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Interaction between the renal excretion rates of β_2-microglobulin and tobramycin in man

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Summary

The renal excretion rate of β_2-microglobulin in man is 127 ± 98 ng/min at alkaline urine pH (pH 7).

Tobramycin, up to intravenous doses of 160 mg (2 mg/kg) does not increase the renal excretion rate of β_2-microglobulin. Tobramycin must have less affinity than gentamicin for the tubular system for active reabsorption of amino groups containing organic compounds. Due to this reduced affinity tobramycin will be absorbed less by the proximal tubular cells, which may be one of the reasons for tobramycin being less toxic than gentamicin.

β_2-Microglobulin excretion can be used as a parameter for the relative binding affinity of aminoglycosides.

Introduction

Gentamicin interferes with the tubular reabsorption of β_2-microglobulin by competitive inhibition when the renal excretion rate of gentamicin exceeds a threshold value of 150 μg/min [1]. The high binding affinity of gentamicin for the proximal tubular reabsorption system may be a determinant of its nephrotoxicity. Tobramycin is considered less toxic than gentamicin as judged by the renal excretion of urinary enzymes NAG, AAP, etc. [2–11].

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This difference in nephrotoxicity may be caused by differences in binding affinity for the tubular reabsorption system. In this investigation the interaction between the renal excretion rates of tobramycin and β_2-microglobulin was studied and compared with the interaction between the renal excretion rates of gentamicin and β_2-microglobulin as described by Walenkamp et al [1].

Materials and methods

Subjects

Five males and one female (age 25–40 years) volunteered for experiments. Each experiment lasted 3 days. The first day was the blank period in which, by collecting two blood samples and every urine sample, the reference values for the renal excretion rate and plasma concentrations of creatinine and β_2-microglobulin were measured.

On the second day, tobramycin was administered by intravenous bolus injection of 1 min at doses of 60, 80 or 160 mg. In one experiment a second dose of 80 mg was given after the first dose of 80 mg. Blood and urine samples were collected at regular intervals during the second and third day.

Drugs

Tobramycin was obtained from Eli Lilly Nederland (Obracin®) (Utrecht, The Netherlands).

Sampling procedures

Plasma. Blood samples of 2 ml were drawn by venepuncture on the first and third day and by an indwelling catheter (Abbocath No. 16) in the left cephalic vein on the second day. Tobramycin was injected into the right cubital vein.

Urine. During the entire experiment urine samples were collected on spontaneous voiding. The urine was made alkaline by the daily intake of 10 g of sodium bicarbonate. An increased urine flow was achieved on the second day by a water load of 0.5 l/h over a period of 8 h after the injection of tobramycin. Urine pH was measured on receipt of the sample with a Copenhagen Radiometer (PMH61).

Assays

Creatinine was measured by an automated Jaffé method (Aurora Selective batch analyser, Ultrolab AB, Bromma, Sweden). Concentrations of β_2-microglobulin were analysed with the Phadebas β_2-microtest (Pharmacia, Uppsala, Sweden). Concentrations of tobramycin were analysed by a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA).

Calculations

The renal excretion rates of β_2-microglobulin, tobramycin and creatinine were calculated by multiplying the urine concentration with the average urine flow during each period of urine collection.

TABLE I

Pharmacokinetic parameters of tobramycin and average plasma concentrations of β_2-microglobulin and creatinine ($\pm$SD)

Subject	Body weight (kg)	Plasma concentrations		Tobramycin		
		β_2-microglobulin (mg/l) ($n=13$)	creatinine (μmol/l) ($n=13$)	$t_{1/2}$ (h)	% excreted (30 h after inj.)	renal clearance (ml/min)
J.H. (160 mg *)	67	1.56 ± 0.13	74.4 ± 1.7	2.08	100	103 ± 46.2
R.W. (160 mg)	74	1.61 ± 0.15	68.1 ± 1.9	3.04	100	84.6 ± 37.8
J.v.d.B. (2×80 mg)	83	1.23 ± 0.13	74.3 ± 2.3	1.88	99	82.6 ± 24.2
Th.d.J. (60 mg)	60	1.05 ± 0.07	47.1 ± 1.1	1.50	93	150 ± 32.2
K.d.G. (80 mg)	68	1.87 ± 0.16	61.6 ± 3.3	1.90	100	95.4 ± 15.5
P.Th. (60 mg)	73	1.74 ± 0.12	82.6 ± 4.3	1.95	98	97.7 ± 23.5

* Tobramycin dose in parentheses.

