Aminoglycoside antibiotics and renal function: changes in urinary $\gamma$-glutamyltransferase excretion

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SUMMARY The urinary excretion of the renal proximal tubular enzyme, $\gamma$-glutamyltransferase ($\gamma$-GT), has been studied in 41 patients receiving tobramycin, gentamicin or streptomycin for a variety of infections. All patients receiving tobramycin or gentamicin have shown increased excretion of $\gamma$-GT in the urine. Only 46% of those receiving streptomycin have shown an increase in $\gamma$-GT excretion and this is of a lesser degree. A change in creatinine clearance which could only be explained by antibiotic administration was detected in three patients (2 on gentamicin, 1 on streptomycin). The degree of elevation of urinary $\gamma$-GT activity was greater when the initial creatinine clearance was lower, and it is therefore suggested that those patients with pre-existing renal dysfunction should be monitored particularly carefully for signs of nephrotoxicity from these antibiotics. Urinary $\gamma$-GT is a useful enzyme in the investigation of renal drug effects.

Although the aminoglycoside antibiotics (the most commonly used of which are streptomycin, neomycin, kanamycin, gentamicin, and tobramycin) are known to be potentially nephrotoxic (Falco et al., 1969) there have been conflicting reports on their degree of nephrotoxicity (Shimizu, 1969; Scottish Gentamicin Symposium, 1975; Wellwood et al., 1975). The recent report of Wellwood et al. (1975) has shown that urinary enzyme assays can be very sensitive in detecting renal effects of gentamicin.

During early studies on the proximal tubular enzyme, $\gamma$-glutamyltransferase ($\gamma$-GT; EC 2.3.2.2.), increased urinary excretion was detected in a patient treated with tobramycin (Beck and Chaudhuri, 1976). The present study shows the effects of gentamicin, tobramycin, and streptomycin on urinary $\gamma$-GT excretion in patients treated for a variety of infections with these antibiotics.

Patients and methods

Forty-one patients were included in the trial receiving either tobramycin, gentamicin or streptomycin. In addition, a 'control' group, consisting of patients receiving other antibiotics, was also investigated.

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The decision as to the need for antibiotic therapy, selection of antibiotic, and duration of therapy was based on clinical diagnosis, general condition of the patient, and presumed or proven bacteriological diagnosis. Patients with renal disease known to cause elevations of urinary $\gamma$-GT were excluded. Many of the patient details are given in Tables 1–3.

A 24-hour urine collection was started as soon as antibiotic therapy was initiated, and venous blood was taken to enable the creatinine clearance to be calculated. Further urine collections and blood samples were taken several times during antibiotic therapy and also after cessation of therapy. Urine collections were stored at 4°C until assay. Venous peak and trough levels of gentamicin and tobramycin were measured in 12 patients. In no case were the peak levels in the toxic range (greater than 10 $\mu$g/ml). Details of other drug therapy were noted, but no attempt was made to exclude patients because of other drug therapy.

Urinary $\gamma$-GT was assayed on well-mixed, undialysed urines with a kinetic method using $\gamma$-glutamyl-p-nitroanilide as substrate (Beck and Chaudhuri, 1976) and the same assay technique was used for serum $\gamma$-GT. Because of the direct correlation which normally exists between urinary $\gamma$-GT excretion (as U/day) and creatinine clearance (Fig. 1), the urinary $\gamma$-GT excretion was expressed as a ratio to creatinine clearance, as previously
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Fig. 1 Relationship between urinary \( \gamma \)-GT and creatinine clearance in normal persons (○) and patients with a variety of renal diseases (●). The \( \gamma \) intercept (8:13) is used in the calculation of the \( \gamma \)-GT:creatinine clearance ratio = \( \frac{\gamma \text{-GT}}{\text{creatinine clearance}} \).

described (Beck and Chaudhuri, 1976). Reference values for this ratio are 0·17–0·52 when \( \gamma \)-GT is expressed as U/24 h and creatinine clearance as ml/min. The reason why different values are given for the regression equation and reference values by Beck and Chaudhuri (1976) and in the present paper is because the former expresses creatinine clearance as ml/sec whereas the latter uses ml/min. Creatinine was assayed by the Jaffe reaction using a Technicon AA1 system.

