Tobramycin nephrotoxicity. A prospective clinical study

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Summary
The nephrotoxicity of tobramycin given at a dose of 4.5 mg/kg/day for a period of 12 days to a group of 90 patients with a mean age of 62.9 years was studied. Toxicity was determined on the basis of 3 main criteria (oliguria <400 ml/24 hr, serum creatinine 0.4 mg increase over a minimum basal level of 1.2 mg/100 ml, BUN 5 mg increase over a minimum of 25 mg/100 ml); and 3 minor criteria (proteinuria, microhaematuria and cylindruria). These parameters were determined before treatment at 7, 10, 14, 17, 21, and 30 days afterwards. The age and coexistence of factors such as hypertension, diabetes, anaemia, cardiac insufficiency, shock and dehydration were considered. Nephrotoxicity level was determined from 3 to 38.8% depending on the criterion used, and is related to hypertension (P < 0.001), age (P < 0.005) and association with ampicillin (P < 0.005). Nephrotoxicity was reversible spontaneously in 96.7% of the cases and no differences have been observed between patients with moderate renal insufficiency and those with normal renal function on the initiation of treatment.

Introduction
Although the toxic effects of the aminoglycosides on the nervous system (eighth nerve), liver, skin and digestive tract are well known, the effects on the kidney are also of importance (Bendush and Weber, 1976). Renal damage may occur by both direct nephrotoxicity or hypersensitivity; the former being dose-related, the latter not. The possible abnormal activation, by the antibiotic, of the renin-angiotensin system and subsequent permanent cortical vasoconstriction in an oliguric phase has also been suggested (Hollenberg et al., 1970; Alcazar et al., 1976).

Tobramycin (nebramycin factor 6) is a relatively new aminoglycoside with an antimicrobial activity similar to that of gentamicin, although with possibly a higher efficacy against Pseudomonas and a lower activity against Staphylococcus (Preston and Wick, 1971; Britt et al., 1972; Delbene and Farrar, 1972; Hof, Schiotz and Paulsen, 1974; Jaffe et al., 1974; Duncan and Penner, 1975). It may be especially useful for pulmonary (Pennington and Reynolds, 1973) and urinary infections (Landes et al., 1975).

As in the case of gentamicin, this new aminoglycoside is not devoid of toxicity, as shown by experiments conducted in animals (Wick and Welles, 1968; Welles et al., 1973; De Rosa et al., 1974) and in man (Tobias, Whitehouse and Wrigley, 1976; Lockwood and Bower, 1973). However, some animal experiments seem to indicate a lower nephrotoxicity of tobramycin as compared to gentamicin (Wick and Welles, 1968; Welles et al., 1973).

The aim of this study was the determination of tobramycin nephrotoxicity in humans.

Patients and methods
Tobramycin was given to a group of 90 patients suffering from various infectious diseases. Their ages ranged between 17 and 97 years, with a mean of 62.9 years. An i.m. dosage of 4.5 mg/kg/day given as 1.5 mg/kg every 8 hr was administered for a period of 12 days in every case. When serum creatinine levels were higher than 1.2 mg/100 ml (normal range from 0.8 to 1.2 mg/100 ml) dosage was adjusted according to a simplified nomogram based on Benner, Kranhold and Bush (1969): Dose every 8 hr = normal dose/serum creatinine (in mg/100 ml).

The following were determined before therapy: blood count, serum blood sugar, proteins, electro-
lytes, creatinine, BUN, plasma and urine osmolarity, quantitative proteinuria and urinary sediment. Factors which might contribute to renal disease, such as arterial hypertension, diabetes, cardiac insufficiency, dehydration, anaemia and shock as well as renal insufficiency (creatinine level >1.4 mg/100 ml) were also evaluated. In each case an effort was made to determine the aetiology of the infectious disease by means of bacteriological techniques.

Serum creatinine, BUN, quantitative proteinuria, urinary sediment and 24-hr urine volumes were measured 7, 10, 14, 17, 21, and 30 days after treatment started. Toxicity was determined on the basis of 3 major criteria (oliguria, <400 ml/24 hr; serum creatinine, 0.4 mg increase over a basal minimum of 1.2 mg/100 ml; BUN, 5 mg increase over a minimum of 25 mg/100 ml); and 3 minor criteria (quantitative proteinuria higher than 750 mg/24 hr; granular casts; microscopic haematuria >20 RBC per high power field) in the absence of reasonable justification for these abnormalities.

In certain cases other antibiotics and diuretics were also given. The statistical study was carried out in the Centro de Cálculo de la Universidad Politécnica de Barcelona (Dr J. M. Domenech) comparing qualitative data by the $\chi^2$ test and quantitative data by Student's $t$ test, with a significance level at $P<0.05$.

