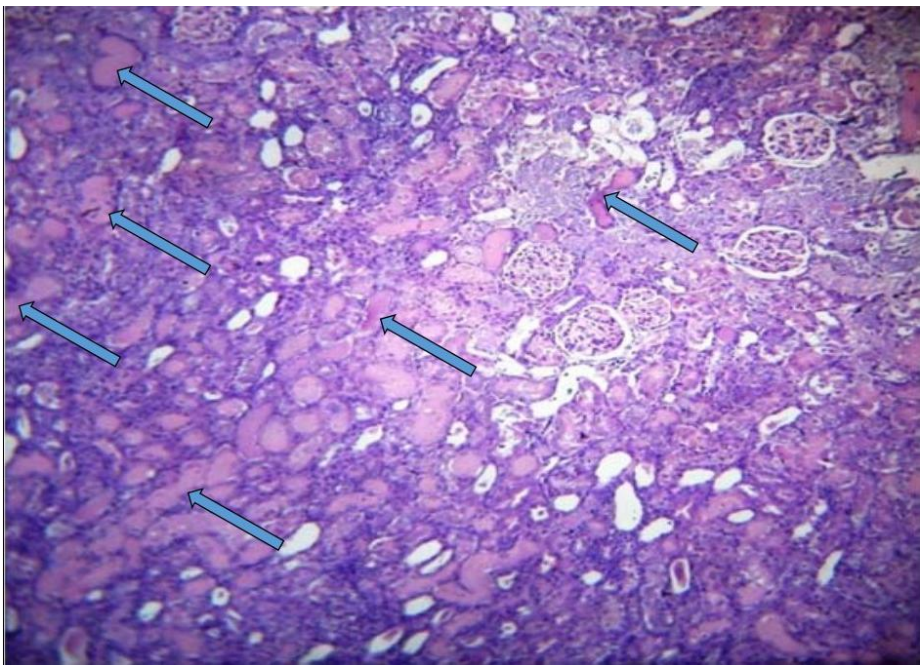

Figure 2. Kidney of Gentamicin-induced rat at day 7 shows hyaline cast (arrows) in renal tubules in their Lumina with H&E stain under light microscope (100X)

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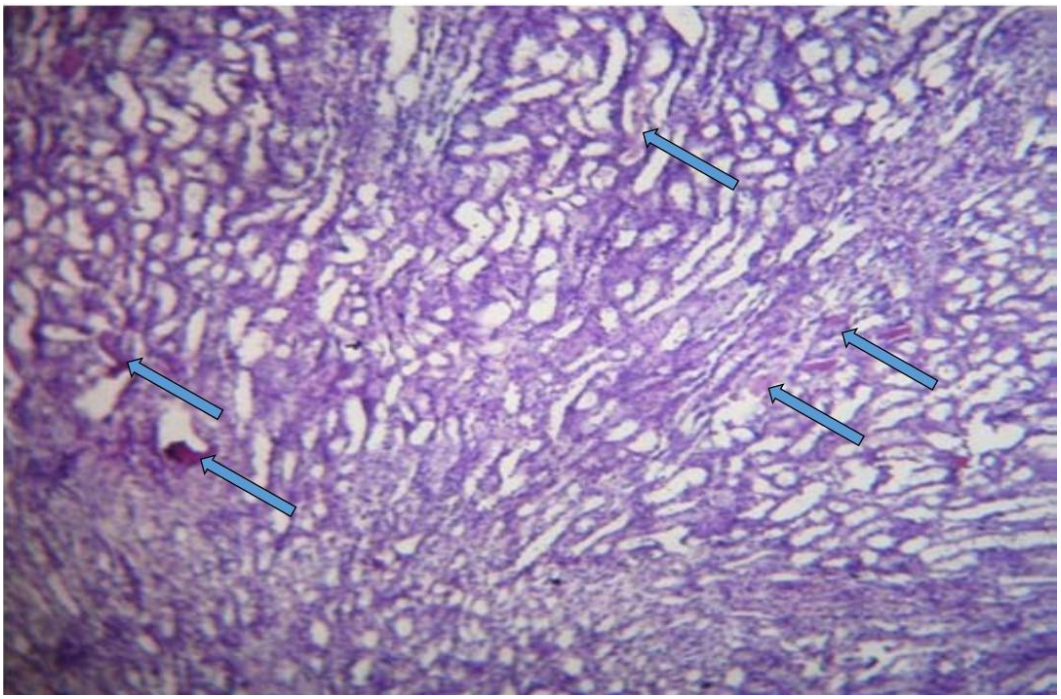

Figure 3. Kidney of Cisplatin-induced rat at day 7 shows renal tubules contain hyaline cast (arrows) with H&E stain under light microscope (100X)

Survey of HD patients

In this study, the survey data provided information of the possible causes of chronic renal failure. Background information of HD patients was reported by Alshafie et al. (2011)**.** Table 3 summarizes the possible causes of renal failure in the 50 HD patients randomly selected for this study. From this table it could be observed that over dose or uncontrolled or long-term treatment with antibiotics seems to have caused renal failure in 3 (6%) of patients in the present study.

