Influence of Steroids on Procalcitonin and C-reactive Protein in Patients with COPD and Community-acquired Pneumonia

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Abstract

Background: The induction of C-reactive Protein (CRP) may be attenuated by corticosteroids, whereas Procalcitonin (PCT) appears to be unaltered. We investigated, whether in community-acquired pneumonia (CAP) a combined antibiotic-corticosteroid therapy may actually lead to different slopes of decline of these inflammatory markers.

Patients and Methods: We studied the slopes of decline of PCT and CRP serum levels during 7 consecutive days as well as clinical parameters in a group of patients with CAP on or off corticosteroids. Patients with underlying COPD received systemic corticosteroids (n = 10), while non-COPD patients (n = 10) presenting with CAP alone formed the control group. All patients were treated with antibiotics.

Results: At baseline, relevant clinical and laboratory characteristics of the two groups were similar. Regarding the decreasing shapes of the curves from PCT and CRP, no significant differences were found (p-value = 0.48 for the groups for CRP, respectively 0.64 for PCT). All patients showed an uneventful recovery.

Conclusion: In patients with COPD and CAP, the time courses over 7 days of PCT and CRP showed a nearly parallel decline compared to non-COPD patients with CAP. Contrary to the induction phase, corticosteroids do not modify the time-dependent decay of PCT and CRP when the underlying infectious disease (CAP) is adequately treated.

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Introduction

Several authors report that the induction of C-reactive protein (CRP) in septic patients is attenuated by corticosteroids [1–3], whereas Procalcitonin (PCT) appears to be unaltered [1, 2]. Accordingly, when judging the process of healing from an infectious disease under antibiotic treatment by analyzing the evolution of CRP, a concomitant corticosteroid therapy could be an important confounding factor. Theoretically, when comparing between groups on or off corticosteroids, CRP should therefore show different slopes of decline, whereas for PCT one might expect almost parallel time dependent decays.

Patients with COPD and CAP often require a corticosteroid treatment in addition to antibiotics [4]. We therefore prospectively investigated the time-courses of PCT and CRP in these patients and compared them with a group of patients with CAP but without underlying COPD.

Patients and Methods

Study Subjects

This is prospective-observational, two-center, longitudinal pilot study, whose protocol and methods were approved by the local Ethics Committee; the investigation was registered in the Clinical Trials.gov-Protocol Registration System [NCT00141973].

During November 2004 and March 2006 we consecutively enrolled all patients presenting to the Emergency Rooms with the clinical suspicion of CAP, when they fulfilled the following inclusion criteria: age ≥ 18 years, written consent, a newly diagnosed CAP associated or not with a known COPD, ≥ 2 SIRS criteria [5]. The diagnosis of CAP and COPD were established according to published recommendations [6, 7]. Exclusion criteria were ongoing or prior (≤ 1 month) therapy with corticosteroids and ongoing antibiotic therapy. Patients with known COPD formed the steroid group while the others served as control group. We enrolled ten patients in the steroid group and ten in the control group. Six patients from the steroid group...
respectively one from the control group were transferred to the ICU’s for non invasive or invasive mechanical ventilation.

**Study Design**

Antibiotic treatment of patients with CAP on/off corticosteroids. We daily registered serum levels of PCT and CRP, white blood count (WBC) and clinical parameters.

**Methods**

Baseline assessment, carried out by study physicians in the Emergency Room, included clinical data, routine blood tests and microbiological sampling. Thereafter the first dose of antibiotics (ceftriaxone and clarithromycin) was given, patients of the steroid group also received an endovenous push of 125 mg of methylprednisolone, followed by prednisone 0.5 mg/kg po once daily. Further antibiotic treatment (choice of drug, duration) was at the treating physicians’ discretion. Recovery was defined as absence of SIRS (0 or 1 criterion fulfilled) combined with the clinical evaluation by the treating physicians. Blood samples were collected daily to determine WBC, CRP and PCT. CRP was measured with Hitachi 912 (Tina-quant®; Roche Diagnostics, Mannheim, Germany). PCT was determined in serum with Kryptor (Brahms Diagnostica GmbH, Berlin, Germany) using the TRACE-technology (Time-Resolved Amplified Cryptate Emission); lower detection limit: 0.02 ng/ml.

**Analysis**

The main parameters were summarized and compared with the baseline. Non-parametric tests were used. Unless specified, Wilcoxon tests were used to compare the different groups. The time course concentrations of PCT and CRP were fitted with a one compartment model so as to estimate the slope of decline and the initial concentration. Non linear mixed effects models were used, followed by log ratio tests when a difference between the control and the steroid group was investigated. The analyses were done with S-Plus® 7.0 Enterprise Developer. A p-value under 5% was considered significant to reject the null hypothesis of a test; results below 10% are also mentioned explicitly given the explorative approach of this pilot study.

**Results**

Patient demographics and baseline data are summarized in table 1. Patients with COPD were sicker by means of SAPS II [8] and length of hospital stay, and were older than those in the control group (p-value 0.07 for all). Microbiological analysis revealed four positive blood cultures with *Streptococcus pneumoniae* in both groups.

Levels of systemic markers of infection are listed in table 2. Median peak values of PCT and CRP on day 1 did not differ statistically between the two groups (p-value = 0.97 for PCT, 0.63 for CRP). The evolution over seven days for the two groups of PCT and CRP is illustrated in figure 1. Regarding PCT, the time courses for both groups were similar: no significant difference was observed with respect to the main parameters used to describe the curves; that is, the coefficient of decrease (p-value = 0.64) and the estimated maximum concentration (p-value = 0.17). For CRP, there is some weak evidence that the concentration in the control group remains globally higher than in the steroid group (area under the curve p-value = 0.057), whereas the maximal concentrations (p-value = 0.60) and the coefficient of decrease (p-value = 0.48) were not statistically different.

