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PROCALCITONIN

PROCALCITONIN IS THE MOST EFFECTIVE MARKER FOR ESTABLISHING THE BACTERIAL ORIGIN OF AN INFLAMMATORY SYNDROME

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Abstract

Procalcitonin, or PCT, is a prohormone whose blood level rises and can be measured routinely, early and specifically during a bacterial infection. PCT is therefore of particular interest because its production is specific to the bacterial, parasitic or fungal origin of the inflammatory syndrome (a viral infection, by contrast, does not induce PCT production) and is very early (a measurable rise within 3 to 6 hours of the onset of infection): it makes it possible to improve medical performance in the early diagnosis of sepsis and in the initiation of appropriate treatment. Procalcitonin is used as a versatile biological marker making it possible to:

1. assist in the aetiological diagnosis of an infection,
2. help determine its severity,
3. monitor its course and the response to treatment,
4. tailor the duration of an antibiotic treatment to each patient.

Serum PCT has been the subject of numerous clinical evaluation studies of fevers of bacterial origin in the fields of intensive care, emergency medicine, general practice and paediatrics (to identify newborns with suspected maternofetal infection who do not require antibiotics, with an NPV close to 100%, and to help in the decision to perform a retrograde cystography in children presenting with a febrile urinary tract infection).

Description

Procalcitonin is a polypeptide composed of 116 amino acids (12.6 kDa). It corresponds to the prohormone of calcitonin (CT). After its synthesis, PCT is stored in secretory granules in all cell types of the body. Only the C cells of the thyroid can cleave this precursor into calcitonin. It should be noted that under normal conditions PCT is also secreted by the neuroendocrine cells of the lung at very low concentrations (which explains the blood concentration found in a healthy individual, which may reach up to 0.05 µg/L). In response to a pro-inflammatory stimulus (involving in particular IL1-β and TNF-α), notably but not exclusively of bacterial origin, PCT granules may be released by all cell types.After an experimental injection of endotoxin, PCT is detectable very rapidly (from the 3rd hour in serum or plasma), with a peak between 6 and 12 hours. Serum PCT production very closely follows the production of pro-inflammatory cytokines (Interleukin 6, TNFα). TNF does indeed appear to be an important mediator in triggering PCT production, whereas IFN alpha, an antiviral, is thought to have an inhibitory effect.

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The half-life of PCT is estimated at approximately 24 h. Thus, procalcitonin has the rare advantage of decreasing very rapidly after eradication of the infectious focus, even if the inflammatory context persists. When the infectious focus is eradicated, a 30 to 50% decrease in the serum PCT level is observed within 24 hours. Its production is nevertheless maintained if the infection persists, as shown by repeated endotoxin injections.

Value

Compared with other biological markers, and in addition to a rigorous clinical examination, PCT is the most effective marker for establishing the bacterial origin of an inflammatory syndrome (although it may also be secreted during a parasitic or fungal infection). The steady fall in PCT levels reflects effective antibiotic treatment. This is why monitoring PCT kinetics may be useful for the surveillance and prognosis of severe bacterial infections, as well as for adjusting the anti-infective strategy. This has been demonstrated in numerous clinical indications, such as in the management of patients suffering from sepsis or septic shock, more particularly ventilator-associated pneumonia (VAP), chronic obstructive pulmonary disease (COPD) or community-acquired pneumonia (CAP).

PCT may also make it possible to consider a concomitant infectious hypothesis in patients presenting with another primary diagnosis. Thus, on admission to the emergency department in patients suffering from heart failure who may present with bacterial pneumonia (an elevated PCT then makes it possible to identify the patients who may benefit from antibiotic treatment.). Finally, low PCT levels (<0.25 µg/L) in patients presenting with clinical signs of infection (CAP, urinary tract infection) indicate a low probability of bacteraemia, and therefore a high probability that any blood culture will be negative.

A role in limiting the use of antibiotics

In a context where the empirical choice of antibiotics is inappropriate in up to 50% of cases and where the durations of antibiotic therapy are often arbitrary, leading not only to adverse effects but also, in the longer term, favouring the emergence of multidrug-resistant bacteria (MDRB), responsible for a high mortality, better management of the question of initiation, of the reassessment of efficacy and of the duration of treatment has become a priority. Among more than 2500 publications on this marker, some ten interventional studies have made it possible to demonstrate the impact of a strategy guided by PCT levels in helping to limit the use and the duration of antibiotic treatments, in intensive care, in community medicine and in emergency departments. Owing to its high sensitivity to most infections, procalcitonin is widely recognised as the most sensitive biomarker for assisting in the diagnosis — or the exclusion — of bacterial sepsis, with a high negative predictive value greater than 95%. International guidelines recommend its use in the optimisation of antibiotic therapy.

