PLASMA NITRIC OXIDE STATUS IN PATIENTS WITH DRUG-INDUCED ACUTE RENAL FAILURE

BY

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ABSTRACT

Background: Drug-induced acute renal failure (ARF) is a medical problem affecting hospitalized patients and patients presented to emergency hospitals. A drug can induce ARF through a prerenal or an intrarenal pathway. Subjects and methods: 12 patients with prerenal ARF and 7 patients with intrarenal nephrotoxic ARF were enrolled in the present study. They were clinically examined and laboratory and radiologically investigated. History of prescribed nephrotoxic medications, rise in serum creatinine levels and ARF manifestations were encountered in all cases. Plasma NO metabolites (NO_2 and NO_3) were determined colorimetrically as a colored azo dye product of Griess reaction . Results: The study showed that nonsteroidal anti-inflammatory agents (41.6%), angiotensin converting enzyme inhibitors (16.6%) and sildenafil citrate, (8.3%) were the single drug-induced prerenal ARF. The remaining cases (33.3%) gave history of multiple drugs intake. On the other hand, aminoglycoside nephrotoxicity occurred in 14.3% of intrarenal ARF patients while, analgesics and/or anti-pyretics caused ARF in 57.14%. At the same time, intrarenal ARF was detected in association with methicillin or cephalosporin administration in the remaining patients (28.6%). The onset of ARF in both series of patients began between four days and two weeks after drug intake (except with sildenafil citrate) while the severity and prognosis were dose-dependent. Plasma NO_2 concentrations among intrarenal ARF patients were not significantly different from those observed in controls. Alternatively, the concentration of plasma total NO-3 (NOx) among prerenal ARF patients were significantly higher than controls. In addition, plasma NO-2 and NOx concentrations of intrarenal ARF were significantly lower than those of prerenal ARF. Conclusion: Plasma total NO_3 (NOx) differentiates between prerenal (high) and intrarenal (normal or low) nephrotoxicity. Hyperkalemia and relatively subnormal NO bioactivity found in intrarenal ARF may explain the high incidence of cardiovascular strokes in them. On the other hand, the excess NO in prerenal ARF participates in development of hypotension and collapse. Discontinuation of the responsible drug is often the only necessary management while avoidance of these drugs is the most effective way to avoid drug-

induced nephrotoxicity.

Key words: *ARF: acute renal failure; GFR: glumerular filtration rate ATN: acute tubular necrosis; NOS: nitric oxide synthase: (i: induced; e: endothelium; c: constitutive; n: neural;) ADMA:asymmetric dimethylarginine.*

INTRODUCTION

Nephrotoxicity is a major side effect in clinical practice, which frequently leads to acute renal failure (ARF). Drug- induced ARF is classified into two categories: (1) Prerenal ARF is a rapidly but commonly reversible uremia caused by renal hypoperfusion. In prernal ARF, there is a reduction in glomerular filtration rate (GFR) with no frank renal parenchymal damage. (2) Intrarenal ARF that may be due to prolonged renal hypoperfusion, resulting in tissue ischemia and acute tubular necrosis (ATN), or due to toxic damage of the nephrons. Any condition that causes prerenal ARF may progress to intrarenal ARF if renal hypoperfusion is severe and prolonged (Mindell and Chertow, 1997; Alexopoulos, 1998; Silva, 2004; Markowtiz and Perazella, 2005). The morbidity and mortality rates in drug-induced uremic patients with serum creatinine levels greater than 3.0 mg/dl remain high, although, a better survival rate in them is not a far hope (Nash et al., 2002).

