LETTER TO THE EDITOR

Copeptin levels upon corticosteroid treatment in acute community-acquired pneumonia

In the past few years, copeptin, which is a stable surrogate marker for arginine vasopressin (AVP) activity, has emerged as a marker for disease severity and as a predictor for outcome in the setting of acute illness.[1 2] Increased levels of copeptin have been shown in septic shock,[1] acute stroke,[3] in myocardial infarction,[4] and in community-acquired pneumonia.[5] However, little is known about the dynamics of copeptin levels in acute illness and about its response to anti-inflammatory treatment. Earliest evidence for corticosteroid-dependent regulation of AVP comes from studies dating back to 1967 showing that administration of corticosteroids reduced AVP levels in patients with adrenal cortisol deficiency. Furthermore, corticosteroid treatment was shown to reduce AVP expression in the posterior pituitary.[6 7] In 2008, a first study addressed the question of corticosteroid-dependent AVP regulation in a human model of endotoxinemia.[8] Thereby, pretreatment with corticosteroids dose dependently inhibited the increase in copeptin levels. However, no study so far has investigated the dynamics of copeptin in acute disease treated with and without corticosteroids in a real-life setting.

We hypothesized that copeptin levels in patients with acute pneumonia treated with corticosteroids show a faster decrease compared with patients not treated with corticosteroids. Therefore, we performed a secondary analysis of a randomized, placebo-controlled trial.[9] Two hundred and eighty-nine patients who were admitted to the University Hospital Basel for community-acquired pneumonia were treated with either 50 mg of adjunct prednisone (n=143) or placebo (n=146) daily. Copeptin levels were measured on the first and third days of hospitalization using an automated immunofluorescent assay in EDTA plasma (Thermo Scientific, BRAHMS).

Table 1 Baseline characteristics

Characteristic/variable	Prednisone (n=143)	Placebo (n=146)
Sex (male)	93 (65.0)	91 (62.3)
Age (y)	72 (±17)	70 (±17)
BMI (kg/m^2)	25.5 (±5.1)	27.7 (±7.7)
PSI (points)	97.7 (±37.7)	92.7 (±36.4)
Days with symptoms	6.4 (±10.4)	6.2 (±8.7)
Body temperature (°C)	38.1 (±0.8)	38.0 (±0.9)
Blood pressure (systolic, mm Hg)	125 (±21)	126 (±22)
Heart rate (min^{-1})	87 (±18)	87 (±18)
Respiratory rate (min^{-1})	21 (±5)	21 (±6)
SaO_2 (%)	94.5 (±3.2)	95.1 (±2.9)
Procalcitonin (ng/mL)	5.4 (±14.3)	4.2 (±13.1)
C-reactive protein (mg/L)	174 (±107)	166 (±117)
White cell count (x10^9/L)	12.9 (±5.6)	11.8 (±6.9)
Chronic obstructive pulmonary disease	31 (21.7)	18 (12.3)
Chronic heart failure	31 (21.7)	29 (19.9)
Cerebrovascular disease	14 (9.8)	13 (8.9)
Renal insufficiency	51 (35.7)	48 (32.9)
Other infections	13 (9.1)	15 (10.3)
Active carcinoma	7 (4.9)	8 (5.5)

Data are reported as means (±SD) or n (%).
BMI, body mass index; PSI, pneumonia severity index.

The effect of prednisone on copeptin was investigated by comparing the difference of copeptin levels between day 1 and day 3. Due to non-normality of the data, a Wilcoxon rank-sum test was performed. A p value <0.05 was considered statistically significant. Analyses and graphics were performed using R software V.i386 3.4.1.

Table 1 shows a summary of the baseline characteristics. Briefly, the majority of patients were male, aged 70 years and had a mean pneumonia severity index score of 95, indicating a high risk for mortality. At baseline, median copeptin levels were 14.2 pmol/L (IQR 7.0–36.8) in the prednisone group and 12.2 pmol/L (IQR

