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Research Article

Usefulness of Procalcitonin in the Suspension of Antibiotics

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Abstract

Background: Procalcitonin is a promising biomarker for the early detection of systemic bacterial infections; its use as a predictor for antibiotic suspension has been studied and has become relevant.

Methodology: A systematic review was carried out through various databases from January 2011 to February 2022; The search and selection of articles was carried out in indexed journals in English. The following keywords were used: Procalcitonin; infections; Sepsis; Bacteria; Virus.

Results: Currently there are different types of inflammatory markers, among which we can highlight procalcitonin, which has become a new biomarker for the early detection of bacterial infections, especially systemic infections. Procalcitonin levels have been shown to increase over 6 to 12 hours, and these values continue to steadily increase 2 to 4 hours after the onset of sepsis. After identifying the condition, it is advisable to measure procalcitonin every 6 to 24 hours, in order to identify the need to change the antibiotic.

Conclusions: The present review offers updated and detailed information on the importance of procalcitonin as a discriminating agent for viral diseases of bacteria and thus whether or not to suspend the antibiotic.

Keywords: Procalcitonin, Infections, Sepsis, Bacteria, Viruses, Bacteria

Introduction

Today there are different laboratory tests for the detection of infectious diseases, including PCR, but they lack the specificity to accurately diagnose bacterial versus non-bacterial infections [1,2]. Procalcitonin is a promising biomarker for the early detection of systemic bacterial infections. Procalcitonin is a 116 amino acid residue that was first explained by *Le Moullec, et al*. in 1984; however, its diagnostic significance was not recognized until 1993 [3,4]. In 1993, *Assicot, et al*. demonstrated a positive correlation between high serum Procalcitonin levels and patients with positive results for bacterial infection and sepsis (e.g., positive blood cultures). It was also shown that these levels do not increase with viral infection, but decrease with antibiotic administration [5,6]. Under normal conditions of homeostasis, preprocalcitonin undergoes initial synthesis by thyroid C cells. Later, this peptide is transformed into procalcitonin through cleavage of a 25 amino acid signal sequence by endopeptidases. The final product, calcitonin, the 32 amino acid hormone responsible for the regulation of serum calcium, is formed after conversion by the enzyme prohormone convertase [7,8].

Infectious diseases remain a major cause of death, disability, and social and economic disruption for millions of people world-

wide. Prevention and treatment strategies for infectious diseases are derived from a thorough understanding of the complex interactions between specific viral or bacterial pathogens and the human host [9,10]. Viruses bind to host cells as a prerequisite for intracellular entry and replication. Because cell surfaces are especially enriched with glycans, numerous viruses target glycans for attachment and entry into cells [8,11]. Children with infectious diseases, both bacterial and viral, are often treated with empirical antibiotics as the first line. Considering both the threat of microorganisms and the toxicity of antibiotics, it is imperative to develop tests at the point of primary care as well as at the in-hospital level to discriminate bacterial from viral infections and to define the indications for antibiotic treatment [7,10, 11,12] It is therefore appropriate to perform this work in order to identify the importance of procalcitonin as a discriminating agent of viral diseases from bacteria and thus the suspension or not of the antibiotic.

Materials and Methods

A systematic review was carried out, searching PubMed, Scielo and ScienceDirect databases, among others. The collection and selection of articles was carried out in English-language indexed journals from 2011 to 2022. As keywords, the following terms were used in the databases according to DeCS and MeSH methodology: Procalcitonin; infections; Sepsis; Bacteria; Viruses. In this review, 102 original and review publications related to the topic studied were identified, of which 32 articles met the specified inclusion requirements, such as articles that were not less than the year 2011, that were full-text articles and that reported on procalcitonin as a predictor of the interruption or not of antibiotic therapy. Exclusion criteria took into account that the articles did not have sufficient information and that they did not present the full text at the time of review.