TABLE II

Urinary pH, urine-flow and renal excretion rate of β_2-microglobulin and creatinine before and after tobramycin administration

Subject	Day	pH	Urine flow (ml/min) ±SD	Renal excretion rate	
				β_2-microglobulin (ng/min) ±SD	creatinine (μmol/min) ±SD
J.H.	0	7.12±0.3 *	5.37±4.37 *	134.3±111	8.01±1.67
(160 mg)	1	7.42±0.30 **	5.33±3.03 **	188.3±142	8.62±1.34
	2	7.16±0.25 ***	3.10±1.60 ***	96.7± 31.4	9.16±1.86
R.W.	0	7.15±0.25	1.03±0.37	56.1± 14.2	6.04±1.95
(160 mg)	1	7.25±0.35	2.20±1.96	95.2± 51.2	7.97±1.90
	2	7.19±0.32	1.06±0.52	80.2± 12.3	8.71±0.54
J.v.d.B.	0	7.22±0.37	2.20±1.72	107.9± 19.1	9.78±1.31
(2×80 mg)	1	7.37±0.28	4.15±3.32	140.5± 53.5	9.69±1.54
	2	7.19±0.25	2.18±1.14	95.7± 20.1	10.66±2.15
Th.d.J.	0	7.25±0.35	1.92±1.65	58.3± 6.65	6.54±0.75
(60 mg)	1	7.45±0.45	4.27±4.20	87.3± 41.0	6.85±0.90
	2	7.42±0.41	2.97±0.83	65.3± 11.9	7.28±2.43
K.d.G.	0	7.20±0.53	0.81±0.18	314.9± 76.8	8.46±1.59
(80 mg)	1	7.35±0.52	1.76±1.19	577.2±722	8.95±2.93
	2	7.33±0.47	2.14±0.37	166.9± 57	8.79±0.56
P.Th.	0	7.18±0.50	3.10±3.82	96.3± 52.1	8.05±1.01
(60 mg)	1	7.51±0.28	5.36±5.06	114.1± 40.6	9.96±1.11
	2	7.62±0.19	1.33±0.43	79.5± 20.7	9.47±0.88

* $n=10$; ** $n=10$; *** $n=10$.

Results

Table I shows pharmacokinetic parameters of tobramycin and the average plasma concentrations of creatinine and β_2-microglobulin in six volunteers over the whole experimental period. The SD of creatinine and β_2-microglobulin plasma concentration show that they did not vary over time, whereas the average is within the normal range.

The average plasma half-life of tobramycin is 2 h, and 30 h after injection 95–100% of the dose is eliminated by the kidneys. The average renal clearance of tobramycin is 102 ml/min and shows a considerable intra- and interindividual variation, but is not dose-dependent.

Table II lists urinary pH, urine-flow and renal excretion rate of β_2-microglobulin and creatinine before and after intravenous tobramycin administration. Urinary pH was alkaline throughout the experimental period, while the urinary flow was adequate to allow frequent spontaneous voiding.

Renal excretion rate of β_2-microglobulin and creatinine were not significantly influenced by tobramycin administration.

Fig. 1 shows the plasma concentration time curve of tobramycin and the renal excretion rate of β_2-microglobulin, creatinine and tobramycin in the volunteer

