Antibiotic blood concentrations in patients successfully treated with tobramycin

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Summary

Thirty-nine patients with severe Gram-negative infections were treated with parenteral tobramycin. Thirty-one (79%) were cured of their infection. Tobramycin was most effective in the therapy of patients with urinary tract infections, arthritis and skin and soft tissue infections and relatively less effective in patients with septicaemia, pneumonia, and osteomyelitis. The infection was cured more frequently in patients who achieved a high ratio between the peak serum concentration of tobramycin and the minimal inhibitory concentration of tobramycin against the pathogenic organism (so-called therapeutic ratio). The ratio was >4.0 in 11 of 13 (85%) assays performed in 12 cured patients, whereas this ratio was achieved in only 3 of 10 (30%) instances in 5 patients in whom the therapy failed ($P < 0.05$). The latter group also included a greater proportion of patients with an ultimately fatal illness, such as lung cancer and uraemia, compared to the former successfully treated group. Adverse effects of tobramycin on renal function were transitory. No significant effect of tobramycin on the hearing was observed.

Introduction

Tobramycin has been found to be an effective drug in the treatment of Gram-negative infections, even when these are resistant to gentamicin (Moellerling, Wennersten and Kunz, 1974). It has greater *in vitro* activity than gentamicin against *Pseudomonas aeruginosa* (Britt *et al.*, 1972; Burger, Sanford and Zweighaft, 1973; Hyams, Sinberkoff and Rahal, 1973; Yourassowsky, Schuntens and Vanderlinden, 1973) and possibly *in vivo* (Burch *et al.*, 1973). The pharmacology of tobramycin (Bechtol and Black 1975; Christopher *et al.*, 1974; Jaffe, Meyers and Hirschman, 1974a; Regamey, Gordon and Kirby, 1973), the *in vitro* susceptibilities of Gram-negative organisms (Geddes *et al.*, 1974; Waterworth, 1972) and its clinical effectiveness (Blair *et al.*, 1975; Carmalt, Cortez and Rosenblatt 1976; Jaffe *et al.*, 1974b; Klustersky, *et al.*, 1974; Schoutens, Vanderlinden and Yourassowsky, 1973) are well documented. The authors have evaluated the results of tobramycin therapy

with respect to each patient's underlying illness, type of infection, and a ratio of peak serum concentration and the minimal inhibitory concentration (MIC) of tobramycin against the patient's own pathogen (so-called therapeutic ratio).

Patients and methods

The study included patients with severe aerobic Gram-negative infections with or without an anaerobic component treated in 1975 and 1976 at the Martin Luther King Jr General Hospital. Thirty-nine patients were treated with tobramycin. Of these 2.6% had a rapidly fatal illness, 33.3% had an ultimately fatal illness, and 64% had a non-fatal illness as defined by McCabe and Jackson (1962). The mean age was 47.9 years. Twenty-four patients were male and 15 were female. The relationship of antibiotic levels, MICs of bacterial pathogens and the results of therapy were analysed in only 17 of these patients since the remainder lacked the necessary pharmacological data. Nephrotoxicity and auditory toxicity were evaluated in 23 of these patients.

In patients with normal renal function, the initial recommended dosage of tobramycin or gentamicin was 1.66 mg/kg administered either i.v. (over 15–30-min interval) or i.m. every 8 hr. In patients with reduced renal function, the calculation of the dose was based on the creatinine level (Bechtol and Black, 1975) and the dose was adjusted according to measured serum concentrations of tobramycin. Some patients also received either carbenicillin for synergistic effect against *Pseudomonas*; clindamycin, chloramphenicol, or ticarcillin for anaerobic infections; or a cephalosporin for *Klebsiella*. The patient was considered cured when clinical signs and laboratory findings indicative of infection (fever, swelling, drainage, leucocytosis, abnormal chest X-ray, abnormal urinalysis and urine culture and abnormal cerebrospinal fluid) returned to normal during the therapy or shortly thereafter. Bacteriological cure or failure was determined on the basis of eradication or persistence of a pathogenic microorganism respectively at the site of infection at the completion of surgery.

