Falsely elevated Digoxin levels detected in patient on concomitant use of Enzalutamide

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ABSTRACT

Enzalutamide may cause falsely elevated Digoxin levels using chemiluminescent microparticle immunoassay analytical method.
This report describes the case of an 81 year old man treated with Enzalutamide since 2019 and Digoxin for the last 15 days before emergency ward admission with falsely elevated Digoxin levels.
The study reveals an analytical interference with the chemiluminescent immunoassay utilized concerning falsely elevated Digoxin levels with concomitant use of Enzalutamide.
In agreement with similar reports in the literature, patients on Enzalutamide, should have the Digoxin levels measured with alternative methods.

Keywords: *Digoxin, Enzalutamide, analytical interference*

CASE PRESENTATION

This report describes the case of an 81 year old man on suppressive hormone therapy since the diagnosis of prostate cancer in 2005. The therapy in particular consisted of Enzalutamide since 2019 and Digoxin during 2017 and again in the last 15 days before hospital admission.

The patient had a medical history of chronic atrial fibrillation, prostate cancer, cholecystectomy, ischemic stroke. The ischemic stroke, previously treated with Vitamin K Antagonists, was then treated with Direct-Acting Oral Anticoagulant therapy after an episode of mesencephalic cerebral hemorrhage.

Upon admission to the hospital, the patient was on Rivaroxaban (15 mg once daily), Pantoprazole (40 mg once daily), Bisoprolol (1.25 mg twice daily), Atorvastatin (10 mg once daily), Enanthone (1 intramuscular vial monthly), Digoxin (0.125 mg once daily) and Enzalutamide (160 mg by mouth once daily).

The patient's general practitioner, upon notification by the laboratory for critical values of Digoxin (>4 µg/L, therapeutic range 0.8-2.0 µg/L), prescribed admission to the emergency department.

Upon admission, the patient presented symptoms of weakness, electrocardiogram changes not specific for Digoxin intoxication and arrhythmia due to chronic atrial fibrillation. The day before admission, the patient had already chosen to take off Digoxin.

The medication with Digoxin was discontinued during hospitalization and upon hospital discharge, as indicated by cardiology counseling.

Enzalutamide therapy was continued during and after hospitalization.

From the emergency department, the patient was then transferred for hospitalization to the geriatric ward. The patient was asymptomatic, electrolytes, creatinine, transaminases and albumin levels were normal. The electrocardiogram showed an arrhythmia due to chronic atrial fibrillation. This remained unchanged during the entire duration of hospitalization.

All monitoring samples of Digoxin, specifically on day 1, 5, 7, 9 and 12 of hospitalization, showed levels 4 µg/L.Digoxin levels were obtained by the

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chemiluminescent microparticle immunoassay (CMIA®, Abbott, Illinois) method with Abbott™ ARCHITECT™ analyzers currently in use in our laboratory. Digoxin levels, which were highly discordant with the clinical status of the patient, required further investigations. Day 12 sample presented a Digoxin concentration >4 µg/L and to 8.23 µg/L with a 1:10 sample dilution.

Two other laboratories, equipped with different analytical methods, carried out further analyses of the specimen taken on day 13. The Digoxin levels were 0.21 µg/L (corresponding to 0.21 ng/mL on Siemens Dimension Vista® System, DIGXN) and 0.42 µg/mL respectively (corresponding to 0,54 nmol/L on ThermoFisher Scientific Homogeneous Particle Immunoturbidimetric Method, DRI®) while the same sample analyzed with CMIA® in our laboratory still showed levels >4 µg/L.

The day 13 sample was then tested for possible known interferences treating it with Human Anti-Murine Antibody (HAMA) (1) and Digoxin-Like Immunoreactive Substances (DLIS) (2) using Heterophilic Blocking Tube (HBT) and Non Specific Antibody Blocking Tube (NABT) (Scantibodies Laboratory, Inc.); in both cases the sample still showed levels of Digoxin >4 µg/L.

