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Procalcitonin in patients with acute and chronic renal insufficiency

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Summary. *Background:* Bacterial infections are associated with a high morbidity and mortality rate in patients with acute and chronic renal failure. Because C-reactive-protein (CRP) is elevated in many patients with renal failure, even in the absence of infection, procalcitonin (PCT) might be useful for the detection of systemic bacterial infections. This cross-sectional observation study measured PCT and CRP in several groups of patients with various types, degrees and treatments of kidney diseases, including patients with sepsis treated with renal replacement therapy.

Patients and methods: We determined PCT and CRP in 85 renal patients with different stages and treatments of renal insufficiency: chronic renal failure (CRF) n = 23, patients undergoing continuous ambulatory peritoneal dialysis (CAPD) n = 20, patients undergoing hemodialysis therapy (HD) n = 42 and in a group of 40 patients with septic conditions, including 20 patients with acute renal failure (ARF). The infectious status of the patients was monitored.

Results: PCT in serum (reference value in healthy controls < 1 µg/l) was within the normal range in patients with CRF and in patients on both short-term HD (< 1 year) and long-term HD (> 1 year) (median of 0.25 µg/l and 0.61 µg/l). However, PCT was elevated in patients on CAPD (median of 1.18 µg/l). In patients with sepsis, PCT was massively elevated in both the presence and absence of ARF. In contrast, CRP (reference value < 5 mg/l) was markedly increased in patients undergoing short- and long-term HD (medians of 14.5 and 51.1 mg/l) but not in patients on CAPD. In patients with CRF and systemic bacterial infections, both PCT and CRP were markedly elevated (median PCT 63 µg/l, CRP 130 mg/l) but, in contrast to PCT, CRP values overlapped in infected and non-infected patients. There was no relevant decrease in plasma concentrations of PCT by hemofiltration or hemodialysis in patients with sepsis.

Conclusion: With the exception of CAPD patients, PCT levels were not significantly affected by renal diseases or treatments but were markedly elevated in the presence of infections. Thus PCT is a valuable marker for early diagnosis of systemic bacterial infections in patients with CRF or patients undergoing HD. In contrast, CRP is elevated in several groups with renal diseases and has low specificity for the diagnosis of bacterial infections.

Key words: Procalcitonin, C-reactive protein, renal failure, hemodialysis, peritoneal dialysis, inflammation.

Introduction

Infections are responsible for high morbidity and mortality in patients with renal failure. Sepsis is one of leading causes of death in patients undergoing hemodialysis therapy (HD), with a mortality rate of 12% [1, 10, 32]. Conventional laboratory parameters for the detection of infections, such as white blood cell (WBC) count, erythrocyte sedimentation rate, and C-reactive protein (CRP), may be affected by the underlying disease, uremia, extracorporeal treatment or immunosuppressive drugs [10, 11]. Parameters such as WBC may be decreased; others such as the erythrocyte sedimentation rate, CRP or other acute-phase proteins may be non-specifically increased [1, 3].

Thus, alternative parameters for the discrimination of infections and other inflammatory events are desirable. Procalcitonin (PCT) is a 116-amino-acid precursor peptide of calcitonin (CT) with a molecular weight of 13,600 Da. CT is almost exclusively synthesized and secreted by C-cells of the thyroid [2, 8]. In plasma and serum of healthy persons, PCT is undetectable or only detectable in low concentration (< 0.1 µg/l). In cases of sepsis, PCT levels can increase to 1000 µg/l with a parallel increase in cytokines TNF-α, IL-1 or IL-6 [1, 3, 4, 7]. The origin, function, secretion and elimination of PCT in infections and sepsis remain unknown. The synthesis and release of PCT is induced by bacterial and, to a lesser extent, by parasitic and fungal infections [2, 9, 31]. In viral, neoplastic or other non-infectious inflammatory diseases there is no increase of PCT or only a weak increase (< 2.0 µg/l) [15–17]. Recent findings have demonstrated that PCT is a mediator for early infection [14]. Compared with other parameters such as CRP or WBC routinely used for monitoring inflammation, determination of PCT has distinct advantages in the diagnosis and follow up of severe bacterial infections.