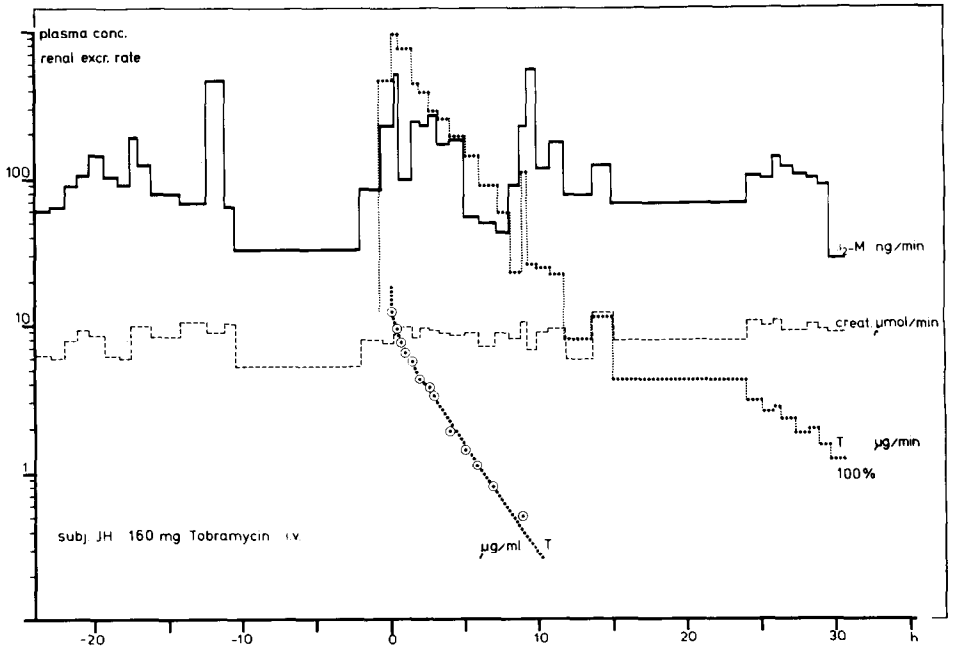

Fig. 1. Plasma concentration time curve to tobramycin (T) and the renal excretion rate time curves of tobramycin (T, µg/min), β_2-microglobulin (β_2-M, ng/min) and creatinine (creat, µmol/min) in a subject after intravenous injection of 160 mg of tobramycin. Tobramycin does not affect the renal excretion rate of β_2-microglobulin.

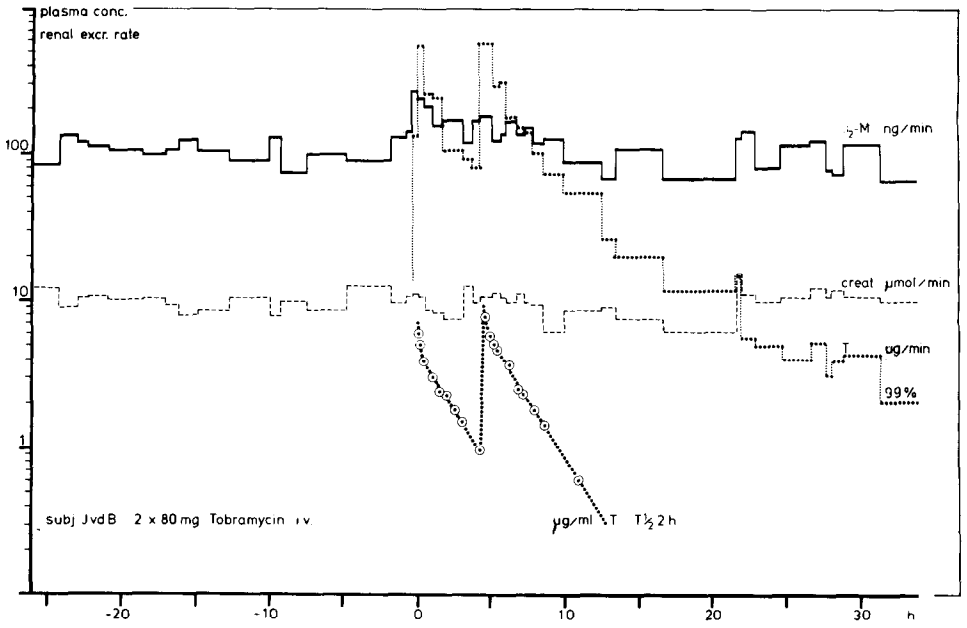

Fig. 2. Plasma concentration time curve of tobramycin (T, µg/ml) and the renal excretion rate time curves of tobramycin (T, µg/min), β_2-microglobulin (β_2-M, ng/min) and creatinine (creat, µmol/min) in a subject after two intravenous injections of 80 mg of tobramycin. Tobramycin does not affect the renal excretion rate of β_2-microglobulin.

receiving the highest single dose of tobramycin. The tobramycin plasma concentration time curve follows apparent first order kinetics 1 h after tobramycin administration. Tobramycin does not influence renal β_2-microglobulin or creatinine excretion.