Nitric oxide (NO) plays a major role in maintaining the high renal blood flow and is also involved in the regulation of glomerular hemodynamics and contractility of mesangial cells, not only under basal but also in toxic acute renal failure (Schramm et al., 1996). NO is critically involved in the functional and morphological alterations observed in drug-induced nephrotoxicity. In the majority of such conditions, NO synthesis appears elevated. The noted increase of NO synthesis appears primarily protective to the remaining renal function (Rivas-Cabanero et al., 1996 & 1997; Mindell and Chertow, 1997; Stroes et al., 1997;Heman et al.,1998; Suschek et al., 2000). However, this increase in NO synthesis and release does not lead to renal vasodilatation, probably due to its decreased bioavailability through its rapid interaction with reactive oxygen species and the simultaneous increase in the release of vasoconstrictors (Goligorsky et al., 2004). Alternatively, decreased endothelium derived NO has been reported in acute renal failure that may be due to depletion of tetrahydrobioptrin, a cofactor for NOSs synthesis (Kakoki et al., 2000). In agreement with these latter findings is that 79% of uremic plasma inhibited both endothelial and inducible NOS activities while the remaining percent stimulated NOS activities (Arese et al., 1995). Altered generation of nitric oxide by the endothelial cells represents an important feature of

endothelial dysfunction that contributes to the pathophysiology of acute renal injury (Goligorsky et al., 2002). So, it has been clearly demonstrated that NO participates in the pathogenesis of ARF and the issue of whether NO is a "good" or "bad" molecule in ARF is currently under extensive investigation (Valdivielso and Blantz, 2002).

The above review shows a controversy about NOS/NO metabolism in drug-induced ARF in experimental models, while studies in this field on human are very rare. So, the present study was initiated to determine the concentration of plasma NO metabolites (NO_2+ NO_3) in patients with drug-induced ARF whether secondary to prerenal or intrarenal drug-induced nephrotoxicity.

SUBJECTS AND METHODS

Serially hospitalized 19 patients with ARF were studied. Before the development of ARF, all these patients were healthy and none had a past history of renal disease. History of nephropathic drug intake was given by all patients. Cases with hemolytic crises, reaction to radio contrast media or hepatorenal failure were not included. On clinical background, none of the uremic patients gave a past history of chronic associating diseases (renal, pancreatic, hepatic, and endocrine disorders). Before investigations, any drug influencing the designed investigations were replaced by biochemically non-effective therapies.

The present study comprized 12 patients suffered from prerenal ARF and the remaining (7 patients) had intrarenal nephrotoxic ARF. No case with postrenal ARF was included in this study. A present history of drug intake, rise of serum creatinine levels, fluid and electrolyte imbalance and abnormal urine analysis results were the keystone of drug-induced ARF diagnosis. Diagnosis of the underlying cause of ARF was based on the history while clinical, radiological, and biochemical examinations pointed to the type and stage of ARF (Schrier et al., 2004). Prerenal ARF due to drug intake is caused by renal hypoperfusion and reduction in glomerular filtration rate without renal parenchymal damage (low effective circulating volume). In contrast, intrarenal drug-induced ARF reflects damage of the nephrons by drug(s) due to prolonged hypoperfusion or directly to their toxic damage.

In addition, 10 healthy persons selected from patients' relatives, blood donors or hospital workers were similarly studied as a reference (control) group. They were matched in age, sex and body mass index (BMI) with the uremic patients.

Informed consent was obtained from all subjects (patients and controls).

Laboratory investigations:

a- Serum and urinary creatinine (Cr), spectrophotometric end point assay (BioMerieux-Vitek Inc., 595 Anglum Drive Hazelwood, Missouri 63042-2395 USA).

b- Serum and urinary Na and K by ion selective electrode (AVL-ISE analyzer 988-3 ,4 Switzerland).

c- Fractional excretion of sodium (FENa) % that measures the activity of the kidneys in resorbing sodium was calculated (Mindell and Chertow, 1997) = (urine Na x serum Cr) / (urine Cr x serum Na) x 100.

d- Plasma (EDTA) nitric oxide metabolites (NO_2^-/NO_3^-) were determined by photometric assay (Moshage et al., 1995) using byproducts of Assay Designs. Inc. (800 Technology Drive Ann Arbor, MI:48108 USA).

Data being parametric, statistical analysis for each group results were presented as mean ± SD. Statistical data of each group of patients were compared with each other and with those for healthy subjects using the Student t test. The significance for any of these tests was set at $P<0.05$ (Knapp and Miller, 1992). Statistical analyses were performed with SPSS 9.0 (SPSS, Inc., Chicago, IL USA).