In patients on HD, potential removal of PCT with high-flux hemodialysis membranes could reduce its value

as an indicator of infection [27]. On the other hand, synthesis of PCT may possibly be stimulated by inflammatory activity triggered by a variety of metabolic and immunological conditions associated with uremia or the dialysis itself, as has been reported for some cytokines [21]. HD per se might change PCT serum levels with no regard to the presence, nature and quality of infection.

There is only limited information, in part contradictory, on the impact of various types of renal failure and/or of renal replacement on plasma PCT concentrations [12, 27, 28, 34, 33]. The aim of the study was to assess PCT and CRP plasma concentrations and the infectious state in several groups of patients with renal failure undergoing various types of renal replacement therapy.

Patients and methods

Patients

A total of 125 patients with renal insufficiency and different types of treatment as listed below were studied (Table 1). These patients were divided into five groups. Apart from renal insufficiency, other diseases, in particular liver disease, jaundice, malignant neoplasma and immunological diseases, as well as enforced physical activity were absent in patients in groups 1–4. The infectious status of patients was monitored using regular leukocyte counts in blood and dialysate. In order to compare the validity of prediction of sepsis using PCT measurement in renal patients, we included group 5 (S) patients with sepsis with and without hemofiltration treatment. PCT is eliminated by hemofiltration and was therefore sampled before HD. We examined the filtration of PCT by HD and hemofiltration in individual patients with sepsis.

Patients in groups 1–4 were in outpatient care; patients in group 5 were treated in the intensive care unit.

Group 1 (CRF) consisted of 23 patients (16 m, 7 f) with chronic renal impairment who had not received dialysis treatment. The median age of these patients was 53 years (31–68 y). These patients had a serum creatinine level of more than 150 µmol/l (median 218; range 133-544 µmol/l). The renal insufficiency was known for a median of three years (1–38 y).

Group 2 (CAPD) consisted of 20 patients (13 m, 7 f) on continuous ambulatory peritoneal dialysis (CAPD) for more than six months. The median age of these patients was 43 years (22–57 y). In these patients renal insufficiency was known for a median of three years (0.5–7 y). Their median creatinine level was 967 µmol/l (425–1756 µmol/l). No recent peritonitis was known.

Group 3 (HD < 1) consisted of 20 patients (11 m, 9 f) with HD for less than a year. The median age of this group was 69 years (45–89 y). Their median time of HD was 48 weeks (8 days – 11.5 months). Their median creatinine level was 614 µmol/l (271–1230 µmol/l).

Group 4 (HD > 1) consisted of 22 patients (12 m, 10 f) who were dialysed for more than a year. The median age of this group was 69 years (33–79 y). The median time of HD for these patients was four years (1.5–16 y). Their median creatinine level was 857 µmol/l (550–1158 µmol/l).

Group 5a: (S) consisted of 20 patients with sepsis (10 m, 10 f) and acute renal failure (ARF), defined as having positive systemic inflammatory response syndrome (SIRS) criteria and bacteremia. The median age of this group was 57 years (45–67 y). The median creatinine was 298 µmol/l (167–451 µmol/l).

Group 5b: (S) consisted of 20 patients with sepsis without ARF (10 m, 10 f), defined as having positive SIRS criteria and bacteremia. The median age of this group was 56 years (48–72 y). The median creatinine was 115 µmol/l (67–135 µmol/l).

The Department of Clinical Chemistry received the clinical data of all patients and the laboratory samples in an anonymous form.

Measurements

Age, sex, duration of HD procedure, type of dialysis membrane, mean blood flow and ultrafiltration rate, weight