Tobramycin serum concentrations were assayed by

an agar-well diffusion assay based upon that for gentamicin (Riff and Jackson, 1971; Winters, Litwack and Hewitt, 1971) using a strain of *Klebsiella* (derived from *K. pneumoniae* ATCC 27779) resistant to commonly used antibiotics except tobramycin and gentamicin. The susceptibilities to tobramycin, gentamicin and amikacin of 242 clinical isolates (including the pathogenic bacteria isolated from the patients in the study) of Gram-negative bacteria were assayed by the International Collaborative Study agar-dilution technique (Washington and Barry, 1974). *Escherichia coli*, *Klebsiella*, *Enterobacter*, and *Serratia* strains were in general more susceptible to gentamicin, whereas *Pseudomonas* strains were more sensitive to tobramycin. On the weight basis, amikacin was less active than either tobramycin or gentamicin.

Results

Treatment with tobramycin resulted in the cure of 31 of 39 (79%) patients (Table 1). Patients with septicaemia, pneumonia, or osteomyelitis, had a less favourable outcome than the rest. Patients with pseudomonal infection were, on the average, younger than the rest, since this group included a large portion of young heroin addicts.

Seventeen patients were evaluated prospectively regarding serum concentrations of the drug and MICs of their pathogens (Table 2). All of these patients had Gram-negative pathogen(s), *Pseudomonas* being the most common and, in addition, some had anaerobic pathogens or *Enterococcus*. The dosage on body weight basis differed among the patients since some patients with severe infections were treated using a low dose of approximately 3 mg/kg/day despite the recommendation to use a high dose of tobramycin.

The patients who received tobramycin (by i.v. or i.m. routines) at a dose of 4.3–5.0 mg/kg/day achieved peak serum concentrations of 4.6–7.6 µg/ml (mean 6.0 µg/ml) and those who received 2.9–3.5 mg/kg/day had peak concentrations of 2.2–2.5 µg/ml (mean 2.4 µg/ml). Twelve patients were cured, and in 5 patients the treatment failed or was only partially effective. Only 2 of the 12 cured patients had a low therapeutic ratio (less than 4.0), whereas 4 of the 5 patients who failed the therapy had such a low ratio. Bacteria isolated from patients not responding to therapy were more resistant to tobramycin than those from patients responding to treatment. Thus, *Pseudomonas* strains isolated from the former patients had an average MIC of 3.3 µg/ml. Carbenicillin was used concurrently with tobramycin in one of 4 patients with *Pseudomonas* infection who failed to respond and in 3 of 8 patients who responded to the therapy. One patient in the group of patients responding to therapy and 2 in the group failing the therapy had an ultimately fatal illness; the majority had a non-fatal underlying disorder such as heroin addiction, diabetes, sickle-cell disease and trauma. The mean age of patients responding to the treatment included one case of lung infection, 4 cases of arthritis and one case of infection from the gastrointestinal tract. The other group comprised 2 cases of lung infection and one case of arthritis. Each group included a comparable proportion of sepsis (25% and 20%) and of urinary tract infection (17% and 20%).

Effect of tobramycin on renal and auditory functions

Renal function was evaluated by serial determinations of serum creatinine in 23 patients on tobramycin and in 18 patients on gentamicin therapy. In the

TABLE 1. Clinical effectiveness of tobramycin in different types of infection and in patients with underlying illness of varying severity

Type of infection or underlying illness			Mean age	Clinical and bacteriological cures	
	No.	(%)		No.	(%)
Septicaemia	5	(13)	47.5	3	(60)
Urinary tract infection	6	(15)	42.2	6	(100)
Lung infection	15	(38)	48.8	11	(73)
Osteomyelitis	5	(13)	63.2	3	(60)
Arthritis	3	(8)	34.6	3	(100)
Skin and soft tissue	5	(13)	44.6	5	(100)
<i>Pseudomonas</i> sp.	23	(59)	42.5	18	(78)
<i>Escherichia coli</i>	4	(10)	51.2	2	(50)
<i>Klebsiella-Enterobacter</i>	8	(20)	57.6	7	(87)
<i>Proteus</i> sp.	3	(8)	63.7	3	(100)
<i>Serratia</i>	1	(3)	58.0	1	(100)
Rapidly fatal	1	(3)	86.0	0	
Ultimately fatal	13	(33)	56.7	10	(77)
Non-fatal	25	(64)	46.3	21	(84)
All patients	39	(100)	47.8	31	(79)