Results

Procalcitonin as an Inflammatory Marker

Currently there are different types of inflammatory markers, among which we can highlight procalcitonin, which has become a new biomarker for the early detection of bacterial infections, especially systemic infections. Procalcitonin does not increase in viral infections, decreasing its values when appropriate antibiotic therapy is administered [13,14]. One of the markers or acute phase reactants most frequently sent to health centers is C-reactive protein, which has a disadvantage in that it lacks the specificity needed to accurately diagnose bacterial versus non-bacterial infections [15,16]. At blood level we can identify normal procalcitonin levels (values lower than 0.05 ng/mL), being elevated or influenced by endotoxins or cytokines such as interleukin 6 (IL-6), Tumor Necrosis Factor (TNF)-alpha and IL-1b, increasing procalcitonin levels up to 100 to 1000 times their normal value [17,18]. The main source of procalcitonin is found at the thyroid level, in thyroid C cells, but it can also be synthesized by extra-thyroid tissues [10,15,18]. In contrast, cytokines, such as interferon (INF)-gamma, which are released after viral infection, lead to a negative regulation of PCT, highlighting another advantage of PCT assays [19,20].

After an initial bacterial infection, procalcitonin levels have been shown to increase from 6 to 12 hours, and these values continue to rise steadily from 2 to 4 hours after the onset of sepsis. Twenty to 24 hours is the half-life that has been recorded so far. One of the ways to demonstrate the efficacy of antibiotics is to identify procalcitonin every so often, since if the antibiotic is effective these levels decrease by 50% every 24 hours [20,21]. It must be taken into account that not in all sepsis states it is advisable to identify the procalcitonin level if it is associated to a factor that may hinder its identification, among these factors we can identify the following: [22-24].

a) Trauma

b) Burns

c) Carcinomas (medullary C-cell, small cell lung and bronchial carcinoid)

d) Immunomodulatory therapy that increases pro-inflammatory cytokines

e) Cardiogenic shock

f) First 2 days of life of the newborn

g) During peritoneal dialysis treatment

h) In cirrhotic patients

Procalcitonin as a Predictor of Antibiotic Initiation and Discontinuation

As previously stated, procalcitonin levels will decrease by 50% in 24 hours after the initiation of the antibiotic, thus demonstrating that, if the antibiotic is not effective in the patient, procalcitonin levels will not decrease to the value necessary to conclude that the antibiotic is effective in the patient. Therefore, this method or these values could be considered as physiological control of the systemic infection presented by the patient [14,20]. Most research has shown that PCT levels show clinical significance when they are in the range of 0.1 to 0.5ng/mL. In addition, research has shown that PCT levels below 0.1 ng/mL have a high negative predictive value (96.3 %) for excluding bacterial infections [25]. Procalcitonin has several cut-off levels applicable in different conditions or diseases that could predict the course of the disease or the cause of the disease. Table 1 shows the main conditions that could be identified or ruled out by procalcitonin: [13,20,22,26,27]. After identifying the condition, it is advisable to measure procalcitonin every 6 to 24 hours, in order to identify the need to change the antibiotic, increase the antibiotic dose, or discontinue the antibiotic implemented for the condition. If procalcitonin levels decrease by 50% after the condition and the initiation of the antibiotic, it is considered that the antibiotic therapy is taking effect [26,27] (Table 1).

It has also been proposed that one of the criteria for discontinuing the antibiotic is when procalcitonin levels decrease or fall below 0.1ng/ml or 80-90% below the initial measurement [28]. Efficient diagnosis of bacterial infections allows physicians to initiate antibiotic therapy when appropriate, thus avoiding misuse and overuse

of antibiotics. As antibiotic resistance continues to increase, it has become increasingly important for physicians to determine different algorithms and laboratory tests to help maintain current antibiotic parameters [29]. Unfortunately, most first-line tests for determining infection, such as blood cultures and C-Reactive Protein (CRP), lack the efficiency and specificity needed to treat patients promptly. Therefore, laboratory tests are still being implemented to adjust cut-off points for procalcitonin to be used promptly and with greater efficacy in clinical practice [28-30].

Table 1: Conditions that could be identified or ruled out by procalcitonin.