RESULTS

(A) Demographic data of the studied cases:

In the total ARF group (19 patients) and the normal control group (10 subjects), the male to female ratios were 12:7 and 6:4 while the mean ages were 44.9 ± 7.7 and 45.3 ± 4.8 years and BMI mean values were 24.1 ± 2.5 and 25.0 ± 1.3 respectively.

(B) The main clinical and laboratory data are shown in Tables from 1 to 5.

DISCUSSION

Drug-induced ARF is one of the common problems seen by nephrologists in emergency hospitals, but its true frequency is probably underestimated. Diagnosis of it is typically only made in uremic patients without another explanation for deteriorating renal function, and is often proved by improvement after drug withdrawal. Failure to recognize drug nephrotoxicity and discontinuation of the offending agent(s) may result in unnecessary morbidity and occasionally, irreversible acute renal failure (Evenepoel, 2004). Despite the progress in pharmaco-therapy, the frequency of hospital acquired drug-induced acute renal failure has increased from less than 5.0% (Mindell and Chertow, 1997) to 6.4% (Nash et al., 2002) of the total ARF affections. More distressing is the finding that mortality associated

with drug-induced acute renal failure has remained high (Nash et al., 2002).

In the present study, the onset of ARF was related to drug therapy, oftenly reversible specifically in prerenal cases and the severity was dose dependent. These results agree with many studies (Alexopoulos, 1998; Evenepoel, 2004; Markowtiz and Perazella, 2005). Prerenal ARF (Table 1) was found to be induced by nonsteroidal anti-inflammatory agents (41.6%), angiotensin converting enzyme inhibitors (16.6%) and sildenafil citrate (8.3%). The remaining (33.3%) was due to combination of drugs. The prerenal changes were peripheral vasodilatation, interference with fluid and electrolyte homoestasis and adverse cardiotoxic changes. Adverse renal effects of conventional nonsteroid anti-inflammatory drugs occur because of inhibiting the synthesis of nonselective cyclooxygenase responsible for synthesis of prostaglandins which are important in the modulation of renal physiology (Gambaro and Perazella, 2003). At the same time, aminoglycoside intrarenal nephrotoxicity with ARF (Table 2) occurred in 14.3% of the investigated patients while combined antibiotics, analgesics and antipyretics caused 57.1% of intrarenal ARF. Administration of certain antibiotics (methicillin and cephalosporin like groups) induced intrarenal ARF in 28.6% of the studied series of patients. Some authors (Silva, 2004; Markowtiz and Perazella, 2005) noticed that all aminoglycosides had the potential to produce nephrotoxicity while others (Boffa et al., 2000) considered antibiotics, in general, as the most common cause of ARF.

These drugs appear to be minimally metabolized within the body and undergo nearly exclusive renal excretion. The role of infection (when present) and subsequent bacterial endotoxin can influence the pathogenesis of drug-induced nephrotoxicity. The clinical course of drug nephrotoxity depends on the primary health status in these patients. In the present study, FENa % (Table 3) was a reliable index for differentiation between both types of ARF. However, Mindell and Cherlow (1997) stated that there was an overlap in the values of FENa% in ARF types. Thus, decreased FENa% was noted in patients with decreased effective circulating fluid volume (Aromoff, 1992).

Cardiac manifestations recorded in this study were due to the noted hyperkalemia of ARF (Table 4). In the present study, full recovery was observed in 73.5% and incomplete recovery was found in only 16.0% while worsening of the condition with development of complications was encountered in 10.5% of cases. Factors of poor prognosis were a poor previous health status and the presence of hidden infection. Oligurea was a high risk of morbidity.

Management of the present cases included: (1) stopping administration of the nephrotoxic drugs (2) encouragement of intravenous fluid infusion for drug elimination (3) dialysis for intrarenal cases till renal function was restored and (4) proper management of any clinical disorder of the vital organs (e.g. cardiovascular, neurovascular and pulmonary systems).