Table 1 Summary of patients and urinary \( \gamma \)-GT results for patients treated with gentamicin

<table>
<thead>
<tr>
<th>Patient and sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Organism</th>
<th>Duration of antibiotic therapy (days)</th>
<th>Peak ( \gamma )-GT:creatinine clearance ratio</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>JR M</td>
<td>76</td>
<td>Acute bronchitis</td>
<td>Pseudomonas aeruginosa</td>
<td>11</td>
<td>6·62</td>
<td>—</td>
</tr>
<tr>
<td>WS M</td>
<td>56</td>
<td>Cor pulmonale</td>
<td>Proteus sp</td>
<td>1. 9</td>
<td>1. 0·80</td>
<td>—</td>
</tr>
<tr>
<td>MR F</td>
<td>78</td>
<td>Necrotic ulcer of right foot with osteitis of metatarsal bone</td>
<td>Nil</td>
<td>2. 16</td>
<td>2. 0·99</td>
<td>Frusemide</td>
</tr>
<tr>
<td>RN M</td>
<td>74</td>
<td>Septicaemia with renal failure</td>
<td>Nil</td>
<td>13</td>
<td>9·49</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>JB M</td>
<td>46</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>13</td>
<td>3·21</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>MG F</td>
<td>69</td>
<td>Fracture of neck of femur</td>
<td>Nil</td>
<td>9</td>
<td>2·71</td>
<td>—</td>
</tr>
<tr>
<td>MM F</td>
<td>67</td>
<td>Cor pulmonale</td>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>3·06</td>
<td>Frumide</td>
</tr>
<tr>
<td>RO F</td>
<td>42</td>
<td>Pneumonia</td>
<td>Klebsiella sp</td>
<td>30</td>
<td>2·64</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>TR M</td>
<td>42</td>
<td>Subphrenic abscess</td>
<td>Nil</td>
<td>10</td>
<td>2·88</td>
<td>—</td>
</tr>
</tbody>
</table>

Results

GENTAMICIN

Table 1 summarises the clinical details and results for the nine patients receiving 10 courses of gentamicin. All patients showed increased levels of urinary \( \gamma \)-GT, ranging from 1·6 to 19 times normal. The peak value for \( \gamma \)-GT occurred at different times during antibiotic administration, but elevated values were found very quickly after the start of antibiotic therapy. It took more than three days for the elevations of \( \gamma \)-GT to occur in only two patients receiving either gentamicin or tobramycin. After the antibiotic was stopped the time for the \( \gamma \)-GT to return to normal was quite variable, ranging from three to more than 38 days.

TOBRAMYCIN

Table 2 summarises the clinical details and results for the eight patients treated with nine courses of tobramycin. All patients showed elevations of urinary \( \gamma \)-GT, ranging from 1·6 to 14 times normal. The time taken for the \( \gamma \)-GT to return to normal after the antibiotic was stopped ranged from one to 45 days.

STREPTOMYCIN

Twenty-four patients received streptomycin for the following conditions: pulmonary tuberculosis (TB) (19 patients), pulmonary and skeletal TB (1), skeletal TB (1), tuberculous meningitis (2), and brucellosis (1). Chemotherapy for tuberculosis in all patients also included rifampicin (or ethambutol), isoniazid, and pyridoxine. Only 11 (46%) of the
patients showed increased levels of urinary γ-GT and the increases ranged from 1:2 to 6 times normal. Increased urinary γ-GT was present within three days in the four patients in whom the beginning of streptomycin therapy was monitored. Four patients were followed after stopping streptomycin. In three the urinary γ-GT returned to normal within five days; the other patient took more than 31 days to return to normal.

Figure 2 summarises the changes in urinary γ-GT for the three aminoglycoside antibiotics.

### CONTROLS

Thirteen patients receiving other antibiotics for a variety of infections were included as a 'control' group. The clinical details and results are summarised in Table 3. Six of these patients showed increased urinary γ-GT activities—four out of five receiving flucloxacillin, one out of two receiving Septrin, and one receiving sulphadimidine.