Systemic Disease or Condition	Procalcitonin Levels	Function of Procalcitonin
Arthritis	0.1 to 0.25ng/mL	Discriminate infectious (septic) arthritis from non-infectious arthritis.
Infections Bacteremia	0.25ng/mL	To rule out bacteremic infections
Bloodstream infection (primary):	0.1ng/mL	Differentiating between a true infection and a contaminated sample
Bronchitis (acute)/ Chronic Obstructive Pulmonary Disease (COPD) Exacerbations:	0.1 to 0.5ng/mL	Reduce (unnecessary) antibiotic exposure in the emergency department and hospital setting without adverse outcomes.
Endocarditis	2.3ng/mL	High diagnostic accuracy for predicting acute endocarditis.
Meningitis	0.5ng/mL	Differentiate viral from bacterial meningitis and subsequently reduce antibiotic exposure.
Neutropenia	0.1 to 0.5ng/mL	To identify systemic bacterial infections in neutropenic patients.
Pneumonia	0.1 to 0.5ng/mL	Reduce antibiotic exposure during hospitalization without adverse outcomes.
Postoperative fever	0.1 to 0.5ng/mL	Differentiate postoperative infections from non-infectious fever.
Postoperative infections	0.5 to 1.0ng/mL	Minimize antibiotic treatment in the surgical ICU without detrimental results.
Severe sepsis/shock	0.25 to 0.5ng/mL	Limit antibiotic treatment in the ICU without detrimental results.
Upper Respiratory Tract Infections	0.1 to 0.25ng/mL	Limit antibiotic treatment in the ICU without detrimental results.
Urinary tract infections	0.25ng/mL	Determine the extent of renal involvement.
Ventilator-associated pneumonia	0.1 to 0.25ng/mL	Minimize antibiotic treatment without detrimental results.

Discussion

The study by Joshua et al, in which they conducted a systematic search of databases using an a priori strategy. Systematic reviews were included that reported an outcome related to antibiotic initiation and/or duration in the setting of respiratory infection. Data extraction was performed by the first author and independently verified by a second author. This paper concluded that the use of procalcitonin leads to a reduction in antibiotic initiation for respiratory illness. It also results in a decrease in antibiotic duration [31]. Another study by Anna et al, concluded that although there are several randomized clinical trials and observational trials evaluating the usefulness of procalcitonin in the early diagnosis of septic events in different clinical settings, there is still uncertainty as to its use in initiating and suspending antibiotic therapy. Since there are different factors that could stimulate the production of procalcitonin and thus obtain false-positive results, the skill of the treating physician plays an important role in this part [32].

All these trials demonstrate that procalcitonin alone would not be advisable to use, as the physician's skill in dealing with the different types of infections and factors that contribute to increased procalcitonin levels in the blood plays an important role here. A strength of the current study is the methodology implemented, with respect to the literature search, and steps in the selection of relevant articles, quality assessment and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among these are the lack of evidence from clinical analysis trials to determine with certainty the efficacy of procalcitonin with respect to the interruption or not of antibiotic therapy in different types of infections, both viral and bacterial, so more studies are needed to answer these questions.

Conclusion

Currently there are different types of inflammatory markers, among which we can highlight procalcitonin, which has become a new biomarker for the early detection of bacterial infections, especially systemic infections. Procalcitonin does not increase in viral infections, decreasing its values when appropriate antibiotic therapy is administered. The main source of procalcitonin is found at the thyroid level, in thyroid C cells, but it can also be synthesized by extra-thyroid tissues, such as the liver, pancreas, kidneys, lungs, intestine and leukocytes.

After an initial bacterial infection, procalcitonin levels have been shown to increase from 6 to 12hours, and these values continue to rise steadily from 2 to 4 hours after the onset of sepsis.

Twenty to 24 hours is the half-life that has been recorded so far. One of the ways to demonstrate the efficacy of antibiotics is to identify procalcitonin every so often, since if the antibiotic is effective these levels decrease by 50% every 24hours. After identifying the condition, it is advisable to measure procalcitonin every 6 to 24hours, in order to identify the need to change the antibiotic, increase the dose of the antibiotic, or discontinue the antibiotic implemented for the condition. If procalcitonin levels decrease by 50% after the condition and the initiation of the antibiotic, it is considered that the antibiotic therapy is working.

Acknowledgement

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Conflict of Interest

None.

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