Clinicopathological Studies On The Role Of Urinary Enzymes In The Diagnosis Of Nephrotoxicity In Dogs

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ABSTRACT

It was reported that lack of early biomarkers for diagnosis of acute renal failure is considered the most important problem hinder the effective therapeutic strategies. This study was performed on fourteen apparently healthy adult male dogs with a mean weight of 13.5 kg. They were demonstrated normal renal function before the study. Dogs were equally divided into two groups each of which contained 7 dogs. Group 1 was kept as a normal control .Group 2 was intramuscularly injected with gentamicin 10mg/kg B.W/d for 17 days . Blood samples were taken from cephalic vein from seven dogs in each group at 6,8, 10, 12,13,14,15,16 and 17 days post treatment. Also random urine samples were collected by cystocentesis and used for estimation of urinary enzymes. Specimens were taken from kidney at 15 and 17 days post treatment for histopathological examination.

The results showed a significant increase in the serum creatinine and blood urea nitrogen at 17 days post treatment in the treated group compared with the normal control. The serum levels of uric acid , total protein, albumin, globulin, sodium and potassium revealed non significant changes all over the experimental periods in the gentamicin treated group.

Urine alkaline phosphatase of dogs treated with gentamicin showed a significant increase at 15 and 16 days post treatment and a highly significant increase at 17 day post treatment. The γ –glutamyltransferase activity was significantly increased at 15, 16 and 17 days post treatment . A significant increase in the urine activity of lactate dehydrogenase was recorded at 16 and 17 days post treatment. The histopathological changes in the kidney of the treated group revealed moderate lesions at 15 days post treatment which became more severe at 17 days.

It could be concluded that urine alkaline phosphatase, γ–glutamyltransferase and lactate dehydrogenase are superior than serum creatinine and blood urea nitrogen in the diagnosis of renal damage.

INTRODUCTION

The development in the treatment of renal diseases especially acute renal failure has faced many problems. Among them the lack of early biomarkers is considered the most important one *(1)* . However, the ability of kidney to recover is depending on the cause, duration of the disease and the extent of the damage. Earlier diagnosis and effective therapeutic strategies are important for improvement of the high mortality rate of acute renal failure *(2-4)*. Also, in drug safety evaluation ,highly sensitive tests for renal injury are needed because the conventional diagnostic tests for renal damage such as serum creatinine and urea concentrations are unfortunately make detection at a relatively late stage. They are neither sensitive nor site specific *(5)*. The creatinine is increased when 65-75% of nephrons become damaged and the urea concentration is affected by many external factors such as whole blood feeding to dogs *(6)*.

So attention has been directed towards the evaluation of urinary enzymes as markers for nephrotoxicity in dogs because the technique is noninvasive and considered to be more sensitive than the conventional tests *(7)*. Urinary enzymes also have the potential of determining the primary site of renal damage *(8)*. Also *(4)* suggested that gamma-glutamyl transferase (γGT) allows early detection of renal tubular damage in dogs. The increase in the brush border enzymes of dogs , including

γGT and alkaline phosphatase (ALP), have been associated with renal proximal tubular damage, while the increase in the lactate dehydrogenase is associated with damage of the entire of the nephron *(7)*.

The aim of the present study is to investigate the clinical diagnostic importance of urinary alkaline phosphatase ,gamma-glutamyltransferase and lactate dehydrogenase as early biomarkers for acute renal failure.

MATERIAL AND METHODS

Animals

This experimental study was performed on fourteen adult apparently healthy male dogs with a mean weight of (13.5 kg). They were demonstrated normal renal function before the study. Dogs were equally divided into two groups each of which contained 7 dogs. Group 1 was kept as a normal control .Group (2) was intramuscularly injected with gentamicin (10mg/kg B.W/d, Alexandria Co. for pharmaceuticals- Alexandria-Egypt) *(9)* for 17 days .

Sampling

Blood samples (5 ml)were taken from cephalic vein from seven dogs in each group at 6,8,10, 12,13,14,15,16 and 17 days post treatment. These samples were collected into a centrifuge tubes for separation of serum by centrifugation for biochemical analysis. Also, random urine samples (10 ml) were collected from each dog by cystocentesis. The samples were centrifuged at 1200 RPM for 10 minutes and the supernatant was used for estimation of urinary enzymes *(10)*.

