

Letter to the Editor

Serum procalcitonin as a biomarker differentiating delayed-type drug hypersensitivity from systemic bacterial infection

To the Editor:

Drug hypersensitivity can present in various ways, and the symptoms and signs are not specific. For this reason, drug hypersensitivity that involves symptoms such as fever is often confused with infectious diseases, and vice versa. If fever with a skin rash develops while several drugs are being administered, it is difficult to tell whether this is caused by drug hypersensitivity or by an uncontrolled infection, especially if antibiotics have been used to treat a suspected bacterial infection.

In fact, the diagnosis of drug hypersensitivity is clinical and is a diagnosis of exclusion, because laboratory measurements are rarely helpful to diagnose it. But because drug hypersensitivity can be life-threatening, early detection and withdrawal of the causative agent is crucial. Drug hypersensitivity mimicking a bacterial infection may lead to the misuse or overuse of antibiotics; systemic corticosteroids may be needed, rather than antibiotics. For these reasons, it is essential to find biomarkers that can differentiate drug hypersensitivity from systemic bacterial infection.

Procalcitonin, with a molecular mass of 14.5 kDa, is the 116 amino acid polypeptide precursor of calcitonin, a calcium regulatory hormone that is produced by the C cells of the thyroid gland.¹ Serum levels of procalcitonin are below the detection limit in healthy subjects, but are generally elevated in patients with a systemic bacterial infection.^{1,2} We conducted this study to determine the usefulness of serum procalcitonin levels in differentiating delayed-type drug hypersensitivity from systemic bacterial infection.

The study involved 95 patients who were admitted with delayed-type drug hypersensitivity to the Department of Allergy at the Asan Medical Center between January 2009 and January 2011. All patients were confirmed to be free of systemic bacterial infection by blood culture at the time of enrollment. We also included 47 patients with proven bacterial infection from our hospital's intensive care unit. The diagnosis of systemic bacterial infection was defined only if pathogens were isolated in blood cultures, and the patients were clinically diagnosed with sepsis by intensive care unit specialists. These patients were free of any skin rash or drug hypersensitivity at the time of obtaining blood. Another 45 healthy subjects with no known underlying disease or drug allergy were recruited as the control group. We reviewed the baseline demographics and laboratory data including the procalcitonin and C-reactive protein (CRP) levels. The procalcitonin level was measured by using an immunoluminometric assay (VIDAS B.R.A.H.M.S. PCT; bioMérieux, Saint Laurent, Quebec, Canada). The threshold of detection of procalcitonin defined by our laboratory is 0.05 ng/mL. Serum procalcitonin levels of more than 0.5 ng/mL were considered abnormal. The CRP level was measured by using a latex immunoturbidimetric assay (Tina-quant CRP [latex] HS Test System; Roche, Basel, Switzerland), and the limit of detection of CRP is 0.1 mg/L. The protocol was approved by the Institutional Review Board and Ethics Committee of Asan Medical Center.

Statistical analysis was performed with SPSS 18 (SPSS, Chicago, Ill). The Kruskal-Wallis test, 1-way ANOVA, or

TABLE I. Serum levels of procalcitonin and CRP in the study groups

	Drug hypersensitivity (n = 95)	Bacterial infection (n = 47)	Normal control (n = 45)	P value
Procalcitonin (ng/mL)	0.53 ± 1.19	24.45 ± 34.39	0.05 ± 0.001	<.001*
CRP (mg/dL)	5.04 ± 5.47	18.56 ± 10.68	0.12 ± 0.17	<.001*

*P < .05.

Pearson's χ^2 test were used to compare the 3 groups (drug hypersensitivity, bacterial infection, and the control group). We constructed estimated receiver operating characteristics curves to evaluate the diagnostic power of procalcitonin and CRP by measuring areas under the curves. Multivariate logistic analysis was used to determine the risk of bacterial infection by using odds ratios (ORs).

Patients in the bacterial infection group were older (65.02 ± 13.94 vs 55.14 ± 15.34 , $P < .001$) and had a higher body mass index (24.16 ± 2.38 vs 22.8 ± 3.81 , $P = .023$) than did the drug hypersensitivity group. There were also more men than women in the bacterial infection group, but the difference was not statistically significant.

In the drug hypersensitivity group, the most common phenotype was maculopapular rash (47, 49.5%), followed by Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (20, 21.0%), and drug reaction and eosinophilia with systemic symptoms (DRESS: 15, 15.8%). Other phenotypes were fixed drug eruption, vasculitis, purpura, and acute generalized exanthematous pustulosis. The most common culprit drugs were cephalosporins (16.8%) and nonsteroidal antiinflammatory drugs, followed by penicillins (9.5%), antiepileptic drugs (8.4%), and allopurinol.

Serum procalcitonin levels were highest in the bacterial infection group, followed by the drug hypersensitivity group and the control group ($P < .001$) (Table I). Ninety-one percent of the patients (44 of 47) in the bacterial infection group had serum procalcitonin levels above 0.5 ng/mL. In the drug hypersensitivity group, 79% (75 of 95) of the patients had serum procalcitonin levels below 0.5 ng/mL. Among 20 patients with drug hypersensitivity whose serum procalcitonin levels were more than 0.5 ng/mL, 80% (16 of 20) had serum procalcitonin levels below 1.67 ng/mL (the best cutoff value determined in this study; see below) and only 4 patients had higher serum procalcitonin levels: 2 of these 4 patients were with SJS/TEN, 1 with DRESS, and 1 with maculopapular rash. Excluding these 4 subjects, the patients with SJS/TEN had the highest serum procalcitonin levels (0.91 ± 1.78 ng/mL), followed by patients with DRESS (0.79 ± 1.54 ng/mL) and maculopapular rash (0.36 ± 0.86 ng/mL) ($P = .011$). There was no significant difference according to culprit drugs in the drug hypersensitivity group.

