



Case Report

Digoxin-specific Fab and therapeutic plasma exchange for digitalis intoxication and renal failure

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ABSTRACT

Treatment of chronic digitalis intoxication includes suspension of drug intake, which may be sufficient in case of mild manifestations, and supportive measures. Severe bradycardia requires the administration of atropine or isoproterenol; placement of a temporary pacemaker may be required in case of absent response to pharmacological therapy. Severe and life-threatening manifestations should be treated with digoxin-specific fragment antigen binding antibodies (Fab). Therapeutic plasma exchange has been suggested, in addition to Fab therapy, to maximize the clearance of Fab-digoxin complexes in patients with renal failure. To date, few case reports have described the use of such a therapeutic approach; currently, extracorporeal methods are not recommended as part of the treatment of digitalis intoxication, and stronger evidence is required to establish their benefit.

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1. Case report

A 69-year-old woman (59 kg weight) was admitted to the emergency department (ED) because of malaise, asthenia, nausea and vomiting during the previous week.

Her medical history included: valvular-ischemic heart disease, with mild reduction of left ventricular function and severe mitral regurgitation; atrial fibrillation; and stage IV chronic kidney disease (CKD), with a baseline serum creatinine of 2.7 mg/dL and estimated glomerular filtration rate (eGFR) of 18 mL/min/1.73 m². During a recent hospitalization, because of inadequate rate control, digoxin was added to her medical therapy, which also included: bisoprolol, torsemide, potassium canrenoate, enoxaparin, levothyroxine, and atorvastatin.

The ECG recorded upon arrival (Fig. 1) showed sinus rhythm with complete atrio-ventricular (AV) block and a ventricular rate of 25–30 bpm. The patient was anuric and blood tests showed worsening renal failure (serum creatinine 4.5 mg/dL, eGFR 10 mL/min/1.73 m²), hyperkalemia (serum potassium 6.9 mmol/L, Fig. 2), and elevated serum digoxin concentration (4.2 ng/mL, Fig. 2). Questioning revealed that, since her last discharge three weeks earlier, she had been taking by mistake a whole 0.250 mg digoxin tablet daily, instead of the prescribed dose of 0.0625 mg, corresponding to one quarter 0.250 mg tablet.

Abbreviations: AV, atrio-ventricular; CKD, chronic kidney disease; ED, emergency department; eGFR, estimated glomerular filtration rate; Fab, fragment antigen binding antibodies; TPE, therapeutic plasma exchange.

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Administration of atropine and isoproterenol was not effective; therefore, a temporary pacemaker was placed. Two vials (80 mg) of digoxin-specific fragment antigen binding antibodies (Fab) were administered (day 1), with reduction of serum potassium concentration to 4.5 mmol/L but only slight improvement of spontaneous ventricular rate (40 bpm) and persistence of oligoanuric renal failure. Total serum digoxin concentration rose to 10 ng/mL. On day 3, the patient underwent a session of therapeutic plasma exchange (TPE) with 5% albumin solution as reposition fluid.

On day 6 a second Fab administration (120 mg) was followed by TPE three hours later. The patient regained a spontaneous rhythm with a heart rate of 60–65 bpm and total serum digoxin concentration dropped from 5.1 to 2.4 ng/mL.

2. Discussion

Cardiac symptoms are the most threatening manifestations of digoxin intoxication. Administration of digoxin-specific Fab is indicated in case of severe manifestations: life-threatening ventricular arrhythmias; symptomatic severe bradycardia and high-grade AV block, up to cardiac arrest, not responsive to atropine; hyperkalemia [1–4]. A high digoxin body load may be considered as an adjunctive indication, given the high mortality associated with this condition [1,3–5].

In case of chronic intoxication, the required dose of Fab can be estimated from the serum digoxin concentration and patient's weight (Table 1) [2–4,6]. A clinical response is usually observed within 60 minutes. Total serum digoxin concentration is expected to rise 10 to 20 times after Fab administration, and its assessment is not recommended to evaluate the efficacy of treatment [2]. The most common cause of