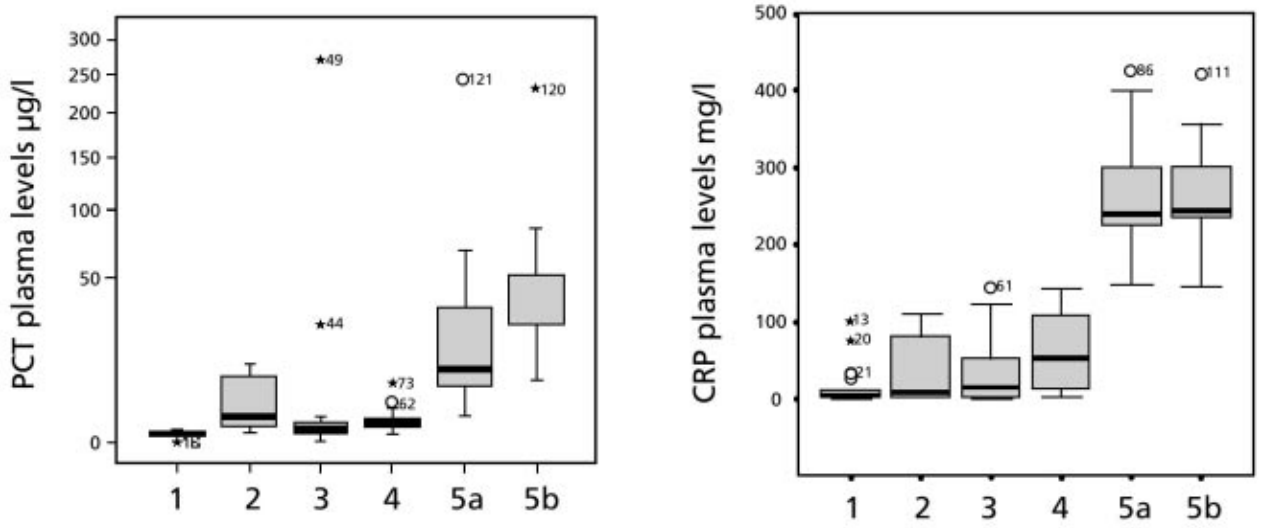

Fig. 1. Box and whisker plots of CRP and PCT levels in four groups of patients with renal insufficiency requiring different treatment regimens and two groups of patients with sepsis, one with and the other without renal insufficiency. Group 1 = renal failure without dialysis (CRF). Group 2 = CAPD. Group 3 = short-term dialysis < 1 year. Group 4 = long-term dialysis > 1 year. Group 5a = sepsis with ARF, Group 5b = sepsis with no ARF. The box shows the area with 50% of all average values. The vertical length of the box is the interquartile range (IQR). The T-beam shows the smallest and the largest value. Values outside these areas are exposed and specifically marked

Table 1. Demographic data of all patients

Variable	Group 1	Group 2	Group 3	Group 4	Group 5a	Group 5b
n Patients	23	20	20	22	20	20
Sex m/f	16/7	13/7	11/9	12/10	10/10	10/10
Age* years	53 (31–68)	43 (22–57)	69 (45–89)	69 (33–79)	57 (45–67)	56 (48–72)
Creatinine* µmol/l	218 (133–544)	967 (425–1756)	614 (271–1230)	857 (550–1158)	298 (167–451)	115 (67–135)
PCT* µg/l	0.1 (0–0.2)	1.1 (0.1–11.5)	0.3 (0–270.5)	0.6 (0.1–6.1)	9.9 (1.3–245)	35 (7–231)
CRP* mg/l	3.8 (1–102)	8.5 (2–110)	14.5 (0–144)	51 (2–143)	240 (148–425)	244 (145–421)
Sepsis	no	no	no	no	yes	yes
Treatment	Ø HD	CAPD	HD < 1	HD > 1	HD	Ø HD

* Median values and ranges are shown.

before and after HD, and type of infection were recorded for each patient. Severe infections were defined as previously published according to clinical and radiological criteria and in each case were confirmed by positive blood cultures or the respective microbiological proof of pathogenic microorganisms. Sepsis was defined as microbiologically confirmed infection in addition to at least two of the following criteria: WBC $> 12.0 \times 10^9$/l or temperature > 38 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or $pCO_2 < 4.3$ kPa.

Two blood samples (10 ml serum tubes) were taken from all HD patients, one before and one after HD treatment. Only one sample was taken from the other patients. The blood samples were collected in test tubes containing no anticoagulant or preservative and, after being allowed to clot, were centrifuged and stored at –60 °C. Specimens were thawed only once, and were assayed within eight hours of thawing.

