STUDIES ON ADRIAMYCIN SIDE EFFECTS ON THE
RENAL FUNCTION AND MORPHOLOGY IN RATS

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INTRODUCTION
Adriamycin (ADR) is an anthracyric antibiotic (Di Marco et al., 1969). It is considered now to be a very effective and useful chemotherapeutic agent in the treatment of many human solid tumors and malignant hematological processes (Carter et al., 1972). However, its extensive use at doses adequate for effective antitumor therapy is restricted by the appearance of a severe cardiotoxicity (Adamson, 1974; Bristow et al., 1978; and Nagineni, 1985). Little is known about the effect of ADR on the kidney function and its relation to any pathological changes. Our study aims to reveal this relation after 4 and 8 weeks of ADR treatment.

Materials and methods
Animals: Experiments were carried out on white male rats weighing between 200-300 grams. They were allowed access to food and water ad. libitum. Five rats were injected i.v. with normal saline twice/week (served as control), and twenty rats arranged in two groups underwent treatment with adriamycin (1 mg/kg b.w. twice/week i.v.) for four weeks and eight weeks respectively. Urine samples were collected over 24 hours period from control and adriamycin treated groups by using metabolic cages. Then the animals were sacrificed for sampling analysis.

Biochemical and histochemical investigations:
Serum and urinary creatinine were determined by the method of Whiting et al., 1982. Creatinine clearance was calculated applying the following formula: Clearance = (P x V / u) m/min.

where P is the plasma concentration (mg/100 ml)
The proximal convoluted tubules
membrane of Bowman's capsule (Figs. 1–4)
was without thickening or basement
membrane. Afferent arteriole and afferent arteriole
showed mild to moderate changes in the kidney.

**Histopathological Findings:**

- The findings were not significant.
- The changes were more severe in sodium content than in potassium content.
- In general, the results of histological analysis showed no significant changes except in the control, where there were no significant changes in the kidney and the sodium content (Na) was reduced.
- Table 3 shows the sodium content (Na) after 4 and 8 weeks, respectively.
- The effects of NaCl on sodium content are significant.
- The treatment with adriamycin resulted in a decrease in sodium content.
- The significance of these changes was established by Table 3, which shows the sodium content (Na) after 4 and 8 weeks.
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**RESULTS**

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**Biochemical Study:**

- The biochemical study showed a significant decrease in the plasma creatinine levels after 4 weeks of adriamycin treatment.
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show cloudy swelling (Fig.1.c). 40% of the treated animals show dilated collecting tubules with eosinophilic red casts in their lumens (Fig.1.D). 60% show, focal interstitial inflammation and fibrosis (Fig.1.A). The mentioned pathological findings are seen in both treated groups, but more marked in 8 weeks treated one.

**DISCUSSION**

The fact that the antitumor antibiotic adriamycin has a glycosidic structure which resembles some glycosides with cardiotoxic effect, and the fact that cardiomyopathy induced by chronic intoxication with adriamycin present very marked alterations in Na and K contents (Olson, 1974) promoted us to study the effect of this drug on the kidney function and morphology and their relation to the Na and K contents of the kidney.

**Biochemical studies:**

In the present work the results showed significant decrease in K content, but not any significant change in Na content in the kidney in all adriamycin treated rats. These results can be interpreted by the preliminary studies of Gosalvez et al., 1979 who showed that adriamycin is a potent inhibitor of Na-K ATPase of native heart microsomes and inhibits K-transport (although not Na-transport) in slices of kidney cortex. In contrast; Richard et al., 1987 found that, the reduction in renal blood flow in adriamycin treated rats contributes to sodium and water retention. An intriguing result is the finding that adriamycin causes a nearly complete inhibition of K-reaccumulation while failing to affect Na excretion. The explanation may be that the drug has uncoupled the sodium transport aspects of the system from its dependency on K. This would represent a novel inhibitory effect in ion transport (Gosalvez et al., 1979).

