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Cisplatin and Adriamycin: A comparative assessment of Rats nephron injury

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***Abstract*—** Assess of short-term physiological and biochemical changes associated with experimentally induced impairment of nephron function in adult male rats. To identify potential neighborhood-level determinants of adopting healthy eats and were able to synthesize evidence indicators for 40 rats into two literature: a group control1 with specific combined tubular injury-rat kidney, or glomerular injury obtaining from Cisplatin (Cis)-obstructive nephropathy models of acute kidney disease through Adriamycin stumble (ADR). Serum urea, blood urea nitrogen (BUN), uric acid and creatinine were measured at 10, 20 and 30 days. The results showed that significantly increased levels of urea, BUN, uric acid and creatinine ($P < 0.01$) with progressive renal function impairment were found in the cisplatin-treated and combined-injury groups as compared to controls. In contrast, minimal biochemical change occurred in day 30 serum following simple treatment with Adriamycin alone, suggesting that initial quantitation of this pathophysiologic model following treatment validation may require more sensitive markers or secondarily activated processes after glomerular structural injury. Overall, additive or synergistic nephron injury due to tubular epithelial toxicity and filtration barrier dysfunction was indicated by the combined model displaying the most advanced impairment. Results confirmed the diagnostic relevance of conventional renal failure markers for nephrotoxicity in experimental models and emphasized their complementarity with early tubular and glomerular biomarkers, histopathological assessment regarding segment specificity of nephron damage.

Keywords **—** renal function tests, cisplatin, Adriamycin, rats.

INTRODUCTION

The kidney is a large, complex organ with critical roles in the regulation of extracellular fluid volume and electrolyte balance; acid-base regulation; endocrine function; and the excretion of metabolic waste products. These functions are dictated by the concerted regulation of glomerular filtration, tubular reabsorption, tubular secretion and renal microvascular modulation. As a result any structural or functional damage in any nephron segment can interrupt nitrogenous waste excretion and mediate measurable changes of blood levels of urea, blood urea nitrogen, creatinine and uric acid. All these classical biochemical markers lack sensitivity in the initial stages of renal injury, but are widely used due to their low costs, reproducibility and established clinical role as helpful markers of functional nephron reserve (1, 2).

Studies using experimental models of nephrotoxicity are important for understanding common mechanisms of kidney injury to develop diagnostic and preventive interventions. Cisplatin is a potent platinum-based antineoplastic agent, however, its dose-limiting toxicity is nephrotoxicity and occurs primarily as a result of organic cation transporter-mediated uptake by proximal tubule epithelial cells (PTECs) that subsequently damages mitochondria through oxidative stress, inflammatory signaling pathways and DNA damage leading to apoptosis or necrosis(3,4). Conversely, Adriamycin (doxorubicin) is routinely used to create rodent models of podocyte injury and proteinuric nephropathy by inducing glomerular injury involving the immunopathological sequelae of podocyte injury, glomerular basement membrane disruption, oxidative stress, and progressive glomerulosclerosis (4). Models both individually, and in combination of the 2 agents represent a practical approach to evaluating tubular-dominant and glomerular-dominant injury patterns as well as mixed nephron injury (5).Recent reports have demonstrated a greater sensitivity of markers such as cystatin C, or urinary enzymes ,e.g., neutrophil gelatinase-associated lipocalin (NGAL), during acute renal injury, and many studies have confirmed their value over traditional serum indices in predicting AKI (6,7). Nevertheless, traditional markers can still be valuable in experimental and veterinary laboratory settings when used in conjunction with timing, injury model, histological findings and the changes of other parameters rather than independently (8-10). Therefore this study assessed serum urea, BUN, uric acid and creatinine serial changes after tubular, glomerular and

combined nephron injury in rats because these markers of nephron segment pathology, as well as renal functional defect.

MATERIALS AND MTHODS

Experimental Animals and Ethical Considerations

The animal studies were performed using 40 male Wistar rats (200 ± 20 g). Animals were aclimatised under standard laboratory condition (22–25 °C, 14 h light/10 h dark cycle) with access to food and water ad libitum on normal pellet diet. Thousands of healthy non-racing or show animals and also hundreds of thousands of racing or show animals can help in research; all procedures must have been approved by the appropriate institutional animal care and ethics committee: UOK.VET.PH.2025.175.

Experimental Design

Rats were randomly strapped into four equal groups (n = 10/group). The control group received normal saline (0.9% NaCl) via IP The tubular injury group was administered one dose of 7 mg /kg BW Cisplatin. Intravenous administration of Adriamycin (5–6 mg/kg BW) was performed once by a tail-vein injection for the glomerular injury group. In case of combined injury with cisplatin and Adriamycin the same scheme was followed. 10, 20, and 30 days after the last challenge samples of blood were collected by retro-orbital plexus. The isolated serum was kept at − 80°C until the biochemical analysis. The authors were not clear if the same animals are being sampled multiple times, or whether different subgroups were sacrificed at each time point since it will affect what statistical model is fit; one of these models (repeated measures) is more appropriate for publication.

