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 ranges from 3.3 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 osmolality, 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 χ^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 septicaemia (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

	<i>n</i>	%
Arterial hypertension	11	12.2
Diabetes mellitus	12	13.3
Cardiac insufficiency	14	15.6
Anaemia	33	36.7
Dehydration	16	17.8
Shock	3	3.3
Renal insufficiency	24	26.8

TABLE 2. Antibiotics and diuretics used in addition to tobramycin

Antibiotic	<i>n</i>	%
Tobramycin alone	34	37.8
Cephalothin	17	18.9
Ampicillin	22	24.4
Fruzemide	4	4.5
Ampicillin + frusemide	3	3.3
Lincomycin	3	3.3
Cephalothin + cloxacillin	3	3.3
Nalidixic acid + frusemide	1	1.1
Nalidixic acid	1	1.1
Nitrofurantoin	1	1.1
Carbenicillin	1	1.1

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 $>$ than 1000 cells/ μ l 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.

FIG. 3. Age (mean $\pm$ 2 s.d.) of patients with $\blacksquare$ and without $\square$ changes.

FIG. 4. Changes in laboratory findings in relation to hypertension. $\blacksquare$ hypertensive; $\square$ normotensive.

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 Debusscher, 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 (Kleinknecht 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; Kleinknecht and Juggers, 1973; Kleinknecht, 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; Gaya, 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.

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