The patient was discharged on day 13 having ruled out Digoxin intoxication. Only Bisoprolol therapy was continued because of heart disease. Digoxin therapy was discontinued as indicated by cardiology counseling during hospitalization.

DISCUSSION

Digoxin is a cardiotonic glycoside and belongs to the digitalis class. This drug is used to treat syndromes caused by atrial flutter, atrial fibrillation and heart failure. Replaced by superior therapies (e.g. beta-blockers and calcium-channel blockers), it is currently used when first-line agents prove not to be effective. Its optimal use lies on the treatment of mild to moderate heart failure in adult patients and to increase myocardial contraction.

Toxicity increases as serum Digoxin concentration reaches 2.0 µg/L. Furthermore, toxicity can occur at lower Digoxin levels in case of other risk factors, such as low body weight, advanced age, decreased renal function, and hypokalemia.

Common mild symptoms of Digoxin intoxication can be nausea, vomiting, and anorexia; visual side effects can include xanthopsia and/or photopsia; other side effects often occur, such as weakness, headache, gynecomastia and rash. At toxic levels, Digoxin is proarrhythmic and it can therefore lead to fatal cardiac arrhythmias. An impaired ventricle is more prone to ventricular tachyarrhythmias and ectopy. Abnormally high serum Digoxin levels stimulate atrial tachycardias, which is suggestive of toxicity. These atrial tachycardias are persistent and resolve when serum Digoxin levels decrease (3).

As previously stated, the patient had previously taken Digoxin therapy in 2017. Digoxin levels detected in 2017 were already above the therapeutic range of 2.0 µg/L and they ranged from 2.23 µg/L to 2.67 µg/L on different occasions in 2017; so the therapy was later discontinued by the cardiologist in favor of Bisoprolol.

By taking into account the patient's medical history, clinical conditions and past and present laboratory data, the laboratory initially decided not to rule out the hypothesis of digitalis intoxication in favor of a possible analytical interference.

According to the Abbott's CMIA® analytical method reference sheet, no drug taken by the patient could cause interference. All the pre-analytical interferents foreseen by the analytical method reference sheet had been excluded in collaboration with doctors and nurses of the geriatric ward. Upon completion of these checks, the sample was processed with other analytical methods which revealed an analytical interference in the method used by the laboratory. Analysis with HBT and NABT ruled out the possible interference caused by HAMA and DLIS. Finally, literature review and the expertise of the analytical method's developers revealed a possible interference from Enzalutamide.

Enzalutamide is an androgen receptor antagonist. Therapy with Enzalutamide is used on patients with castration-resistant prostate cancer that had previously failed other forms of treatment. Enzalutamide is available as capsules of 40 mg with typical oral dose of 160 mg once daily. Common side effects include fatigue, diarrhea, anorexia, weight loss, constipation, joint and muscle pain, hot flushes, headaches, dizziness, and edema. Rare side effects include seizures and posterior reversible encephalopathy (4).

This case shows that the CMIA® Abbott method is unreliable and produces erroneously elevated serum Digoxin levels when patients are on Enzalutamide whether or not they are on Digoxin therapy. Previous publications also describe similar falsely elevated Digoxin levels detected in patients on therapy with Enzalutamide (5,6).

The mechanism, as described by Steimer et al., is postulated to be an interaction between the antibody used in the chemiluminescent magnetic microparticle immunoassay method and Enzalutamide's oxo-imidazoline moiety, which is in close proximity to the lactone ring. The degree of interference may depend on the timing of intake of both drugs and absorption (7).

In conclusion, the authors agree with the recommendations found in literature: clinicians and clinical laboratory professionals involved in the diagnostic and therapeutic processes should be aware that the chemiluminescent microparticle immunoassay report either falsely high Digoxin levels with concomitant Enzalutamide therapy even when the patient is not on Digoxin.

In such cases it is recommended to confirm Digoxin level with an alternative method without known interference (8,9).

Analytical methods such as UPLC-MS/MS or similar liquid chromatography-tandem mass spectrometry methods (10) bring new perspectives which help avoiding this analytical interference and others of similar type.

CONFLICT OF INTEREST

None

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