Procalcitonin used as a marker of infection in the intensive care unit

Hector Ugarte, MD; Eliezer Silva, MD; Dany Mercan, MD; Arnaldo De Mendonca, MD; Jean-Louis Vincent, MD, PhD, FCCM

From the Departments of Intensive Care (Dr. Ugarte, Silva, Mendonca, and Vincent) and Clinical Chemistry (Dr. Mercan), Erasme University Hospital, Free University of Brussels, Belgium, Belgium.

Address requests for reprints to: Dr Jean-Louis Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. E-mail: jlvincen@resulb.ac.be.

CRITICAL CARE MEDICINE 1999;27:498-504
[Click here for reference links. (18 references linked.)]

Objective: To determine the value of procalcitonin (ProCT) as a marker of infection in critically ill patients.

Design: Prospective, observational study.

Setting: Medicsurgical department of intensive care (31 beds).

Patients: One hundred eleven infected and 79 noninfected patients.

Interventions: None.

Measurements and Main Results: ProCT and C-reactive protein (CRP) concentrations were monitored daily. The best cutoff values for ProCT and CRP were 0.6 ng/mL and 7.9 mg/dL, respectively. Compared with CRP, ProCT had a lower sensitivity (67.6 vs. 71.8), specificity (61.3 vs. 66.6), and area under the receiver operating characteristic curve (0.66 vs. 0.78, p < .05). The combination of ProCT and CRP increased the specificity for infection to 82.3%. In the infected patients, plasma ProCT, but not CRP, values were higher in nonsurvivors than in survivors. Infected patients with bacteremia had higher ProCT concentrations than those without bacteremia, but similar CRP concentrations. ProCT levels were particularly high in septic shock patients.

Conclusions: ProCT is not a better marker of infection than CRP in critically ill patients, but it can represent a useful adjunctive parameter to identify infection and is a useful marker of the severity of infection. (Crit Care Med 1999; 27:498-504)

Key Words: C-reactive protein; inflammatory response; fever; white blood cell count; diagnosis; prognosis; sepsis; septic shock; survival

Although sepsis defines the typical body response to infection, acutely ill patients frequently present signs of sepsis such as fever, tachycardia, hyperventilation, and leukocytosis, even when no infection can be demonstrated. The widespread administration of antibiotics to all such patients carries problems of antibiotic resistance, drug toxicity, and financial considerations. There is a need for effective and accurate biological or biochemical tests to support, or exclude, the diagnosis of infection. Sepsis response...
involves the release of a wide array of mediators, which has led to the suggestion that some of these mediators could be used as markers of infection or sepsis severity [1,2]. However, these same inflammatory agents may be released in association with a variety of diseases such as trauma, pancreatitis, ischemia and reperfusion, and even heart failure in the absence of identified infection [3,4]. In practice, no inflammatory agents are reliable enough to differentiate acute bacterial infection from other types of inflammation and to guide the therapy of infection in critically ill patients.

In addition to the white blood cell (WBC) count, C-reactive protein (CRP) is currently the most widely used parameter to support the diagnosis of infection. CRP is an acute-phase reactant produced by the liver in response to tissue injury or infection [5]. The magnitude of peak CRP values has been shown to be proportional to the amount of damage after tissue injury [6-8]. However, although large increases occur in response to infection, no definite correlation between infection and the change in CRP has been documented [9]. Nevertheless, some authors have demonstrated that CRP may be useful in diagnosing the onset of sepsis in acutely ill patients [9] and in indicating successful treatment [7].

Recently, plasma procalcitonin (ProCT) concentrations have been proposed as an indicator of the presence of infection [10-14]. ProCT concentrations are very low in healthy individuals but have been shown to increase markedly after endotoxin administration in healthy volunteers [15] or during severe systemic infection and septic shock in patients [10]. The exact origin of ProCT in sepsis remains unclear, but its association with the presence and severity of infection make plasma ProCT levels a potentially important additional parameter in the assessment of the critically ill patient.

We sought to further define the value of plasma ProCT concentrations in the diagnosis of infection by measuring parameters of infection (i.e., WBC count, plasma ProCT, and CRP concentrations), daily in acutely ill patients. We also analyzed the relationships between plasma ProCT and CRP concentrations and mortality rate, and between plasma ProCT and CRP concentrations and the presence of shock.