### IN VITRO STUDIES

Addition of tobramycin and gentamicin to fresh normal urines at concentrations which may be attained during treatment did not affect γ-GT activity (Table 4).

### RENAL FUNCTION

Figure 3 shows that the degree of increase in the urinary γ-GT was inversely related to the initial creatinine clearance, and that this applied to all three antibiotics.

Three patients showed changes in creatinine clearance which could only be related to treatment with the antibiotic. WS received two courses of gentamicin for a chronic diabetic foot ulcer. His creatinine clearance fell from 116 ml/min to 82 ml/min during his first course and further to 70 ml/min during his second course. RN showed an increase in creatinine clearance from 29 ml/min during gentamicin therapy to 42 ml/min 13 days post-gentamicin. DE showed an increase in creatinine clearance from 84 ml/min during streptomycin therapy to 101 ml/min post-streptomycin.

### SERUM γ-GT

Serum γ-GT was measured in all patients. Sixty-one per cent showed increased activities, but there was
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Table 3  Summary of patients and results for 'controls' on other antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Patient and sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Organism</th>
<th>Peak (γ)-GT: creatinine clearance ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin + Ampicillin</td>
<td>JO F</td>
<td>61</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>0.59</td>
</tr>
<tr>
<td>Flucloxacillin + Amoxycillin</td>
<td>MD M</td>
<td>69</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>0.80</td>
</tr>
<tr>
<td>Flucloxacillin + Ampicillin</td>
<td>AM F</td>
<td>83</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>1.18</td>
</tr>
<tr>
<td>Flucloxacillin + Ampicillin</td>
<td>WR M</td>
<td>57</td>
<td>Pneumonia</td>
<td>Staphylococcus aureus</td>
<td>1.11</td>
</tr>
<tr>
<td>Flucloxacillin + Ampicillin</td>
<td>DM M</td>
<td>65</td>
<td>Pneumonia</td>
<td>Haemophilus influenza</td>
<td>1.48</td>
</tr>
<tr>
<td>Septrin</td>
<td>AM M</td>
<td>73</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>***</td>
</tr>
<tr>
<td>Septrin</td>
<td>CM F</td>
<td>65</td>
<td>Congestive cardiac failure</td>
<td>Streptococcus pneumonia</td>
<td>1.00</td>
</tr>
<tr>
<td>Sulphadimidine + Penicillin</td>
<td>PM M</td>
<td>50</td>
<td>Meningitis</td>
<td>Neisseria meningitidis</td>
<td>1.52</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>JM F</td>
<td>69</td>
<td>Pneumonia</td>
<td>Streptococcus pneumonia</td>
<td>***</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>MO F</td>
<td>64</td>
<td>Congestive cardiac failure</td>
<td>Pneumonia</td>
<td>0.40</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>MD M</td>
<td>49</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>0.34</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>AP M</td>
<td>74</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>0.37</td>
</tr>
<tr>
<td>Ampicillin + Tetracycline</td>
<td>PM F</td>
<td>76</td>
<td>Peritonitis</td>
<td>Nil</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic renal failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

***The values were too low to be measured, but they were normal for chronic renal failure.

Table 4  Lack of effect of tobramycin and gentamicin on urinary \(γ\)-GT in vitro. Each value is the mean for three urines.

<table>
<thead>
<tr>
<th>Concentration of added aminoglycoside (μg/ml)</th>
<th>Tobramycin (γ)-GT (U/l)</th>
<th>Gentamicin (γ)-GT (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24.9</td>
<td>24.9</td>
</tr>
<tr>
<td>50</td>
<td>24.8</td>
<td>24.5</td>
</tr>
<tr>
<td>100</td>
<td>25.4</td>
<td>24.7</td>
</tr>
<tr>
<td>200</td>
<td>24.4</td>
<td>25.5</td>
</tr>
<tr>
<td>400</td>
<td>24.7</td>
<td>25.3</td>
</tr>
</tbody>
</table>

Fig. 3  Relationship between initial creatinine clearance and urinary \(γ\)-GT response for patients on the aminoglycoside antibiotics.