Biochemical study

The tested biochemical parameters included serum creatinine according to **(11)** , blood urea nitrogen *(12)* , uric acid *(13)* serum total protein *(14)*, albumin *(15)* and serum globulins were calculated as the difference between total protein and albumin. Serum sodium and potassium were measured by using flame photometer . Urine alkaline phosphatase (ALP) was determined *(16)*, γ glutamyle transferase (γGT) *(17)* and lactate dehydrogenase (LDH) *(18)* .

Histopathological examination

Specimens were taken from kidney at 15 and 17 days of age. The specimens were fixed in 10 % neutral buffered formalin and were embedded in paraffin. Sections of five micron thickness were prepared and stained with hematoxylin and eosin (H & E) *(19)*.

Statistical analysis

Results of tested parameters were statistically analyzed *(20)* using the MSTAT – C computer program.

RESULTS

Serum biochemical findings

Table (1) shows a significant increase in the serum creatinine level (17.05%) and blood urea nitrogen level (13.36%) at 17 days post treatment in the gentamicin treated group compared with the normal control. Non significant change was noticed in the serum level of uric acid.

Table (2) shows non significant changes in the serum levels of total protein, albumin and globulin all over the experimental periods in the gentamicin treated group compared with the normal control.

Table (3) reveals non significant changes in the serum levels of sodium and potassium in the different periods in the gentamicin treated group compared with the normal control.

Urinary enzymes

Urine activity of alkaline phosphatase of dogs treated with gentamicin showed a significant increase at 15 and 16 days post treatment by (12.14% and 19.01%) respectively. A highly significant increase (31.57%) was reported at 17 day post treatment. The γ–glutamyltransferase activity was significantly increased by (9.20% , 11.65% and 12.52%) at 15, 16 and 17 days post treatment with gentamicin respectively. A significant increase in urine activity of lactate dehydrogenase was recorded by (11.10%) and (15.32%) at 16 and 17 days post treatment respectively (Table 4).

Pathological changes

Macroscopically the kidney of gentamicin treated group was slightly smaller than the normal control. Microscopically at 15 days post treatment the renal parenchyma suffered from focal coagulative necrosis of some renal tubules represented by granular eosinophilic cytoplasm with karyolysis of their nuclei which encircled with round cells mainly periglomerular (Fig. 1). Some glomeruli had dilated glomerular space with partially destroyed glomerular tufts. The kidney of dogs 17 days post treatment showed diffuse subcapsular necrotic changes of renal tissue manifested by cytoplasmolysis and pyknosis or karyolysis of their nuclei together with thickened renal capsule (Fig. 2). Other tubules had swollen renal epithelium, fragmented eosinophilic cytoplasm with absence of the majority of their nuclei beside hyaline casts inside the lumina of some tubules (Figs. 3&4). Moreover lobulation of some glomerular tufts was encountered in the renal corpusles of some nephrons.

Table 1. Some renal function testes of dogs (mean values ± SE)

Groups	Parameters	Periods (day)								
		6	8	10	12	13	14	15	16	17
Gp. (1)	Creatinine (mg/dl)	0.86 ±0.05	0.87 ±0.04	0.87 ±0.05	0.87 ±0.06	0.88 ±0.06	0.86 ±0.06	0.88 ±0.06	0.88 ±0.05	0.88 ±0.04
Gp. (2)		0.86 ±0.05	0.88 ±0.06	0.89 ±0.07	0.89 ±0.07	0.90 ±0.07	0.89 ±0.08	0.93 ±0.08	0.94 ±0.08	1.03* ±0.05
% difference		+0.00	+1.15	+2.30	+2.30	+2.27	+3.49	+5.68	+6.82	+17.05
Gp. (1)	Blood urea nitrogen (mg/dl)	17.29 ±0.97	17.14 ±0.63	17.00 ±0.53	17.28 ±0.42	17.29 ±0.47	17.43 ±0.48	17.43 ±0.53	17.29 ±0.64	17.14 ±0.51
Gp. (2)		17.14 ±0.86	17.43 ±0.84	17.43 ±0.57	17.71 ±0.52	17.86 ±0.59	18.14 ±0.60	18.29 ±0.68	18.71 ±0.91	19.43* ±0.78
% difference		-0.87	+1.69	+2.53	+2.49	+3.30	+4.07	+4.93	+8.21	+13.36
Gp. (1)	Uric acid (mg/dl)	3.94 ±0.11	3.94 ±0.09	3.98 ±0.11	3.98 ±0.07	3.99 ±0.09	3.97 ±0.10	3.97 ±0.07	3.97 ±0.09	4.00 ±0.13
Gp. (2)		3.99 ±0.10	3.97 ±0.12	4.02 ±0.10	4.04 ±0.10	4.04 ±0.08	4.06 ±0.10	4.09 ±0.09	4.14 ±0.12	4.19 ±0.11
% difference		+1.27	+0.76	+1.01	+1.51	+1.25	+2.27	+3.02	+4.28	+4.75

*Significant at P≤0.05

Table 2. Changes in serum total protein, albumin and globulins of dogs (mean values ± SE).