MATERIALS AND METHODS

The study included 205 consecutive adult patients admitted to the intensive care unit (ICU) at the Erasme University Hospital in Brussels, from September 1996 to November 1996 and from January 1 to February 14, 1997 but excluded elective surgical patients without complications. The study was approved by the Institution Ethics Committee and informed consent was waived in view of the lack of need for additional blood sampling. All patients were examined for signs and symptoms of infection at the time of admission and daily thereafter. Clinical and laboratory data were collected, including temperature, heart rate, respiratory rate, arterial pressure, WBC count, ProCT, and CRP. Depending on the clinical symptoms, samples were collected for culture of blood and other body fluids.

Three groups were defined on the basis of clinical, laboratory, and bacteriologic findings.

Infected Patients. The infected patient group constituted 111 who became infected at any time during their ICU stay, as determined by a definable source of infection and/or positive blood cultures. All of these patients were treated with antibiotics.

Noninfected Patients. The noninfected patient group constituted 79 patients without bacteriological or clinical signs of infection. These patients did not receive antibiotic therapy.
Possibly Infected Patients. The possibly infected patient group constituted 15 patients who developed clinical signs of systemic inflammatory response but had no defined source of infection. The inflammatory response in all of these patients could be attributed to their diagnoses, which included recent surgery, pancreatitis, or intracerebral bleeding. All had negative blood cultures and all were treated with antibiotics. Since the diagnosis of infection was doubtful, these patients were excluded from analysis.

The primary diagnosis was recorded at the time of admission using the diagnostic category of the Acute Physiology and Chronic Health Evaluation II score [16]. We used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of sepsis [17] to identify patients with sepsis, patients with septic shock, and, in the noninfected group, patients with systemic inflammatory response syndrome (SIRS).

Day 0 was defined as the day of admission in noninfected patients. In the infected group, day 0 was the day when the patient became infected and systemic antibiotic therapy was started. Blood samples were obtained from an arterial catheter every morning at 08:00. The samples were processed by the same person. CRP was measured by direct immunoturbidimetry (Tina-Quant[trade mark sign], Boehringer Mannheim, Germany). The samples were stored at -20[degree sign]C for

Statistical Analysis. To compare independent samples we used the Mann-Whitney U-Wilcoxon test and to compare proportions we used the chi-square test. The best cut-off value was chosen using Youden's Index. Receiver operating characteristic (ROC) curves and the respective areas under the curve [18] were calculated. Since many values fell below the detection limit, to construct the ROC curves we used a randomization method to define the values of ProCT that were <0.5 ng/mL. We also used the maximum ProCT and CRP concentrations on day 0 and day 1 to calculate the sensitivity, specificity, positive and negative predictive value, and ROC curve. Statistical calculations were done with the Statistical Program for Social Science, SPSS, Chicago, IL. All variables are expressed as median. A p < .05 was considered significant.

RESULTS

Admission diagnoses of the 190 patients included in the analysis are presented in Table 1. The age range was from 11 to 90 yrs (median age 63). Males constituted 65% (n = 124) of the patient population. Of the 190 patients, 111 (58%) were infected at some time during their ICU stay and 79 (42%) were not infected. Fifty-three patients died, giving a crude mortality rate of 28%. There was no significant difference in mortality rate between the infected and noninfected groups. The median duration of stay was longer in infected than in noninfected patients (Table 2). The WBC values were increased in both groups with no statistically significant differences between the two.

Table 1. Primary admission diagnoses of the 190 patients
Using Youden's Index, the best cutoff value for ProCT was 0.6 ng/mL and for CRP was 7.9 mg/dL. The ProCT values were >0.6 ng/mL in 68% of the infected patients but were >0.6 ng/mL in only 39% of the noninfected patients (p < .05). The CRP values were >7.9 mg/dL in 72% of the infected patients but were >7.9 mg/dL in only 33% of the noninfected patients (p < .05). The distributions of maximum ProCT and CRP concentrations in each group of patients during the first 24 hrs are shown in Figure 1. There was no significant correlation between the maximum ProCT and CRP concentrations in the noninfected (r = .10) and infected (r = .06) groups during the first 24 hrs.

