Oral pefloxacin in the treatment of CAPD peritonitis

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Summary

Continuous ambulatory peritoneal dialysis (CAPD), a widely used replacement therapy for end stage renal failure, is frequently complicated by bacterial peritonitis. The infecting organisms are mainly staphylococci and gram negative aerobes. Pefloxacin is a fluorinated quinolone with good in-vitro activity against these pathogens. The objective of this open non comparative study is to determine the effectiveness and safety of oral pefloxacin mesylate as a single first line antimicrobial treatment of CAPD peritonitis. 28 episodes of CAPD peritonitis were treated with a stat dose of pefloxacin 800 mg. followed by 400 mg. 12 hourly for about 15–18 days. A pefloxacin sensitive organism was isolated in 17 episodes. 11 episodes were culture negative. Treatment results showed a cure in seventeen (60.7%), no treatment response in seven (25%), and relapses in four (14.2%). Side effects encountered were not serious except for one incident of a generalized seizure.

We conclude that oral pefloxacin is convenient, safe and effective enough as a single first line antimicrobial treatment for CAPD peritonitis.

Key words: Peritoneal dialysis, Peritonitis, Pefloxacin.

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is now a widely used replacement treatment for end stage renal failure[1-4]. However, peritonitis remains a frequent complication, often resulting in increased morbidity, hospital visit and stay, and on occasions, the termination of CAPD[5-7]. Various antibiotic regimens have been shown to be effective for the treatment of CAPD peritonitis[8-10].

At the University Hospital in Kuala Lumpur (UHKL), our usual treatment for CAPD peritonitis was intraperitoneal cefuroxime and an aminoglycoside (gentamicin from 1980 – 1988, netilmicin from 1989–1990). The intraperitoneal antibiotics were continued for at least seven days after the peritoneal fluid had cleared. Treatment was then continued with an appropriate oral antibiotic for a further fourteen days. This extended treatment regimen requires prolonged and probably unnecessary hospital stay in a majority of the cases.

Pefloxacin, a fluorinated quinolone, has a broad antimicrobial spectrum that covers most of the causative organisms usually encountered in CAPD peritonitis[11-14]. It achieves good intraperitoneal concentrations even when administered orally[15]. These properties should make pefloxacin an effective and convenient first line antimicrobial for the treatment of CAPD peritonitis. We report here our results with oral pefloxacin in the treatment of CAPD peritonitis.

Material and Method

During the period from August 1988 to January 1990, sixty-one episodes of CAPD peritonitis were diagnosed at the UHKL. With written patient consent, thirty (49%) episodes occurring in twenty patients were treated with oral pefloxacin and they provided the material for this study. Men and women between the ages of 18 to 70 years with a diagnosis of "peritonitis" were entered into the study.

Excluded from the study were twenty-one episodes where written consent was not obtained. Nine other episodes were excluded because antibiotic treatment had already been started. The remaining one did not fulfill the age criteria.

The trial design was an open and non comparative one. The initial turbid peritoneal effluent was sent for microscopic examination and culture. Oral pefloxacin was adminstered as a loading dose of 800 mg. followed by 400 mg. 12 hourly. Culture and sensitivity results were reviewed at 48 hours. Culture negative cases were included in the study but resistant cases were not. Assessment for "treatment response" was made at 96 hours. Treatment was continued for a further fourteen days after achieving "treatment response". Patients were reviewed daily for the occurrence of any side effects. Assessment was again made at the end of treatment and at follow-up two weeks later. All treatment failures were treated with appropriate intraperitoneal antibiotics (which included ceftazidime and vancomycin).

Definitions

"Peritonitis" was diagnosed when the turbid peritoneal effluent showed a white cell count of >100/ul and of which >50% were polymorphonuclear leucocytes. "Treatment response" was defined as clearing of peritoneal effluent (<100 WBC/ul) with relief of peritonitis symptoms. A "cure" was treatment response with culture-negative effluent at the end of treatment and at follow up. All events other than cure were deemed to be "failures". This included "no response," "relapse" and "drop-out." "No response" referred to the inability to achieve or sustain treatment response within 96 hours of initiating treatment. "Relapse," for those initially culture positive, referred to recurrence of peritonitis caused by the same organism, during treatment or within two weeks of stopping treatment. For those initially culture negative, relapse referred to recurrence of peritonitis during treatment or within two weeks of stopping treatment, irregardless of peritoneal effluent culture results. A "dropout" was an incident when the trial drug had to be substituted by another drug because of unacceptable side effects.

