A Trap In Measuring Of Plasma Digoxin Level After Stopping Of A Treatment

ZIJAD DURAKOVIC[1]
ASAF DURAKOVIC[2]
SENADIN DURAKOVIC[3]
NAIMA COROVIC[4]
IBRAHIM RAMIC[5]

Summary

In this paper, a course of the disease of a 68-year-old patient treated with medigoxin for congestive heart failure is presented. After being withdrawn from his treatment at the hospital, the patient was administered spironolactone and furosemide. The plasma digoxin level at entry was 1.1 nmol/L, after five days it reached 3.2 nmol/L, and after ten days was 2.3 nmol/L. The patient had a normal renal function. The interference of spironolactone and its metabolites with the digoxin radioimmunoassay was discussed as a possible explanation for this phenomena.

The interaction of some drugs such as verapamil[4], nifedipine, ACE inhibitors, amiodarone, quinidine[6], spironolactone[7-9] and digoxin is well known. By different mechanisms, these drugs increase plasma digoxin concentration. After the withdrawal of that therapy, concentration of digoxin gradually decreases, since it is primarily eliminated by the kidneys. We report a case in whom plasma level of digoxin increased when digoxin was withdrawn.

Report of a Case

A 68-year-old man (S.S.) was admitted to the Emergency Unit of the Department of Internal Medicine because of congestive heart failure. He was hospitalized from March 5 to 17, 1990.

The patient has been well until 17 years earlier, when ischemic cardiomyopathy was diagnosed. Thereafter he was treated for heart failure on several occasions. The ECG tracings at that time showed anteroseptal scar, upper anterior fascicular block, first degree atrioventricular block and few monomorphic ventricular extrasystoles. A few months before admission, he had been receiving medigoxin at a dosage of 0.1 mg daily, isosorbide dinitrate 6x5 mg per os, captopril 3x12.5 mg. One month before entry the patient experienced the onset of fatigue, dyspnea provoked by smallest physical effort, swelling of the abdomen and lower extremities, and abnormal frequency of micturition.

On examination the patient was a man 165 cm in height, weighted 57 kg, and was dyspnoic at rest. There was a history of tricuspidalization. Diminished breath sounds and several crepitations were heard at the base of the right lung. The heart sounds were rhythmic, quiet, and protosystolic murmer (grade 2/6) was heard. The blood pressure was 140/90 mmHg (18.6/12.0 kPa), and his pulse

1. Department of Internal Medicine, Rebro University Hospital, Medical Faculty University of Zagreb, Croatia.
2. DVA Medical Center, Wilmington, Delaware, USA.
3. Faculty of Biotechnology, University of Zagreb.
4. Institute for Medical Research and Occulational Health, Zagreb, Croatia.
5. Department of Internal Medicine, Medical Center Brcko, Bosnia and Herzegovina.

rate was 80 per minute. The liver edge was palpable for 2 cm.

Laboratory examination revealed the following: the serum creatinine was from 79 to 88/umol/L and the creatinine clearance was 64.1 ml/min (1.07 ml/s). The potassium was 4.2, while the other findings showed normal results, including CK and LD. The ECG at admission showed pathologic left electrical axis, sinus rhythm of 78/min, trifascicular block, first degree atrioventricular block with the PQ-interval of 0.36 to 0.38 s, upper anterior fascicular block and a focal right bundle-branch block, anteroseptal scar with the ST-segment elevation and several monomorphic ventricular extrasystoles. The corrected Q-T interval was 0.477 s (normal value for males up to 0.477 s) and was determined according to the formula:

$$\frac{\text{measured } QT_s}{\sqrt{\text{R-R interval}_s}}$$ 10, 11

The plasma digoxin concentration at entry was 1.1 nmol/L (therapeutic concentration: 0.9-2.6). Roentgenogram of the chest and heart disclosed massive vascular hiluses without the enlargement of the mediastinum, and an enlarged left cardiac silhouette.

