Serum drug levels to diagnose non-adherence in acute decompensated heart failure

Miroslav Solar\textsuperscript{a,b}, Radek Pelouch\textsuperscript{a,b}, Viktor Vorisek\textsuperscript{c}, Vera Furmanova\textsuperscript{c}, Jiri Ceral\textsuperscript{a,b}

Background. The aim of this study was to analyze medication non-adherence by measuring serum drug levels (SDL) in patients presenting with acute decompensated heart failure (ADHF).

Methods. Included in the study were chronic heart failure patients presenting with signs of acute decompensation. Blood sampling for the measurement of SDL was performed shortly after presentation. SDL were measured using liquid chromatography coupled with mass spectrometry. The estimation of SDL was calculated from the recommended chronic cardiac medications with the exception of drugs administered as part of the acute treatment prior to blood sampling. The patients were labeled as non-adherent when any one of the evaluated medications was not found in the serum.

Results. Fifty patients with ADHF were prospectively enrolled. All of the evaluated drugs were detected in the sera of 28 (56\%) patients. Non-adherence was diagnosed in the remaining 22 (44\%) patients. None of the evaluated medications was detected in the sera of 5 (10\%) patients.

Conclusion. The estimation of SDL indicates that non-adherence to the recommended chronic therapy is a common problem among patients presenting with ADHF. This method should be an essential aspect of routine clinical evaluation in these patients.

Key words: acute heart failure, drug non-adherence, pharmacotherapy, serum drug levels

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\textsuperscript{a}Department of Internal Medicine, Faculty of Medicine in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic
\textsuperscript{b}1st Department of Internal Medicine – Cardioangiology, University Hospital Hradec Kralove, Czech Republic
\textsuperscript{c}Institute of Clinical Biochemistry and Diagnostics, University Hospital Hradec Kralove, Czech Republic

Corresponding author: Miroslav Solar, e-mail: miroslav.solar@fnhk.cz.

INTRODUCTION

Acute decompensated heart failure (ADHF) is a common reason for emergency room visits and unplanned hospitalizations. One of the factors contributing to acute decompensation is non-adherence to recommended medication\textsuperscript{1,2}. The diagnosis of non-adherence is clinically important in order to plan proper management of heart failure patients. However, the diagnosis of non-adherence is challenging in the real life clinical setting.

The adherence to prescribed medication can be evaluated by pill counts, rates of prescription refills and electronic medication monitors\textsuperscript{3}. Monitoring techniques have high specificity in the detection of non-adherence; however, Sensitivity is reduced because no technique is able to document if the prescribed drugs were actually ingested\textsuperscript{4}. The measurement of serum or urinary drug levels is a novel approach for adherence assessment that provides reliable information on whether the recommended medications were taken\textsuperscript{5-9}, and we used this approach to analyze the prevalence of medication non-adherence in patients presenting with ADHF.

METHODS

The study was approved by the Local Ethics committee, and the participants gave written informed consent. Chronic heart failure patients presenting with signs of acute decompensation were enrolled. The diagnosis of ADHF was made based on the progression of heart failure symptoms and signs of fluid retention and/or pulmonary congestion. Blood sampling for the measurement of serum drug levels (SDL) was performed shortly after presentation at the emergency department or hospital admission.

The determination of serum drug levels

The determination of serum drug levels was performed by liquid chromatography coupled with mass spectrometry (LC-MS) (ref.\textsuperscript{10,11}). Prior to the chromatographic separation, the serum samples were prepared by liquid-liquid extraction using a mixture of ethyl acetate and dichloromethane. The chromatographic separation was performed on a reversed-phase column with gradient flow of the mobile phase (0.05 M formic acid and acetonitrile). The detection of the analyzed substances was performed on a linear ion-trap mass spectrometer (LTQ XL, Thermo Scientific) using electrospray ionization. The parameters of the mass spectrometer were adjusted for each individual analyte (analyzed drug). Pooled blank sera from healthy volunteers were used for method opti-
Interpretation of the results

Because clinical interpretation of serum drug concentrations is difficult, any quantifiable amount of the evaluated drug was interpreted to mean that the drug was taken. By applying this criterion for non-adherence, we eliminated uncertainties and ethical bias from the interpretation of low concentrations of the evaluated medications in the serum.