DISCUSSION

In the experimental rats, the occurrence of drug-induced nephrotoxicity was documented in the Cis and GM groups by many criteria including: significant number of deaths among the rats during the experimental period, 13 rats out of 20 (65%) in the GM group (Alshafie et al., 2011). There was a significant ($P<0.05$) increase in serum Ur, Cr and potassium levels (Table 1). These results are in agreement with Daniel (1998) who concluded that the increased death rate in case of GM treated rats is due to uremia, hyperkalemia, septicemia, and gastrointestinal hemorrhage.

Cisplatin

The marked increase (Table 1) in serum Ur, and Cr levels in Cis treated group compared to the control group were in agreement with Arhoghro et al. (2012) and Saumya et al. (2011) who observed that, Cis injected rats had encountered acute kidney dysfunction as evidenced by elevation in serum Ur, Cr and uric acid decreased urine output and body weight with multiple histological damages. As mentioned earlier for GM the drug-induced histopathological changes are important causes of renal failure as shown in figure 2 when comparisons were made with the control group at the 7th day of the experiment. The histopathological changes that occurred at 3rd, 9th, and 11th days were reported by Alshafie and Nour (2011). Moreover, Khoshnoud et al. (2011) showed that, serum Cr and Ur levels were significantly elevated ($P<0.05$) in the animals treated with Cis compared to the normal control group. The increase of serum Ur and Cr levels were 6.5 and 5.8 folds, respectively. Jisha et al. (2008) as well, documented in Cis treated group a similar increase in serum Ur and Cr. Cis treatment resulted in a two fold increase in the serum urea and creatinine levels as compared to that of the untreated control group. The results of this study also agreed with the findings of Zhanjun et al. (2011) who concluded that mice treated with Cis showed earlier and greater increases in the levels of Ur and serum Cr. Furthermore, Udeani et al. (1996) observed a decline in renal function four days after Cis therapy, with a concomitant increase in serum Cr and blood Ur concentrations. Conklin (2000) mentioned that evidence suggests Cis-induced nephrotoxicity is due to the reactive oxygen species and the renal antioxidants. Ayman et al. (2006) indicated that, kidney damage induced by Cis treatment was characterized by alterations in kidney function, as evidenced by the continuing increase in serum Cr and blood urea nitrogen (BUN) levels. Interestingly, serum Cr increased significantly than BUN after Cis treatment, which may be due to the acute nephrotoxicity as suggested by Arunkumar et al. (2011). Furthermore, Cis-induced renal

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oxidative stress, the inflammatory response, and the histopathological injury had led to renal dysfunction (Mukhopadhyay et al., 2012).

The serum sodium level of Cis injected group in this study (Table 1) was different from had found by Peyrade et al. (1997), who concluded that Cis treatment resulted in hyponatremia that requires specific management. Also, Shafaq and Tabassum (2011) mentioned significant decrease in plasma sodium level of CIS treated rats when compared to the control group, the changes in the antidiuretic hormone secretion have been reported as the underlying mechanism for Cis chemotherapy induced hyponatremia (Lequn et al., 2002). Furthermore, hyponatremia might be attributed to the effects of the circulating uremic toxins, which resulted in accumulation of sodium inside the cell and loss of potassium as stated by Kosa and Silva (1980). Cis treatments can lead to hyponatremia in 4 to 10% of cases due to salt wasting with hypomagnesemia and normokalemia. In addition, functional renal failure and associated hyponatremia and hypotension were observed by Peyrade et al. (1997). Our study did not observe hyponatremia in Cis-treated rats.