Biochemical Measurements

Serum concentrations of urea, BUN, uric acid and creatinine were measured by commercial colorimetric kits (Biolabo SA; France) in accordance with the manufacturer's instructions. All methodological details (e.g., quality control procedures, mention of the calibration and wavelength and enzyme analyzer model used, intra- and inter-assay variation), anything that enhances the basis for reproducibility.

Statistical Analysis

Data were expressed as mean ± SE. The original analysis was using one-way ANOVA and LSD post-hoc comparison $P \leq 0.05$. A tow way ANOVA or conditional-repeated-measures ANOVA would be statistically stronger if the same animals were followed over time compared to this design incorporating both treatment groups and time points.

RESULT AND DISCUSSION

Current data regarding the effects of cisplatin on acutely injured (tubular injury model) renal and combined tubular-glomerular injury represent simple and progressive (mostly BUN and Creat- more consistent total derangement) (11,12). Although the first observation from our studies is being biologically plausible as cisplatin actively entered proximal tubular epithelial cells resulting in mitochondrial damage, and excessive production of reactive oxygen species (ROS)(13), lipid peroxidation, inflammation and activation of apoptotic/necrotic pathways (14), there still are some more key features that must be investigated to confirm(15). The loss of the integrity of alpha tubules depletion excretory capacity and retention nitrogenous waste products. These sequential changes between day 10 and day 30 probably reflect either functional deterioration or continued resolution after a nephrotoxic injury (16). The increase in serum urea shoulder in cisplatin treated and combined injury suggests a globally impaired functional reserve with diminished clearance of nitrogenous waste from spaces into vascular access as shown in table (1). Similar to urea, the BUN also found an increment after exposure of rats to cisplatin (Abdeen et al. In a study by Lewis et al (15), this change was combined with oxidative stress, tubular necrosis and inflammatory renal injury. This other observation is the higher urea response of the combined model, (9) which suggests that functional impairment exceeds additivity expected for two independent lesions -that is, tubular epithelial cell necrosis (histological damage), and glomerular filtration barrier disruption (13) or that sequential loss in more than on site compresses over all excess metabolic waste clearance greater than either injury acting separately (6,7,16).

Table 1. Serum urea concentration (mg/dl) Timed in control and experimental groups.

Group	Mean ±SE of Urea (mg/dl)			L.S.D.
	10 Days	20 Days	30 Days	
G1	31.62 ±0.57 B a	32.54 ±0.39 B a	32.81 ±0.42 C a	1.406 NS
G2	36.05 ±0.22 A b	36.88 ±0.29 A a	37.34 ±0.14 B a	0.684 NS
G3	31.79 ±0.56 B a	31.79 ±0.43 B a	31.75 ±0.51 C a	1.517 NS
G4	35.75 ±0.25 A c	37.65 ±0.32 A b	38.84 ±0.43 A a	1.031 *
L.S.D.	1.275 *	1.073 *	1.182 *	---
Means having with the different big letters in same column and small letters in same row differed significantly. * (P≤0.05).				

The BUN had one of the highest responses with time in treated animals especially in those receiving cisplatin (from 16.22 ± 0,66 mg/dl day 10 to 26.94 ± 1,55 mg/dl day30). Such evolution suggests persistence disorder of nitrogen excretion. Blood urea nitrogen (BUN): mirror of plasma urea concentration, and widely used estimate for determining overall glomerular filtration and tubular handling. As shown in figure (2), for combined injury, we observed that BUN on day 10 was already significantly elevated and remained steeper through day 30 than the other groups of animals suggesting that exposure to both nephrotoxins results in either immediate or near maximal functional compromise. In this model BUN was recognized as an important conventional marker, but must

be interpreted along with creatinine and hydration status rather than in isolation(17).

Table 2. Blood urea nitrogen (BUN; mg/dl) serum by time in control and experimental groups.

Group	Mean ±SE of BUN (mg/dl)			L.S.D.
	10 Days	20 Days	30 Days	
G1	13.88 ±0.36 C a	13.47 ±0.54 B a	13.12 ±0.32 B a	1.262 NS
G2	16.22 ±0.66 B c	21.16 ±1.61 A b	26.94 ±1.55 A a	4.064 *
G3	13.40 ±0.63 C a	13.02 ±032 B a	13.62 ±0.25 B a	1.326 NS
G4	21.22 ±0.42 A b	22.21 ±0.43 A b	24.88 ±0.45 A a	1.314 *
L.S.D.	1.589 *	2.632 *	2.461 *	---
Means having with the different big letters in same column and small letters in same row differed significantly. * (P≤0.05).				