The patients were labeled as non-adherent when any of the evaluated medication, with the exception of furosemide, was not found in the serum. The adherence assessment for furosemide reflected the short plasma half-life of this drug; if furosemide was not detectable in the serum and there was a delay greater than 6 hours between the presumed drug ingestion time and blood sampling time, the respective result was considered inconclusive and excluded from the final analysis.

Because the results of the adherence assessment were not readily available, the results did not impact the immediate clinical management of the patients enrolled; however, the results were accessible during the follow-up visits.

All of the statistical calculations were performed using the MedCalc® software, version 11.6 (Mariakerke, Belgium).

RESULTS

Fifty patients with ADHF were prospectively enrolled. Seven patients were treated on an outpatient basis, and 43 were hospitalized. One patient died during hospitalization. The principal characteristics of the patients are summarized in Table 1.

Based on clinical evaluations prior to SDL results availability, the episode of decompensation was attributed to acute myocardial ischemia in 5 patients, acute infection in 5, tachyarrhythmia in 2, uncontrolled arterial hypertension in 1, progressive valvular disorder in 1, and anemia in 1. In 1 patient, acute heart failure was caused by an inappropriate medication switch, and 3 patients overtly admitted medication non-adherence. The precipitating cause of acute decompensation remained unclear in 31 (62%) patients.

All of the evaluated drugs were detected in the sera of 28 (56%) patients. Non-adherence was diagnosed in the remaining 22 (44%) patients. There was no other explanation for the decompensation in 13 of the 22 non-adherent patients. The detailed SDL results are described in Table 2.

DISCUSSION

The study was motivated by observations of patients with difficulties controlling arterial hypertension. In these patients, the estimation of serum or urinary drug levels appears to be a valuable examination to enable the differentiation between true resistant hypertension and medication non-adherence.

Surprisingly, in ADHF patients enrolled in our study, the non-adherence rate was similar to that observed in patients presenting with difficult-to-treat hypertension.
hypertension, causes troublesome and limiting symptoms. To the best of our knowledge, the use of serum or urinary drug levels for the adherence assessment in heart failure patients has not been reported before. The previous studies assessing medication adherence in heart failure patients are based mainly on the self-reporting or the analysis of prescription refills, and the frequency of non-adherence may have been underestimated.

Compared to other techniques, the estimation of serum drug levels allows reliable and easily accessible identification of actual non-adherence to the recommended medication; this information may be of high clinical value when searching for causes of acute cardiac decompensation in individual patients.

We can only speculate about the reasons for the frequent non-adherence among patients enrolled in this study. In our opinion, the non-adherence among ADHF patients resulted mainly from the underestimation of the importance of the chronic pharmacotherapy in the treatment of chronic heart failure. Drug related side effects leading to the interruption of recommended medications might also play a role. We have no reason to assume that socio-economic factors contributed to the observed non-adherence; the health care system in our country enables unlimited prescription for cardiac medications at negligible costs for those with very low incomes.

Confirmed non-adherence is a clinically relevant finding that indicates a need for a special attention. Instead of searching for new therapeutic options, non-adhering patients require focused counseling and close supervision. In our experience, extensive communication may help to establish good relationships with the patient and to manage the problem successfully.

The study has the following limitations:

First, we were not able to reliably assess the adherence to angiotensin-converting enzyme inhibitors due to analytical limitations.

Second, in a significant number of patients, furosemide was excluded from the adherence assessment because it was administered intravenously as an acute pre-hospital treatment or there was a long time delay between the presumed ingestion time and the blood sampling time for SDL measurement.

Third, it is important to note that the single assessment of SDL provides information about actual adherence only. Therefore, it is possible that among the patients, who were labeled as adherent in our study, some patients started to take the recommended medical therapy shortly before presentation when heart failure symptoms deteriorated. These limitations may have led to an underestimation of the real occurrence of non-adherence.

Although the number of patients in our study was small, we do not believe that increasing the number of patients would principally change the study results given the considerable non-adherence rate.

CONCLUSION

The estimation of serum drug levels indicates that non-adherence to the recommended chronic therapy is a common problem among patients presenting with acute decompensated heart failure. We believe that this test should become a component of complex clinical assessment of acute heart failure patients.

ABBREVIATIONS

ADHF, Acute decompensated heart failure; SDL, Serum drug levels.

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