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Ordering of the Serum Angiotensin-Converting Enzyme Test in Patients Receiving Angiotensin-Converting Enzyme Inhibitor Therapy

An Avoidable but Common Error

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BACKGROUND: Serum angiotensin-converting enzyme (ACE) levels may be decreased by use of ACE inhibitor (ACEI) medication. In this study, we determined how often ACE levels were measured in patients receiving ACEI therapy.

METHODS: ACE levels analyzed over a 54-month preintervention time period at an academic medical center were reviewed retrospectively for tests performed during ACEI therapy. These data were compared with a large, deidentified dataset of ACE levels measured at a national reference laboratory; in vitro studies of ACEI inhibition; and liquid chromatography time-of-flight mass spectrometry detection of lisinopril in a subset of clinical specimens.

RESULTS: Over a 54-month period, 1,292 patients had ACE levels measured, with 108 patients (8.4%) receiving ACEI therapy at the time of testing. ACE levels measured for patients receiving ACEI therapy were substantially lower. In general, clinical teams did not recognize a medication effect on ACE levels. Introduction of a warning prompt in the electronic health record reduced the ordering of ACE levels in patients receiving ACEIs by >60% in a 17-month postintervention time period. The deidentified dataset of ACE levels at a reference laboratory showed a bimodal distribution, with a peak of very low ACE levels. Using liquid chromatography time-of-flight mass spectrometry, the presence of lisinopril was confirmed in a subset of specimens with low ACE activity. In vitro studies of two different ACE assays showed significant inhibition of activity at clinically relevant concentrations.

CONCLUSIONS: Assessment of ACE activity is often measured for patients receiving ACEIs, potentially leading to low ACE concentrations and inaccurate interpretations.

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ABBREVIATIONS: ACE = angiotensin-converting enzyme; ACEI = angiotensin-converting enzyme inhibitor; AMR = analytical measurement range; CPOE = computerized provider order entry; EDTA = ethylenediaminetetraacetic acid; EHR = electronic health record; LC-TOF-MS = liquid chromatography time-of-flight mass spectrometry; UIHC = University of Iowa Hospitals and Clinics

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Sarcoidosis is a multiorgan disease of unknown etiology.[1,2] The presence of noncaseating granulomas on histology is essential for diagnosis.[3] Measurement of serum angiotensin-converting enzyme (ACE) activity is used frequently in the diagnostic workup and management of sarcoidosis.[4,5] Elevated ACE levels are common in active sarcoidosis although they are not specific to the disease. ACE levels may be increased in a variety of other clinical conditions, including histoplasmosis, hyperthyroidism, Gaucher disease, psoriasis, amyloidosis, and respiratory distress syndrome of the newborn.[5,6] It has been known for > 3 decades that therapy with ACE inhibitors (ACEIs) (eg, captopril, enalapril, lisinopril, and so forth) can substantially reduce serum ACE activity.[7-11] Thus, the measurement of serum ACE levels is not reliable in patients taking ACEIs. However, health providers ordering ACE levels may be unaware of patient medications at the time of laboratory test ordering or may simply not consider the impact of medication therapy on testing. The widespread use of ACEIs for a variety of clinical indications[12,13] makes it likely that measurement of ACE levels will be ordered for some patients taking ACEIs.

In this study, we conducted several analyses to determine how often ACE levels are measured in patients receiving active ACEI therapy and the impact of this preanalytical (ie, before specimen reaches the clinical laboratory) error. First, at an academic medical center, we determined from retrospective analysis how often measurement of ACE levels were ordered in patients receiving ACEI therapy. We then determined the impact of implementing a warning prompt and, later, a best practice alert, in the electronic health record (EHR) order entry system to reduce this preanalytical problem. Second, we analyzed a large, deidentified dataset of ACE levels measured at a national reference laboratory. Third, we confirmed the presence of lisinopril in a subset of specimens with ACE levels < 5 U/L. Last, we carried out in vitro studies on the inhibition of ACE activity by ACEIs or their active metabolites.