Serum digoxin analysis on admission was done on 2 ml serum added to 0.05 ml heparin by the radioimmunoassay method by commercial kits supplied by Pharmacia, Sweden[2]. Coefficient of variability between single determinations and within one determination was 9.3% and 5.2%, respectively. The digoxin concentration on entry was 1.1 nmol/L.

Course of the Illness

The patient was treated with captopril at a dosage of 3x12.5 mg, isosorbide dinitrate at a dose of 4x5 mg per os, spironolactone, 100 mg daily, together with furosemide at a dosage of 2x40 mg i.v.: in the first two days and then in dosage of 2x80 mg daily per os from the third to the fifth day and after that 80 mg per day per os. The patient was not administered digitalis glycoside. Diuresis was permanently good throughout the period of treatment: 24 hours following the entry it was 650 ml and the blood pressure 140/90 mmHg (18.6/12.0 kPa). On the fifth hospital day the diuresis was 1700 ml, the blood pressure 120/80 mmHg (16.0/10.6 kPa), and the pulse 72. On that day the digoxin concentration in plasma was even 3.2 nmol/L. The dose of furosemide was diminished to 80 mg daily. The ECG showed the corrected Q-T interval of 0.449 s. There were no ventricular extrasystoles, the PQ-interval ranged from 0.30 to 0.32 s, while the other findings were unchanged. On the tenth hospital day plasma digoxin concentration was 2.3 nmol/L, the blood pressure 105/70 mmHg (13.9/9.3 kPa), and the diuresis 2700 ml. The corrected QT-interval of 0.469 s was recorded in an ECG, and the PQ-interval ranged from 0.28 - 0.30 s.

Discussion

The case described here demonstrates a presentation of a 68-year-old patient with cardiac decompensation who had been treated with 0.1 mg of medigoxin daily for congestive heart failure until the admission to the hospital. On entry an electrocardiogram indicated the PQ-interval of 0.38 s suggesting the digitalis effect. During the treatment the clinical picture of heart failure disappeared, while plasma digoxin concentration disclosed higher and higher values, despite the withdrawal of medigoxin. The patient was treated with spironolactone at a dosage of 100 mg per day. Diuresis was normal, while the blood pressure tended to fall. Plasma digoxin concentration on the tenth hospital day was lower, namely, 2.3 nmol/L than on the fifth hospital day when it was 3.2 nmol/L. Diuresis was normal.

It has been questioned, how is it possible that despite withdrawal of digoxin from the therapy, its plasma concentrations increased. This was not due to a mistake in the analytical technique, since the method was checked every day. One of the drugs used in this patient was furosemide, an agent that promotes the discharge of water from the body and decreases the volume of drug distribution, in this case of digoxin. It also improves the absorption and biological availability of the drugs that are

orally administered, in this case of spironolactone. As a result of this, furosemide could have a very small effect on this phenomenon.

Since the admission to the hospital, the patient was receiving spironolactone at a dose of 100 mg per day. It is well known that spironolactone and its metabolites interfere with the determination of digoxin by means of a radioimmunoassay and change digoxin kinetics, respectively. Digoxin is mainly eliminated by the kidneys[7-9]. Spironolactone treatment decreases extrarenal clearance of digoxin by inhibiting tubular excretion. The obtained digoxin concentrations on the fifth and tenth hospital days suggest most probably a pharmacodynamic interaction between digoxin and spironolactone. However, the question has to be placed concerning the decreased plasma digoxin concentration on the tenth hospital day. The reasons may be different. On the one hand, we have been probably measuring on the fifth hospital day the residual plasma digoxin and spironolactone whose biological availability was increased by the furosemide administration. The blood pressure in the treatment period showed a tendency of lowering, in contrast to the period before the discharge when it disclosed normal values. Since, the biological availability of some drugs depends significantly on blood pressure values, it may be postulated that it has decreased on the tenth hospital day, what might be the explanation for the aforementioned plasma digoxin concentration.

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