Creatinine was determined on a Dade-Behring Dimension Analyser using a kinetic Jaffé method from Dade-Behring (DADE Behring Vertriebs GmbH & Co., Liederbach, Germany). The reference range for this method is 42–106 µmol/l.

CRP was determined using the Dade-Behring turbidimetric CRP assay on a Dade-Behring Dimension Analyser. In healthy controls the upper reference limit for this method is 5 mg/l.

PCT was determined using the LUMItest PCT kit (Brahms Diagnostica GmbH. Berlin, Germany) on a Behring Berilux 400 Analyser. In healthy controls the upper reference limit for this method is 0.5 µg/l. This assay is a sandwich-type chemiluminescence assay using an antibody against the calcitonin epitope of PCT (tracer antibody) and an antibody against the katacalcin epitope (capture antibody). Functional sensitivity of the assay, defined as the concentration determined with an interassay CV of 20%, is 0.3 µg/l. The interassay CV within the observed clinical range is 5–10%.

A Multiflow 60 filter (Hospal, France) was used for hemofiltration and an F6HPS membrane (Fresenius, Germany) for HD. PCT was analysed in plasma and sampled before and after the filter/membrane and in the final eluate.

Statistica for Windows (StatSoft, Inc., Tulsa) was used for statistical calculations and plotting of data.

Results

Two patients had to be excluded from group 3 because they had human anti-mouse antibodies (HAMA) leading to false high values for PCT. These patients had undergone renal transplantation and rejection treatment with mouse antibodies.

The PCT and CRP plasma values of all groups are shown in Fig. 1. PCT levels were significantly elevated in CAPD patients but not in patients with CRF or in those on short-term or long-term HD. The highest PCT and CRP plasma values were observed in group 5 (S). There was no correlation between PCT and CRP levels (correlation coeff. r = 0.00034, 95% confidence interval from –0.45 to + 0.45). In patients with systemic bacterial infections, peak PCT levels reached 270 µg/ml, but there was no relationship between PCT levels and the seriousness of the infection or the type of microorganism. After starting antibiotic therapy, PCT levels fell constantly (Fig. 2), in parallel with the clinical recovery.

CRP levels were significantly higher in renal patients with systemic bacterial infections ($p < 0.001$) than in groups 1–4, and peak levels were intensified, as for PCT. There was an overlap of CRP values between groups 5a and 5b (Fig. 2). The specificity and sensitivity of PCT were both 94% for bacterial infections in renal diseases in all patients. The corresponding specificity and sensitivity for CRP were 49% and 98%.

In-out concentration differences in the hemofiltration/dialysis analysis showed no appreciable extraction ratio. We measured plasma PCT (µg/l) before and after the hemofiltration filter/HD membrane and in eluate/dialysate in two patients with sepsis. The PCT concentration was

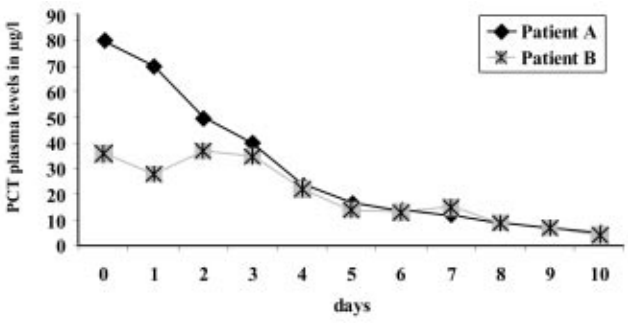

Fig. 2. Time course of PCT values over ten days in two patients after starting antibiotic therapy

32.4 µg/l before the filter/membrane and 32.04 µg/l afterwards. For HD we found PCT 2.58 µg/l before the membrane and 2.35 µg/l afterwards. PCT in the dialysate was 7.29 µg/l in hemofiltration and 0.49 µg/l in HD.

Discussion

The results of this comparative study suggest that in renal failure patients' serum PCT may serve as an accurate marker of systemic bacterial infections or sepsis. PCT is a much better predictive parameter for bacterial infections than CRP, confirming earlier publications that PCT helps to differentiate sepsis from an inflammatory syndrome and therefore helps in recognition and earlier treatment of serious infections in patients with kidney diseases [18, 19] or patients undergoing HD [13, 14].

