Nephrotoxicity of Pyrroloquinoline Quinone in Rats
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ABSTRACT
When pyrroloquinoline quinone (PQQ) was intraperitoneally injected into rats daily for 4 days at a dose of 11.5 mg/kg body weight/injection, functional and morphologic changes of the kidneys were clearly observed. The most prominent finding was necrotic and degenerative changes of the proximal tubular epithelium as well as hematuria and an elevation of serum creatinine concentration.

Key words: Nephrotoxicity, Pyrroloquinoline quinone, Renal tubules

Table 1. Blood biochemistrya

<table>
<thead>
<tr>
<th>Group</th>
<th>BUN (mg/dl)</th>
<th>Cr</th>
<th>GOT (IU/l)</th>
<th>GPT</th>
<th>ALP</th>
<th>LDH</th>
<th>Glc (mg/dl)</th>
<th>TG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlb</td>
<td>23.7 0.53 47 37 118 83</td>
<td>203 137</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>2.3 0.07 10</td>
<td>11</td>
<td>24</td>
<td>40</td>
<td>27 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PQQb</td>
<td>62.5 1.48c 93c 71d 131</td>
<td>87 176 48c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.5 0.46 23</td>
<td>24</td>
<td>37</td>
<td>26</td>
<td>16 12</td>
<td></td>
<td></td>
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<tr>
<td>SD</td>
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</table>

a Statistical differences between the mean values were determined by Student’s t-test after analysis of variance. Cr, creatinine; Glc, glucose; and TG, triglyceride.

b There were 5 rats in each group.

c p < 0.05.
d p < 0.001.
sugar, protein, ketone bodies, bilirubin, urobilinogen and occult blood using Multi-Sticks III (Miles-Sankyo Co., Ltd., Tokyo). Serum glutamate pyruvate transaminase (GPT), glutamate oxalocacetate transaminase (GOT), blood urea nitrogen (BUN), serum creatinine, triglyceride, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) were routinely examined with a Gilford Auto-analyzer (Impact 400).

No significant difference of changes in the body weight of rats between the PQQ and Control groups was observed. Examination of the urine revealed an increased excretion of protein, glucose, ketone body and occult blood. BUN and serum creatinine levels were significantly higher in the PQQ group, and serum triglyceride contents were significantly lower in this group (Table 1). Serum GOT and GPT activities were also higher in the PQQ group than in the Control group, although ALP and LDH activities were not elevated. Swelling of the kidneys was observed macroscopically at autopsy, and the weight of the kidneys as well as % of body weight also increased, although only the latter was significant (Table 2).

In the PQQ group, vacuolar degeneration, atrophy and necrosis of the proximal tubular epithelium in the renal cortex were observed microscopically (Fig. 1). Dilatation and regeneration of the tubules were also observed in 2 rats of the PQQ group (Table 3). However, few changes of the glomerulus were observed in any of the rats treated with PQQ. A slight decrease in glycogen deposition and an increase in the mitotic process were observed also in the liver, but pathological findings of the spleen were not observed in the PQQ-treated rats.

Biological and toxic effects of PQQ on mammals have not been elucidated yet. PQQ contents in the animal tissues and the minimum toxic dose of PQQ are also unknown. The present preliminary study revealed that PQQ induced functional and histological changes in the kidneys, particularly proximal tubular changes, although the mechanism of PQQ nephrotoxicity is not clear. The high concentrations of PQQ metabolites in the kidneys may injure the proximal tubular component of the renal cortex. The further studies on the dose dependency of PQQ, the route of PQQ administration and the time

![Fig. 1. Microscopic findings of PQQ-treated rats (No. 10).](image-url)
course of renal injury in PQQ nephrotoxicity are
now under study in our laboratory.

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