In contrast, uric acid following markedly role as significant peak by day 20 in cisplatin group and partial decrease at the end of study (30 Day). Uric acid can be measured in the serum, and its passive tubular secretion and reabsorption have been shown to change after acute tubular injury through loss of normal protein expression or function (18),to interpret elevated uric acid with caution as during early stage it reflects (19,20), however at this timing suggest nod nephrotoxicity increases other combination spirit metabolism were triggered reveal cisplatin-induced damage modify more accurate conclusion must practice raise about kidney tissue passively secret low concentration versus active dependence on time point uricase activity decreases mutagen about rodent human differences note lab marked purine clearance paralleled (21,22). To reinforce this view, measurements of oxidative stress markers, xanthine oxidase activity or histological tubular score should be performed.

Table 3. Serum uric acid level (mg/dl) in control and experimental groups over time

Group	Mean ±SE of Uric acid (mg/dl)			L.S.D.
	10 Days	20 Days	30 Days	
G1	3.35 ±0.06 B a	3.42 ±0.05 C a	3.45 ±0.08 C a	0.206 NS
G2	4.75 ±0.13 A b	7.08 ±0.17 A a	4.67 ±0.33 B b	0.691 *
G3	3.35 ±0.06 B a	3.36 ±0.08 C a	3.52 ±0.11 C a	0.257 NS
G4	4.91 ±0.30 A b	5.91 ±0.19 B a	5.72 ±0.31 A ab	0.821 *
L.S.D.	0.499 *	0.408 *	0.699 *	---
Means having with the different big letters in same column and small letters in same row differed significantly. * (P≤0.05).				

Creatinine was continually elevated in both the cisplatin and combined injury groups, and is considered the classical measure of reduced filtration capacity (4). Inevitably, serum creatinine at the bedside is a pretty poor measure of very early renal injury from insult but if it is persistently elevated there must have been large losses of renal functional reserve. (12). In relation to the absence of a statistically significant within-group time effect, one plausible explanation could be observed in G2; as numbers seem numerically elevated over time but with greater variability at day 30 and less participants. Therefore, it would have been useful to report effect size, confidence intervals and exact P values in the manuscript. At the level of group, a hierarchical time effect to accrue nephron injury was more steady but still important in the aggregate (21).

This relatively small biochemical alteration in the Adriamycin-alone group is not a limitation, but a point that should be interpreted with caution. Traditionally, Adriamycin nephropathy is modelled as a podocyte injury followed by proteinuria and glomerular basement membrane damage (followed by development of glomerulosclerosis). (22). Serum urea and creatinine may remain near normal with moderate or early glomerular injury due to substantial nephron functional reserve compensating for loss of filtration. So, in the next versions of this study urinary proteins, albuminuria, serum albumin, lipid profile, kidney weight index and histopathological scoring for glomerular and tubular lesions are recommended to be added. As for the more definitive validation of the Adriamycin model as a glomerular injury model (23).

Table 4. serum creatinine concentration (mg/dl) in control and experimental groups.

Group	Mean ±SE of Creatinine (mg/dl)			L.S.D.
	10 Days	20 Days	30 Days	
G1	0.543 ±0.01 B a	0.525 ±0.01 B a	0.550 ±0.01 B a	0.0275 NS
G2	1.065 ±0.05 A a	1.341 ±0.10 A a	1.611 ±0.30 A a	0.567 NS
G3	0.543 ±0.01 B a	0.541 ±0.01 B a	0.551 ±0.01 B a	0.0329 NS
G4	1.116 ±0.09 A b	1.291 ±0.09 A ab	1.533 ±0.08 A a	0.270 *
L.S.D.	0.157 *	0.208 *	0.465 *	---
Means having with the different big letters in same column and small letters in same row				

differed significantly. * (P≤0.05).

For all combined injury models, the systems-level biochemical profile was significantly more informative than either model alone for discrimination purposes. Injury to both the tubular epithelium and glomerular filtration barrier would therefore be expected to restrict filtration, negatively impact tubular secretion and reabsorption, provoke oxidative and inflammatory pathways, and hasten the accumulation of wastes. Results from the current study are therefore in agreement with hypotheses suggested by one or more previous studies indicating that conventional renal indices were correlated directly to severity and progression of experimental nephron injury only when multiple compartments within the nephron were compromised (24,25).

CONCLUSION

The cisplatin experimental renal injury, especially the acute tubular injury model and also an additional synergy between tubular-glomerular injury that afforded extremes in mortality level of 90% in rats produces elevations in serum urea, BUN, uric acid and creatinine. However, provided urine, histopathological, oxidant stress and early molecular markers are indicators of nephron segment selective damage and August greater specificity in diagnosis.

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