Endothelial dysfunction in ARF may result from accumulation of uremic toxins. These include a variety of guanidino compounds which have been shown to be nitric oxide synthase modulators both in vitro and in vivo (DeDeyn et al., 2003). Thuraisingham and Yaqoob (2003) reported that there was an increased NO release, but this was associated with excess consumption of it in uremia. NO metabolites (NOx) in the plasma of hemodialysis nephrotoxic patients showed higher concentrations, both pre- and post-dialysis compared to controls. This is not a simple retention by ARF since culture of endothelial cells in uremic plasma demonstrated increased NO release compared to controls. At the same time, Noiri and Colleagues (1996) concluded that, excess NO were produced via induced NOS (iNOS) in the course of acute renal failure and hemodialysis modified the state of plasma NOS activity in uremia. So plasma taken after hemodialysis session showed a reduced inhibitory activity since, molecules reducing NOS activity were accumulated in the ultrafiltrate.

In the present study, there was significantly higher concentrations of plasma NO stable metabolites in the form of total nitrates (NOx) in prerenal ARF patients compared to healthy control group (Table 5). The high plasma NOx concentrations can be attributed to the rapid inactivation of the excessively released NO. Moreover, it is likely that renal dysfunction may decrease clearance of such NO metabolites, amongst which NO-3. In this respect, Suto et al. (1995) showed that approximately 50% of the ingested nitrates are excreted in the urine. Subsequently, total nitates (NOx) will be retained in the circulation in cases with renal insufficiency. In this respect and based on pharmacological and experimental studies, some authors (Conger et al., 1995; Can et al., 2000) suggested an impaired production of plasma NO in ARF. Alternatively others (Rivas-Cabanero et al., 1997) found that in ARF, NO is formed in excessive amounts due to an augmented expression of both iNOS and endothelial NOS (eNOS) but not neuronal NOS (n NOS). Altered generation of NO by endothelial cells or reduced NO bioavailability represents an important feature of endothelial dysfunction (Arese et al., 1995; Goligorsky et al., 2002). Conger et al. (1995) have demonstrated that vasorelaxation in response to stimuli generating endothelium-derived relaxing factor was inhibited in ARF.

With regard plasma NOx concentration in intrinsic (intrarenal) ARF patients, it showed no significant difference from the control group. However, there was a significant decrease in comparison to the corresponding prerenal ARF value (Table 6). These findings can be explained by the possibility of NO conversion to peroxynitrite which is implicated in cytotoxicity. Of interest is that plasma NOx levels (obtained under condition of dietary nitrate control) do not give stand-alone information about NO production, particularly when renal function is impaired. Reduced synthesis of the vasoactive substances (e.g. NO and prostaglandins) in renal disease might predispose such patients to drug-induced nephropathy. Subsequently, Can et al. (2000) postulated that L-argininc supplementation had beneficial effects in gentamycin-induced acute renal failure. The nitric oxide released from vascular endothelium played a protective role in gentamycin nephrotoxicity (Goto et al., 2004).

The result of the present study assumed an increased NO production in prerenal ARF and a decreased production of it in intrarenal affections. Both conditions are harmful for the corresponding patients' and contribute to the pathophysiological diverge seen in them.

Table (1): The main medical data in prerenal ARF patients.

Cases		Pre existing disease	Prescribed drug	Duration of therapy	Major presenting signs and symptoms
No.	%				
5	41.6	Autoimmune diseases-osteoartheritis	Non steroidal anti-inflammatory	4 days	• Hypotension, Collapse and cardiovascular incompetence • Acute renal failure
2	16.6	Hypertension	Angiotensin converting enzyme inhibitor	4 days	
1	8.3	Senile impotence	Slidenafil citrate	2 hours	
4	33.3	Prolonged unknown fever	Mixed drugs (antibiotics, antipyretics and analgesics)	4 days	

Table (2) : The main medical data in intrarenal ARF patients.