Materials and Methods

Retrospective Analysis: University of Iowa

The University of Iowa Hospitals and Clinics (UIHC) is a state academic medical center that serves as a tertiary and quaternary care center. The medical center includes cardiovascular, medical, surgical-neurologic, pediatric, and neonatal ICUs, along with a level I trauma center. Retrospective analysis was performed over the time frame of April 23, 2009, to April 24, 2015 (71 months) using an Institutional Review Board-approved protocol (University of Iowa IRB-01 committee protocol No. 201504806). During this time period, the EHR for UIHC was Epic (Epic Systems, Inc), which uses computerized provider order entry (CPOE). The final 17 months of this time frame included CPOE interventions (see the CPOE Interventions: University of Iowa section).

The EHR was searched for all laboratory orders of ACE levels during the time period of retrospective analysis. In patients who had multiple ACE levels over time, only the chronologically first level was used. Data retrieved during the search included the following details at the time of laboratory order: patient age and sex, outpatient clinic or inpatient unit, quantitative ACE level, and active ACEI therapy. Chart review was performed in all instances in which an ACEI prescription was active during an encounter during which an ACE level was measured. In a small number of cases, chart review revealed that the ACEI prescription was started during the encounter but after the ACE level was measured. Nine ACEIs were on the pharmacy formulary of the medical center during at least some of the period of retrospective analysis: benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and trandolapril.

Parameters for the ACE assay used at UIHC have been summarized in a previous report.[14] Additional details are provided in e-Appendix 1. Statistical analysis was performed in SPSS (PASW Statistics 18) (IBM Corporation). Nonparametric Mann-Whitney *U* tests were used for comparison of ACE levels in patients who either did or did not have active ACEI prescription at the time of ACE level.

CPOE Interventions: University of Iowa

Following a strategy that has been successful for other examples of laboratory test misuse,[15] we implemented interventions within the CPOE to reduce the ordering of ACE levels in patients receiving ACEIs. A warning prompt with a hard stop in the EHR was in place for the final 17 months of the retrospective time period; this prompt had the following verbiage: "When intended for diagnosis of sarcoidosis, this testing should NOT be performed in patients taking ACE inhibitors (benazepril, captopril, enalapril, lisinopril) as these drugs dramatically lower ACE levels and make testing unreliable." The processing instructions for the person drawing the blood sample for the serum ACE level had the following statement: "Testing is unreliable in patients taking ACE inhibitors (benazepril, captopril, enalapril, lisinopril) as these drugs dramatically lower ACE levels." In the final 4 months of the retrospective time period, an additional CPOE intervention was in place. This was a "Best Practice Alert" in the EHR that presented the following warning when an ACE level was ordered for a patient actively receiving an ACEI prescription (this included all ACEI formulations on the UIHC formulary). The Best Practice Alert warning verbiage was "This patient is on an ACE-Inhibitor which can alter ACE levels. Please discuss holding ACE-Inhibitor therapy for 48 hours before obtaining ACE levels." The ordering provider had the option to discontinue the ACE level order or to provide a reason for overriding the warning.

Retrospective Analysis: ARUP Laboratories

ARUP Laboratories, a nonprofit enterprise of the University of Utah, is a national clinical and anatomic pathology reference laboratory. Using an Institutional Review Board approved protocol (University of Utah Institutional Review Board protocol No. 00082990), a deidentified list of 70,000 consecutive ACE assay results measured at ARUP was obtained from the data warehouse. Results from specimens without a supplied sex were excluded. Because the extract was deidentified, this dataset did not permit the exclusion of potential multiple ACE results from the same patients. Details on the ACE assay used at ARUP are provided in e-Appendix 1. The analytical measurement range (AMR) for this assay is 5 to 150 U/L. Specimen results less than AMR are reported as < 5 U/L. In this article, ARUP "< 5 U/L" results in the retrospective analysis have been converted to 2 U/L to facilitate graphical display.

Specimen Retrieval and Testing

Previously collected clinical serum and plasma specimens at ARUP were obtained from frozen storage (−20°C) and deidentified in accordance with an Institutional Review Board-approved protocol (University of Utah Institutional Review Board protocol No. 0007275). ACE testing