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Case Report

Digoxin intoxication–induced encephalopathy in a patient with chronic kidney disease

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ABSTRACT

Digoxin is a drug with a narrow therapeutic range. We present an 88-year-old woman with chronic kidney failure who was suspected of having digoxin intoxication when she developed nausea, vomiting, loss of appetite, lethargy, and unconsciousness after taking digoxin 0.25 mg daily for 1 week. A blood test revealed a high digoxin concentration of 5.42 ng/mL. The patient experienced bradycardia, hypotension, acute renal failure, and hyperkalemia. Electroencephalography revealed global brain dysfunction. She was given a temporary pacemaker and several rounds of dialysis. The digoxin concentration in the patient's blood was monitored every 2 days, and she gradually regained consciousness as the level of digoxin decreased to the normal range within 2 weeks. Patients with chronic renal failure should be monitored and tested before the administration of digoxin to titrate the dose. The drug plasma concentration should be carefully monitored for 5–7 days after drug administration. Patients' renal function, associated electrolyte concentrations, and drug levels should be tested regularly to ensure drug safety.

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1. Introduction

Digoxin is a drug with a narrow therapeutic range. Nevertheless, with the progress in pharmacokinetics, the serum concentration of digoxin can be maintained at a safe level to reduce the possibility of digoxin toxicity.

The symptoms of digoxin toxicity include blurred vision, diarrhea, and nausea in mild cases, and unconsciousness and vertigo in severe cases. Therefore, it is extremely important that extra attention be paid to elderly patients who regularly receive digoxin. These patients should receive special instructions on dosage and administration time. Although cases of digoxin toxicity are common, few studies have described one of the adverse effects of digoxin toxicity—encephalopathy. The present article focuses on a patient with chronic kidney disease, who underwent digoxin treatment for 1 week and subsequently developed severe digoxin toxicity with encephalopathy and bradycardia, which persisted for 2 weeks. We also discuss the safety concerns related to the use of digoxin in such patients.

2. Case report

An 88-year-old woman with a medical history of chronic kidney disease (blood urea nitrogen, 55 mg/dL; creatinine, 2.5 mg/dL) and heart failure was referred to the emergency room of our hospital because of unconsciousness (Glasgow Coma Scale score: E2, V4, M5–6) and oliguria. In the emergency room, she was diagnosed with sinus bradycardia (heart rate, 56 beats/min); hypotension (blood pressure, 90/47 mmHg); and acute renal failure (blood urea nitrogen, 148 mg/dL; creatinine, 6.6 mg/dL). She was transferred to the respiratory intensive care unit for observation and treatment. Her recent medication history revealed that she had been taking digoxin 0.25 mg daily for heart failure for 1 week and had subsequently developed nausea, vomiting, loss of appetite, and lethargy; hence, digoxin toxicity was suspected. A blood test revealed that the serum digoxin concentration was 5.42 ng/mL (Table 1).

The patient experienced bradycardia, hypotension, acute renal failure, and hyperkalemia (potassium level, 6.64 mmol/L) in the respiratory intensive care unit. As hyperkalemia had the potential to worsen the bradycardia, emergency dialysis was performed to lower the potassium levels, and a temporary cardiac pacemaker was implanted to manage the bradycardia and hypotension. After several rounds of dialysis, renal function was restored to her baseline level, and her urine volume increased. Subsequently, the

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Table 1
Biochemical data obtained during the patient's admission.

Test/value	Normal range	Baseline value	At the time of admission	Day 2	Day 3	Day 6	Day 9	Day 12	Day 19
BUN (mg/dL)	6–20	55	148	—	95	80	110	45	
CRE (mg/dL)	0.5–1.2	2.5	6.6	—	5.2	4	4.2	2.1	
K (mEq/L)	3.4–5.1	5.09	5.8	6.64	3.44	4.09	3.38	2.91	4.00
Mg (mg/dL)	1.3–2.5	—	—	6.9	4.3		3.6		3.8
Digoxin (ng/mL)	*0.8–2.0*	—	*5.42*		*4.45*	*3.17*	*2.32*	*1.53*	*1.22*
GCS (total score)			4		11	10	11	13	13

BUN = blood urea nitrogen; CRE = creatinine; GCS = Glasgow Coma Scale; K = potassium; Mg = magnesium.

dialysis was terminated. Because the patient remained unconscious, computed tomography of the head was performed to rule out the possibility of stroke. Electroencephalography revealed global brain dysfunction. Her blood digoxin concentration was monitored every 2 days, and the patient gradually regained consciousness as the blood level of digoxin decreased to the normal range within 2 weeks (Table 1). During this period, the patient's heart rate also returned to normal. She was discharged from the hospital a week after the removal of the temporary pacemaker.

3. Discussion

The diagnosis of digoxin-induced encephalopathy in our patient was confirmed by exclusion of other organic brain lesions and recovery of consciousness after the decline in digoxin levels. The mechanism of the pharmacological action [1] of digoxin is the inhibition of the α-subunit of Na^+/K^+ ATPase that enhances myocardial contractility. Moreover, digoxin increases vagal activity, leading to a decrease in the heart rate [2] by means of a decrease of intraventricular conduction and increase of the refractory period and diastolic filling time. Both digoxin and digitoxin, the unaltered form of digoxin, are reabsorbed by the small intestine. However, because digoxin has a long half-life compared with its dosage interval and a very long distribution phase, simple pharmacokinetic equations can be used to individualize dosages when postdistribution serum concentrations are used. Digoxin is excreted about 50–70% unchanged by the kidneys, and the elimination half-life is about 1.5–2 days in adult anuric patients, and 3.5–5 days in patients with renal impairment [3–5]. As digoxin has a narrow therapeutic index, its therapeutic and toxic effects should be monitored with the serum digoxin concentration (SDC). The standard SDC for treatment of atrial fibrillation with a rapid ventricular rate is 1.0–2.0 ng/mL, and for symptoms of congestive heart failure, it is <1.0 ng/mL. However, some studies have suggested that a high SDC (>1.0 ng/mL) leads to increased mortality [6].