TABLE 2. Relationship between the outcome of the therapy and the value of the therapeutic ratio

Outcome	No. of patients	Organism	Bacterial pathogens		Tobramycin			
			No. of strains	No. strains eradicated	Average MIC ($\mu\text{g/ml}$)	Average peak serum level ($\mu\text{g/ml}$ of serum)	Therapeutic ratio	No. of cases with therapeutic ratio < 4.0†
Cured*	12	<i>Pseudomonas</i>	8	8	1.2	4.9	4.5	2
		<i>Proteus mirabilis</i>	2	2	0.3	8.2	27.2	0
		<i>Klebsiella</i>	1	1	0.3	7.9	26.0	0
		<i>Enterobacter</i>	1	1	1.2	5.5	4.6	0
		<i>Escherichia coli</i>	1	1	0.6	7.9	13.2	0
Partial** or none	5	<i>Pseudomonas</i>	4	0	3.3	5.0	1.5	4
		<i>Pr. mirabilis</i>	3	2	0.8	5.1	10.5	1
		<i>Klebsiella</i>	2	2	0.7	2.1	11.8	1
		<i>E. coli</i>	1	1	2.0	7.6	3.8	1

* Infections included 3 cases of sepsis, 2 of urinary tract infection, 4 of arthritis, 2 of skin and soft tissue infections and one case of infection originating from the gastrointestinal tract. One patient had an ultimately fatal illness (multiple sclerosis) and 11 patients had a non-fatal illness (heroin addiction, diabetes, trauma, sickle-cell disease and heart surgery).

** Infections included one case of sepsis, 2 of lung infection, one of urinary tract infection, and one of infection originating in the gastrointestinal tract. Two patients had an ultimately fatal illness (lung cancer), 2 had decubitus ulcers and one had perforated appendicitis and uraemia due to sepsis.

† Significance of the difference in the proportions of therapeutic ratio < 4.0 in the 2 groups is < 0.05.

tobramycin group, serum creatinine rose in 7 (30%) patients by an average of 2.5 mg/dl, but it returned to normal in at least 2 patients, following the therapy. In the gentamicin group, creatinine rose in 6 (48%) patients, all with pre-existent renal damage, by an average of 1.0 mg/dl. Cochlear function was followed by serial audiograms at frequencies of 125 to 8000 Hz in 8 patients who had a prolonged course of tobramycin therapy (range 13–47 days, average 25.1 days). Changes were minimal and were observed predominantly in the high-frequency range (6000 Hz). Five patients had a loss of 10–20 dB and three patients had a gain of 10–20 dB during the therapy.

Discussion

In this study, tobramycin was remarkably effective in the therapy of Gram-negative infections of all types but relatively less so in infections of the lung, bone and in septicæmia. Particularly pleasing was the favourable response to the combined tobramycin and carbenicillin regimen of infections due to *Pseudomonas* sp. The relatively less effective response to tobramycin in Gram-negative pneumonia may be related to the low concentration of tobramycin in the lung. In one patient dying with pseudomonal pneumonia, the post-mortem revealed consolidation and microabscesses in the whole lung. Since aminoglycosides administered systemically penetrate poorly into normal pulmonary secretions (Klasterky *et al.*, 1974) in a consolidated lung, the concentration would be expected to be low. Recently, a patient with pseudomonal pneu-

monia, initially not responding to systemic therapy, was cured with simultaneous endotracheal nebulization of the drug and administration of up to 8 mg of tobramycin/kg/day which achieved a peak serum concentration of 12 $\mu\text{g/ml}$.

Most patients who failed the therapy had a low therapeutic ratio, usually as a result of a high MIC of the pathogenic organism rather than because of low peak serum concentration. The peak antibiotic serum concentration is a useful index, since it approximates the peak tissue concentration (Barza *et al.*, 1974). Pharmacological reasons for the failure of gentamicin therapy were similarly advanced (Jackson and Riff, 1971). The group of patients failing the tobramycin therapy also included a greater proportion of lung infections and of lung cancer and uraemia as underlying illness compared to the successful group. Further experience is needed to determine whether raising the serum concentration of the drug might defeat (a) pathogens with a greater resistance; (b) infections in patients with severe underlying illnesses; (c) Gram-negative lung infections.

