Serum C-reactive protein concentration in the management of infection in patients treated by continuous ambulatory peritoneal dialysis

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SUMMARY In a prospective study over 21 months, serum C-reactive protein (CRP) concentration was measured serially in 39 consecutive patients undergoing continuous ambulatory peritoneal dialysis. All patients with peritonitis mounted a CRP response, and the height of the response correlated well with the severity and extent of the peritoneal damage. Patients who recovered uneventfully after antimicrobial treatment showed a prompt fall in CRP from its peak value towards normal. In contrast, each patient in whom the serum CRP value remained raised after antimicrobial treatment had a complicated course. During routine outpatient follow up the serum CRP value remained within the normal range in the absence of intercurrent complications.

These results, together with the commercial availability of rapid and precise assays for CRP, indicate that serial CRP measurements may be useful in monitoring the efficacy of antimicrobial treatment during episodes of peritonitis and in the recognition of intercurrent complications in patients undergoing continuous ambulatory peritoneal dialysis

Peritonitis is the major complication of continuous ambulatory peritoneal dialysis (CAPD) and results in considerable morbidity in some patients.¹⁻⁴ Recurrent episodes may limit the use of this treatment by destroying the integrity of the peritoneal lining or resulting in widespread adhesions. Early diagnosis and prompt antimicrobial treatment of intraperitoneal sepsis are therefore imperative. Other important problems in the management of these cases include the early assessment of the efficacy of antimicrobial treatment and determining the duration of their use in treating this common complication.

Major rises in the serum concentration of C-reactive protein (CRP), the classic acute phase protein, are seen in most bacterial infections. The extent of the increase usually corresponds reasonably well with the severity of the infection.^{5,6} After successful antimicrobial treatment the serum concentration of CRP rapidly falls back towards the normal range. Methods are now available for the rapid and precise estimation of serum CRP concentration. Serial measurements are particularly useful in monitoring the response to treatment of infec-

tions in cases that are not readily accessible to standard microbiological techniques, such as infections of the central nervous system⁷⁻⁹ and neonatal septicæmia.¹⁰

These features suggest that serial measurement of serum CRP in patients undergoing CAPD may be useful as an objective index of the efficacy of antimicrobial treatment of peritonitis and as a guide to determining the duration of treatment. We report here a prospective study of the serum CRP values in 39 consecutive patients undergoing CAPD.

Patients and methods

PATIENTS

Thirty nine consecutive patients undergoing CAPD were studied prospectively between September 1982 and June 1984. Twenty two were male and 17 female, with a mean age of 47 years, range 21-69. There were 23 Caucasian, 12 Asian, 2 West Indian, 1 Iranian, and 1 Phillipino patients. During the study 19 patients had renal transplants (15 cadaveric and 4 live donors), of whom two later returned to CAPD, and three patients went on to haemodialysis. Eighteen patients continued on CAPD throughout the study. The mean duration of study for all 39 patients was 9.3 months (range 1-21).

SERUM MEASUREMENT

Blood was taken for estimation of the serum CRP concentration from each patient when seen in the CAPD outpatient clinic and at least three times a week during inpatient antimicrobial treatment for peritoneal infection. Serum CRP was assayed by electroimmunoassay, as described elsewhere.¹¹ Intra-assay and inter-assay replicates gave results with a coefficient of variation of less than 10%. Ninety nine per cent of normal healthy people have CRP concentrations of less than 10 mg/l.¹²

PERITONEAL INFECTION

Peritonitis was diagnosed when the peritoneal dialysis fluid effluent became cloudy in patients with or without overt clinical signs and symptoms of peritonitis. Microbiological tests on peritoneal fluid were performed in the routine clinical laboratories. Treatment with cefuroxime (250 mg/l of dialysis fluid) was given to all patients before the results of peritoneal fluid culture were known. Patients with peritonitis were initially admitted to hospital for two to five days, and then treatment was continued at home (total course, 14 days). Other antimicrobial drugs were used, depending on bacterial sensitivities.

STATISTICAL ANALYSIS

Differences in results of the various objective measurements between groups of patients were sought using Wilcoxon's rank sum test.

