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Procalcitonin - potential, limitations and availability

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ABSTRACT

Bacterial infections and sepsis are major problems in critically ill patients. Timely diagnosis and therapy reduce morbidity and mortality. Many studies have included the investigation of various biomarkers whose elevated concentrations can indicate sepsis; among them, PCT proved to be most useful.
PCT is synthesized in the thyroid gland as a prohormone of calcitonin. In healthy individuals the PCT concentration is <0.1 ng/mL.
The advantage of the PCT is a high negative predictive value for the exclusion of sepsis, with the cut-off value of 0.5 ng/ml. A concentration between 2 and 10 ng/ml indicates strong sepsis, whereas a value ≥10 ng/ml is associated with septic shock. In addition to the diagnosis of sepsis, the measurement of PCT concentration is useful for the introduction and monitoring of antibiotic therapy, which is performed according to an algorithm based on the cut-off value for PCT.
Immunoassays are used to measure PCT concentrations in serum or plasma. It is possible to determine the concentration in whole blood by using point-of-care testing. In pathological conditions that are not associated with sepsis, PCT is useful as a prognostic indicator of disease complications. Some studies suggest that PCT is a potential early indicator of acute coronary syndrome.

Key words: procalcitonin, bacterial infection, sepsis, intensive care unit

INTRODUCTION

Bacterial infections and sepsis are major problems in critically ill patients, particularly those in intensive care units. The timely diagnosis and introduction of therapy reduces related morbidity and mortality. Most of the biomarkers routinely used for the diagnosis of sepsis (e.g., C-reactive protein (CRP), white blood cell count) are not specific and sensitive for the early detection of sepsis. For years, various studies have been searching for a potential biomarker for the diagnosis of sepsis. Characteristics of a good biomarker for sepsis include short half-life, a specific increase of the concentration in sepsis and concentration decrease during treatment with appropriate antibiotic therapy. Studies have included investigations of various cytokines (1), copeptin (2), atrial natriuetic peptide (ANP) and the pro-ANP (3), but the best characteristics as a potential biomarker for the diagnosis of sepsis were shown by procalcitonin (PCT).
In 1993, the first study was published that showed that high concentrations of PCT are present in patients with bacterial infection and sepsis. (4)

Biochemical characteristics of procalcitonin

PCT is a peptide composed of 116 amino acids. Physiologically, it is synthesized in the C cells of the thyroid gland as a prohormone of calcitonin (calcitonin is a hormone that plays a role in calcium homeostasis). In addition, a low PCT concentration is produced in neuroendocrine cells of the lung and small intestine. In physiological conditions, PCT is secreted in very small concentrations, and its concentration in healthy individuals is <0.1 ng/mL. (5) Increased secretion of PCT is stimulated by inflammatory cytokines, bacterial endotoxin and bacterial lipopolysaccharides from certain organs (liver, kidney and lungs). (6) Depending on the severity of bacterial infection, the concentration can rise up to 1,000-fold than that found in healthy individuals. PCT half-life is approximately 22-26 hours. After stimulation, concentration in blood rises within 2-4 hours, and the maximum concentration is achieved within 6-12 hours. These characteristics give it a significant advantage over CRP, whose concentration in the blood starts to rise 6-10 hours after stimulation. In addition to increased concentration in bacterial infection, elevated CRP concentrations are also found in viral infections and in all conditions associated with inflammation.

WHY IS IT NECESSARY TO DETERMINE PCT CONCENTRATION?

It is necessary primarily in order to detect sepsis at a very early stage, and to monitor antibiotic therapy (to check if therapy is effective and when it can be discontinued).
The defined cut-off for exclusion of bacterial infection and sepsis is the PCT concentration of ≤0.2 ng/mL, whereas values exceeding 0.5 ng/ml suggest that sepsis is possible. (7) The concentrations of PCT ≥2 and ≤10 ng/ml indicate severe sepsis, while the value of ≥10 ng/mL is associated with septic shock. SIRS (systemic inflammatory response syndrome) and MODS (multiple organ dysfunction syndrome) can also be followed by elevated concentrations of PCT, but they are usually lower than in sepsis, while local bacterial infection usually does not cause an increased PCT concentration.
Microbiological methods are still the gold standard for determining the cause of bacterial infection and sepsis. A drawback of this method is the time required for analysis results. When there is a possibility of sepsis, it is necessary to use a biomarker that will either confirm the diagnosis or reject it. Procalcitonin is a biomarker that possesses such capability because we can safely determine whether sepsis is present or not based on its measured concentration. Results of some studies indicate the possibility of differentiating Gram-positive bacterial infection from Gram-negative us-