Fig. 2 shows the same data in the volunteer receiving two injections of tobramycin with a 5-h interval and the results are essentially the same as in Fig. 1.

Fig. 3 shows the renal excretion rate of β_2-microglobulin plotted against corresponding renal excretion rate of tobramycin in each urine sample from the six volunteers.

The normal range for the β_2-microglobulin excretion rate (127 ± 98 ng/min at pH 7) as assessed from the blank period before tobramycin administration is also plotted.

Fig. 4 shows the same data together with the β_2-microglobulin excretion rate plotted against the corresponding renal excretion rate of gentamicin derived from previous work (Walenkamp et al 1983 [12]). It is obvious that gentamicin strongly influences β_2-microglobulin excretion rate, whereas tobramycin does not over the whole dose range.

Discussion

The renal excretion rate of β_2-microglobulin is a valuable means of assessing the instantaneous effects of aminoglycosides on the proximal tubular cells. Walenkamp

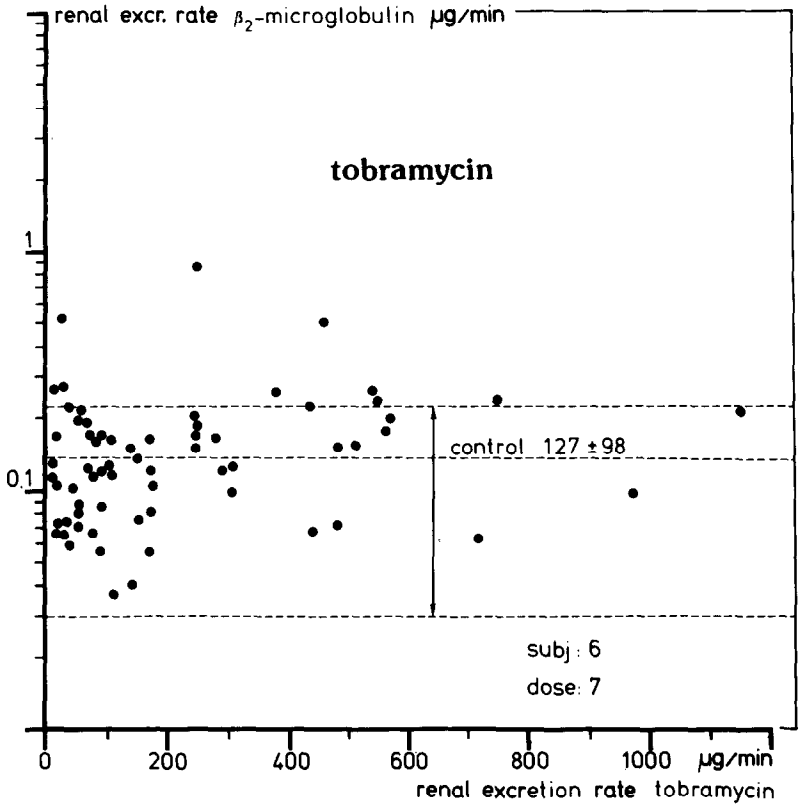

Fig. 3. The renal excretion rate of β_2-microglobulin plotted against the corresponding renal excretion rate of tobramycin in all urine samples. The renal excretion rate of β_2-microglobulin is not affected by the presence of tobramycin.

et al [1] showed that gentamicin was able to inhibit the tubular reabsorption of β_2-microglobulin when the gentamicin renal excretion rate exceeded the threshold value of 150 µg/ml.