Results

SERUM CONCENTRATION OF CRP IN PERITONITIS

During the study serum CRP concentrations were measured during 30 episodes of peritonitis in 18 individuals undergoing CAPD. All patients with peritonitis mounted a CRP response, the peak value (median 69 mg/l, range 15–225) occurring two to four days after the onset of abdominal symptoms or signs. There was no significant difference in the peak CRP concentrations between peritonitis caused by *Staphylococcus epidermidis* (median 82 mg/l, range 61–161), *Staph aureus* (median 118 mg/l, range 76–193), or Gram negative bacteria (median 63 mg/l, range 34–225) (Fig. 1). In contrast, episodes of peritonitis where no bacteria were cultured from the peritoneal fluid (culture negative infection) had a significantly lower peak serum CRP value (median 42 mg/l, range 15–119) ($p < 0.01$) (Fig. 1). There was one episode of *Candida albicans* peritonitis (not shown in Fig. 1), where the peak serum CRP concentration was 217 mg/l.

After the two episodes of peritonitis associated with the highest peak serum CRP concentration

Fig. 1 Peak serum C-reactive protein (CRP) concentrations in 29 episodes of peritonitis in 18 patients undergoing continuous ambulatory peritoneal dialysis. Horizontal bars are medians. Ninety nine per cent of normal healthy individuals have serum CRP values below 10 mg/l (broken lines).

(*Escherichia coli*, 225 mg/l; *Cand albicans*, 217 mg/l), the patients were unable to continue CAPD because of widespread adhesions causing mechanical problems.

During the study there were two episodes of localised infections at the site of exit of the peritoneal catheter from the abdominal wall, and the peak serum CRP concentrations were 10 and 15 mg/l.

CHANGES IN SERUM CRP CONCENTRATION DURING SUCCESSFUL TREATMENT OF PERITONITIS

In all patients serum CRP concentrations started to fall within 48 h of the start of antimicrobial treatment that proved successful. The mean time after the start of treatment for the serum CRP concentration to return to normal in 19 episodes of peritonitis was eight days (range 5–11). In the remainder of the

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successfully treated cases, the serum CRP concentration had not returned to normal when the patients were sent home, but all showed an uninterrupted fall before their discharge.

There were no differences in the time for the serum CRP concentration to fall to normal in episodes of peritonitis caused by *Staph epidermidis* (mean 7 days, range 5–9; n = 5), *Staph aureus* (mean 9.5 days, range 8–11; n = 2), Gram negative bacteria (mean 8 days, range 6–10; n = 4) and culture negative infection (mean 8 days, range 5–11; n = 8).

CHANGES IN SERUM CRP CONCENTRATION DURING TREATMENT OF PERITONITIS WITH COMPLICATIONS

In three episodes of peritonitis the serum CRP concentration did not return to normal within 7–10 days of the introduction of antimicrobial treatment, and in two cases there followed a second episode of peritoneal infection. In one case a different pathogen was isolated from the dialysis fluid during the second episode, which then responded to a course of the appropriate antimicrobial drug. There was clinical improvement and the serum CRP concentration returned to normal. In the second case the same organism (*Staph aureus*) was isolated in the second as in the first episode of peritonitis. A second course of antibiotics was again unsuccessful, and only after the peritoneal catheter was changed did the infection resolve completely and the serum CRP concentration return to normal.

In the third case (Fig. 2) there was no clinical improvement or fall in serum CRP concentration after the introduction of cefuroxime for culture negative peritonitis. Despite the addition of vancomycin, the serum CRP value continued to rise. A subsequent dialysis fluid culture revealed *Pseudomonas aeruginosa*, and with the introduction of gentamicin treatment there was a prompt fall in the serum CRP concentration and clinical improvement.

SERUM CRP CONCENTRATION DURING ROUTINE OUTPATIENT FOLLOW UP

Serial serum CRP values were obtained on each occasion that 37 patients attended the CAPD outpatient clinic. Of these, three showed persistently raised serum CRP concentrations in the absence of any peritoneal infection. Two of these patients complained of a dull ache at the site of their failed renal transplant graft, which was thought to be secondary to chronic rejection. The serum CRP concentrations during these five month periods varied between 21 and 50 mg/l and 56 and 88 mg/l in the respective patients. One patient's renal graft was later

Fig. 2 Serial serum C-reactive protein (CRP) concentrations in a 36 year old man who developed peritonitis while undergoing continuous ambulatory peritoneal dialysis. Culture of peritoneal dialysis fluid (PDF) was initially negative, and he received intraperitoneal cefuroxime. His serum CRP concentration continued to rise, however, despite intravenous vancomycin on day 7. On day 9 *Pseudomonas aeruginosa* was cultured from the peritoneal dialysis fluid. After the introduction of intraperitoneal gentamicin, the serum CRP fell rapidly to normal within nine days.

removed, and the serum CRP value returned to normal.