Results

Of the thirty episodes of peritonitis treated with pefloxacin, eleven (36%) were culture negative. Of the positive cultures, (Table I), two isolates, *Corynebacterium* and *Micrococcus* species were pefloxacin resistant (MIC > 16 mg/1). These were withdrawn from the study, leaving twenty-eight cases for final analysis. One episode was due to an unusual combination of *S. epidermidis* and *Acinetobacter* species, while another yielded a methicillin resistant but pefloxacin sensitive (MIC 2mg/1) *S.epidermidis. Pseudomonas* and fungal organisms which were not infrequently encountered in CAPD peritonitis were not isolated in this study group. Table II shows the overall cure rate of 60.7% with pefloxacin. Of the eleven failed cases, seven were subsequently cured with intraperitoneal antibiotics (Table III). The remaining four required catheter removal to achieve eventual cure (Table

III). Included was the patient with methicillin resistant *S. epidermidis* peritonitis and concomitant catheter tract infection which did not respond to intraperitoneal vancomycin.

Table I
Results of peritoneal fluid cultures

Isolates	Number
Staphylococcus epidermidis	7
Staphylococcus aureus	4
Acinetobacter spp	3
Enterobacter spp	3
Alcaligenes sp	1
Corynebacterium sp*	1
Micrococcus sp*	1
Negative cultures	11
Total	31

pefloxacin resistant organisms excluded from the study

Table II
Treatment outcome of CAPD peritonitis with pefloxacin

	Culture positive		Culture negative		Overall	
Cure	11		6		17	(60.7%)
Failure						
relapse	1		3			
no response	4		2			
dropout*	1		0			
Subtotal	6		5		11	(39.3%)
Total	17	(60.7%)	11	(39.3%)	28	(100%)

Patient discontinued pefloxacin treatment because of recurring dizziness.

Minor adverse events consisting of nausea, vomiting, myalgia and lethargy were noted in ten (33%) of the patients. There were two incidences of drug side effects resulting in drug withdrawal. In one case, there was severe giddiness and in the other, a generalized seizure.

Discussion

The infective organisms isolated in our series of peritonitis reflect the usual range seen with CAPD peritonitis[12,16,17]. These organisms have shown good in vitro sensitivity to pefloxacin (87% had pefloxacin MICs <4mg/1). The *Corynebacterium* and *Micrococcus* species isolated were not usual causative pathogens associated with CAPD peritonitis[18]. The culture negative peritonitis episodes

were difficult to analyse. Many of our outstation patients not infrequently start peritoneal lavage at home and also omit bringing the original turbid dialysate fluid when they come to hospital. This practice is thought to increase our incidence of culture negative peritonitis. We also did not attempt to isolate anaerobes from the peritoneal fluid. It is possible that the two culture negative cases (Table III) which did not respond at all to either pefloxacin or intraperitoneal cefuroxime, netilmicin or vancomycin were anaerobic bacterial peritonitis although colonic diverticular diseases and intestinal perforations were not seen in them. They were cured only after removal of the peritoneal catheter.

Table III
Outcome of treatment failures

	Cure with intraperitoneal antibiotics		Failed intraperitoneal antibiotics	
Culture positive				
dropout	1	(Acinetobacter)	0	
relapse	1	(S. epidermidis)	0	
no response	3	(S. aureus) (Enterobacter) (Alcaligenes)	1	(S. epidermidis)
Culture negative				
relapse	1	(Klebsiella)	1	(Acinetobacter)
	1	(S. epidermidis)		
no response	0		2	
Total	7		4	

The culture negative peritonitis had a higher pefloxacin failure rate (45.5%) when compared to the culture positive peritonitis (35.3%). However, this did not reach statistical significance. It also had a higher catheter removal rate of 27% compared to 5% in the culture negative peritonitis. As the infective organisms in culture negative peritonitis were unknown, treatment with appropriate antimicrobial agent could not be ensured.