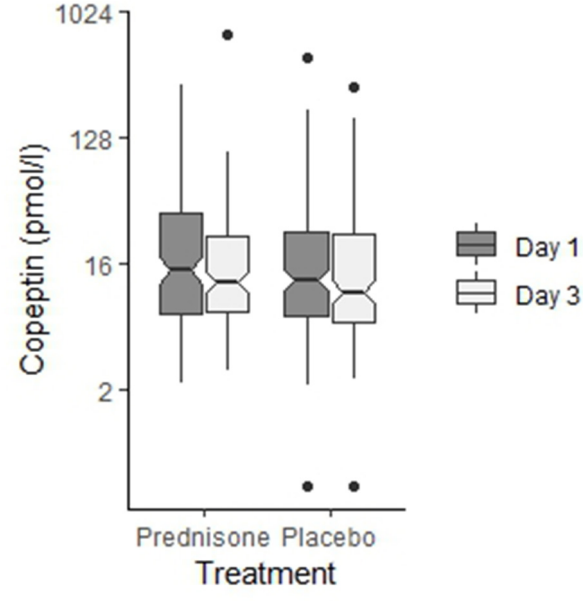

Figure 1 Box plots of the copeptin levels over time in the 2 treatment groups (dark grey: day 1, light grey: day 3).

6.7–26.9) in the placebo group. On day 3, median copeptin levels were 11.6 pmol/L (IQR 7.1–25.6) in the prednisone group and 10.0 pmol/L (IQR 6.1–26.3) in the placebo group (figure 1). Forty-eight hours from baseline, the median decrease in copeptin levels was 1.3 pmol/L in the prednisone, and 1.2 pmol/L in the placebo group, which was neither clinically nor statistically significant (p=0.25).

The main result of our study is that corticosteroid treatment with 50 mg of prednisone did not reduce copeptin levels to a higher extent than placebo over time. These findings stand in contrast to previous studies. de Kruif *et al* showed a dose–response decrease of copeptin on corticosteroid treatment. On first sight, this is surprising, since we even used a higher dose equivalent of corticosteroids (ie, 50 mg of prednisone) than in the endotoxemia model where doses of 3, 10, and 30 mg were used. However, there are substantial differences between the 2 studies. First, in contrast to this study, the study by de Kruif *et al* was performed in healthy volunteers with an experimental model of illness. Importantly, in the endotoxemia model, corticosteroids were given before administration of lipopolysaccharide (LPS). In contrast, the patients in our study received corticosteroids only after admission to hospital, meaning that inflammation due to infection was already at its maximum. Furthermore, the largest effect was observed 4 hours after LPS administration. Our study compared the effect at 48 hours from baseline. Finally, in contrast to community-acquired pneumonia, LPS-induced illness is self-limiting within several hours, whereas the subjects in our study had already suffered several days from the disease. Therefore, the effect of corticosteroids on AVP neurons seems to be only present in patients who are pretreated with corticosteroids before inflammation reaches its maximum.

Our study has strengths and limitations. Strengths are the large sample size and the real-life setting. Limitations are the lack of interval measurements and the retrospective analysis.

We conclude that in a real-life setting in patients with ongoing infection, corticosteroids do not have an effect on the dynamics of copeptin at 48 hours after treatment start.

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REFERENCES

1 Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. *Peptides* 2005;26:2500–4.
2 Odermatt J, Bolliger R, Hersberger L, *et al*. Copeptin predicts 10-year all-cause mortality in community patients: a 10-year prospective cohort study. *Clin Chem Lab Med* 2016;54:1681–90.
3 Katan M, Fluri F, Morgenthaler NG, *et al*. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. *Ann Neurol* 2009;66:799–808.
4 Khan SQ, Dhillon OS, O'Brien RJ, *et al*. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. *Circulation* 2007;115:2103–10.
5 Müller B, Morgenthaler N, Stolz D, *et al*. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. *Eur J Clin Invest* 2007;37:145–52.
6 Ahmed AB, George BC, Gonzalez-Auvert C, *et al*. Increased plasma arginine vasopressin in clinical adrenocortical insufficeincy and its inhibition by glucosteroids. *J Clin Invest* 1967;46:111–23.
7 Erkut ZA, Pool C, Swaab DF. Glucocorticoids suppress corticotropin-releasing hormone and vasopressin expression in human hypothalamic neurons. *J Clin Endocrinol Metab* 1998;83:2066–73.
8 de Kruif MD, Lemaire LC, Giebelen IA, *et al*. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensive Care Med* 2008;34:518–22.
9 Blum CA, Nigro N, Briel M, *et al*. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015;385:1511–8.