The increase in serum potassium levels observed in experimental group in this study (Table 1) is consistent with the findings of Marshal (1988). Marshal (1988) documented the presence of a hyperkalemia after the progression of renal failure, and attributed that to the decreased excretion of potassium. Moreover, Lajer et al. (2005) concluded after repeated Cis treatments in rats that, Cis treatment exerted a negative effect on total potassium balance, although the difference between Cis-treated and the control rats was not significant at the end of their follow up. However, Shafaq and Tabassum (2011) reported a non-significant increase in serum potassium level in Cis treated rats as compared to the control. Surgam and Kahn (1986) explained that hyperkalemia might be related to the secondary hyperparathyroidism following uremia, and could be due to impairment renal excretion of potassium. Soliman et al. (1989) observed that the administration of parathyroid hormone to experimentally uremic rats caused a marked rise in plasma potassium level. In contrast to these findings, Khoshnoud et al. (2011) argued that Cis injection at a dose of 5 mg/kg did not change serum potassium levels significantly when compared with control group. Lajer and Daugaard (1999) argued that electrolyte disturbances such as hypomagnesaemia (60%), hypocalcaemia (89%), hypophosphatemia (57%), hypokalemia (95%) and elevations in serum Cr and Ur were observed after Cis-based chemotherapy. Our results agree with those reported in the literature in that Cis treatment resulted in a decrease in serum potassium.

Gentamicin

GM is a widely used antibiotic against serious and life-threatening infections, but its usefulness is limited by the development of nephrotoxicity (Randjelovic et al., 2012). Drug-induced nephrotoxicity is an important cause of renal failure as shown in Figure 2 when comparisons were made with the control group at the 7th day of the experiment. The histopathological changes that occurred at 3rd, 9th, and 11th days were reported by Alshafie and Nour (2011). The nephrotoxicity produced by GM can be due in part to an imbalance of pro-oxidant and antioxidants (Poormoosavi et al., 2010). The significant increase in serum Ur and Cr observed in this study (Table 1) is in agreement with that found by Marwan and Afaf (2012) in that GM produced highly significant ($P<0.001$) increase in the concentration of serum Ur and Cr and confirmed that GM produced nephrotoxicity. Furthermore, Poormoosavi et al. (2010) showed that the administration of GM to rats once daily for seven days reduces glomerular function, as reflected by the increased serum Ur and Cr concentrations. The increase in serum Ur and Cr levels were documented in the GM treated group compared to the control rats, were also in agreement with Freddy et al. (2009) who demonstrated that the mean serum Cr and Ur levels had significantly increased, after nine days of treatment with GM in comparison to that of the control group. Moreover, Patil et al. (2010) used GM at a dose of 100 mg/kg in rats and reported similar results to those observed in this study. Administration of GM alone at a dose of 100 mg/kg/day for eight days resulted in an increased level of serum Cr with evident nephrotoxicity (Eldin et al., 2008). Shaibu and Aminu (2009) confirmed the increase in serum levels of Cr and Ur after intramuscular injections of GM at a dose of 80 mg/kg body weight/day produced nephrotoxicity, as evidenced by the continuing increase in serum Ur and Cr. This was also confirmed by Nasim et al. (2006) who showed that rat groups injected subcutaneously with GM for seven days, euthanized on days 8 and 15, revealed highly significant ($P<0.001$) increases in Cr and Ur serum levels and histological change suggestive of nephrotoxicity. Nenad et al. (2008) observed that, aminoglycoside antibiotics are toxic to the kidneys and would result in renal failure during prolonged use, and the experimental models of GM-induced nephrotoxicity have shown histopathological, ultra structural and functional alteration with BUN, uric acid and serum Cr increase leading to acute renal insufficiency. This is consistent with the findings on this study. Nagai (2006) mentioned that, as aminoglycosides are taken up into the cells of the renal proximal tubules, and because they remain in these cells for a long time, result in nephrotoxicity. The GM damage was believed to be related to the generation of Reactive Oxygen Species (ROS) in the kidney (Martínez et al., 2002). ROS induces vasoconstriction, decreases Glomerular Filtration Rate (GFR) and also induces cellular injury and necrosis via lipid peroxidation and protein modification (Edson and Terrell, 1999).

The decrease in serum sodium levels observed in Table 1 in the GM-treated group compared to the control rats, is similar to the findings of Francescato et al. (2012) who mentioned that, rats injected with GM for nine days and