The median plasma ProCT concentrations in noninfected and infected patients were 0.5 and 2.5 ng/mL (p < .05), respectively. The median CRP concentrations in noninfected and infected patients were 5.6 and 12.1 mg/dL (p < .05), respectively. The two patients with the highest ProCT levels in the noninfected group (61 and 28 ng/mL) had a recent transplant of kidney or liver, respectively. Neither of these patients had signs of organ rejection. Median ProCT and CRP levels remained higher in the infected than in the noninfected patients, but the WBC count was not significantly different (Figure 2).

(Figure 3) shows the ROC curves for the maximum ProCT and CRP concentrations and the maximum WBC count during the first 24 hrs. The area under the ROC curve was higher for CRP than ProCT (0.78 vs. 0.66, p < .05). The combination of ProCT and CRP levels resulted in higher specificity than was
obtained by either CRP or ProCT alone (Table 3).

Figure 3. Receiver operating characteristic curves of C-active protein (thick solid line), procalcitonin (dotted line), and white blood cell count (thin solid line) in the diagnosis of infection.

<table>
<thead>
<tr>
<th>ProCT levels</th>
<th>Noninfected (w/o SIRS)</th>
<th>Noninfected (w/ SIRS)</th>
<th>Septic</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>&lt;0.5 ng/mL</td>
<td>&lt;0.5 ng/mL</td>
<td>0.8 ng/mL</td>
<td>4.3 ng/mL</td>
</tr>
</tbody>
</table>

Median ProCT levels during the first 96 hrs were <0.5 ng/mL in noninfected patients without SIRS, <0.5 ng/mL in noninfected patients with SIRS, 0.8 ng/mL in septic patients, and 4.3 ng/mL in septic shock patients. The ProCT levels in the septic shock patients were significantly higher than in the sepsis subgroup (p < .05). Median CRP levels in each group were 5.1, 6.6, 10.8, and 12.6 mg/dL, respectively, and there were no significant differences between the various subgroups (Figure 4). Infected patients with bacteremia had higher ProCT levels than patients without bacteremia during the first 4 days (Figure 5). The levels of CRP were similar for both groups. There was no relationship between the type of bacteria and CRP or ProCT levels.

Figure 4. Bar graph of median procalcitonin (ProCT) and C-reactive protein (CRP) during the first 96 hrs in four subgroups: noninfected (white bars); systemic immune response syndrome (light gray bars); sepsis (dark gray bars); septic shock (black bars). *p < .05

We also assessed the relationship between the plasma ProCT and CRP concentrations and the mortality rate among the infected patients. Median plasma ProCT values in survivors and nonsurvivors during the first 96 hrs were 0.9 and 3.4 ng/mL, respectively (p < .05). Median plasma CRP values were 10.4 and 11.9 mg/dL, respectively (p = NS). Among the infected patients, ProCT levels increased more and...
remained higher in the nonsurvivors. In contrast, CRP levels were similar in both groups (Figure 6).

Figure 6. Time course of median (with interquartile range) serum procalcitonin (ProCT) (top) and C-reactive protein (CRP) (bottom) concentrations in surviving (open circles) and nonsurviving (solid circles) infected patients. *p < .05

(Figure 7) shows two representative examples of the time course of ProCT and CRP values in two patients who developed infection at different times during their ICU stay. The first patient was admitted with pancreatitis and intra-abdominal infection and had a favorable course with antibiotic treatment. The second patient was admitted with a brainstem stroke and developed bronchopneumonia on day 6, which resolved with antibiotic therapy. The fluctuations in ProCT and CRP levels in both patients were parallel.

Figure 7. Time course of procalcitonin (open circles) and C-reactive protein (solid circles) concentrations in two patients who developed infection at different times during their intensive care unit stay. The first patient was admitted with pancreatitis and intra-abdominal sepsis. The second patient was admitted with a brainstem stroke and developed bronchopneumonia on day 6. Both patients were successfully treated with antibiotics.