In the third case, high serum CRP concentrations (median 105 mg/l, range 27–208) over eight months were noted in an Indian patient for no apparent reason. At operation for the insertion of a cadaveric kidney enlarged iliac lymph nodes were noted. The renal transplant was cancelled, and biopsy and culture of the nodes revealed *Mycobacterium tuberculosis*. After antituberculous chemotherapy the serum CRP value returned to normal within two months.

In the remaining 34 patients, 93% of serial CRP measurements (mean number of assays per patient = 8, range 1–23) remained within the normal range in the absence of other intercurrent complications (Fig. 3).

Discussion

The results of this study show that peritonitis in patients undergoing CAPD is a potent stimulus to CRP production. The increase in the circulating concentration of CRP is an entirely non-specific response to most forms of infection, inflammation, and tissue damage⁵ and is not therefore diagnostic of peritoneal infection per se. The height of the CRP response, however, does correlate well with the sev-

Fig. 3 Serum C-reactive protein (CRP) measurements in 34 patients taken when they routinely attended the continuous ambulatory peritoneal dialysis clinic. The results are expressed in percentages, and the shaded areas are those values outside the normal range.

erity and extent of the tissue damaging process in a number of infectious, inflammatory, and neoplastic disorders.⁵ In this respect, it is interesting to note in this study that in the two cases of peritonitis associated with the highest CRP values, the patients were unable to continue with CAPD owing to irreversible peritoneal damage. Furthermore, cases of culture negative peritonitis had a significantly lower peak CRP response than infections where a pathogen was cultured from the dialysis fluid. Such culture negative cases account for 31–90% of episodes of peritoneal infection in these patients.² The low isolation rate is thought to be related to the small number of bacteria in the infected dialysis fluid. The lower CRP response in these cases in our study suggests that the degree of peritoneal inflammation and damage is also less in this group.

Having made a diagnosis of peritonitis in a patient undergoing CAPD, there are considerable differences of opinion on both the choice of antimicrobial drug and the duration of its use.^{1,2} Recurrent infections are common in some patients. Whether they are due to relapse or to reinfection is usually difficult to determine. This distinction is, however, important for estimation of the success rate of the antimicrobial treatment. The results of the present study, albeit in only a small number of patients, suggest that serial monitoring of serum CRP concentrations may help to resolve these dilemmas. A successful outcome to antimicrobial treatment was in all cases associated with a fall in serum CRP values within 48 h of the start of treatment, and the value returned to normal within 5–11 days. In contrast, in two

patients the serum CRP values did not fall promptly with antimicrobial treatment, and an organism resistant to the first line antimicrobial drug was later found. In another case recurrent peritoneal infections with the same bacteria were noted, and on each occasion the serum CRP was still raised 10 days after the start of antimicrobial treatment. Only when the peritoneal catheter was replaced did the recurrent infections stop and the serum CRP level return to normal. This suggests that in this case the patient was having recurrent relapses owing to ineffective treatment of a presumed focus of infection within the catheter, rather than having further reinfections.

Patients undergoing CAPD are immunosuppressed by virtue of their renal failure and are therefore more at risk of systemic infections, which may be difficult to detect or diagnose or involve unusual organisms.⁴ Serum CRP measurement is known to provide a useful screening test in outpatient practice in specialties such as rheumatology,¹³ gastroenterology,¹¹ and nephrology^{14,15} and at routine medical examinations. The value is not influenced by the many factors that affect measurement of the erythrocyte sedimentation rate.¹⁶ A raised serum CRP concentration should therefore always alert the physician to the presence of an organic tissue damaging disease process. This point is emphasised in our study by the Indian patient with persistently raised serum CRP values over eight months, in whom abdominal tuberculosis was subsequently found. Routine screening of the serum CRP concentration in this group of patients should therefore provide a rapid sensitive, and precisely quantifiable non-specific index of the patient's well being.

The above conclusions suggested by this study must be confirmed by further prospective investigations in which stat CRP values are provided to the clinicians throughout the course of the patient's management. The technology for rapid precise assay of serum CRP is readily available commercially and, although not used in the present study, the methods of homogeneous enzyme or fluoroimmunoassay (Syva Co, Palo Alto, California, USA) or rate immunonephelometry (Beckman Instruments Inc, Fullerton, California, USA) are capable of providing results within 1 h of obtaining the serum. General access to such methods should greatly facilitate the application of serum CRP measurements in this and related areas of clinical practice.

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