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Letter to the Editor

Appropriateness of ordering serum angiotensin-converting enzyme during renin-angiotensin-aldosterone system inhibitor therapy

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Sarcoidosis is a multisystem inflammatory disease of unknown etiology that manifests as non-caseating granulomas, predominantly in the lungs and intrathoracic lymph nodes, but possibly affecting any organ. Sarcoidal granulomas produce angiotensin-converting enzyme, and measurement of serum angiotensin-converting enzyme (SACE) activity is frequently part of the diagnostic workup of sarcoidosis. However, the value of SACE levels in diagnosing sarcoidosis remains controversial, due to suboptimal test specificity and sensitivity. [1] It is well established that treatment with ACE inhibitors (ACEIs) reduces SACE levels, making the measurement of SACE activity during ACEI treatment unreliable. [2–4] Angiotensin II receptor blockers (ARBs) offer an alternative route to block the renin-angiotensin-aldosterone system (RAAS). The effect of ARBs on SACE levels is unknown. In a retrospective study, we investigated the influence of RAAS-inhibitor therapy (ACEIs and ARBs) on SACE measurement and the implications of this interaction in clinical practice.

Retrospective analysis was performed of SACE levels recorded in the medical records of a cohort of patients evaluated in the general internal medicine department of the University Hospitals of Leuven, Belgium, between January 1st, 2013 and January 1st, 2016. From the electronic health records (EHR) we collected: age, sex, quantitative SACE level, active treatment with RAAS inhibitor, glucocorticoids or other immunosuppressive agents, arguments in favor of sarcoidosis or an alternative diagnosis. SPSS (version 24, IBM corporation) was used for statistical analysis. The significance of the group comparisons was determined by chi-square test and the non-parametric Mann–Whitney or Kruskal–Wallis tests. P values < 0.05 were considered significant.

In the time frame of 36 months, 903 SACE levels were analyzed, of which we excluded 138 test values of patients who had multiple measurements during the time period of the retrospective analysis (only the first measurement was considered). Furthermore, we excluded 19 test values obtained during simultaneous treatment with glucocorticoids and/or immunosuppressive agents. We included 746 SACE levels. Of these, 9.8% (n = 73) and 4.3% (n = 32) were measured during ACEI and ARB treatment, respectively. No patient was treated with direct renin inhibitors.

There is a significant difference in SACE levels between the ACEI and ARB treatment groups ($p < 0.001$). The SACE levels in patients treated with ACEI therapy are significantly lower compared to the group without RAAS inhibitor ($p < 0,001$). On the contrary, no significant difference is found between the SACE levels in patients treated with ARB therapy compared to the group without RAAS inhibitor ($p = 0,725$) (Fig. 1).

The lowest SACE levels were disproportionately found in patients with ACEI treatment. Of the SACE levels measured during ACEI treatment, 54.7% were suppressed (≤10 U/L), in contrast to the ARB- and no-RAAS inhibitor groups, where < 1% of SACE levels were suppressed (≤10 U/L). Among the elevated SACE levels (≥53 U/L), 4.7% of these values were measured during ARB treatment compared to 4.5% in the group of normal SACE levels (10–52 U/L).

In 7% of patients with a suppressed SACE level, measured during ACEI treatment, the SACE level was explicitly mentioned as a contributing argument against the diagnosis of sarcoidosis. In the ACEI treatment group, the diagnosis of sarcoidosis was established in 11% based on clinical, radiological and histological evidence, compared to 19% in the ARB group and 16% in the no-RAAS inhibitor group ($p = 0,48$).

