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Gentamicin ototoxicity in continuous ambulatory peritoneal dialysis

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Abstract

A prospective study was undertaken of 10 chronic renal failure patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) complicated by repeated bouts of peritonitis treated with gentamicin. Each 10-day treatment course consisted of a 120 mg loading dose, followed by 16 mg in 2l of peritoneal dialysate, given four times a day. Serum gentamicin analysed by enzyme immunoassay showed a mean level of 5.2 μg/ml, (range 3.7 to 6.6 mg/ml) four hours after the loading dose. Similar levels, well within the therapeutic range, were maintained on the 3rd, 5th, 7th and 9th days of intraperitoneal gentamicin therapy, suggesting no accumulation of gentamicin in the serum. Pure tone audiometry, electronystagmography and clinical assessment were performed during each course of treatment. Although no evidence of ototoxicity was found during the first two courses of gentamicin, but disequilibrium and bobbing oscillopsia were present during the third and fourth courses of gentamicin. These findings could be explained by cumulative injury to the vestibular apparatus caused by repeated therapeutic insults.

Key words: Peritoneal dialysis, continuous ambulatory; Kidney failure, chronic; Gentamicins, ototoxicity

Introduction

Gentamicin, an aminoglycoside carrying a potential risk of ototoxicity, is used routinely as a first line antibiotic therapy for peritonitis in Chronic Renal Failure (CRF) patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) at the Nephrology Department, General Hospital, Kuala Lumpur. Since patients frequently develop recurrent peritonitis, repeated courses of gentamicin are required. The gentamicin is administered intraperitoneally via the peritoneal dialysate in courses lasting 10 days. This study was undertaken to investigate the risks of drug-induced ototoxicity due to repeated courses of therapy and to correlate serum gentamicin levels with ototoxicity.

Materials and methods

The study covered a one year period (July 1990 to June 1991) on all end-stage renal disease patients on CAPD treated with gentamicin for the complication of peritonitis. The drug was administered intraperitoneally in the dialysate. Signs of ototoxicity were monitored by audio-vestibular assessment. Patients falling into the following categories were excluded from the study.

(a) Pre-existing sensorineural hearing loss.
(b) Narrow auditory canal.
(c) Discharging ear or perforated tympanic membrane.
(d) Concurrent administration of ototoxic drugs. As the patients were routinely treated with loop diuretics (frusemide) for their chronic renal failures, it was necessary to discontinue administration of these drugs prior to commencement of gentamicin therapy.

The routine of CAPD comprised four daily cycles in each of which 2l of dialysate was introduced within five minutes, retained intraperitoneally for 4–5 hours and drained within 10 minutes. The overnight cycle was retained for a longer duration (10–12 hours). Patients developing peritonitis at any time during the course of CAPD were treated initially with 120 mg gentamicin administered via the dialysate intraperitoneally, followed by 16 mg in the dialysate in each subsequent cycle over a course of 10 days.

Blood samples were collected for serum gentamicin assay on days one, five, seven and nine prior to commencing dialysis. On day five, an additional blood sample for serum gentamicin was collected before the last dialysis for the day was commenced. The analysis was carried out by the enzyme immunoassay technique, using an EMIT Analyser Unit. Patients were questioned every alternate day concerning hearing loss, vomiting, vestibular disturbance

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TABLE I
SERUM GENTAMICIN LEVELS (μG/ML) DURING ONE COURSE OF THERAPY VIA CAPD

Patient number	Age (years)	Serum CAPD gentamicin levels according to duration in day						Body weight (Kg)
		1st day (4 h*)	3rd day	5th day (am)	5th day (pm)	7th day	9th day	
1	57	5.9	5.9	5.1	5.7	4.6	4.0	57
2	50	4.5	3.6	4.3	5.3	6.4	4.8	55
3	38	3.9	3.4	3.1	3.7	4.0	3.9	105
4	43	–	3.2	3.8	3.9	3.7	3.4	66
5	47	5.7	5.9	6.8	6.8	7.9	6.3	57
6	50	5.9	6.1	6.2	7.7	6.8	6.5	48
7	36	6.2	4.6	4.2	4.3	3.9	3.8	62
8	60	3.7	3.4	4.4	4.2	4.7	4.8	68
9	50	4.5	3.8	4.6	5.0	4.5	4.3	61
10	58	6.6	4.1	4.7	–	5.7	5.8	65
	48.9 ± 8.16	5.2 ± 1.07	4.4 ± 1.15	4.7 ± 1.09	5.2 ± 1.36	5.2 ± 1.41	4.8 ± 1.09	64.4 ± 15.45