ing the concentration of PCT. In actuality, PCT concentration is higher in infections with Gram-negative bacteria compared to infection with Gram-positive bacteria. (8) As stated above, in addition to diagnosis, measuring the concentration of PCT is useful for the introduction and monitoring of antibiotic therapy. Monitoring of therapy is performed according to an algorithm based on the cut-off values for PCT. (9)

THE ROLE OF THE CLINICAL LABORATORY IN THE DIAGNOSIS OF SEPSIS - HOW WE CAN DETERMINE THE CONCENTRATION OF PROCALCITONIN

The concentration of PCT can be measured in serum and plasma (EDTA or heparin). As PCT is a biomarker whose concentration is necessary to be determined as quickly as possible, the use of plasma is recommended because it has advantages over serum in terms of preanalytical requirements (a plasma sample can be centrifuged immediately after blood sampling, which significantly reduces the turnaround time). The first assays to determine the concentration of PCT were based on manual immunochemistry methods (Brahms PCT LIA). (10) Assays which are used to determine the concentration of PCT are based on an immunochemical reaction (antigen-antibody reaction). A type of immunochemical reaction is a sandwich ELISA, which is based on the formation of an antibody-procalcitonin-antibody complex. All assays for the determination of PCT concentrations are standardized according to the BRAHMS PCT LIA assay, but are adapted for use on different analysers (table 1). A comparison of results obtained by different assays shows good correlation. (10) In addition to tests which are used on biochemical analysers in clinical laboratories, PCT concentrations can be determined using point-of-care tests (POCT) (Brahms PCT-Q assay). (11) These assays are semi-quantitative and use whole blood for analysis, with results that are available in less than 30 minutes. A limitation of POCT is that these tests are unable to precisely monitor changes in PCT concentration trends, which is needed to monitor a patient's clinical status.

IS PCT CONCENTRATION DETERMINATION CLINICALLY SIGNIFICANT IN OTHER PATHOLOGICAL CONDITIONS NOT RELATED TO SEPSIS?

Many studies have investigated the significance of determining the concentration of PCT in various types of inflammation that are not associated with sepsis, or the possible benefit of determining the concentration of PCT in infections without sepsis. In acute pancreatitis, the significance of determining PCT levels is limited; PCT is useful as a prognostic indicator of disease complications and adverse outcomes. (16) The usefulness of PCT in urinary tract infections involves the exclusion of bacterial diseases with a cut-off value of 0.25 µg/L (0.25 ng/ml) (17). With the PCT cut-off value of 0.1 (0.25) ng/ml, it is possible to differentiate patients with septic and non-septic arthritis. (18) The role of procalcitonin is investigated in pathogenesis of atherosclerosis and myocardial infarction as a possible early marker of acute coronary syndrome. (19)

CONCLUSION

Procalcitonin as a biomarker for bacterial infections and sepsis has advantages over those biomarkers used in routine practice as it can be detected early in the blood. The concentration of PCT increases within 2-4 hours in bacterial infections. Concentrations of less than 0.5 ng/ml have a high negative predictive value for the exclusion of sepsis. Regardless of the increase in the concentration of PCT in some infections not associated with sepsis, it is certain that a value of >2 ng/mL indicates sepsis and a value exceeding 10 ng/mL indicates septic shock. It has been shown that PCT determination is also important for monitoring antibiotic therapy where a significant decrease in PCT concentration indicates unnecessary use of antibiotics therapy.

Table 1. Comparison of PCT immunoassays (11-14).

	Sample volume (µL)	Duration of analysis (min)	Measuring range (ng/mL)	Analytical sensitivity (ng/mL)
ADVIA Centaur B·R·A·H·M·S PCT	100	29	0.02 - 75	<0.02
B·R·A·H·M·S PCT sensitive KRYPTOR	50	19	0.02 – 50	<0.02
VIDAS® B·R·A·H·M·S PCT	200	20	0,05 – 200	<0.05
ELECSYS® B·R·A·H·M·S PCT	30	18	0.02 – 100	<0.02

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