Creatinine is a substance that has a maintained plasma level by its continuous endogenous production due to muscle catabolism and is indirectly affected by diet. Given a constant rate of production, and for negligible tubular reabsorption and extra renal losses, the plasma level of creatinine depends directly on the GFR and considered to be a good index of the degree of impairment of GFR. All adriamycin treated rats has developed nephrotoxicity by the time of study as judged by an increased plasma creatinine and decreased its concentration in the urine (Table 1), thus leading to
SUMMARY

The present study is a trial to correlate local findings of focal glomerulosclerosis of the kidney with administration of long duration treatment of Adrenylamine (ADP) which is widely used in Canada.

A new function of the drug, with investigation of kidney function needed to avoid the cumulative effect of treatment is mentioned. Adrenylamine changes creatinine clearance in ADP treated rats can be explained by the pathological changes detected in the adrenylamine treated kidneys with changes in kidney structure and intertubular cloudy swelling and interstitial inflammation with fibrosis. These results are consistent with the findings of other experiments.}

The renal changes appear to be

| Vol. 20, No. 3 & 4, July-August-1990 | 12 |

Studies on Adrenylamine Side Effects etc.
chemotherapy. Previous studies revealed cases of heavy proteinuria following single injection of 5 mg/kg ADR. Marked alteration in sodium and potassium contents were seen in cases of cardiomyopathy induced by chronic intoxication with ADR. We are interesting to study the relationship between renal sodium and potassium contents and proteinuria, in Adriamycin treated rats (1 mg/kg b.w. twice a week for 4 and 8 weeks), and the renal function and morphology. The results showed impaired renal function as revealed by the significant increase in plasma creatinine and decreased urinary creatinine and creatinine clearance in ADR treated rats. ADR treatment also produced significant decrease in plasma proteins and proteinuria. Sodium content of the kidney was not significantly changed, while potassium content was significantly decrease in ADR treated rats. These finding are consistent with the pathological examination which show glomerular sclerosis, cloudy swelling of the proximal convoluted tubules, dilated collecting tubules with protein casts and inflammation of the interstitial tissue. These changes are more marked in 8 weeks ADR treated rats. The study advise interrupted courses of ADR in the long treatment periods, with investigations for the kidney function.

Table (1): Plasma (P) and urinary (U) creatinine in mg/l, and creatinine clearance (C) in ml/minute, in control and Adriamycin treated rats.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Adriamycin (1mg/kg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>U</td>
<td>C</td>
<td>P</td>
</tr>
<tr>
<td>Mean</td>
<td>7.26</td>
<td>304.6</td>
<td>0.51</td>
<td>7.80</td>
</tr>
<tr>
<td>± S. E</td>
<td>0.08</td>
<td>1.66</td>
<td>0.006</td>
<td>0.06*</td>
</tr>
<tr>
<td>% of change</td>
<td>+7.44</td>
<td>-18.98</td>
<td>-15.69</td>
<td>+32.23</td>
</tr>
</tbody>
</table>

n = 5
* = Significantly different from control (P < 0.005).

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Table (3): Renal sodium (Na) and potassium (K) contents in control and adriamycin treated rats.

<table>
<thead>
<tr>
<th>8 Weeks</th>
<th>4 Weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>K</td>
<td></td>
</tr>
<tr>
<td>23.97</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>1.43</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>0.58</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>2.92</td>
<td>2.92</td>
<td></td>
</tr>
<tr>
<td>2.06</td>
<td>3.88</td>
<td></td>
</tr>
<tr>
<td>3.72</td>
<td>2.42</td>
<td></td>
</tr>
</tbody>
</table>

% of change

Mean ± S.E.

Table (2): Total plasma proteins (mg/100 ml) in control and adriamycin treated rats.

<table>
<thead>
<tr>
<th>8 Weeks</th>
<th>4 Weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>K</td>
<td></td>
</tr>
<tr>
<td>27.36</td>
<td>10.94</td>
<td></td>
</tr>
<tr>
<td>5.86</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>6.58</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

% of change

Mean ± S.E.
Fig. 1: Effect of adriamycin on the survival percent in white rats.

Fig. 2: Protein excretion in adriamycin treated rats results are expressed as mean ± SD.
Fig. 7. Sections in the kidneys of adriamycin treated rats. H&E (x400). Show two.

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REFERENCES


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