Aminoglycosides (amino group containing organic compounds) are reabsorbed by the same systems as those which reabsorb endogenous proteins and the amino acids [13–15]. The number of amino groups per molecule may be determinant for the binding to the brush border membrane [15,17]. The fact that tobramycin, in contrast to gentamicin, does not inhibit tubular reabsorption of β_2-microglobulin, has to be explained by differences in binding affinity of the three compounds for the reabsorption system (gentamicin-β_2-microglobulin-tobramycin). Fig. 4 shows that even a tobramycin renal excretion rate of 1200 µg/min does not enhance renal excretion of β_2-microglobulin. This means that the binding affinity of tobramycin for the tubular reabsorption system must be at least ten times less than that for gentamicin.

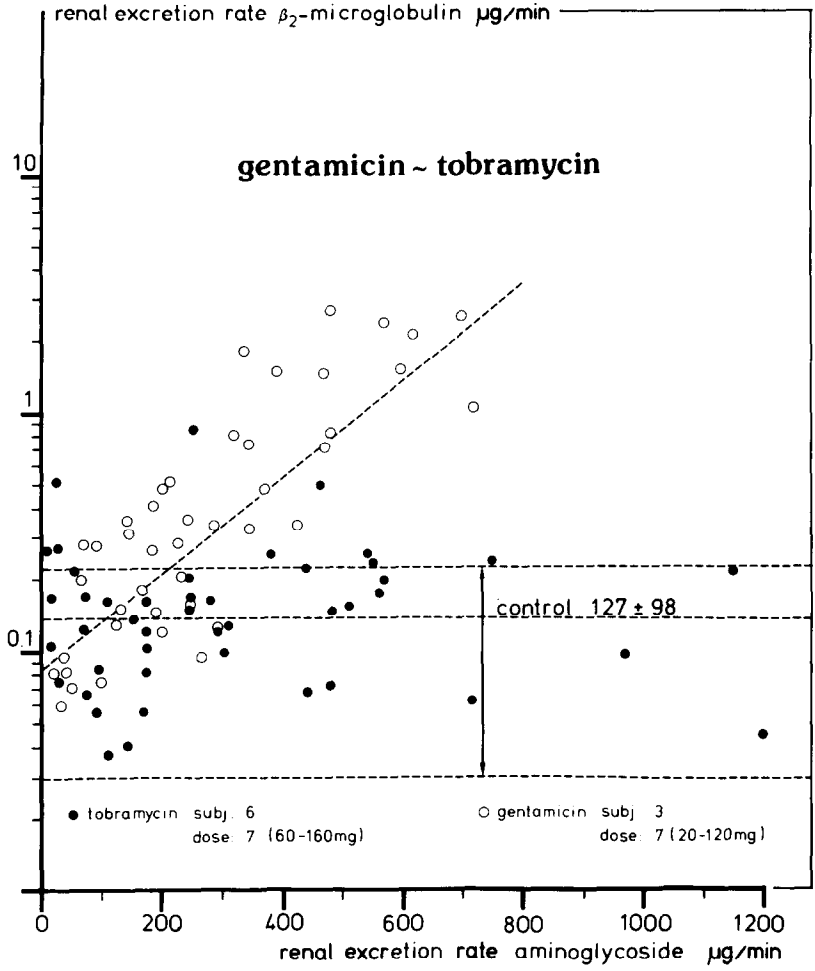

Fig. 4. The renal excretion rate of β_2-microglobulin plotted versus the renal excretion rate of tobramycin (Fig. 3) and the renal excretion rate of gentamicin (data taken from [1]). A threshold renal excretion rate of gentamicin of approximately 150 µg/ml can be observed at which the increase in renal excretion of β_2-microglobulin becomes visible (1). This effect is absent with tobramycin.

Increasing the dose and, thereby, the renal excretion rate of tobramycin would reveal the threshold value for tobramycin at which the renal excretion rate of β_2-microglobulin increases. However, this dose will be beyond the normal clinical dosage. The finding that tobramycin is less nephrotoxic than gentamicin [2–11], i.e. after entering the proximal cell, may be correlated with the relative lower affinity for the tubular reabsorption system(s) than has gentamicin. In this respect β_2-microglobulin may be a parameter which indicates relative affinities for reabsorption of aminoglycosides and the consecutive effects in the cell.

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