Our overall cure rate of 60.7% (Table II) showed that oral pefloxacin is effective as a single antimicrobial agent for the treament of CAPD peritonitis. Rose et al[19] using an almost similar oral pefloxacin treatment protocol obtained a cure rate of 47% in their seventeen peritonitis episodes. Their high failure rate (9 of 11) in the gram positive peritonitis led to their caution against using pefloxacin treatment for such cases. Antibiotic resistance was not the main reason for treatment failure in the paper. We were unable to explain this difference in treatment response. Denis et al[20] reported a cure rate of 66.7% in their fifteen cases of CAPD peritonitis treated with intravenous and oral pefloxacin. Chan et al[21] used oral ofloxacin, another quinolone, and achieved a cure rate of 83.3% in the 18 episodes reported.

Some intra-peritoneal antibiotic protocols have achieved cure rates of about 80% or more (12,16,17,22,23). These authors have used combinations of second or third generation cephalosporins,

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aminoglycoside and vancomycin. These are very potent but costly antibiotics and their intra-peritoneal usage requires extra skilled care and an extended hospital stay unless the patients can be taught to administer the antibiotics themselves. These regimens are similar to our second line or "rescue" regimen.

Our lower cure rate with oral pefloxacin could also be accounted for by a probable difference in the definition of "cure" which was not defined in the above reports. We had three patients (Table III), who "relapsed" within two weeks of stopping oral pefloxacin and were therefore considered as "failures". They were treated with intraperitoneal antibiotics (although the organisms were still sensitive to pefloxacin) and were cured. Another patient (Table III) with previous aminoglycoside-induced ototoxicity refused to continue with pefloxacin because of recurring dizziness. At the time of stopping pefloxacin, he was already clinically cured of peritonitis. Including these four as "cure" would have produced a cure rate of 75%.

Another reason for a lower cure rate with oral pefloxacin might be the low peritoneal drug level which exists immediately after a bag exchange. As the new bag of peritoneal fluid contains no antibiotics, it will take some time before the drug level in the peritoneal fluid reaches bactericidal level. Our unpublished data showed that peritoneal fluid pefloxacin level may be below 0.5 mg/1 for the first half hour after bag exchange even when the serum levels are > 5 mg/L. It is not known if these repeated low drug concentration periods, which take place with each bag exchange, and occur four to six times daily in CAPD, would adversely affect the outcome of treatment.

The side effects encountered were minor and subjective, making it especially difficult to evaluate in renal failure patients on dialysis. Eight patients were entered into the pefloxacin trial on more than one occasion. Three of them did not report any adverse reaction at all. Three other patients reported adverse reactions which however did not recur on subsequent usage. Included was the patient who had stopped pefloxacin treatment because of severe dizziness. Only two patients had the same complaint of nausea and vomiting on using pefloxacin the second time. These two symptoms were, however, quite common in CAPD peritonitis itself.

The one episode of seizure was the only serious adverse reaction noted during the trial period. The event occurred after eleven days of pefloxacin treatment in a 58-year-old woman who had no history of epilepsy. No seizure recurrence was noted after stopping pefloxacin. There was no peritonitis-related death recorded during the duration of the study.

Blood pefloxacin levels were not measured in our patients. We were therefore unable to correlate the side effects and treatment outcomes with pefloxacin blood levels.

Conclusion

The treatment of CAPD related peritonitis with oral pefloxacin achieved a cure rate of 60.7%. Pefloxacin provided an adequate spectrum of antimicrobial coverage for the infective organisms isolated in our series of CAPD peritonitis. Intra-peritoneal antibiotics remained an effective second line or "rescue" treatment in the few cases with resistant organisms and in those who failed to respond to pefloxacin despite in vitro sensitivity. A pefloxacin serum-peritoneal fluid pharmacokinetics study is now required to help define the best time interval for bag exchanges in CAPD peritonitis when oral pefloxacin is used for treatment.

Side effects encountered were minor and subjective in nature and frequently non-recurring with subsequent rechallenge. Oral pefloxacin obviates the need to introduce antibiotics into the dialysis bags. This greatly reduces the number of times the "closed" dialysis fluid flow system is breached. Oral

treatment is also convenient and it reduces the need for hospital stay. We conclude therefore that oral pefloxacin is safe, convenient and effective enough for use as a single first line antimicrobial for the treatment of CAPD peritonitis.

Acknowledgements

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