Although serum creatinine rose in 7 (30%) 23 patients treated with tobramycin and in 6 (46%) of 13 treated with gentamicin, the rises appeared to be transitory on follow-up. No significant adverse effect on hearing was observed.

In vitro, tobramycin has been shown to be the most active aminoglycoside against *P. aeruginosa* (Britt *et al.*, 1972; Burger *et al.*, 1973; Hyams *et al.*, 1973; Waterworth, 1972). The present results confirm a greater susceptibility of *Pseudomonas*

tobramycin and a greater susceptibility to gentamicin of *Esch. coli*, *Klebsiella*, *Enterobacter* and *Serratia* strains. Recently, amikacin has been proposed as an aminoglycoside of choice in the initial treatment of a compromised host with severe, presumable Gram-negative sepsis (Hewitt and Young, 1977). Amikacin has been shown to be effective in infections with gentamicin- and tobramycin-resistant organisms, including infections unsuccessfully managed with gentamicin (Bartlett, 1977). Although amikacin has the broadest antibacterial spectrum of all aminoglycosides, it is less active against *P. aeruginosa* than tobramycin (Moellering *et al.*, 1974). Since the importance of bacterial species varies in different hospitals and frequently *P. aeruginosa* assumes a major role, in the authors' opinion, the selection of an aminoglycoside antibiotic should be based on the knowledge of the locally important pathogens and their susceptibilities.

Additionally, in this trial, it was found that tobramycin causes nephrotoxicity less frequently than does gentamicin, very much like the result of Smith *et al.* (1980), following their double-blind comparison of nephrotoxicity of gentamicin and tobramycin.

Acknowledgment

We are grateful to Thamina and Frank Low for technical assistance, and to Patricia Edson for editorial assistance.