Discussion

All of the aminoglycoside antibiotics are potentially nephrotoxic, as has been shown in animal studies (Falco et al., 1969). It has been reported that there has been a reluctance to use gentamicin, particularly in the presence of renal impairment (Scottish Gentamicin Symposium, 1975), but most of the published reports on nephrotoxicity mention only an occasional patient showing deterioration in renal function, and this is often in combination with other drug therapy, particularly the cephalosporins (Shimizu, 1969; Falco et al., 1969; Fillastre et al., 1973; Kleinknecht et al., 1973; Cabanillas et al., 1975). Klastersky et al. (1974) compared tobramycin and gentamicin and noted 'azotaemia' in one patient on the former and in two on the latter antibiotic out of a total of 62; while an international study reported by Speirs (1976) found 1.3% of renal abnormalities, chiefly nitrogen retention, out of 2789 patients treated with tobramycin.

However, Wellwood et al. (1975) have shown that urinary excretion of renal enzymes is affected commonly during gentamicin therapy and that there

OTHER DRUGS

Tables 1–3 show that many of the patients were receiving other drug therapy, but no relationship between the degree of elevation of urinary \(γ\)-GT and other drug therapy could be discerned in these patients.
may be ultrastructural changes in both humans and rats (Wellwood et al., 1976).

The present studies using the proximal tubular enzyme, \( \gamma \)-GT, have confirmed the findings of Wellwood. All patients treated with tobramycin and gentamicin have shown elevated activities of urinary \( \gamma \)-GT, but less than half the patients treated with streptomycin have shown such a change, and where elevations are present they are of a lesser degree. The lesser response of the streptomycin group is in keeping with the comparative nephrotoxicities of the aminoglycoside antibiotics reported by Falco et al. (1969). Kanamycin has also caused an increase in urinary \( \gamma \)-GT activity (Beck and Chaudhuri, 1976).

Three of the 41 patients showed changes in creatinine clearance which could only be ascribed to treatment with the aminoglycoside, but these were of a fairly mild nature. However, an important relationship was found to exist between the degree of elevation of the urinary \( \gamma \)-GT and the initial creatinine clearance: the poorer the initial renal function, then the greater was the response to the aminoglycoside antibiotic. In the present study a greater number of patients on streptomycin than on the other antibiotics had normal creatinine clearances and therefore would be expected to show a lesser \( \gamma \)-GT response. But Fig. 3 shows that even similar creatinine clearances are compared, the \( \gamma \)-GT response to gentamicin and tobramycin appears greater than the response to streptomycin.

Klastersky et al. (1974) reported that two of the three patients who showed ‘azotaemia’ after tobramycin or gentamicin therapy had high serum creatinine levels before treatment. Unfortunately details as to the degree of ‘azotaemia’ are not given. The nephrotoxicity of other drugs may also be dependent on the level of renal function (Warren et al., 1974).

Although most of the patients were also receiving other drug therapy, no relationship could be found between the \( \gamma \)-GT response, either temporally or in degree, and any other treatment. But obviously a more controlled trial is needed, especially for the influence of frusemide on the aminoglycoside response (Dodds and Foord, 1970). One of the surprising findings of the present study was that ‘control’ patients on flucloxacillin also showed elevations of urinary \( \gamma \)-GT. Reports of nephrotoxicity of flucloxacillin have not been found, although nephritis is a very rare complication of high-dose penicillin or methicillin therapy (Baldwin et al., 1968; Simenhoff et al., 1968).

The aminoglycoside antibiotics are of great value in the control of many severe infections, and clinically important nephrotoxicity is rare. However, renal enzyme changes due to these antibiotics are common and are more marked in patients with pre-existing renal dysfunction; therefore treatment with these antibiotics should be remembered as a possible cause of deterioration in renal status, particularly in such patients. Urinary \( \gamma \)-GT is a useful enzyme for the study of renal drug effects.

We should like to thank the following clinicians for allowing us to study patients under their care: Drs P. McKenzie, W. C. Love, R. S. Kennedy, D. Summers, and Dr Madkour. We should also like to thank Dr J. Thomson, Bacteriology Department, Belvidere Hospital, for her interest and help with the study.

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