Cases		Pre existing disease	Prescribed drug	Duration of therapy	Major presenting signs and symptoms
No.	%				
1	14.3	Urinary tract infection	Aminoglycoside	14 days	(1) Hypersensitivity reaction. (2) Normotensive (3) Urinary volume depletion and urinary deposit of RBCs and casts. (4) ARF
2	28.6	Prolonged unknown fever	Methicillin and cephalosporin antibiotics	7&10 days	
	57.1	Variable	Multiple drugs	8-12 days	

Table (3): Data of significance in urine analysis of both ARF groups.

	Prerenal	Intrinsic ARF
Specific gravity	~1.020	1.010 (fixed)
FENa%	<1.0	>1.0
Albuminurea	Nil - trace	++
Casts	Hyaline (few)	Epithelial & Granular

Table (4): Selected kidney function tests (serum creatinine, sodium and potassium concentrations) statistical data in normal control group versus ARF patients.

Data	Creatinine mg/dl	Sodium mmol/l	Potassium mmol/l
Normal control	1.05±0.2	137.1±4.4	3.90±0.4
ARF patients	6.8±1.5	136.6±3.8	5.15±1.7
p-value	<0.001	>0.90	<0.001

Table (5): Statistical data of plasma NO stable metabolites as NO_2 and NO_x ($NO2+ NO_3$) in the studied groups.

Items (studied groups)		NO_x µmol/L	NO_2 µmol/L
[A] Normal control group	X ± SD	36.2±6.3	11.4±1.5
[B] Prerenal ARF group	X ± SD	49.5±8.3	12.2±1.8
[C] Intrarenal ARF group	X ± SD	32±9.5	10.5±2.4
P: A versus B		0.001	0.624
P: A versus C		0.567	0.345
P: B versus C		0.001	0.012

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دراسة عن وضع أوكسيد النيتريك فى بلازما الدم فى حالات الفشل الكلوى الحاد الناتجة عن تعاطى أدوية

المشتركون فى البحث

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إن معدل حالات الفشل الكلوى الحاد الناتج من تعاطى بعض الأدوية العلاجية بالمستشفيات قد إزداد بصورة ملحوظة، ومن ضمن الأدوية المؤدية للفشل الكلوى نأتى المضادات الحيوية والاستيريدات المضادة للالتهاب بصفة عامة من أهم الأسباب . لهذا كان الغرض من هذه الدراسة هو بيان دور أوكسيد النيتريك فى حالات السمية الكلوية الناتجة عن تناول بعض الأدوية الشائعة الاستعمال، أجريت هذه الدراسة على ١٩ شخصاً وقد تم تقسيمهم إلى ٣ مجموعات كالآتى : مجموعة ضابطة من عشرة أفراد، مجموعة مصابة بفشل كلوى حاد لأسباب غير كلوية ونتيجة تعاطى أدوية علاجية وتتكون من ١٢ حالة والمجموعة الثالثة لمرضى الفشل الكلوى الحاد (٧ حالات) نتيجة الإصابة بالتهاب وتحلل أنسجة الكلى نتيجة للأدوية المستخدمة، ولقد أخذت عينات دم لبيان مستوى الكرياتينين والبوتاسيوم بمصل الدم وأيضيات أوكسيد النيتريك بالبلازما.

وقد تم تحليل النتائج الإكلينيكية والمعملية إحصائياً ووجد الآتى : وجود زيادة واضحة فى الكرياتينين والبوتاسيوم، كما وجد أن معدلات أيضيات أوكسيد النيتريك بالدم عالية فى مرضى الفشل الكلوى الناتج عن أسباب غيركلوية بينما كان معدل هذه الأيضيات فى المرضى المصابون بتحلل أنسجة الكلى فى مستوى أقل نسبياً من المعدل الطبيعى وهذه النتائج توضح أهمية وضع أوكسيد النيتريك فى حالات الفشل الكلوى فبينما معدل أوكسيد النيتريك ببلازما الدم يقل فى مرضى الكلى الأولى فإنه يزيد فى مرضى الفشل الكلوى الثانوى الناتج عن إختلال الدورة الدموية، وهذا يوضح أسباب الاختلاف الإكلينيكى فى هاتين المجموعتين.