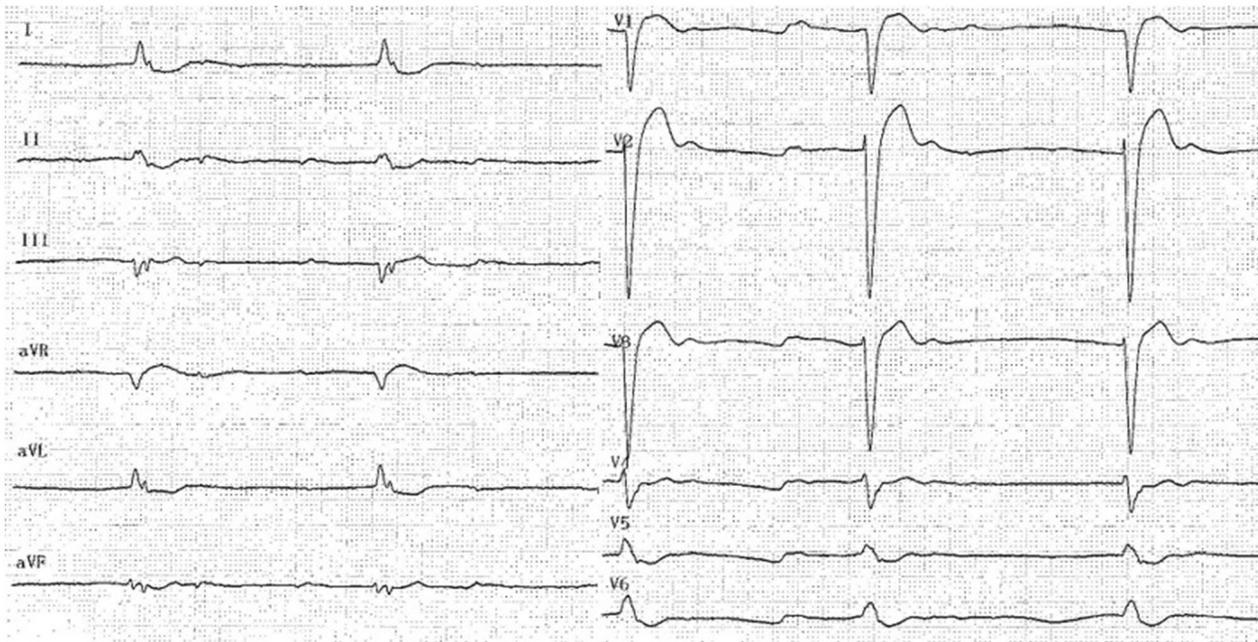


Fig. 1. ECG at admission in the emergency department.

absent or incomplete clinical response is inadequate dosing; in such a case, a second Fab administration may be considered [6].

Treatment of severe digoxin intoxication with concomitant renal failure is particularly challenging: both digoxin and Fab are mainly renally excreted, hence their half-lives are extremely prolonged (Table 2) [7]. To enhance digoxin clearance, extracorporeal removal techniques have been considered. However, free digoxin cannot be removed by any extracorporeal method, given its large volume of distribution and its mainly extravascular allocation (Table 2) [7,8]. Hemodialysis or hemofiltration are not effective in the removal of high molecular weight Fab-digoxin complexes, whereas the use of TPE for this purpose has been reported [7,9,10]. However, TPE after Fab administration is not routinely recommended, and does not significantly enhance digoxin clearance [8]. Only few case reports have described this approach in the treatment of digoxin intoxication complicated by renal failure [7,9–11]. Our choice of treating the patient with TPE was mainly driven by the persistence of oligoanuric renal failure, requiring renal replacement therapy until its resolution. The estimated optimal timing for TPE is 1 to 3 hours after Fab administration [7].

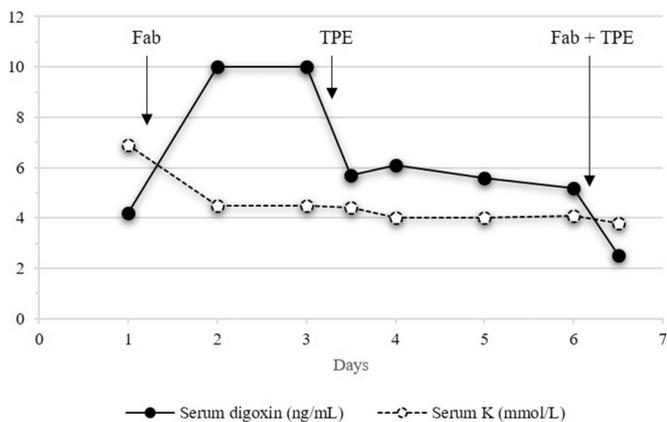


Fig. 2. Our patient's serum digoxin and potassium concentrations during treatment. Fab: digoxin-specific fragment antigen binding antibodies; K: potassium; TPE: therapeutic plasma exchange.

Our patient experienced only a partial response after the first Fab administration. Fab underdosage might be one possible explanation: treatment of a chronically intoxicated 59 kg patient would have required 3 vials of Fab (120 mg) [2,4]. Another possibility is inaccurate measurement of serum digoxin concentration, an eventuality reported for very high serum digoxin levels with some assay kits [4]. After this inadequate Fab administration, a late TPE session did not improve our patient's clinical status.

The second Fab dose was calculated assuming that the serum digoxin concentration available to us was very close to the free serum digoxin fraction. This artifice was necessary since our laboratory was not equipped with an assay for the measurement of free serum digoxin concentration. The administration of 120 mg of Fab was closely followed by a second TPE session. The combination of a more adequate Fab dosage and a closer TPE session was probably the key of treatment efficacy.

3. Conclusion

Treatment of digitalis intoxication in patients with renal failure may be challenging, given the renal clearance of both free digoxin and Fab-digoxin complexes. TPE after Fab administration does not significantly enhance digoxin clearance and is not routinely recommended, although few case reports described its successful use [7–11]. TPE optimal timing is uncertain, but a TPE session up to three hours after Fab administration probably maximizes Fab-digoxin clearance.

Table 1

Calculation of the dose of digoxin-specific Fab [2,4,6].

Acute ingestion

Step 1. Calculation of the body load of digoxin: Body Load (mg) = Ingested Amount (mg) * 0.8

where 0.8 corrects for digoxin tablet bioavailability

Step 2. Calculation of the Fab dose: Dose (number of vials) = Body Load (mg) / 0.5

Chronic intoxication

Calculation of the Fab dose: Dose (number of vials) = [Serum Digoxin

Concentration (ng/ml) * 5.6 * Weight (kg)] / 1000 * 0.5

where 5.6 corrects for the volume of distribution of digoxin

Table 2

Main pharmacokinetic aspects of digoxin and digoxin-specific Fab [3,4,7,8,12–14].

Variable	Digoxin	Digoxin-specific Fab
Volume of distribution, L/kg	5–8	0.3–0.4
Renal clearance, %	60–70	50–70
Half-life (normal renal function), hours	36–48	16–30
Half-life (renal failure), hours	46–330	59–137

Although our patient apparently benefited from this treatment, stronger evidence is required to establish whether this approach improves survival and hospitalization length.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

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