Practical Laboratory Medicine 2 (2015) 22–28

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm

Multicenter comparison of automated procalcitonin immunoassays

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ARTICLE INFO

Article history:
Received 10 June 2015
Received in revised form
3 July 2015
Accepted 7 July 2015
Available online 17 July 2015

Keywords:
Procalcitonin
Sepsis
Bacterial infections
Immunoassay
Multicenter study

ABSTRACT

Objectives: A multicenter study to compare results of BRAHMS Kryptor PCT with those obtained using four BRAHMS-partnered procalcitonin (PCT) automated immunoassays (DiaSorin Liaison, BioMérieux Vidas, Roche Cobas E601 and Siemens Advia Centaur) and the Diazyme immunotubidimetric assay implemented on four clinical chemistry platforms (Abbott Architect c16000, Siemens Advia 2400, Roche Cobas C501 and Beckman Coulter AU5800).

Design and methods: One hundred serum samples from in-patients with PCT values between 0.10 and 58.7 ng/mL were divided into aliquots and tested with the nine different reagents and analyzers. BRAHMS PCT Kryptor results were used as reference.

Results: Compared to BRAHMS PCT Kryptor, significant differences in results were observed on Vidas, Advia Centaur, Architect, Cobas C501 and AU5800. However, the correlation coeffiecients (r) with BRAHMS PCT Kryptor were between 0.899 and 0.988. The mean bias was less than $\pm$ 1.02 ng/mL, except for Vidas (2.70 ng/mL). The agreement at three clinically relevant cut-offs was optimal: between 83–98% at 0.50 ng/mL, 90–97% at 2.0 ng/mL, and 98% at 10 ng/mL. The comparison of Diazyme PCT across the four clinical chemistry analyzers yielded high correlation coefficients (r between 0.952 and 0.976), a mean bias less than $\pm$ 0.9 ng/mL, acceptable agreement at 0.5 ng/mL (> 82%), and high concordance at the 2.0 ng/mL (> 97%) and 10 ng/mL (> 98%) cut-offs.

Conclusions: The methods and applications evaluated in this multicenter study are aligned with BRAHMS PCT Kryptor and can be used for predicting the risk of progression to systemic inflammation in patients with bacterial infections using the conventional PCT diagnostic thresholds.

1. Introduction

Procalcitonin (PCT), a 116 amino acid peptide with molecular weight 14.5 kDa, belongs to the calcitonin superfamily of peptides. The protein is encoded by the *CALC-1* (Calcitonin Gene-related Peptide 1) gene on chromosome 11 [1]. The original product of this gene, a 141 amino acid peptide known as pre-PCT, undergoes a proteolytic cleavage of the 25 amino acid signal peptide to produce the PCT molecule, which is then further processed to generate the mature, 32 amino acid-long calcitonin. Under physiological conditions, the transcription of *CALC-1* gene is suppressed in non-neuroendocrine tissues, so that the C cells of the thyroid gland are responsible for the entire synthesis of PCT and calcitonin [1].

In the presence of microbial infections, the synthesis of PCT is dramatically amplified in all parenchymal tissues and differentiated cell types, so that its concentration in blood may increase by several orders of magnitude, up to one thousand-fold [1]. The PCT response to the infection closely mirrors the severity of the inflammatory reaction. More specifically, higher values are associated with severe disease,

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http://dx.doi.org/10.1016/j.plabm.2015.07.001

whereas a declining concentration usually reflects disease resolution [2]. This paradigmatic behavior is now widely used for diagnosis and monitoring of bacterial infections. In particular, PCT values between $\geq$0.5 and 2.0 ng/mL are suggestive of moderate risk for progression to systemic inflammation, between 2.0 and 10 ng/mL are suggestive for high risk for progression to systemic inflammation, whereas values $\geq$10 ng/mL are associated with a high probability of developing severe sepsis and septic shock [1]. Recent evidence also suggests that the measurement of PCT may be helpful for the diagnosis of bacterial peritonitis [3], as well as for guiding antibiotic therapy in patients with localized (i.e., community acquired pneumonia) and systemic bacterial infections [4].

Although there is currently no agreed reference technique for PCT measurement, the BRAHMS PCT Kryptor method has been directly developed from the original BRAHMS luminometric immunoassay (LIA), and was the first automated method cleared by the FDA for the diagnosis of severe sepsis and septic shock [5]. Several diagnostic companies such as DiaSorin, BioMérieux, Siemens and Roche have since partnered with BRAHMS for developing automated PCT assays on their proprietary platforms, using different technologies (i.e., immunoluminometric, enzyme-linked immunofluorescent, chemiluminescent and electrochemiluminescent immunoassays). More recently, a latex-enhanced immunotubidimetric assay has also been developed by Diazyme, to be used on a vast array of clinical chemistry analyzers. Nevertheless, due to the lack of a PCT reference material, it remains uncertain whether the current clinical PCT cut-offs would apply to all the available procalcitonin immunoassays, or if monitoring using different methods would be clinically reliable when patients are transferred between healthcare facilities. Therefore, the aim of this multicenter study was to compare results of the BRAHMS Kryptor PCT with those obtained using four BRAHMS-partnered PCT automated immunoassays and the Diazyme immunotubidimetric assay implemented on four different clinical chemistry platforms.