H* = Hours after loading dose.

and other symptoms suggestive of ototoxicity. Pure tone audiometry (PTA) and the Fitzgerald-Hallpike caloric test with electronystagmography (ENG), were performed before commencing gentamicin therapy, on the 3rd, 5th, 7th and 9th days of therapy and one week after completion. All clinical audiometric and vestibular examinations were performed by the same operator.

Results

A total of ten patients were treated for more than one episode of peritonitis with gentamicin. The average age was 49.9 ± 8.16 years (mean ± SD) and average weight was 64.4 ± 15.45 Kg. In all the patients the serum creatinine level before the dialysis was above 1000 μmol/l. Data on serum gentamicin levels during the first course of treatment for each of the ten patients are shown in Table I. Since similar levels were obtained for each patient during subsequent courses of therapy, only one representative set of data is shown for the four courses of therapy (Table II).

Interval between courses of gentamicin

Among the ten patients in the study, four patients had four courses of treatment, three had three courses, while the remaining three had two courses of intraperitoneal gentamicin therapy. The average intervals between treatments for these three groups of patients were 1.6 months (range 1 to 2.3 months), 2.6 months (range 1.8 to 3.3 months) and 0.75 months (range 0.5 to 1 month) respectively.

Serum gentamicin levels

A graph showing serum gentamicin levels at different times during each course of therapy is shown in Figure 1. The average serum gentamicin level attained four hours after the loading dose was 5.2 ± 1.07 μg/ml (3.7 to 6.6 μg/ml) while on the 3rd, 5th, 7th and 9th days of therapy the levels were 4.4 ± 1.15 μg/ml (3.2 to 6.1 μg/ml), 4.7 ± 1.09 μg/ml (3.1 to 6.8 μg/ml) respectively. The evening level on the 5th day was 5.2 ± 1.36 μg/ml). Analysis of variance revealed no significant difference between any of these levels.

Audiometric assessment

The criterion of threshold shift was taken as 15 dB at any two frequences between 125 Hz and 8 KHz or 25 dB at a single frequency. Based on these criteria, audiometric threshold alterations were found to be within normal limits in all cases even after repeated courses of treatment (Table III).

Caloric testing (with ENG)

The caloric test (Fitzgerald-Hallpike) showed normal responses in all patients prior to, and at the end of, the first two courses of therapy. However, of the seven patients who presented for a third course of gentamicin therapy, four had already development bilateral canal paresis. This situation remained unaltered at the end of the course of therapy.

A fourth course was required by four of the original seven patients. Two of these, whose labyrinths were normal after the third course, were found to have bilateral diminution in the caloric responses when they presented for the fourth course. The other two cases, who already showed partial labyrinthine damage at the third course of treatment had by this time, no remaining labyrinthine function in either ear. These findings remained unaltered in all four patients at the end of the fourth course (Table IV).

Discussion

The peritoneal cavity in the adult can easily accommodate 2 l of dialysate at any one time (Smithivas *et al.*, 1971; Gary, 1972; Mohan *et al.*, 1973). Each daily course of CAPD gentamicin consisted of a 120 mg loading dose and 16 mg subsequently at approximately five hourly intervals. Four hours after the commencement of gentamicin, the average serum levels were within the therapeutic range. Similar gentamicin serum levels were obtained on the 3rd, 5th, 7th and 9th days. Futhermore, on subsequent hospitalizations for recurring peritonitis, each additional course of intraperitoneal gentamicin showed a similar pattern. Although these levels attained the therapeutic range, they were far below the toxic threshold (10 to 12 μg/ml).