ACEI are frequently used to treat a number of heart-related conditions, including high blood pressure, heart failure, heart attack, and to precent kidney damage associated with high blood pressure and diabetes. Despite the limited sensitivity and specificity of an elevated SACE measurement for diagnosing sarcoidosis (41.4% and 89.9% respectively), it often remains part of the diagnostic work up. [1] We confirm that SACE levels in patients actively receiving ACEI therapy are significantly lower than in patients receiving ARB therapy or no RAAS-inhibitor therapy. Although the inhibition of the SACE activity by ACEI therapy has been established for over thirty years, one in ten SACE levels was ordered during ACEI treatment in our tertiary care center, suggesting insufficient consideration of the influence of medical therapy on laboratory values in sarcoidosis workup. Routine implementation of an EHR warning prompt for active ACEI treatment, as proposed by Krasowski et al., might prevent misinterpretation when ordering SACE activity. [5]

In our study population, no significant difference was observed between the SACE levels in patients measured during ARB treatment and patients without RAAS inhibitor therapy. In addition, the ARB

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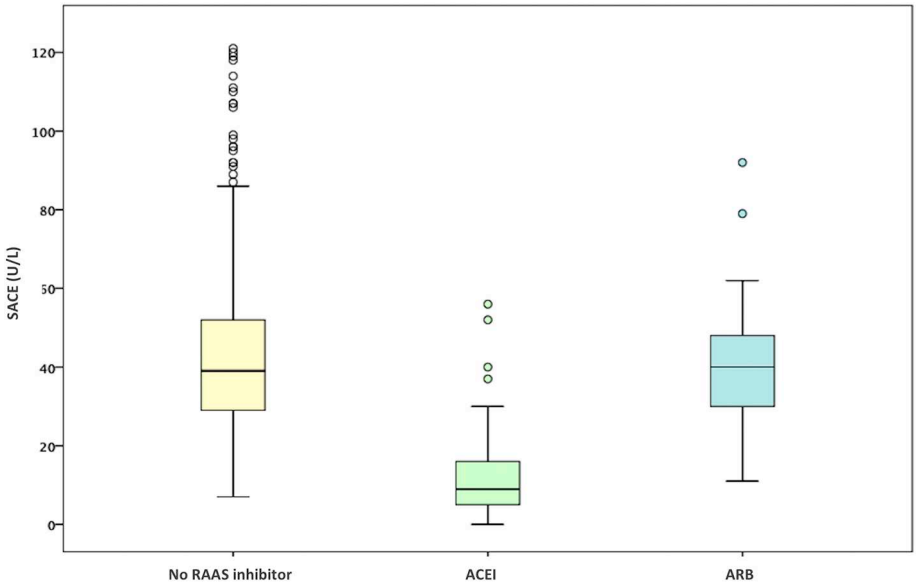

Fig. 1. Boxplot showing the distribution of SACE activity during treatment without RAAS inhibitor (n = 641) vs. ACEI (n = 73) vs. ARB (n = 32). SACE = serum angiotensin-converting enzyme; RAAS = renin angiotensin aldosterone system; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

group is not overrepresented in patients with a SACE level of ≥ 53 U/L, suggesting there is no influence of ARB treatment on SACE activity. Subsequently, we can conclude SACE activity can be safely interpreted during ARB treatment in sarcoidosis workup.

The frequent use of SACE measurement in sarcoidosis workup emphasizes the need for more performant biomarkers. Better understanding of environmental factors and progress in whole genome gene expression profiling may provide an opportunity to develop a new generation of biomarkers associated with sarcoidosis.

1. Conclusion

In summary, our data confirm that measurement of SACE levels during ACEI treatment is unreliable, possibly misguiding and should be discouraged. ARBs, in contrast, do not affect SACE activity, making interpretation of SACE levels during ARB therapy possible, although consideration of limited test sensitivity and specificity is advised.

Competing interests

The authors have no competing interests.

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A. Betrains[a], P. Vermeersch[c], S. Vanderschueren[b,*]
[a] *Clinical Department of Internal Medicine, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium*
[b] *Clinical Department of General Internal Medicine, University Hospitals Leuven Research Department of Microbiology and Immunology, Laboratory for Clinical Infectious and Inflammatory Disorders, KU Leuven, Herestraat 49, 3000 Leuven, Belgium*
[c] *Clinical Department of Laboratory Medicine, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium*
E-mail address: steven.vanderschueren@uzleuven.be (S. Vanderschueren)

* Corresponding author at: Department of General Internal Medicine, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium.