Low-dose ACTH testing does not predict treatment response to corticosteroids in community-acquired pneumonia

C.A. Blum[1,2,4], P. Schuetz[2], N. Nigro[1], B. Winzeler[1], B. Arici[1,2], J. Refardt[1], S.A. Urwyler[1], M. Briel[1,3], B. Mueller[2], M. Christ-Crain[1]

[1]University Hospital Basel, Departments of Endocrinology, Diabetology and Metabolism, Internal Medicine and Clinical Research, Switzerland; [2]Medical University Clinic, Kantonsspital Aarau, Switzerland; [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; [4]Service d'Accueil des Urgences, CHU Pitié-Salpêtrière, Paris, France

BACKGROUND

It is highly debated whether the attenuated increase of circulating cortisol to ACTH stimulation predicts treatment response to corticosteroids in patients with critical illness,[1,2] and the use of the low-dose ACTH test is controversial.[3,4] We investigated whether ACTH testing predicts treatment response to corticosteroids in patients with community-acquired pneumonia (CAP).

METHODS

We performed a low dose (1 µg) ACTH test on admission in a prospective randomized, double-blind, placebo-controlled multicenter trial comparing prednisone 50 mg for seven days to placebo in patients hospitalized with CAP. The results of the main study showed a benefit of corticosteroids in community-acquired pneumonia.[5] Cortisol was measured at baseline and 30 min after stimulation with 1µg ACTH. We performed Cox regression models for time to clinical stability to compare baseline and stimulated cortisol levels between both treatment groups.

RESULTS

347 patients in the prednisone group and 331 patients in the placebo group completed ACTH test and were evaluated.
Baseline data are shown in table 1.
Time to clinical stability in patients with a basal cortisol > median (571 nmol/L) was significantly longer in both groups (4.4 vs. 2.1 days, p<0.0001 in the prednisone and 5.0 vs. 3.0 days in the placebo group, p=0.0003; see Figures 1 and 2). This occurred in 176 (51%) patients in the prednisone group and 163 (49%) patients in the placebo group.

Table 1. Baseline Characteristics.
Data are shown as median (IQR) or n (%).

Characteristic	Prednisone group, n=347	Placebo group, n=331
Age	73 (61-83)	73 (60-82)
Male sex	221 (61%)	210 (63%)
PSI class I-III*	169 (49%)	178 (54%)
PSI class IV-V	178 (51%)	152 (46%)
C-reactive protein	162 (85-250)	170 (79-250)
Leukocytes	12.2 (8.9-15.7)	11.9 (8.7-15.6)
Baseline cortisol	577 (400-750)	565 (391-764)
Stimulated cortisol	877 (714-1039)	851 (711-1064)
Diabetes mellitus	67 (19%)	66 (20%)
COPD	66 (19%)	54 (16%)
Cerebrovascular disease	39 (11%)	26 (8%)
Renal insufficiency	109 (31%)	111 (34%)
Neoplastic disease	22 (6%)	22 (7%)

*The Pneumonia Severity Index is a clinical prediction rule for morbidity and mortality in CAP. Classes I-III are low-risk and IV-V high-risk.

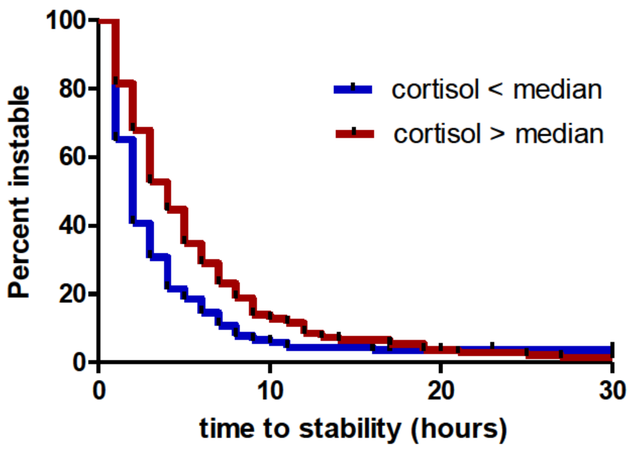

Figure 1. Time to clinical stability according to baseline cortisol, prednisone group

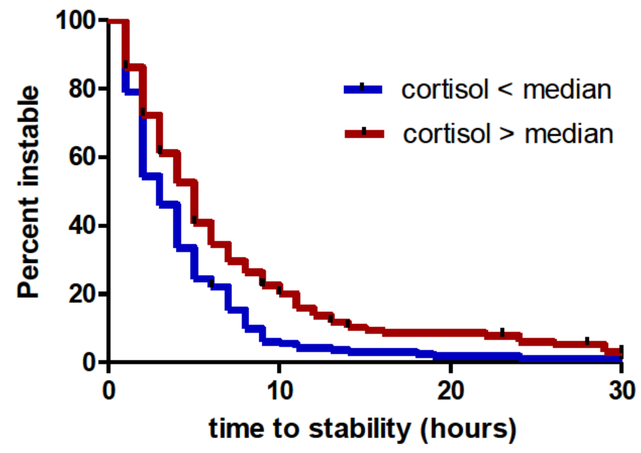

Figure 2. Time to clinical stability according to baseline cortisol, placebo group

However, in Cox regression model, basal plasma cortisol levels did not predict treatment response to prednisone (p for interaction = 0.942 for cortisol >median of 571 nmol/L and p for interaction = 0.664 for the proposed cutoff of cortisol > 938 nmol/L in other studies[6]).
Similarly, neither a delta cortisol < 250 nmol/L after ACTH stimulation (p for interaction = 0.840) nor the combination of basal cortisol and delta cortisol predicted treatment response to corticosteroids (p for interaction = 0.824 for combination delta cortisol <250 nmol/L+baseline cortisol 571 nmol/L and p for interaction = 0.821 for the combination delta cortisol < 250 nmol/L+baseline cortisol > 938 nmol/L).

CONCLUSION

Even though corticosteroids shorten time to clinical stability in CAP, our data suggest that a low-dose ACTH test does not predict treatment response to corticosteroids in patients with CAP of any severity.
This suggests a pharmacological effect of corticosteroids in patients with critical illness or CAP and argues against a critical illness-related corticosteroid insufficiency (CIRCI).

REFERENCES

1. Annane D. Corticosteroids for severe sepsis: an evidence-based guide for physicians. Ann Intensive Care. 2011 Apr 13; 1(1):7.
2. Venkatesh B, Cohen J. The utility of the corticotropin test to diagnose adrenal insufficiency in critical illness: an update. Clin Endocrinol. 2015 Dec 18.
3. Siraux V. et al. Relative adrenal insufficency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. Crit Care Med. 2005 Nov; 33 (11):2479-86.
4. Annane D. Low dose adrenocorticotropic hormone test is not ready for routine adrenal function testing in the intensive care unit Crit Care Med 2005 Nov; 33(11): 2688-9.
5. Blum CA et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2015 Jan 16. pii: S0140-6736(14)62447-8.
6. Annane D. et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000 Feb 23, Vol 283, No.8.

CORRESPONDENCE

Dr. med. Claudine Blum
Service d'Accueil des Urgences
CHU Pitié-Salpêtrière
Paris, France
claudineblum@yahoo.com
0041 76 303 07 57

DOI: 10.3252/pso.eu.17ece.2015