Groups	Parameters	Periods (day)								
		6	8	10	12	13	14	15	16	17
Gp. (1)	Total protein (gm/dl)	6.16 ±0.12	6.13 ±0. 12	6.16 ±0.11	6.20 ±0.12	6.15 ±0.10	6.17 ±0.13	6.14 ±0.12	6.13 ±0.13	6.14 ±0.15
Gp. (2)		6.16 ±0.11	6.10 ±0.11	6.01 ±0.14	6.00 ±0.14	5.96 ±0.14	5.94 ±0.15	5.88 ±0.15	5.86 ±0.17	5.76 ±0.16
% difference		0.00	-0.49	-2.44	-3.23	-3.10	-3.73	-4.23	-4.40	-6.19
Gp. (1)	Albumin (gm/dl)	3.00 ±0.09	3.00 ±0.09	3.02 ±0.07	3.02 ±0.07	3.03 ±0.05	3.03 ±0.08	3.02 ±0.08	3.02 ±0.09	2.99 ±0.11
Gp. (2)		2.99 ±0.05	2.98 ±0.08	2.91 ±0.11	2.89 ±0.08	2.89 ±0.11	2.88 ±0.11	2.86 ±0.09	2.83 ±0.10	2.79 ±0.08
% difference		-0.33	-0.66	-3.64	-4.30	-4.62	-4.95	-5.29	-6.29	-6.69
Gp. (1)	Globulins (gm/dl)	3.16 ±0.14	3.13 ±0.09	3.14 ±0.04	3.18 ±0.05	3.12 ±0.06	3.14 ±0.06	3.12 ±0.05	3.11 ±0.05	3.15 ±0.06
Gp. (2)		3.17 ±0.06	3.12 ±0.11	3.10 ±0.10	3.11 ±0.10	3.07 ±0.11	3.06 ±0.11	3.04 ±0.12	3.03 ±0.13	2.97 ±0.12
% difference		+0.32	-0.32	-1.27	-2.20	-1.60	-2.55	-2.56	-2.57	-5.71

Table 3. Changes in serum sodium and potassium of dogs (mean values ± SE).

Groups	Parameters	Periods (day)								
		6	8	10	12	13	14	15	16	17
Gp. (1)	Sodium (mmol/l)	142.71 ±1.02	143.24 ±0.86	143.14 ±0.67	143.29 ±0.68	143.43 ±0.61	143.00 ±0.58	143.14 ±0.51	143.00 ±0.62	143.14 ±0.86
Gp. (2)		144.00 ±0.82	143.71 ±0.68	143.71 ±0.75	143.00 ±0.76	143.00 ±0.87	142.29 ±0.81	141.86 ±0.82	141.57 ±0.84	141.14 ±1.01
% difference		+0.90	+0.33	+0.40	-0.20	-0.30	-0.50	-0.89	-1.00	-1.40
Gp. (1)	Potassium (mmol/l)	4.37 ±0.10	4.37 ±0.11	4.39 ±0.14	4.38 ±0.12	4.39 ±0.09	4.36 ±0.11	4.36 ±0.10	4.37 ±0.09	4.39 ±0.09
Gp. (2)		4.35 ±0.09	4.36 ±0.10	4.38 ±0.13	4.38 ±0.11	4.41 ±0.10	4.43 ±0.11	4.47 ±0.11	4.50 ±0.10	4.55 ±0.11
% difference		-0.46	-0.23	-0.23	+0.00	+0.46	+1.6	+2.52	+2.97	+3.64

Table 4. Changes in urine ALP, γGT and LDH of dogs (mean values ± SE).