References

- BARTLETT, J.G. (1977) Amikacin treatment of pulmonary infections involving gentamicin-resistant Gram-negative bacilli. *American Journal of Medicine*, **62**, 945.
- BARZA, M., BRUSCH, J., BERGERON, M.G. & WEINSTEIN, L. (1974) Penetration of antibiotics into fibrin loci *in vivo*. III. Intermittent vs. continuous infusion and the effect of probenecid. *Journal of Infectious Diseases*, **129**, 73.
- BECHTOL, L.D. & BLACK, H.R. (1975) Tobramycin in renal impairment. *American Journal of Medical Science*, **269**, 317.
- BLAIR, D.R., FEKETY JR, F.R., BRUCE, B., SILVA, J. & ARCHER, G. (1975) Therapy of *Pseudomonas aeruginosa* infections with tobramycin. *Antimicrobial Agents and Chemotherapy*, **8**, 22.
- BRITT, M.C., GARIBALDI, R.A., WILFERT, J.N. & SMITH, C.B. (1972) *In vitro* activity of tobramycin and gentamicin. *Antimicrobial Agents and Chemotherapy*, **2**, 236.
- BURCH, K., NICHOLS, R.D., QUINN, E.L., COX, F., FISHER, E.J., MADHAVEN, T. & POHLOD, D. (1973) A clinical trial of tobramycin with pharmacological and microbiological studies. *Henry Ford Hospital Medical Bulletin*, **21**, 135.
- BURGER, J.M., SANFORD, J.P. & ZWEIGHAFT, T. (1973) Tobramycin: bacteriological evaluation. *American Journal of Medical Science*, **265**, 125.
- CARMALT, E.D., CORTEZ, L.M. & ROSENBLATT, J.E. (1976) Clinical experience with tobramycin in the treatment of infections due to Gram-negative bacilli. *American Journal of Medical Sciences*, **271**, 285.
- CHRISTOPHER, T.G., KORN, D., BLAIR, A.D., FORREY, A.W., O'NEILL, M.A. & CUTLER, R.E. (1974) Gentamicin pharmacokinetics during hemodialysis. *Kidney International*, **6**, 38.
- GEDDES, A.M., GOODALL, J.A.C., SPEARS, C.E., GILLET, A., ANDREWS, J. & WILLIAMS, J.D. (1974) Clinical and laboratory studies with tobramycin. *Chemotherapy*, **20**, 245.
- HEWITT, W.L. & YOUNG, L.S. (Ed) (1977) Symposium on Amikacin. *American Journal of Medicine*, **62**, 863.
- HYAMS, P.J., SINBERKOFF, M.S. & RAHAL, J.J. (1973) *In vitro* bactericidal effectiveness of four aminoglycoside antibiotics. *Antimicrobial Agents and Chemotherapy*, **3**, 87.
- JACKSON, G.G. & RIFF, L.J. (1971) *Pseudomonas* bacteremia: Pharmacologic and other bases for failure of treatment with gentamicin. *Journal of Infectious Diseases*, **124** (Suppl.), S185.
- JAFFE, G., MEYERS, B.R. & HIRSCHMAN, S.Z. (1974a) Pharmacokinetics of tobramycin in patients with stable renal impairment, patients undergoing peritoneal dialysis, and patients on chronic hemodialysis. *Antimicrobial Agents and Chemotherapy*, **5**, 611.
- JAFFE, G., RAVREBY, W., MEYERS, B.R. & HIRSCHMAN, S.Z. (1974b) Aminoglycoside tobramycin for therapy of infections due to Gram-negative bacteria. *Antimicrobial Agents and Chemotherapy*, **5**, 75.
- KLASTERSKY, J., GEUNING, C., MOUAWAD, E. & DANEAU, D. (1972) Endotracheal gentamicin in bronchial infections in patients with tracheostomy. *Chest*, **6**, 117.
- KLASTERSKY, J., HENSGENS, C., HENRI, A. & DANEAU, D. (1974) Comparative clinical study of tobramycin and gentamicin. *Antimicrobial Agents and Chemotherapy*, **5**, 133.
- MCCABE, W.R. & JACKSON, G.G. (1962) Gram-negative bacteremia. I. Etiology and ecology. *Archives of Internal Medicine*, **110**, 847.
- MOELLERING, R.C., WENNERSTEN, C. & KUNZ, L.J. (1974) Emergency of gentamicin-resistant bacteria: Experience with tobramycin therapy of infections due to gentamicin-resistant organisms. *Journal of Infectious Diseases*, **134** (Suppl.), S40.
- MOELLERING, R.C., WENNERSTEN, C., KUNZ, L.J. & POITRAS, J.W. (1977) Resistance to gentamicin, tobramycin and amikacin among clinical isolates of bacteria. *American Journal of Medicine*, **62**, 873.
- REGAMEY, C., GORDON, R.C. & KIRBY, W.M.M. (1973) Comparative pharmacokinetics of tobramycin and gentamicin. *Clinical Pharmacology and Therapeutics*, **14**, 396.
- RIFF, L.F. & JACKSON, G.G. (1971) Pharmacology of gentamicin in man. *Journal of Infectious Diseases*, **124** (Suppl.), S98.
- SCHOUTENS, E., VANDERLINDEN, M.P., YOURASSOWSKY, E. (1973) Tobramycin: Clinical and microbiological evaluation. *International Journal of Clinical Pharmacology*, **8** (Suppl.), 207.
- SMITH, C.R., LIPSKY, J.J., LASKIN, O.L., HELLMANN, D.B., MELLITS, E.D., LONGSTRETH, J. & LIETMAN, P.S. (1980) Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. *New England Journal of Medicine*, **302**, 1106.
- WASHINGTON II, J.A. & BARRY, A.L. (1974) Dilution tests procedures. In: *Manual of Clinical Microbiology* (Ed by Lennette, E.H., Spaulding, E.H. & Truant, J.P.) 2nd edn, p. 410. American Society of Microbiology, Washington, D.C.
- WATERWORTH, P.M. (1972) The *in vitro* activity of tobramycin compared with that of other aminoglycosides. *Journal of Clinical Pathology*, **21**, 973.
- WINTER, R.E., LITWACK, K.D. & HEWITT, W.L. (1971) Relation between dose and levels of gentamicin in blood. *Journal of Infectious Diseases*, **124** (Suppl.), S90.
- YOURASSOWSKY, E., SCHUNTENS, E. & VANDERLINDEN, M.P. (1973) *In vitro* evaluation of tobramycin and gentamicin on bacterial strains isolated from clinical material. *Chemotherapy*, **18**, 337.