The WBC and the body temperature at study entry were similar (p-value = 0.73 and 0.14, respectively). The decline of the body temperature (mean difference between day 1 and day 7: –1.9 °C, p-value < 0.001) and the WBC (mean difference between day 1 and day 7: –5.0 G/l, p-value 0.004) are illustrated in figure 1. All patients showed an uneventful recovery.

**Discussion**

This pilot trial prospectively assessed the time courses of PCT and CRP in two groups of patients with CAP, whereof one group was constituted by patients with COPD, requiring corticosteroids. As the induction of CRP in septic
patients is attenuated by corticosteroids [1–3], we hypothesized that this inflammatory marker may actually present different slopes of decline between the two groups.

From a clinical point of view all patients had an uneventful recovery from the CAP. Concerning PCT and CRP we observed a rapid and almost parallel decline of both inflammatory serum markers in the two groups. Thus, contrary to the previously mentioned suggestions [1–3] and to our hypothesis, the combination of antibiotics and steroids in a population of patients with COPD presenting with CAP did not produce a significant difference in the slope of decline in serum CRP levels as compared to a population of patients with CAP treated with antibiotics alone.

How could this apparent contradiction be interpreted? There are at least two plausible explanations: first, our observation only considered patients with CAP at a very early stage of the disease, whereas the results from the other authors have referred to septic patients of different origins [1, 2], to different stages of disease [1–3], to patients with an ongoing antibiotic treatment [2, 3] or (part of them) with ongoing corticosteroids [1] and to discontinuous measurements of serum inflammatory markers (day 1, day 2 and day of discharge) [1]. Second, the immediately instituted antibiotic therapy led to rapid and complete healing of all our patients while the other authors reported longer LOS and also unfavourable outcomes [1–3]. It is important to emphasize, that by means of our data we can only comment on the baseline serum levels and the consecutive slopes of decline of the inflammatory markers, e.g. from the very moment, an adequate therapy has been introduced. The disparity of our results with those presented by the previous authors [1–3] emphasizes that serum values of inflammatory parameters can not be interpreted without the clinical context: an ongoing bacterial infection – unresponsive to antibiotics – will be a potent inflammatory stimulus that maintain synthesis of PCT and CRP, unless corticosteroids ultimately interfere with the latter. Once the bacterial infection is adequately treated, the induction of inflammatory parameters will no longer be stimulated, and by consequence there is no further possibility of interference for corticosteroids. Thus, one will only observe the decline of CRP and PCT, that should correspond to their proper half lives.

The time courses of the WBC and the body temperature from the control group showed a similar decline as reported elsewhere [9], whereas the analogous traces for the steroid group were altered in a well known matter: the antipyretic effect of corticosteroids leaded to a initially more rapid thermal decrease but a slower drop of the WBC due to a prednisone-induced leukocytosis.

### Table 2

<table>
<thead>
<tr>
<th>Steroid (n = 10)</th>
<th>Control (n = 10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/ml)</td>
<td>2.31 ± 2.79</td>
<td>0.97</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>236.0 ± 163.1</td>
<td>0.03</td>
</tr>
<tr>
<td>WBC (G/l)</td>
<td>14.9 ± 6.7</td>
<td>0.14</td>
</tr>
<tr>
<td>T (°C)</td>
<td>38.1 ± 1.6</td>
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Data expressed as median ± median absolute deviation.
Our pilot study has several limitations: first, due to the reduced number of patients in both groups our study was certainly underpowered for detecting a significantly different kinetics of the two serum markers. Given the variability of the data, a number of at least 70 patients would be necessary to detect a significant difference of ≥ 0.5 day for half-life, with a probability of at least 80%. Second, the patient assignment to the two study groups (and hence the need for concurrent corticosteroid therapy) was not random but determined by the presence of underlying COPD. Theoretically COPD – a systemic disease – could have affected PCT and/or CRP production, modifying either the baseline values and/or their time-dependent decay. Thus, although the serum values of the biochemical markers did not differ statistically between the two groups it might have been incorrect to assume that they had similar inflammatory states. Indeed, patients form the steroid group actually had a significantly higher SAPS II and generally showed a trend toward more severe illness (older age, lower PaO₂/FiO₂, higher need for ICU care, more comorbidities). Notwithstanding these hypothetical limitations, adequately treated patients from the steroid group showed a nearly parallel decline of PCT and CRP, respectively, when compared to the control group. We therefore suppose, that in this particular situation (uneventful recovery from CAP under antibiotic therapy) the presence of COPD did not introduce such inherent inconsistencies between groups as to consequently prohibit a comparison. Unfortunately there is no ideal patient population to suggest for studying the effect of steroids on these inflammatory markers: such a study would dictate either withholding steroids when they are clinically indicated or administering steroids in a situation when this is not the standard of care.

Finally, one might argue that only septic patients without clinical signs of recovery present dissociated slopes of decline between PCT and CRP, when subjected to corticosteroid treatment. We thus suppose, that our results are rather complementary than contradictory to those of the other studies [1–3]. As our pilot study generates a hypothesis with clinical implications, further confirmation upon a larger, homogenous population is required. We conclude, that in patients affected by COPD and presenting with CAP, the slopes over 7 days of PCT and CRP showed a nearly parallel decline compared to those with CAP but without COPD. Contrary to the induction phase, our results suggest that corticosteroids might not modify the time-dependent decay of CRP when the underlying infectious disease (CAP) is adequately treated.

References