In one study [7], 6–23% of admitted patients had digoxin intoxication, and the mortality rate was up to 41%. Digoxin intoxication presents with the following symptoms [8]—psychological symptoms: delirium, fatigue, exhaustion, confusion, dizziness, and encephalopathy; visual symptoms: blurred or yellow vision; gastrointestinal symptoms: nausea, vomiting, abdominal pain, and loss of appetite; and cardiac symptoms: abnormally high electrical conductivity and autorhythmicity of the cardiac myocytes. When a patient shows any symptoms of digoxin intoxication, the blood digoxin concentration should be checked immediately.

In our patient, acute renal failure led to the decrease in the amount of body fluid, which intensified the digoxin intoxication and then caused the gastrointestinal side effect. The complications included bradycardia, hypotension, and encephalopathy. The symptoms of intoxication included vomiting, ventricular tachycardia, ventricular fibrillation, sinoatrial node arrest, atrioventricular block, visual impairment, weakness, sinus bradycardia, atrial fibrillation, and ventricular arrhythmia.

Digoxin-induced encephalopathy was also reported in two clinical cases published by Greenway et al [8] in 1995. We summarize and compare these three cases in Table 2.

Previous studies [9–11] have indicated that the most commonly observed symptoms of digoxin intoxication include lethargy and loss of consciousness. Elderly patients are generally at a much higher risk of digoxin intoxication than younger individuals. Moreover, in patients with chronic kidney disease, imbalances of body fluids and electrolytes often occur, which makes evaluation of the digoxin dosage extremely critical. During dose titration, extreme care should be taken with regard to renal function and electrolyte levels.

Table 2
Summary of the digoxin-induced encephalopathy [8].

Case number	Age (y)	Gender	Symptom	Digoxin level (ug/L)	Stop digoxin level	Serum creatinine level	Medication record
1	68	Female	1-wk history of profound somnolence	>5	1 wk later, digoxin level was back to 0.3 ug/L	Not mentioned in the article	Furosemide 120 mg, spironolactone 100 mg, prednisolone 5 mg, ranitidine 150 mg, digoxin 250 ug, all daily, with isosorbide mononitrate 20 mg and nifedipine SR 10 mg both twice daily
2	66	Female	Unconsciousness	4.2	3 d later, digoxin level was 0.7 ug/L	Not mentioned in the article	Digoxin 250 ug daily, captopril 25 mg tid, furosemide 250 mg bid, warfarin 4 mg daily
Our case	88	Female	Unconsciousness and oliguria	5.42	2 wk later, digoxin level was back to 1.22 ug/L	5.2 mg/dL	Digoxin 250 ug daily, furosemide 40 mg daily, clopidogrel 75 mg, perindopril & indapamide 2 mg & 0.625 mg/tab daily, isosorbide mononitrate 20 mg twice daily

The patient reported in this article received digoxin as the only medication before intoxication; thus, the possibility of a drug interaction was automatically eliminated. The patient's poor renal function and the failure to remove digoxin through blood dialysis delayed the removal of digoxin from the patient's body. Although dialysis can treat hyperkalemia, it can also worsen digoxin intoxication by lowering the potassium level. Therefore, if the digoxin concentration in a patient's blood does not reach a normal level, the potassium concentration in the serum should be carefully monitored, and supplements should be given when the potassium concentration is low. As a result of this delay, we were able to observe the development of digoxin-induced encephalopathy and the regaining of consciousness caused by the elimination of digoxin.

Supportive treatment for digoxin intoxication should be performed depending on the clinical symptoms. First, digoxin administration should be terminated immediately. Activated carbon can be used to lower the serum digoxin level in cases of acute intoxication.

Digoxin antibodies (digoxin immune Fab, Digibind) can be administered when the aforementioned treatments do not relieve the patient's symptoms. According to the study by Kelly and Smith [12], the dosage of digoxin-specific antibodies can be calculated using the following formula:

$$\text{Dosage of Fab fragments (mg)} = [50{,}000\ (\text{Da}) \times \text{total amount of digoxin in the body (mg)}]/\text{molecular weight of digoxin (781 Da)}$$

Approximately 90% of patients show the effects of the antibodies 19 minutes after injection. Generally, a significant relief of symptoms will be observed within 30–60 minutes after injection. Gastrointestinal symptoms are eliminated first, followed by irregular heart rhythms. Digoxin toxicity is expected to be relieved 3–4 hours after the injection [13]. The half-life of the digoxin-specific Fab fragments is approximately 17.1 hours, and symptoms are unlikely to recur once the patient has been treated with the antibody. However, as the half-life of digoxin is much longer than that of the digoxin-specific Fab fragments, patients with renal failure and those who have taken high amounts of digoxin may still be at a risk of recurrent digoxin overdose and should be closely monitored [14].

4. Conclusion

Digoxin is a drug that requires extensive education on its use. Patients with kidney disease should have periodic checkups to monitor renal function, levels of associated electrolytes, and the serum drug concentration. They should also have periodic evaluations of both possible drug interactions that could affect digoxin absorption and metabolism and the patient's drug administration status and compliance.

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