Groups	Parameters	Periods (day)								
		6	8	10	12	13	14	15	16	17
Gp. (1)	ALP (U/l)	10.83 ±0.21	10.79 ±0.32	10.82 ±0.51	10.74 ±0.48	10.82 ±0.62	10.93 ±0.68	10.96 ±0.50	10.85 ±0.56	10.80 ±0.68
Gp. (2)		10.62 ±0.37	10.81 ±0.26	11.04 ±0.49	11.30 ±0.45	11.47 ±0.48	11.70 ±0.50	12.29* ±0.34	12.92* ±0.60	14.21** ±0.93
% difference		-1.94	+0.19	+2.03	+5.21	+6.01	+7.04	+12.14	+19.01	+31.57
Gp. (1)	γGT (U/l)	29.86 ±1.10	30.00 ±1.27	29.86 ±1.18	30.14 ±0.99	30.00 ±0.69	29.71 ±0.84	29.57 ±0.43	29.43 ±0.92	29.71 ±0.99
Gp. (2)		29.14 ±1.16	29.29 ±1.25	29.57 ±1.56	29.86 ±1.60	30.29 ±1.32	30.29 ±1.23	32.29* ±1.04	32.86* ±1.18	33.43* ±1.25
% difference		-2.41	-2.37	-0.97	-0.93	+0.97	+1.95	+9.20	+11.65	+12.52
Gp. (1)	LDH (U/l)	15.83 ±0.58	15.86 ±0.34	15.86 ±0.50	15.71 ±0.52	15.86 ±0.34	16.00 ±0.61	16.14 ±0.55	15.94 ±0.43	15.86 ±0.59
Gp. (2)		15.80 ±0.80	16.14 ±0.80	16.14 ±0.51	16.29 ±0.52	16.71 ±0.78	17.14 ±0.67	17.43 ±0.72	17.71* ±0.61	18.29* ±0.81
% difference		-0.19	+1.77	+1.77	+3.69	+5.36	+7.12	+7.99	+11.10	+15.32

*Significant at P≤0.05 ** Significant at P≤0.01

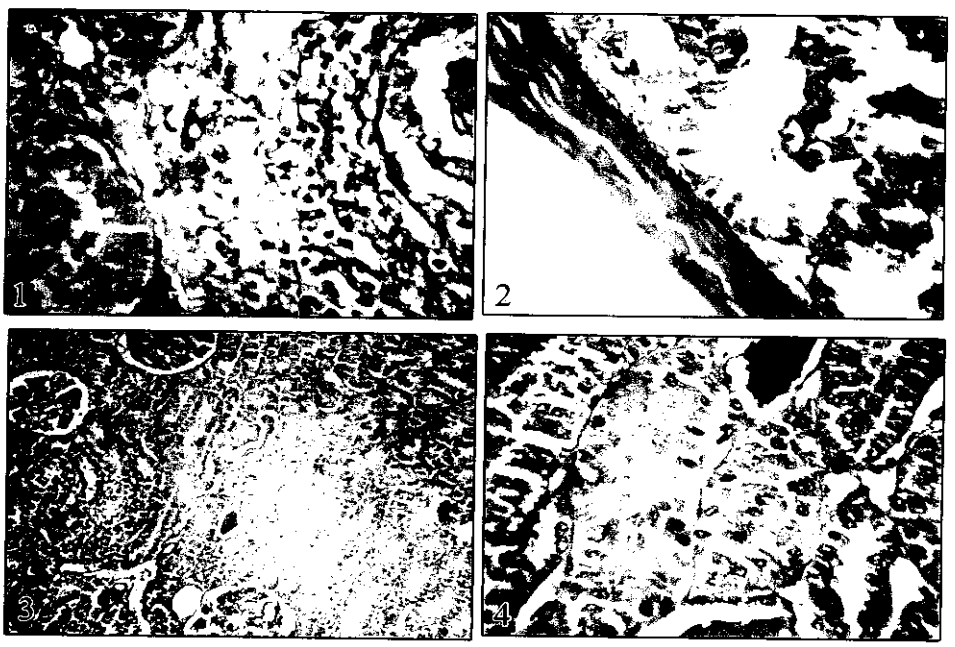

Fig.1. Kidney of dog (15 day post treatment) showing focal coagulative necrosis of some renal tubules with presence of periglomerular round cells aggregation (H & E x 1200).

Fig.2. Kidney of dog (17 day post treatment) showing diffuse subcapsular necrosis with thickened renal capsule. (H & E x1200).

Fig.3. Kidney of dog (17 day post treatment) showing diffuse coagulative necrosis with hyaline casts inside the lumina of some renal tubules (H & E x 300).

Fig.4. Kidney of dog (17 day post treatment) high power of the previous figure to show the necrotic changes of renal epithelia and hyaline casts (H & E x 1200).