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euthanized two days after the end of this treatment, presented a higher plasma Cr and Ur levels, and increased sodium excretions. Also, Marwan and Afaf (2012) showed that serum electrolytes had significantly ($P<0.001$) changed in GM-treated rats as compared with control animals. Lower value of serum sodium indicates the inability of the kidney to conserve sodium and chloride. Hemodilution too may be involved in the decrease of serum sodium levels via the excess of water intake, and or increased production of metabolic water (Marwan and Afaf, 2012). Moreover, Poormoosavi et al. (2010) documented that serum sodium level had significantly decreased in GM group, however the serum potassium level significantly increased in GM group. On the other hand, Nenad et al. (2008) observed no statistically significant differences between the values of serum sodium concentrations in the GM group and the control group. The observed hyponatremia in the experimental groups treated with GM might be due to increased aldosterone production which affects the intracellular distribution of sodium potassium pump, leading to an increase of potassium and a decrease of sodium in tissues in uremic patients (Akmal et al., 1985). Another suggestion was advanced by Massary (1983) in that the decreased serum sodium level could be related to the metabolic acidosis accompanied uremia. The decreased serum sodium level in this study was not in agreement with the findings of Khalida et al. (2011) who mentioned that level of serum sodium had slight ($P>0.05$) increased in GM group, whereas level of serum potassium had significantly decreased in groups of rabbits receiving GM compared to the control group. The differences between experimental animals might have lead to the different results.

Regarding hyperkalemia observed in this experiment (Table 1) our results were in agreement with Poormoosavi et al. (2010) who mentioned that GM-induced nephrotoxicity is characterized by a decrease in the glomerular filtration rate, hyponatremia, hyperkalemia, and direct tubular injury. Moreover, Weinberg et al. (2009) stated that the risk of hyperkalemia in GM group is small. The increases of potassium appeared to be due to reduced excretion of potassium aggravated by leakage of intracellular potassium into blood stream as a result of GM- induced damage to the renal tubular epithelium (Marwan and Afaf, 2012). In contrast with these findings, Afzal et al. (2012) recorded a significant fall in serum potassium levels on day 16 in the animals treated with GM compared to the group treated with pyridoxal phosphate, where potassium levels remained similar to that observed on the First day. Khalida et al. (2011) stated that the administration of GM resulted in a significant decrease in serum potassium throughout the experiment. However, Enver et al. (2003) argued that in the GM-induced nephrotoxicity in experimental rats, potassium and sodium levels were altered by the treatment.

Survey of hemodialysis patients

The survey data revealed that 6% of the HD patients had renal failure that was attributed to antibiotics. Taking GM, particularly in diabetics, without close medical supervision, and the consumption of NSAIDs are being considered major causes of chronic renal failure. Because of the risk involved, it is recommended that taking such drugs should be avoided, or if necessary taken under strict medical supervision, which does not usually happen in developing countries, especially Africa. Adu and Tse (2001) suggested that the major causes of renal disease in such patients include drug toxicity and glomerulonephritis. Acynthia (2008) concluded that, drugs are a common source of acute kidney injury. The results obtained in this study are in agreement with the above mentioned investigations. The possible association of rheumatoid arthritis and chronic renal failure observed in this study is in agreement with Karstila et al. (2007) who reported that the occurrence of rheumatoid arthritis has varied between 5 and 50 percent in patients with chronic kidney disease which might be related to NSAIDs and antibiotics treatment. Drugs are shown to cause nephrotoxicity and exert their toxic effects by one or more common pathogenic mechanisms. However, Gilbert (1991) observed that, despite the mechanism of drug induced renal failure, the drug is actively concentrated in the renal cortex and proximal tubular cells where it reaches maximum concentration. Hence, high drug concentrations or multiple dosing are expected to be more harmful to the kidneys. This is of particular concern in countries of Africa where the lack of knowledge of the harmful effects of drugs, and the ease with which antibiotics are obtained might have resulted in drug toxicity and the associated kidney failure.

CONCLUSION

Several factors and drugs, such as antibiotics and a variety of other pharmaceutical agents, are known to be toxic to the kidneys. Renal toxicity commonly occurs after administration of these nephrotoxic agents. Nephrotoxicity has been listed as one of the major side effects of the drug GM, whose plasma half-life is increased when the glomerular filtration rate is low. On the other hand, a single dose Cis injection may cause impairment of renal functions and cause severe histopathological injury that would lead to the development of renal failure. The traditional measures of renal damage, elevated Cr and Ur levels usually occur after significant kidney damage has taken place. This study showed that the histopathological changes in renal tissues in Cis and GM-induced renal failure appeared in early stage of renal dysfunction in comparison to the changes in serum levels of traditional biomarkers such as urea and creatinine. More

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studies are needed to determine the correlations between biochemical markers and histopathological changes that may be used in prediction equations to assess earlier the drugs-induced toxicity in the kidneys before renal failure.

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Competing Interest

The authors declare that there are not significant personnel, professional or financial competing interest that might have influenced the presentation of the results of the study described in this manuscript.

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