Aminoglycoside antibiotics and renal function: changes in urinary γ-glutamyltransferase excretion

PETER R. BECK, RUTH B. THOMSON1, AND AJAY K. R. CHAUDHURI
From the Department of Biochemistry, Royal Infirmary, Glasgow G4 0SF and the Department of Infectious Diseases, Belvidere Hospital, Glasgow

SUMMARY The urinary excretion of the renal proximal tubular enzyme, γ-glutamyltransferase (γ-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 γ-GT in the urine. Only 46% of those receiving streptomycin have shown an increase in γ-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 γ-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 γ-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, γ-glutamyltransferase (γ-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 γ-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.

1Present address: Royal Hospital for Sick Children, Glasgow

Received for publication 11 October 1976

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 γ-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 µg/ml). Details of other drug therapy were noted, but no attempt was made to exclude patients because of other drug therapy.

Urinary γ-GT was assayed on well-mixed, undialysed urines with a kinetic method using γ-glutamyl-p-nitroanilide as substrate (Beck and Chaudhuri, 1976) and the same assay technique was used for serum γ-GT. Because of the direct correlation which normally exists between urinary γ-GT excretion (as U/day) and creatinine clearance (Fig. 1), the urinary γ-GT excretion was expressed as a ratio to creatinine clearance, as previously
Aminoglycoside antibiotics and renal function: changes in urinary \( \gamma \)-glutamyltransferase excretion

Fig. 1 Relationship between urinary \( \gamma \)-GT and creatinine clearance in normal persons (○) and patients with a variety of renal diseases (●). The \( y \) intercept (8·13) is used in the calculation of the \( \gamma \)-GT:creatinine clearance ratio:

\[
\text{Creatinine clearance (ml/min)} = 0.34x + 8.13
\]

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 76</td>
<td>Acute bronchitis</td>
<td>Pseudomonas pyocyanea</td>
<td>11</td>
<td>6·62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WS M 56</td>
<td>Diabetes mellitus</td>
<td>Proteus sp</td>
<td>1, 9</td>
<td>1·0-80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR F 78</td>
<td>Nephrotic ulcer of right foot with osteitis of metatarsal bone</td>
<td>Staphylococcus aureus</td>
<td>2, 16</td>
<td>2·0-99</td>
<td>9·49</td>
<td>Frusemide Lincomycin</td>
</tr>
<tr>
<td>RN M 74</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>13</td>
<td>3·21</td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>JB M 46</td>
<td>Fracture of neck of femur</td>
<td>Nil</td>
<td>9</td>
<td>2·71</td>
<td></td>
<td>Amoxicillin Spironolactone Frusemide</td>
</tr>
<tr>
<td>MG F 69</td>
<td>Pneumonia</td>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>3·06</td>
<td></td>
<td>Frusemide Salbutamol Prednisolone</td>
</tr>
<tr>
<td>MM F 67</td>
<td>Cholangitis</td>
<td>Klebsiella sp</td>
<td>20</td>
<td>2·64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RO F 42</td>
<td>Prophylaxis</td>
<td>Nil</td>
<td>7</td>
<td>4·29</td>
<td></td>
<td>Frusemide</td>
</tr>
<tr>
<td>TR M 42</td>
<td>Subphrenic abscess</td>
<td>Nil</td>
<td>10</td>
<td>2·88</td>
<td></td>
<td>Oxyrenolol Lincomycin</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 \(\gamma\)-GT and the increases ranged from 1·2 to 6 times normal. Increased urinary \(\gamma\)-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 \(\gamma\)-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 \(\gamma\)-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 \(\gamma\)-GT activities—four out of five receiving flucloxacillin, one out of two receiving Seprin, 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 \(\gamma\)-GT activity (Table 4).

### RENAL FUNCTION

Figure 3 shows that the degree of increase in the urinary \(\gamma\)-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 \(\gamma\)-GT

Serum \(\gamma\)-GT was measured in all patients. Sixty-one per cent showed increased activities, but there was
Aminoglycoside antibiotics and renal function: changes in urinary $\gamma$-glutamyltransferase excretion

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 $\gamma$-GT:creatinine clearance ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin + Amoxicillin</td>
<td>JO F</td>
<td>61</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>0-39</td>
</tr>
<tr>
<td>Flucloxacillin + Amoxicillin</td>
<td>MD M</td>
<td>69</td>
<td>Bronchopneumonia</td>
<td>Nil</td>
<td>0-80</td>
</tr>
<tr>
<td>Flucloxacillin + Amoxicillin</td>
<td>AM F</td>
<td>83</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>1-18</td>
</tr>
<tr>
<td>Flucloxacillin + Amoxicillin</td>
<td>WR M</td>
<td>17</td>
<td>Pneumonia</td>
<td><em>Staphylococcus aureus</em></td>
<td>1-11</td>
</tr>
<tr>
<td>Flucloxacillin + Amoxicillin</td>
<td>DM M</td>
<td>65</td>
<td>Pneumonia</td>
<td><em>Haemophilus influenzae</em></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></td>
<td></td>
<td></td>
<td>Congestive cardiac failure</td>
<td>Streptococcus pneumoniae</td>
<td>1-00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Empyema</td>
<td>Neisseria meningitidis</td>
<td>1-52</td>
</tr>
<tr>
<td>Sulphadimidine + Penicillin</td>
<td>PM M</td>
<td>50</td>
<td>Meningitis</td>
<td>Streptococcus pneumoniae</td>
<td>***</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>JM F</td>
<td>69</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>0-40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congestive cardiac failure</td>
<td>Nil</td>
<td>0-34</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>MO F</td>
<td>64</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>0-37</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>MD M</td>
<td>49</td>
<td>Pneumonia</td>
<td>Nil</td>
<td>0-55</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 $\gamma$-GT in vitro. Each value is the mean for three urines.