Compared with C-reactive protein (CRP) — another biomarker frequently used to facilitate the diagnosis of sepsis — procalcitonin has a shorter lifespan and its concentration rises earlier during a bacterial infection. These kinetics potentially allow an earlier diagnosis and better monitoring of the progression of sepsis.

Procalcitonin and Sepsis

Sepsis is defined as the concomitant presence of a systemic inflammatory response syndrome (SIRS) and an infection. For the clinician, it is important to differentiate rapidly between sepsis and SIRS without infection, and to apply the appropriate treatment, in particular antibiotic therapy.

The distinction between these two entities is difficult. A number of non-specific clinical and biological signs are found in both pictures: fever, tachycardia, signs of shock. Furthermore, neither the complete blood count nor CRP is sufficiently discriminating. Numerous studies have shown that procalcitonin could be used as a first-line test in cases of suspected sepsis. Moreover, the various populations studied have made it possible to identify procalcitonin as a good marker of a positive blood culture.

Procalcitonin and Sepsis

The distinction between bacterial meningitis and viral meningitis is a problem for the clinician, meningitis being a therapeutic emergency. The procalcitonin level shows a sensitivity of 94 to 100% and a specificity of 93 to 100%, which makes procalcitonin a very good marker of bacterial meningitis. The main value of measuring procalcitonin in this context is the therapeutic management of meningitis with a negative direct examination, in particular in the case of meningitis with a mixed CSF formula. minating. Numerous studies have shown that procalcitonin could be used as a first-line test in cases of suspected sepsis. Moreover, the various populations studied have made it possible to identify procalcitonin as a good marker of a positive blood culture.

Procalcitonin and Bronchopneumopathies

In infections, the lungs represent one of the main portals of entry. A definite diagnosis is difficult for the clinician because, in certain cases, the combination of clinical and paraclinical findings is not sufficient. This leads to a massive prescription of antibiotics with, as a consequence, a far from negligible extra cost and the emergence of resistant bacterial strains. It would appear that procalcitonin is, in this particular case, a genuine therapeutic decision-making tool. Researchers set up a study which demonstrated the benefits of procalcitonin in the use of antibiotics in the hospital setting. This study showed that procalcitonin was an excellent decision-making tool in an emergency context, in this specific setting of lower respiratory tract infections.

Procalcitonin and Systemic Diseases

Fever is a reason for consultation in patients receiving immunosuppressive treatment for a systemic disease. The difficulty of the diagnosis lies in the distinction between a flare-up of the disease and an infectious complication, which is a therapeutic emergency because of the immunosuppressive treatment. Procalcitonin appears to be a good discriminating factor, although a number of situations give rise to false positives. These results suggest that it is imperative to look for an infectious focus during a febrile peak in all systemic diseases, even if the procalcitonin level may rise during flare-ups.

Procalcitonin: Prognostic Marker

Alongside the diagnostic use of the marker, the prognostic applications are perhaps more interesting. They had already been identified in the study carried out by Assicot. The children presenting with the most severe infectious states were also those who had the highest procalcitonin levels. The procalcitonin level is correlated with the severity scores used in intensive care, such as APACHE III (acute physiology and chronic health evaluation), to assess the severity of community-acquired pneumonia. With regard to mortality, procalcitonin levels were higher in the patients who died than in the survivors.

Consequently, it may be considered that the rise in procalcitonin is directly proportional to the severity of the sepsis and therefore to the prognosis. Conversely, a rapid decrease in the procalcitonin level in patients under treatment makes it possible to anticipate a favourable outcome.

Assay

Various kits are available to the medical laboratory, but all are based on the principle of a sandwich-type immunometric assay using, on the one hand, an anti-calcitonin antibody and, on the other hand, an antibody directed against katacalcin (the C-terminal peptide of PCT). The use of two antibodies guarantees the specific detection of the precursors of calcitonin, and not of the mature hormone. The kits differ from one another in the technology used to detect the antibody1–PCT–antibody2 complexes formed, and in the type of analyser used. Laboratoire Sion possesses state-of-the-art technology for a rapid and effective procalcitonin assay in 30 minutes.

Difficulties in interpreting a procalcitonin assay

Certain non-infectious situations may be the cause of a rise in the PCT concentration.

- Newborns: PCT may be elevated in the first days following birth, but this level falls rapidly after 48 hours.
- Severe trauma, extensive burns.

Certain thyroid cancers Certain infectious situations may give a negative PCT result. For example:

Incipient bacterial infection (early assay), localised infectious focus

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