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Gentamicin administration via peritoneal dialysis fluid: the risk of ototoxicity

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Abstract

In a prospective study on 47 patients, 16 mg of gentamicin per two litres dialysate was administered intraperitoneally at every cycle of intermittent peritoneal dialysis, carried out over the course of several days. Serum gentamicin sampling, pure tone audiometry and caloric tests were performed before and during the treatment. The gentamicin levels reached at the end of the thirtieth cycle were observed to be low. In view of this, the risk of acute ototoxicity was considered to be minimal. This was confirmed by the absence of clinical audiometric or vestibulometric evidence of toxicity.

Introduction

Gentamicin, an aminoglycoside with a potential risk of ototoxicity, (Hewitt, 1973; Gilman *et al.*, 1985) is widely used at the Nephrology Department, General Hospital, Kuala Lumpur for chronic renal failure patients on intermittent peritoneal dialysis complicated by peritonitis. The gentamicin is administered intraperitoneally via the peritoneal dialysate. A study was undertaken to investigate the possible development of drug-induced ototoxicity and to correlate serum gentamicin levels with the incidence of toxicity.

Materials and methods

The study was carried out over a two-year period (April 1986–April 1988). All patients suffered from chronic renal failure requiring Intermittent Peritoneal Dialysis. Gentamicin was administered to those cases who developed peritonitis as a complication of the treatment. The drug was given intraperitoneally in the dialysate. Signs of ototoxicity were monitored by audiovestibular assessment and patients with the following abnormalities were excluded from the survey:

1) Pre-existing sensorineural hearing loss.
2) Narrow external auditory canal.
3) Discharging ears or perforated tympanic membrane and
4) Concurrent administration of ototoxic drugs by other routes.

Each course of peritoneal dialysis comprised repeated dialysing cycles, eight to ten times per day lasting three to four days. At each cycle, two litres of dialysate was introduced within five minutes, retained intraperitoneally for 30 min and subsequently drained within 10 mins.

Patients developing peritonitis at any time during the course of intermittent peritoneal dialysis were treated with 16 mg of gentamicin per dialysing cycle given in the two litres of dialysate. Those requiring a further course of the antibiotic at the end of the intermittent peritoneal dialysis regime were treated by the intramuscular route. Examination of patients and measurement of gentamicin levels were limited to the intraperitoneal dialysis period only.

Blood samples were collected for serum gentamicin assay at the end of the first, fifteenth and thirtieth cycles after the commencement of gentamicin therapy. The enzyme immuno-assay technique, using the EMIT Analyser Unit was used for the analysis.

Patients were questioned every alternate day concerning hearing loss, vomiting, giddiness or vertigo and other relevant symptoms of ototoxicity. Pure tone audiometry and caloric testing employing the Hallpike method and Frenzel glasses were performed before commencing gentamicin therapy and at the end of first, fifteenth and thirtieth cycles of the dialysis. All clinical audiometric and vestibular examinations were performed by the same operator in a standardized quiet environment on the Nephrology ward. Recordings of the air and bone audiometric thresholds and calorimetric results in both ears were retained for analysis.

Results

A total of 47 patients were treated with gentamicin. The average age was 48.6 ± 10.2 years (mean ±SD) and the average weight was 40.2 ± 11.7 kg. The serum creatinine level was 1487 ± 399.9 umol/l. Data on serum gentamicin levels of 93 specimens from these 47 patients were pooled and are projected graphically in Figure 1.

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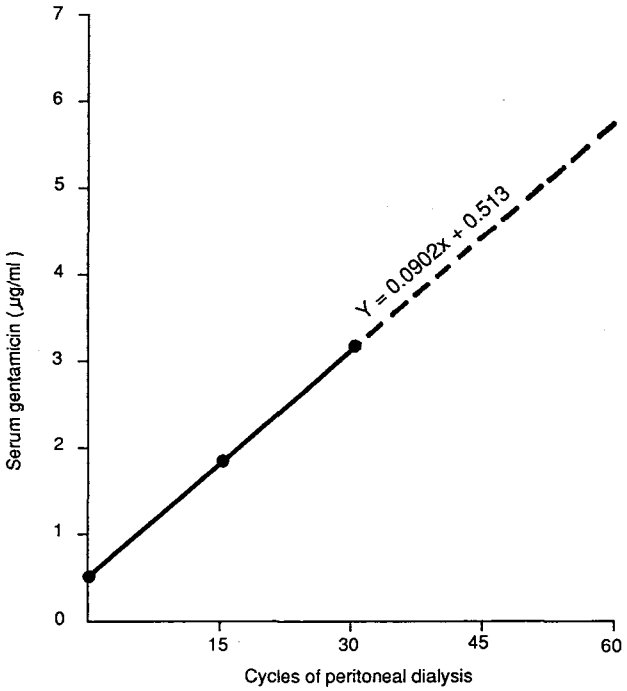

FIG. 1

Graph showing the relationship between serum gentamicin levels and cycles of peritoneal dialysis in patients with end stage renal failure (n = 93).

Data on serum levels in 12 patients who completed the course of 30 cycles of gentamicin administered via the peritoneal route are shown in Table I. The mean (±SD) serum gentamicin values at the first, fifteenth and thirtieth cycles were 0.44 ± 0.38, 2.0 ± 0.91 and 3.2 ± 1.16 µg/ml respectively. Seven of the blood specimens obtained from the first cycle were below the detectable limit of 0.1 µg7ml and only one specimen had a value above 1.0 µg/ ml (Table I). At the fifteenth and thirtieth cycles, there were only two values each above 3 and 5 µg/ml respectively. The serum gentamicin levels at the thirtieth cycle of intraperitoneal dialysis ranged from 1.9 to 5.3 µg/ml.