The equilibration of peritoneal gentamicin with serum usually requires a period of 12 hours of continuous dialysis. The additional administration of 16 mg gentamicin at every cycle is designed to ensure that serum therapeutic levels are maintained (Selvador and Christina, 1981). A

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TABLE II

SERUM GENTAMICIN LEVELS AND AUDIOVESTIBULAR ASSESSMENT OF A CAPD PATIENT DURING FOUR COURSES OF THERAPY

Date of gentamicin course	Serum CAPD gentamicin levels (μg/ml) in days						Pure tone audiogram results	Caloric test results	Clinical vestibular assessment
	1st day (4 h*)	3rd day	5th day (am)	5th day (pm)	7th day	9th day			
19.5.90	5.9	5.1	5.1	5.7	4.6	4.0	No change[0]	Normal	Nil
11.6.90	–	2.7	3.1	3.9	3.2	5.3	No change[0]	Normal	Nil
19.8.90	3.2	2.7	3.3	2.8	3.5	3.6	No change[0]	Minimal response	Disequilibrium
2.9.90	5.2	5.2	4.2	4.7	3.5	–	No change[0]	Absent	Disequilibrium and bobbing oscillopsia

[0] = alteration of less than 15 dB.
H* = Hours after loading dose.

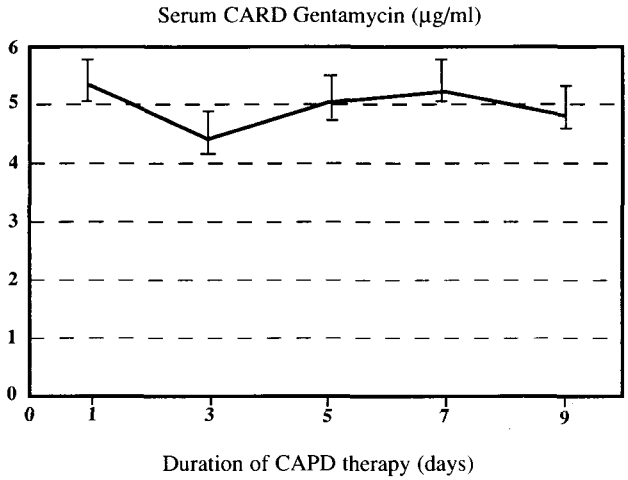

FIG. 1

Mean serum gentamicin levels (μg/ml) of 10 patients by duration of CAPD therapy.
Mean therapeutic level = 5.2 μg/ml; toxic level = 10-12 μg/ml.

steady level is rapidly attained, probably in less than five hours, due to the high loading dose and the relatively long retention time in the peritoneal cavity i.e. five hours compared with 30 minutes in simple peritoneal dialysis (Gendeh *et al.*, 1991).

All ten patients in the study failed to show any clinical or audio-vestibulometric evidence of ototoxicity after two courses of intraperitoneal gentamicin. However, six of the seven patients undergoing additional courses showed evidence of vestibulotoxicity. Although serum levels showed no obvious accumulation of gentamicin during each course, the vestibulotoxicity exhibited by these six patients after the cessation of therapy suggested cumulative damage to the vestibular apparatus from repeated 'therapeutic' insults with gentamicin combined with a slow excretion rate. This resulted in progressive degeneration of the vestibular receptor organs.

The precise mechanism by which gentamicin exerts its toxic effects upon the inner ear in patients exposed to repeated therapeutic doses of gentamicin is not known. When gentamicin is administered intraperitoneally, it is

TABLE III

AUDIOMETRIC RESULTS

Patient number	Courses of CAPD gentamicin: 1st course PTA (dB) R	1st course L	2nd course R	2nd course L	3rd course R	3rd course L	4th course R	4th course L
1	−5	+5	+5	−5	−10	−5	–	–
2	+5	−5	−5	+10	+5	−10	−10	+10
3	−5	+10	+5	−10	+5	−10	−10	+10
4	−5	+5	+5	−5	–	–	−5	+10
5	+5	−5	−10	−5	–	–	–	–
6	−5	+5	+5	−5	−10	−10	–	–
7	−5	+5	−5	−10	−5	+10	+10	−10
8	−5	−5	−5	+5	–	–	–	–
9	+10	−5	−10	+5	+10	−5	–	–
10	−5	−5	−5	+10	+5	−10	–	–

PTA = Pure Tone Audiometry (average threshold alterations at any two frequencies mainly at 4 and 8 kHz). Chi square = 2.1; Probability = 0.000095; DF = 3.
R = right ear. L = left ear.