The patients knew that they were being given a new antibiotic and that the frequency of blood extractions was for the study of the drug's possible toxicity. Patients who did not accept the protocol or from whom all the required measurements could not be obtained were excluded from the study.

**Results**

There were 58 male and 32 female patients of mean age 62.9 years. Infectious diseases for which the antibiotic was given were pneumonia (54 cases), urinary infection (24 cases), cholecystitis (9 cases) and septicemia (3 cases). Causative agents were *Pneumococcus* sp. (10 cases), *Escherichia coli* (14 cases), *Staphylococcus* sp. (3 cases), *Streptococcus* sp. (3 cases), *Klebsiella* sp. (3 cases), *Proteus* sp. (2 cases), *Serratia* sp. (2 cases) and unknown in 53 cases. Associated significant conditions and treatment are shown in Tables 1 and 2. A total of 83 changes occurred in 35 patients (38-8%).

Abnormalities observed were changes in serum creatinine in 18 cases (20%), BUN in 16 (17.8%), granular casts in 23 (25.6%) (this being the most frequent change), haematuria in 13 (14.4%), proteinuria in 10 (11.1%) and oliguria in 3 (3.3%). Qualitative analysis of these abnormalities shows that the change of serum creatinine and of BUN occurs simultaneously in most cases (Fig. 1).

Of 66 patients with normal renal function when the treatment was started (Group I), 13 showed changes in serum creatinine (19.7%) and 11 on BUN (18.7%). Mean values are shown in Fig. 2. The highest alteration occurred 14 days after treatment was started, and then the 2 values fell in parallel, becoming normal at 30 days. Of the remaining 24 patients with moderate renal insufficiency (serum creatinine ≤3 mg/100 ml) at the start of treatment, 5 had raised serum creatinine and BUN levels (20.8%).

**Table 1.** Associated conditions predisposing to renal damage

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>11</td>
<td>12.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12</td>
<td>13.3</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>Anaemia</td>
<td>33</td>
<td>36.7</td>
</tr>
<tr>
<td>Dehydration</td>
<td>16</td>
<td>17.8</td>
</tr>
<tr>
<td>Shock</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>24</td>
<td>26.8</td>
</tr>
</tbody>
</table>

**Table 2.** Antibiotics and diuretics used in addition to tobramycin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin alone</td>
<td>34</td>
<td>37.8</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>17</td>
<td>19.8</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>22</td>
<td>24.4</td>
</tr>
<tr>
<td>Frusemide</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>Ampicillin + frusemide</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Cephalothin + cloxacillin</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Nalidixic acid + frusemide</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

The average age of patients was significantly higher in those with changes in serum creatinine ($P<0.01$), BUN ($P<0.005$), microscopic haematuria ($P<0.005$) and proteinuria ($P<0.05$) (Fig. 3).

No significant correlation was observed between nephrotoxicity and sex, type of infection, diabetes, cardiac insufficiency, dehydration or anaemia. During the course of treatment, eosinophilia >1000 cells/μl occurred in 21 patients but was not related with nephrotoxicity.

Comparison of hypertensive patients with the rest showed a higher incidence of rises in serum creatinine ($P<0.01$), casts ($P<0.001$) and haematuria ($P<0.001$) in the former group (Fig. 4). Likewise, rises in BUN in patients receiving tobramycin plus ampicillin (6 of 22) were more frequent than in those treated with tobramycin only (one out of 34) ($P<0.005$). However, the tobramycin-cephalothin combination did not produce a higher incidence of nephrotoxicity.
Tobramycin nephrotoxicity

There was an almost identical incidence of changes suggestive of nephrotoxicity in those with normal and impaired renal function before treatment.

In all patients except 3, all changed levels returned to normal with stopping the treatment – adjustment of the dosage only was necessary. One of the 3 exceptions was an 82-year-old with chronic pyelonephritis and cardiac insufficiency who had a serum creatinine of 2-1 mg/100 ml at 30 days. The other 2 patients died from non-renal causes with final serum creatinine levels of 2-8 and 4-3 mg/100 ml.

Discussion

The administration of tobramycin to animals produces changes in the proximal tubule which, by optical and electron microscopy, are similar to those produced by gentamicin and consist of vacuolation and myeloid bodies in the tubular epithelium cell lysosomes; these changes are interpreted as the phagocytes remains of organoids from altered cells (Welles et al., 1973; De Rosa et al., 1974; Kosek, Mazze and Cousins, 1974; Szwed et al., 1974; Patel et al., 1975). The toxicity of tobramycin in man seems to be lower than that of gentamicin and

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Table: Qualitative changes

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Qualitative changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>18</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>16</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>Casts</td>
<td>23</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>13</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>10</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Oliguria</td>
<td>3</td>
<td>3.3</td>
<td></td>
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</table>

Fig. 1. Quantitative and qualitative representation of the 83 changes of renal function observed in 35 patients.