Serum CRP levels were also highest in the bacterial infection group (Table I). When we applied the best cutoff value, 19 patients in the drug hypersensitivity group had false-positive results. Excluding these patients, the serum CRP level was highest in the SJS/TEN group (8.5 ± 6.85 mg/dL), followed by patients with

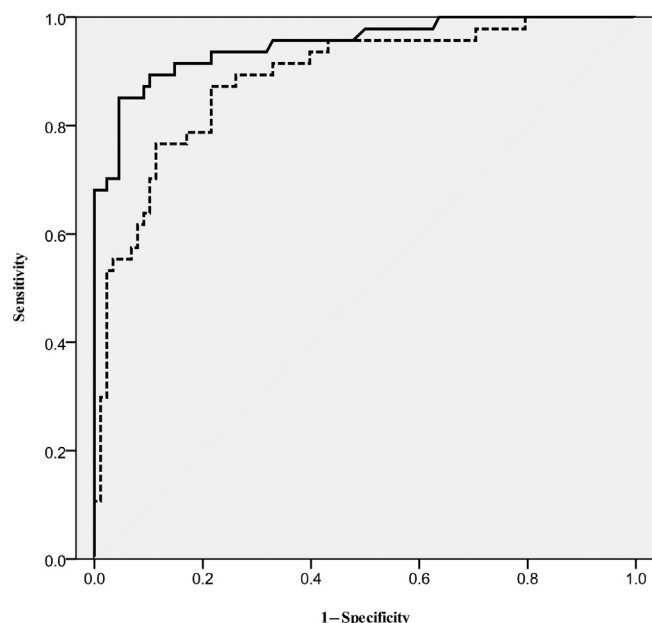


FIG 1. Receiver operating characteristics curves for serum procalcitonin and CRP levels in differentiating drug hypersensitivity from bacterial infection. The area under the curve for procalcitonin was 0.95 (95% CI, 0.91-0.99) and for CRP, it was 0.85 (95% CI, 0.82-0.94).

DRESS (4.55 ± 3.54 mg/dL) and maculopapular rash (3.51 ± 3.21 mg/dL), although these results were not statistically significant.

The area under the curves of the receiver operating characteristics curve for procalcitonin was higher than that for CRP (0.95, 95% CI, 0.91-0.99 vs 0.88, 95% CI, 0.82-0.94). The best cutoff value for the serum procalcitonin level to differentiate drug hypersensitivity from bacterial infection was estimated to be 1.67 ng/mL, and sensitivity and specificity at that value were 85.1% and 95.5%, respectively. Serum CRP level had the highest sensitivity and specificity at 6.67 mg/dL (sensitivity 87.2% and specificity 78.4%, respectively) (Fig 1).

Multivariate logistic regression analysis including age, body mass index, and serum CRP level showed that high procalcitonin was a stronger risk factor for bacterial infection than for drug hypersensitivity; the OR was 2.917 (95% CI, 1.620-5.252; $P < .001$). Age and serum CRP level were also risk factors for bacterial infection, but the ORs of these variables were lower than those of serum procalcitonin.

We found that serum procalcitonin is a good biomarker because it can distinguish delayed-type drug hypersensitivity from bacterial infection with a greater sensitivity and specificity than does the serum CRP level. To our knowledge, this is the first study to evaluate the diagnostic usefulness of serum procalcitonin levels in patients with drug hypersensitivity.

It is well known that high serum procalcitonin levels occur mainly in systemic bacterial infections,¹ and studies have shown that serum procalcitonin levels are below 0.50 ng/mL in malignant tumors, pulmonary infarction,³ viral infection,⁴ and autoimmune diseases.² Procalcitonin levels show more sensitivity and specificity than do CRP levels for distinguishing bacterial infections from disease flares in autoimmune disease.⁵ According to a recent study, 56 patients with systemic inflammatory responses including malignancy, viral infection, allergy, and drug-induced

inflammation had a significantly lower frequency of positive procalcitonin tests (≥ 0.5 ng/mL) than did a bacterial infection group.⁶

Interestingly, serum procalcitonin levels tended to increase according to the severity of the drug hypersensitivity phenotypes. Mean serum procalcitonin level was higher in patients with SJS/TEN than in those with DRESS and maculopapular rash. This suggests that serum procalcitonin level may depend on the severity of inflammation, although it is lower in the drug hypersensitivity group than in the bacterial infection group. A meta-analysis has shown that procalcitonin levels are closely correlated with the severity of sepsis and outcomes.⁷

On multivariate analysis after adjusting for other variables, serum procalcitonin levels were more predictive than CRP levels, although both were independent risk factors for bacterial infection. A previous study showed that serum CRP and IL-6 levels could be lowered by corticosteroid administration, unlike serum procalcitonin levels.^{8,9} Therefore, we expect that high serum procalcitonin level may be a useful biomarker for distinguishing drug hypersensitivity from bacterial infection, even when patients are being treated with corticosteroids or other immunosuppressive agents.

Our study involved patients with rare diseases in a single hospital, and so the number of cases was small and the study was cross-sectional. In addition, we included only sepsis patients with proven bacteremia to differentiate from drug hypersensitivity definitely. Therefore, the predictive value of serum procalcitonin level may be diminished in patients with less severe infection. Another limitation is that we did not follow up the levels of procalcitonin. Further study of the correlation between serum procalcitonin level and drug hypersensitivity is needed.

In conclusion, the levels of serum procalcitonin may be a better biomarker than serum CRP levels for distinguishing delayed-type drug hypersensitivity from systemic bacterial infection. Appropriate use of serum procalcitonin levels could help physicians make critical life and death decisions.

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