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TABLE IV
CALORIC TEST RESULTS

Patient Number	Courses of CAPD gentamicin															
	1st course				2nd course				3rd course				4th course			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim	Abs	Abs	Abs	Abs
2	+	+	+	+	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim
3	+	+	+	+	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim
4	+	+	+	+	+	+	+	+		–		–		–		–
5	+	+	+	+	+	+	+	+		–		–		–		–
6	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim		–		–
7	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim	Abs	Abs	Abs	Abs
8	+	+	+	+	+	+	+	+		–		–		–		–
9	+	+	+	+	+	+	+	+	+	+	+	+		–		–
10	+	+	+	+	+	+	+	+	Dim	Dim	Dim	Dim		–		–

R = Right ear.
L = Left ear.
\+ = Normal response.
Dim = Diminuation of response.
Abs = Absence of response.

carried to the labyrinthine fluids through the blood. Hawkins *et al.* (1967) suggested other possibilities including secretion into the perilymph from the vessels of the spiral ligament or into the endolymph from the stria vascularis. Another possible route is by way of the vas spirale in the basilar membrane and the cortilymph. In the inner ear, perilymph and endolymph are in direct contact with the vestibular and cochlear sensory cells. Ototoxicity may therefore be largely dependent on the gentamicin levels in these fluids.

The specific ototoxic effects observed in this study suggest a cumulative concentration of gentamicin in the inner ear fluids due to multiple courses of treatment in combination with the prolonged half-life of gentamicin in the perilymph compared to other body fluids (Federspil *et al.*, 1976). It has been postulated that the highly negatively-charged gentamicin becomes bonded with the strongly positively-charged mucopolysaccharides in the inner ear. Thus binding to tissue proteins may account for the delayed removal of gentamicin from the perilymph. Furthermore it is believed that inflammatory changes in the middle ear increase the perilymph concentration of gentamicin. Voldrich (1965) suggested that this might be due to the general inflammatory effect causing leakage of tight junctions with consequent increase in the diffusion of gentamicin from the capillaries to the inner ear structures. It has been reported that gentamicin is probably eliminated from the inner ear by reabsorption by the stria vascularis. It is possible that repeated intraperitoneal gentamicin administration results in damage to the latter, thus slowing down the rate of transfer across the membrane. Thus alterations in the processes of absorption and elimination may contribute to the retention of gentamicin in the inner ear longer than in the blood stream. Diffusion back into the plasma is facilitated when the serum concentration of the blood is low.

Gentamicin exhibits a four-fold greater affinity for the vestibule than the cochlea thereby explaining the vulnerability of the vestibular apparatus to the drug (Tran Ba Huy and Defferennes, 1988). Thus the vestibular sense organs are the first to manifest the effects of repeated gentamicin exposure with clinical evidence of ototoxicity. The cristae of the semicircular canal are more vulnerable to damage than the saccular and utricular maculae (Tran Ba Huy and Deffrennes, 1988). The vestibular damage is usually permanent but with the passage of time, the patient may adapt to the disability by using visual and proprioceptive information to maintain balance (Ramsden and Ackrill, 1982).

The serum trough levels seem to correlate with the occurrence of ototoxicity better than the peak levels (Line *et al.*, 1970) The trough concentration of gentamicin should be less than 1 μg/ml to avoid ototoxicity before the next dose is given. Since gentamicin is excreted more slowly in patients with renal impairment, the regular occurrence of peak serum levels of over 5 μg/ml inevitably leads to higher trough levels with higher risk of ototoxicity.

We conclude that the administration of repeated courses of gentamicin for recurrent peritonitis in CAPD patients carries a significantly higher risk of ototoxicity than in single-course therapy. An alternative and safer antibiotic should therefore be sought for the treatment of peritonitis in this group of patients.

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