<table>
<thead>
<tr>
<th>Concentration of added aminoglycoside (µg/ml)</th>
<th>Tobramycin $\gamma$-GT (U/l)</th>
<th>Gentamicin $\gamma$-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>25-7</td>
</tr>
<tr>
<td>200</td>
<td>24-4</td>
<td>24-7</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 $\gamma$-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

...
may be ultrastructural changes in both humans and rats (Wellwood et al., 1976).

The present studies using the proximal tubular enzyme, γ-GT, have confirmed the findings of Wellwood. All patients treated with tobramycin and gentamicin have shown elevated activities of urinary γ-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 γ-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 aminoglycosides, but these were of a fairly mild nature. However, an important relationship was found to exist between the degree of elevation of the urinary γ-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 γ-GT response. But Fig. 3 shows that even similar creatinine clearances are compared, the γ-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 γ-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 fluoxacillin also showed elevations of urinary γ-GT. Reports of nephrotoxicity of fluoxacillin 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 γ-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.

References


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


Reports and Bulletins prepared by the Association of Clinical Biochemists

The following reports and bulletins are published by the Association of Clinical Biochemists. They may be obtained from The Publishing Department, British Medical Journal (ACB Technical Bulletins), B.M.A. House, Tavistock Square, London WC1H 9JR. Overseas readers should remit by British Postal or Money Order.

SCIENTIFIC REPORTS (price £1.00/$2.00 each)


4 An Evaluation of five Commercial Flame Photometers suitable for the Simultaneous Determination of Sodium and Potassium March 1970 P. M. G. BROUGHTON and J. B. DAWSON

SCIENTIFIC REVIEWS (price £1.00/$2.00 each)

1 The Assessment of Thyroid Function March 1971 F. V. FLYNN and J. R. HOBBS


3 Biochemical Tests for the Assessment of Fetoplacental Function May 1975 C. E. WILDE and R. E. OAKLEY

4 Tests of Exocrine Pancreatic Function, March 1977 A. H. GOWENLOCK

TECHNICAL BULLETINS (price £1.00/$2.00 each)

9 Determination of Urea by AutoAnalyzer November 1966 RUTH M. HASLAM

11 Determination of Serum Albumin by AutoAnalyzer using Bromocresol Green October 1967 B. E. NORTHAM and G. M. WIDDOWSON

13 An Assessment of the Technicon Type II Sampler Unit March 1968 B. C. GRAY and G. K. MCGOWAN

14 Atomic Absorption Spectroscopy: an outline of its principles and a guide to the selection of instruments May 1968 J. B. DAWSON and P. M. G. BROUGHTON


16 A Guide to Automation in Clinical Chemistry May 1969 P. M. G. BROUGHTON

17 Flame Photometers: a comparative list of 17 instruments readily available in Britain August 1969 P. WILDING

19 Spectrophotometers: a comparative list of low-priced instruments readily available in Britain May 1970 C. E. WILDE and P. SEWELL

20 Quantities and Units in Clinical Biochemistry June 1970 P. M. G. BROUGHTON

21 Filter Fluorimeters: A comparative list of 18 instruments September 1970 H. BRAUNSBERG and S. S. BROWN

22 Bilirubin Standards and the Determination of Bilirubin by Manual and Technicon AutoAnalyzer Methods January 1971 BARBARA BILLING, RUTH HASLAM, and N. WALD

23 Interchangeable Cells for Spectrophotometers and Fluorimeters September 1971 S. S. BROWN and A. H. GOWENLOCK

24 Simple Tests to Detect Poisons March 1972 B. W. MEADE et al.

25 Blood Gas Analysers May 1972 K. DIXON

26 Kits for Enzyme Activity Determination September 1972 S. B. ROSALKI and D. TARLOW

27 Assessment of Pumps Suitable for Incorporation into Existing Continuous Flow Analytical Systems November 1972 A. FLECK et al.

28 Routine Clinical Measurements of Transferrin in Human Serum September 1973 K. DIXON

29 Control Materials for Clinical Biochemistry (5th edition) September 1973 J. F. STEVENS

30 Notes on the Quality of Performance of Serum Cholesterol Assays September 1973 S. S. BROWN

31 Determination of Uric Acid in Blood and in Urine July 1974 R. W. E. WATTS

32 A Survey of Amino Acid Analysers Readily Available in the United Kingdom September 1974 J. E. CARLYLE and P. PURKISS

33 Definitions of some Words and Terms used in Automated Analysis November 1974 A. FLECK, R. ROBINSON, S. S. BROWN, and J. R. HOBBS

34 Measurement of Albumin in the Sera of Patients January 1975 LINDA SLATER, P. M. CARTER, and J. R. HOBBS


36 Factors Influencing the Assay of Creatinine November 1975 J. G. H. COOK
Aminoglycoside antibiotics and renal function: changes in urinary gamma-glutamyltransferase excretion.

P R Beck, R B Thomson and A K Chaudhuri

doi: 10.1136/jcp.30.5.432

Updated information and services can be found at: [http://jcp.bmj.com/content/30/5/432](http://jcp.bmj.com/content/30/5/432)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to: [http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to: [http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to: [http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)