DISCUSSION

This study showed that administration of gentamicin caused damage to the renal tissue as clarified by both the clinico – and histopathological means .This renal damage was reflected at 17 days post treatment by a significant increase in the serum levels of creatinine and blood urea nitrogen. Such biochemical changes, in the present work, are the outcome of nephropathy which is manifested by diffuse subcapsular necrosis with thickened renal capsule and diffuse coagulative necrosis with hyaline casts inside the lumina of some renal tubules .Numerous have been referred to renal toxicity of gentamicin. The common understanding is that accumulation of the aminoglycosoides, particularly in the renal proximal cells, accounts for direct cytotoxicity *(9, 21 , 22).* The serum levels of uric acid, total protein, albumin, globulin, sodium and potassium showed non significant changes .This indicates that serum creatinine and blood urea nitrogen are more sensitive than them as they need more time to be changed. The urine activity of ALP is significantly increased from the 15 day post treatment which became highly significant at 17 day. Alkaline phosphatase is a brush border enzyme which is more sensitive for even mild renal damage and this is clarified by the histopathological findings which revealed focal necrosis of some renal tubules with presence of periglomerular round cells aggregation. This support the previously obtained result by many authors *(23, 24)* who suggested that urinary ALP can be used as an early indicator for acute renal damage. Regarding to the activity of γ glutamyl transferase a significant increase was recorded at 15 day post treatment till the end of the experiment. Nearly similar result was obtained *(9)* who reported a significant increase in the γGT preceded the significant increase in the serum creatininee value by four days. Moreover *(4) mentioned that* γGT can used as an early biomarker for renal damage. Concerning to the result of lactate dehydrogenase, it seemed to be the least sensitive one in the measured enzymes as it showed a significant increase at 16 day post treatment. Nearly this result is in accordance with *(25).*

It could be concluded that urine ALP, γGT and LDH are more sensitive as early biomarkers for renal damage than serum creatininee and blood urea nitrogen. The most sensitive one was ALP and the least was LDH

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الملخص العربى

دراسات باثولوجية إكلينيكية على دور إنزيمات البول فى تشخيص التسمم الكلوى فى الكلاب

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النقص فى الدلالات المبكرة لتشخيص الفشل الكلوى الحاد يعتبر من أهم المشاكل التى تعيق التقدم فى استراتيجيات العلاج. أجريت هذه الدراسة على عدد ٢٠ كلب بالغ وكانت وظائف الكلى لهذه الكلاب طبيعية قبل أجراء الدراسة. قسمت هذه الكلاب إلى مجموعتين كل مجموعة منها تحتوى على ١٠كلاب.

المجموعة الأولى : هى المجموعة الضابطة اما المجموعة الثانية فقد تم حقنها عضليا بالجنتامايسين (١٠مجم/كجم وزن حى / يوم) لمدة ١٧ يوم أخذت عينة الدم من عدد ٧ كلاب من كل مجموعة عند اليوم ٦ و٨ و١٠ و ١٢ و ١٣ و ١٤و ١٥ و ١٦ و ١٧ يوم بعد العلاج.

وأيضا أخذت عينات عشوائية للبول من المثانة واستخدمت فى قياس أنزيمات البول. وتم أخذ عينات من الكلى عند عمر ١٥ و ١٧ يوم بعد العلاج لإجراء الفحوصات الباثولوجية. أظهرت النتائج عن وجود زيادة معنوية فى الكرياتينين والبولينا عند اليوم ١٧ بعد العلاج مقارنة بالمجموعة الأولى ولم يظهر أى تغير معنوى فى حمض البوليك والبروتين الكلى والزلال والجلوبيولين والصوديوم والبوتاسيوم فى السيرم على مدار التجربة.

أظهر إنزيم الفوسفاتيز القلوى فى البول زيادة معنوية عند اليوم ١٥ و١٦ وزيادة معنوية جداً عند اليوم ١٧ كما اظهر إنزيم الجاما جلوتاميل تراسفيريز زيادة معنوية عند اليوم ١٥ و ١٦ و١٧ .

وكذلك اظهر إنزيم اللاكتيت ديهيدروجينيز زيادة معنوية فى اليوم ١٦ و ١٧ بعد المعاملة وأظهرت الكلى تغيرات باثولوجية متوسطة عند اليوم ١٥ واشتدت عند اليوم١٧.

وستخلص من ذلك ان إنزيم الفوسفاتيز القلوى و إنزيم الجاما جلوتوميل تراسفيريز و إنزيم اللاكتيت ديهيدروجينيز أكثر حساسية من الكرياتينين والبولينا فى تشخيص التلف الكلوى.