Serum Angiotensin-Converting Enzyme Activity in Rats with Gentamicin-Induced Nephrotoxicity

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Results are means±SEM (n=5). a Gentamicin was injected intramuscularly daily for 6 days and serum obtained on the 7th day.

b Captopril was injected intraperitoneally once and serum obtained 1 h later.

c One unit is defined as amount of enzyme required to release 1 mmol of hippuric acid/min at 420 nm substrate. This method correlates well (r = 0.99) with results from an HPLC method for measuring hippuric acid [4]. Nephrotoxicity was assessed by measuring the serum concentration of creatinine by an automated spectrophotometric method (Beckman Autoanalyzer 2) and by renal histology. Statistical comparisons of the control group and each individual treatment were carried out by Student’s t test. A value higher than 0.05 was considered to be insignificant.

The results of this work indicated that the antibiotic produced dose-dependent increases in serum creatinine concentration and renal tubular necrosis indicative of nephrotoxicity. Captopril produced complete inhibition of ACE activity. Gentamicin, at the doses used, did not significantly affect the enzyme activity (table 1). These results suggest that

Dear Sir,

Chronic inhibition of angiotensin-converting enzyme (ACE) has been shown to modulate gentamicin nephrotoxicity in rats [1]. It is not known, however, whether treatment with gentamicin at nephrotoxic doses would affect the basal activity of ACE, and the present experiment attempts to investigate this. For comparative purposes, ACE was measured in rats treated with the known ACE inhibitor captopril.

Female Sprague-Dawley rats weighing about 250 g were used. They were fed ad libitum on a nutritionally adequate pelleted diet and tap water. Room temperature was kept at 22–24°C. Animals (n = 25) were divided into five equal groups (designated 1-5). Group 1 was kept as control and was injected intramuscularly with normal saline at a dose of 0.25 ml/rat. Groups 2, 3 and 4 were injected intramuscularly with gentamicin (Roussel Labs, UK) at doses of 20, 40 and 80 mg/kg/day for 6 days. These animals were killed 24 h after the last dose. Group 5 was injected intraperitoneally with captopril (Squibb, Egypt) at a single dose of 25 mg/kg, and rats were killed 1 h after the injection, as this is the time reported to allow for maximum inhibition of the enzyme [2]. Animals were killed by stunning and decapitation. Trunk blood was collected in centrifuge tubes, allowed to clot at 5°C and then cen-trifuged to obtain serum. The kidneys were rapidly removed, and pieces thereof were placed in 10% formol
saline pending histopa-thological examination. After processing, kidney sections were stained with HE and examined by light microscopy by a histo-pathologist unaware of the treatments. Serum ACE activity was measured spectro-photometrically by the method of Neels et al. [3] using hippuryl-L-histidyl-L-leucine as a substrate.

Table 1. Activity of ACE in serum of rats treated with gentamicin or captopril

<table>
<thead>
<tr>
<th>Control</th>
<th>Gentamicin, 20 mg/kg</th>
<th>40 mg/kg</th>
<th>80 mg/kg</th>
<th>Captopril 25 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.40±0.02</td>
<td>0.51±0.05</td>
<td>0.59±0.05</td>
<td>1.12±0.08</td>
</tr>
<tr>
<td>ACE, U/l</td>
<td>214.2 ± 10.2</td>
<td>240.7 ± 31.7</td>
<td>231.8 ± 29.1</td>
<td>237.7 ± 32.0</td>
</tr>
</tbody>
</table>

any possible interaction of gentamicin and ACE inhibitors may not involve inhibition of ACE by this antibiotic.

ACE activity has been shown to be increased in certain pathological conditions including hyperthyroidism, diabetes, silicosis and alcoholic liver disease [3]. The enzyme activity is decreased in conditions like tuberculosis, chronic asthma and lung cancer.

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References