Fig. 2. Mean changes (± s.e. mean) in the serum creatinine and BUN during treatment of patients with normal renal function. ● Increase in serum creatinine. ▲ Increase in BUN. ○ No change in serum creatinine. △ No change in BUN.
ranges from 1.5 to 4.4% (Bendush and Weber, 1976; Neu, 1976) although this might be attributable to the greater care exercised when administering tobramycin, based on the previous experience with gentamicin. Toxicity is revealed by the presence of granular casts, microscopic haematuria, proteinuria, progressive azotaemia and oliguria (Appel and Neu, 1977). Cylindruria has been considered as an early sign of nephrotoxicity (Neu, 1976).

Nevertheless, there is no single criterion which is accepted by all authors as establishing antibiotic-induced nephrotoxicity: Khalmeter, Kamme and Hallberg (1978) define it as progressive azotaemia and increase in serum creatinine with parallel decrease in glomerular filtration; Dosik et al. (1978) define it as an increase of 150% in serum creatinine over the initial level and a BUN increase >40 mg/100 ml; Lau et al. (1977) only require a 100% increase in serum creatinine over a minimum basal level of 1.3 mg/100 ml; Lerner, Seligsohn and Matz (1977) consider a 50% increase in serum creatinine over a minimum level of 1.4 mg/100 ml; Lane, Wright and Blair (1977) require a criterion similar to that of the present authors, i.e. a 0.4 mg/100 ml increase in serum creatinine over the basal level in patients with a serum creatinine <3 mg/100 ml and
an increase of 0.9 mg/100 ml in patients with an initial serum creatinine > 3 mg/100 ml, as well as increases of BUN > 5 mg/100 ml over the basal level. Finally, some authors establish this by the simple presence of casts without alterations of serum creatinine (Giamarellou et al., 1978a). All these reports support the fact that the toxicity levels defined in the literature show wide variations with a range from 1.5% (Bendush and Weber, 1976) to 48% (Giamarellou et al., 1978a) depending on the criterion used.

In the present study, only 3 patients, all seriously ill, 2 of whom died, showed oliguria with progressive azotaemia. One had neoplastic disease in which nephrotoxicity is most likely to occur (Klastersky, Hensgens and Debuyscher, 1975; Plager, 1976). On the basis of this criterion, the toxicity in this series was only 3.3%. In accordance with the criterion of Dosik et al. it was 4.4%, according to Lau et al., 6.6%, according to Lerner’s 13.3%, based on the present authors’ main criteria and those of Lane et al. 20% and, finally, according to the present authors’ minor criteria or those accepted by Giamarellou et al. (1978a), 38.8%. This is why, although 38.8% of the patients presented some kind of change of the parameters studied, only 20% of them required dosage adjustment because of increases in serum creatinine. Cylindruria, the most frequent abnormality, did not correlate with the other changes in most of the cases.

As already noted by other authors (Kleinhecht and Juggers, 1973; Kahlmeter et al., 1978) age and arterial hypertension were related to a higher incidence of changes in some of the parameters studied. Those patients with moderate renal insufficiency on initiation of treatment did not show a higher degree of toxicity, in contrast with the findings of others (Appel and Neu, 1977); this is attributed to the strict control of serum creatinine levels and subsequent dosage adjustments.

In the last years, many cases of nephrotoxicity have been reported after using an aminoglycoside with other antibiotics, particularly the association gentamicin-cephalothin (Bobrow, Jaffe and Young, 1972; Fillastre, 1973; Fillastre et al., 1973; Kleinhecht and Juggers, 1973; Kleinhecht, Ganeval and Droz, 1973; Mendez and Ortiz, 1974; Plager, 1976). Cephalothin, when given in high dosage, can produce proximal tubular lesions and acute tubular necrosis in animals (Carling et al., 1975) and in man (Burton et al., 1974; Engle et al., 1975; Pasternak and Stephens, 1975). However, certain experimental (Carling et al., 1975) as well as clinical studies do not confirm such a hypothesis (Fanning, Jick and Gump, 1975; Gay, Klastersky and Schimpff, 1975; Giamarellou et al., 1978b). In the present study no differences were observed between those patients receiving tobramycin only or tobramycin plus cephalothin. Ampicillin nephrotoxicity has been reported (Benner, 1970). The present authors found a higher degree of toxicity when ampicillin was associated with tobramycin. As far as they know, the latter has not previously been reported.

From the results obtained it can be concluded that the nephrotoxicity of tobramycin ranges from 3.3 to 38.8% depending on the criterion used. On the basis of main criteria it reaches a maximum of 20% and it subsides spontaneously without need for discontinuing the antibiotic in 96.7% of the cases. The presence of moderate renal insufficiency on starting treatment does not predispose to toxicity provided dosage is adjusted.

References