These gentamicin values were in keeping with those obtained from the 93 pooled blood specimens of all 47 patients in the study. The total intraperitoneal gentamicin cycles administered per patient ranged from 9 to 44 with a mean value of 26.3 cycles. The total intraperitoneal gentamicin dose per patient ranged from 144 mg to 704 mg, the mean being 402.5.

Serum gentamicin levels related to cycles of peritoneal dialysis

A linear graph comparing serum gentamicin levels with cycles of peritoneal dialysis is shown in Fig. 1. An increase in the number of cycles of dialysis causes a linear increase in the serum gentamicin levels at the fifteenth and thirtieth cycles of peritoneal dialysis. Thus, the projected values at the forty-fifth and sixtieth cycles show maximum attainable levels of 4.5 µg/ml and 6 µg/ml respectively.

Analysis of audiometric and vestibular data following gentamicin therapy

The audiometric threshold alterations were within normal limits in all cases. The level of significance of threshold shift was taken as 15 dB at any two frequencies (between 128 Hz and 8 Kz) or 25 dB at a single frequency.

There was no evidence of vestibular changes (no nystagmus, dysequilibrium or bobbing oscilopsia). Caloric tests showed no evidence of canal paresis or directional preponderance.

Discussion

The peritoneal cavity is a potential space which in the adult can accommodate comfortably two litres of dialysate at any one time (Gary, 1971; Smithivas *et al.*, 1971; Mohan *et al.*, 1973). Sixteen milligrams of gentamicin in 2000 ml of dialysis fluid (8 µg/ml) was infused in to the peritoneal cavity. If the total dose of gentamicin were absorbed from the peritoneum, this would be concentrated into the rather small volume of distribution (Vd) of approximately 14 l (Gilman *et al.*, 1985) resulting in a concentration of around 1 µg/ml, even at first dosing. This level would increase rapidly with each subsequent administration of gentamicin and would thus approach 10 µg/ml by the tenth cycle.

However, the foregoing results showed that this situation did not arise as the mean serum gentamicin level at the thirtieth cycle of dialysis being only 5.3 µg/ml. This level was far below the toxic threshold (10 to 12 µg/ml). The reason for this can be attributed to a number of factors: concentration gradient, speed of absorption and volume of distribution.

The initial dilution of gentamicin in the two litres of peritoneal dialysate, markedly lowers the concentration gradient. Furthermore, the dialysate present in the peritoneum continues to exert its dialysing effect on the gentamicin which has been absorbed. Thus serum therapeutic levels are not attained, even after repeated intraperitoneal gentamicin administrations, albeit the level in the peritoneal fluid itself is more than adequate to treat the peritonitis.

The equilibration of peritoneal gentamicin with serum usually requires a period of 12 h and the additional administration of intramuscular gentamicin is important to ensure therapeutic levels in the body (Selvador and

TABLE I

SERUM GENTAMICIN LEVEL (µG/ML) OF 12 PATIENTS RECEIVING 16 MG PER CYCLE VIA PERITONEAL DIALYSIS FLUID

Patient number	Cycles of peritoneal dialysis			Body weight (kg)	Serum creatinine (µg/ol)
	1st	15th	30th		
1	ND*	1.3	2.5	46	2568
2	ND*	1.1	2.1	52	1527
3	0.2	1.4	3.0	61	2036
4	ND*	2.3	4.0	49	1014
5	ND*	1.2	2.3	55	1246
6	0.2	1.0	2.3	57	1828
7	ND*	2.8	3.3	66	1722
8	ND*	1.1	1.9	44	1684
9	ND*	2.8	3.6	57	1110
10	1.1	2.4	2.4	63	974
11	0.3	3.1	5.3	36	1220
12	0.4	3.5	5.2	56	1338
Mean ±SD	0.44 ± 0.38	2.0 ± 0.91	3.2 ± 1.16	53.5 ± 8.59	1522 ± 472

*ND = not detectable.

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Christina, 1981). Thus, even if higher doses of intraperitoneal gentamicin are administered, the equilibration of gentamicin with the serum does not reach serum therapeutic levels due to the short retention time of the individual cycle in the peritoneal cavity.

Gentamicin, has a small volume of distribution in patients with normal renal function. In chronic renal failure patients, however due to fluid retention, there is a slightly larger volume of distribution which tends to decrease the concentration in the plasma. Furthermore in renal dialysis another two litres of peritoneal fluid is added to this intrinsic volume of distribution (Vd), thereby significantly expanding the total volume of distribution for the patient.

The above factors doubtless all play a part in ensuring that the serum gentamicin levels remain below the threshold level of ototoxicity. In our study these levels remained very low with only a gradual rise and were subtherapeutic even at the thirtieth cycle despite the fact that the patients were receiving about 160 mg gentamicin per day.

Theoretically, if the graph in Figure 1 is presumed to be a straight line, then, using this line of best fit, the serum gentamicin ototoxic threshold as 10 μg/ml would be reached only when the number of cycles per peritoneal dialysis approached 110.

We conclude therefore that standard intra-peritoneal gentamicin therapy for peritonitis on chronic renal failure patients is virtually without risk of ototoxicity.

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