DISCUSSION

ProCT is a peptide that is virtually undetectable in the circulation of healthy human individuals. High serum ProCT concentrations have been described in patients with bacterial sepsis [10,11] and in healthy volunteers with systemic signs of sepsis after injection of endotoxin [15]. The exact source and function of ProCT in septic patients remains uncertain, but the amount of ProCT produced and the degree of increase in plasma levels may be correlated with the extent of the inflammatory reaction to infection. Assicot et al. [10] showed that patients with systemic viral and localized bacterial infections had lower plasma ProCT levels than patients with systemic infections and bacteremia. Al-Nawas et al. [11] reported higher ProCT levels in patients with clinically documented infection than in those merely fulfilling the SIRS criteria.

The present study included a typical, heterogeneous ICU population. In comparing the sensitivity and specificity of serum ProCT and CRP in the diagnosis of infection, we considered three groups of patients, as has been recommended [19]: a) those with documented infection; b) those without infection; and c) those with possible infection. The latter group was eliminated from the analysis. We found the best
Cut-off values were 0.6 ng/mL for ProCT and 7.9 mg/dL for CRP. Similar cut-off values for ProCT have been reported [11], although cut-off values for CRP levels have been a little more variable, ranging from 4 mg/dL in infected neutropenic adult patients [20] to 10 mg/dL in neonatal septicemia [21] and infected surgical patients [2]. As anticipated, the sensitivity of ProCT and CRP increased with time after the diagnosis of infection. ProCT demonstrated a slightly lower sensitivity and specificity than CRP values, but the combination of ProCT and CRP was much more specific in ascertaining the diagnosis of infection. In 337 patients with suspected sepsis, Al Nawas et al. [11] reported a sensitivity of 60% and a specificity of 79% for ProCT, similar values to those we obtained. Although they measured plasma CRP concentrations, they did not show the sensitivity and specificity for CRP values. However, in neonates at risk of sepsis, Berger et al. [21] found that CRP may achieve a specificity of 96% and a sensitivity of 78%, higher levels than we observed. It is interesting to note that the WBC count was similar in both the infected and the noninfected groups in our study, indicating that the WBC count may reflect the stress response to the inflammatory condition but that it is not specific for infection. In our experience (also illustrated in Figure 7), ProCT levels do not increase earlier than CRP levels and do not contribute to an earlier diagnosis. ProCT should not replace CRP as a marker of infection in ICU patients, but the combination of both parameters can indicate the presence of infection with greater specificity.

We found that ProCT levels, but not CRP levels, were much higher in infected patients with shock than in those without shock, and our results also showed greater ProCT levels in infected nonsurvivors than in survivors. These results could be due to ongoing inflammation as a result of uncontrolled infection, although decreased ProCT clearance due to renal and/or hepatic dysfunction cannot be ruled out. Other investigators [22] have made similar observations. Control of infection with appropriate therapy has been associated with a decrease in ProCT levels in other studies [10,23], as well as in our own. Hence, monitoring of serum ProCT concentration may be useful in following the response to therapy in septic patients.

We found higher levels of ProCT in infected patients with bacteremia than in patients without bacteremia, even though bacteremia may not be associated with higher mortality rates [24]. Recent reports [25,26], have suggested that mean ProCT concentrations were higher in patients with Gram-negative bacteremia or in patients with increased endotoxin levels, but we did not observe higher levels in patients with Gram-negative bacteremia.

In view of our findings, we recommend the following steps in the diagnosis of infection in ICU patients. First, obtaining clinical and bacteriologic findings remain the essential first step in the diagnosis of infection, and should not be replaced by any blood test. However, when these findings are equivocal, CRP remains the best discriminant test because of its good sensitivity and specificity, as the WBC count does not clearly discriminate between infected and noninfected patients. If the CRP level is >7.9 mg/dL, the diagnosis of infection can be further confirmed by a ProCT concentration of >0.6 mg/mL. ProCT levels can also be a good marker of disease severity and outcome, and could be useful in monitoring treatment of critically ill patients, and perhaps in defining populations for inclusion in clinical trials.

REFERENCES [Click here for reference links. (18 references linked.)]

intensive care unit patients: Diagnostic signs in nosocomial infection. Crit Care Med 1993; 21:1175-1180