2. Materials and methods

2.1 Study design

This multicenter study was based on 100 serum samples from inpatients (52 from the intensive care unit, 12 from the emergency department, 15 from the infective diseases unit and 21 from other medical and surgical wards) referred to the laboratory of the University Hospital of Parma for routine PCT measurement during a single working day. The samples were selected to cover the most clinically significant PCT concentrations (0.10–58.7 ng/mL) measured using the local routine immunoassay (BRAHMS PCT Kryptor system, BRAHMS, Hennigsdorf, Germany) (Fig. 1). The blood samples were immediately centrifuged upon arrival in the laboratory, serum was separated and divided into seven aliquots of 0.6 mL each. The first aliquot was used for routine PCT assessment, whereas the remaining six aliquots were frozen at -70 °C. After one week of storage, the aliquots were transported to the participating centers, under controlled conditions of temperature and humidity. Specifically, four reusable dry gel packs containing carbopol gel (2×200 mL and 2×500 mL) were frozen at -70 °C and then placed into certified transport boxes at the sample collection center [6]. The mean time of shipment to the participating centers was 92 min (range: 54–106 min). Upon arrival, the aliquots were stored frozen at -70 °C until all sites had received the shipment. The aliquots were then thawed at room temperature on the same day, and simultaneously analyzed in each center with all reagents and methods, including retesting on BRAHMS PCT Kryptor.

2.2 Methods description

The complete description of reagents and instrumentation is shown in Table 1. In brief, the BRAHMS PCT Kryptor system is an

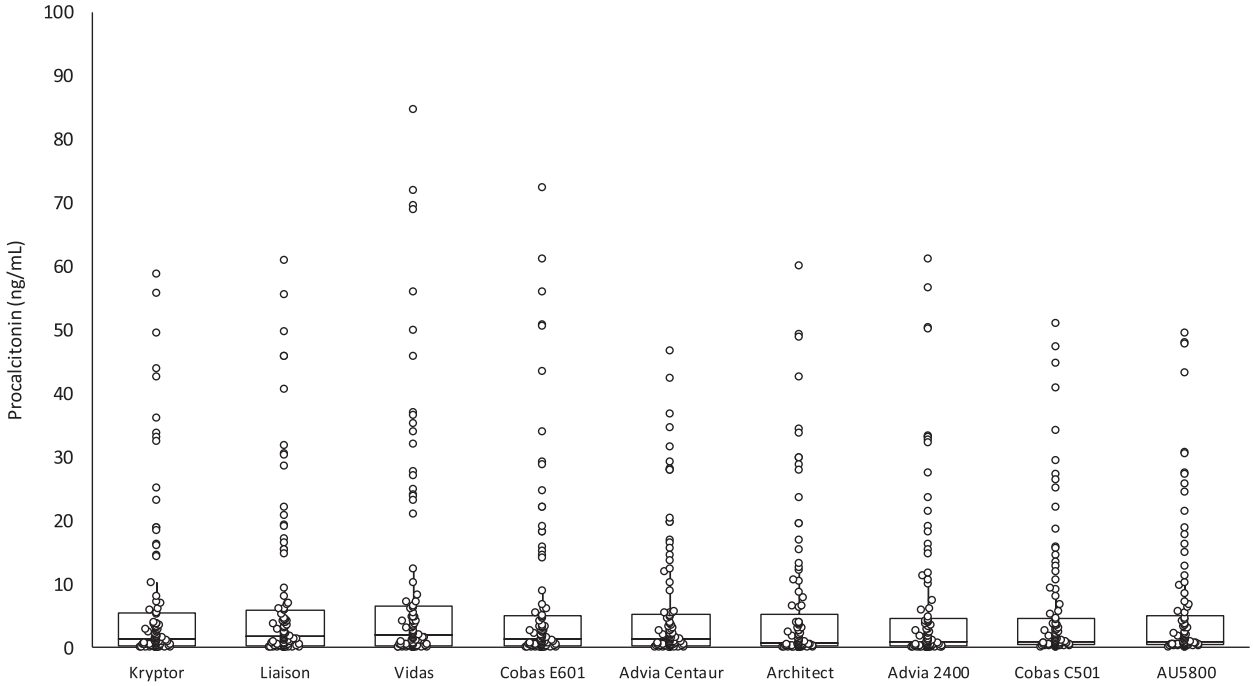

Fig. 1. Distribution of procalcitonin values (median and interquartile range) obtained with the different reagents and instruments (see Table 1 for details).