Unlike CRP, PCT is thought to be specific for bacterial infection and sepsis. However, elevated PCT serum levels are found in the absence of infection or sepsis in patients with renal insufficiency treated with CAPD [13]. It might be speculated that the pressure of intra-abdominal fluid volume and or the dialysis catheter tube might lead to chronic endotoxinemia and hence to moderate PCT elevation. In general, the origin of circulating PCT is not known and the reason for elevation of PCT levels in CAPD patients remains to be elucidated [7]. HD and hemofiltration eliminated PCT from the blood; however, in CAPD the dialysate PCT levels were low [5].

Comparison of patients with different stages of renal functional impairment found no evidence that loss of excretory renal function affected the circulating level of PCT. Moreover, many patients with end-stage renal disease on HD therapy had normal PCT levels. Consequently, the mild increase of mean PCT observed in our patients cannot be ascribed to a decrease in renal excretion of PCT as a result of reduced renal function, but seems to be associated with the release of PCT mediated by uremia or by extracorporeal treatment. There is little information on the accurate location of PCT or the mechanisms responsible for its release [7, 20]. When comparing patients with sepsis with or without ARF (groups 5a and 5b), HD per se did not affect the accuracy of PCT in indicating infection. Obviously HD per se does not significantly stimulate PCT release in sepsis.

Therefore, unlike CRP, PCT remains a valid and specific diagnostic parameter for identifying bacteremia and sepsis in HD patients. All patients with renal insufficiency and sepsis had elevated PCT levels. In contrast, CRP increased up to 10 times above the upper reference limit of 5mg/l in all HD patients, including those without sepsis. Further, some patients showed unexpectedly high levels above 100 mg/l. Although elevated CRP is common among HD patients, we were surprised to see so many values above 50 mg/l. The highest values were observed in chronic HD patients. In contrast, PCT was only slightly raised in some cases on long-term HD. Thus, PCT determination has proven to be a useful diagnostic tool for monitoring infectious events such as shunt sepsis in HD patients but not for CAPD patients. Although the in-out concentration differences show no significant extraction ratio, the dialysate and especially the hemofiltrate contain PCT.

Although the molecular weight of PCT is 13,600 Da and is thus ultrafilterable, PCT, unlike Troponin-T, does not accumulate in renal insufficiency [14]. The renal excretion of PCT does not seem to play a major role in the elimination of PCT [22, 24]. The main elimination pathway is obviously localized in different organs; PCT is most probably extracted by the liver [23].

There is unquestionable indication that bacteria-derived products induce PCT secretion in the neuroendocrine system and in circulating mononuclear cells [11]. In healthy persons, injection of endotoxin from Gram-negative bacteria is responsible for a rapid increase in PCT plasma levels, which reach a maximum six hours after endotoxemia [21–23]. In contrast, PCT did not increase or only increased to a mild degree in viral or localized infections [18, 24]. An increase of PCT plasma levels seems to be part of the cytokine release syndrome and could be triggered by proinflammatory cytokines [21, 25]. Elevated PCT plasma levels have also been described in a non-infectious, post-traumatic SIRS, and after coronary artery bypass surgery [26–28]. Consequently, activation of monocytes by uremia, linked with diminished cytokine clearance or endotoxins from infected dialysate, could be responsible for the small increase of PCT plasma levels in some HD patients. Earlier analysis in chronic HD patients [29] and a study by Herget-Rosenthal et al. [14] pointed out that a serum PCT level of 1.5 ng/ml was an appropriate cut-off in HD patients. Cut-off values of 0.5 and 1.5 ng/ml have also been suggested for distinguishing between bacterial infection and non-infection in patients with normal renal function [18, 19, 30, 35]. In our study, all serum PCT levels in HD patients with infections were significantly above 1.5 ng/ml and there was no coincidence between infected and non-infected patients. CRP was of limited use for the discrimination of inflammatory response and bacterial infection in HD patients.

In conclusion, in patients with renal failure (with exception of patients on CAPD) PCT seems to be much more specific for bacterial infections than CRP. Even though evaluation of PCT plasma levels will not be a substitute for clinical assessment and microbiological examination, it is useful for detecting bacterial infections.

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