

Clinical signs and symptoms of toxic serum digoxin levels in neonates

Mehmet Mutlu¹, Yakup Aslan¹, Şebnem Kader¹, Filiz Aktürk-Acar¹, Embiya Dilber²

Division of ¹Neonatology and ²Department of Pediatric Cardiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey. E-mail: drmehmetmutlu38@hotmail.com

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Digoxin is widely used in the treatment of congestive heart failure and some arrhythmias. Digoxin toxicity may occur easily because digoxin has a narrow therapeutic index. This retrospective study was conducted to evaluate the clinical signs and symptoms of toxic serum digoxin levels in neonates. Medical reports of the neonates who had serum digoxin concentrations >2 nanogram/milliliter (ng/ml) were reviewed in terms of patient demographics, serum digoxin concentrations, signs and symptoms of digoxin toxicity, serum digoxin and electrolyte levels, renal function tests, electrocardiograms, echocardiography, and treatments applied. Digoxin toxic levels were identified in the 13 neonates. Of the 13 neonates with digoxin toxic level, 9 (69%) were term and 8 (62%) were female. Twenty-three percent (3/13) of newborn infants were symptomatic. Symptomatic patients had statistically significantly higher serum digoxin levels, at 7.76 ± 2.76 (5.4-10.8) ng/ml, than asymptomatic patients, at 3.31 ± 1.09 (2.02-4.95) (p=0.036). Symptoms related to toxic digoxin levels were observed in the three neonates with plasma digoxin levels >5 ng/ml. Gastrointestinal and central nervous system symptoms were the major clinic findings. Despite high digoxin levels, no digoxin-related arrhythmia was observed on electrocardiography, other than sinus bradycardia. Two premature neonates were treated with digoxin-specific antibody Fab fragments (DigiFab®) and hypokalemia developed in both of them. Our data suggests that symptoms related with digoxin toxic levels were observed in neonates with plasma digoxin levels >5 ng/ml. Serum digoxin levels should be measured in case of signs and symptoms of digoxin toxicity or risk factors for such toxicity.

Keywords: digoxin, neonate, toxic level, clinical signs and symptoms.

Digoxin is a cardiac glycoside widely used in the treatment of congestive heart failure (CHF) and some arrhythmias. Digoxin indirectly increases intracellular calcium in myocardial cells by inhibiting the sodium-potassium pump in the cell membrane. Increased intracellular calcium raises cardiac contractility. Conditions predisposing to digoxin toxicity include impaired renal clearance in neonates, particularly premature infants, dehydration, electrolyte imbalance (hypokalemia, hypercalcemia, hypomagnesemia), hypoxia, hypothyroidism, drug interactions (e.g. amiodarone and

quinidine), and alkalosis.¹⁻³ Serum digoxin concentrations in the range of 0.8–2 nanogram/milliliter (ng/ml) are regarded as normal.¹ Digitalis toxicity may easily occur since digoxin has a narrow therapeutic index.

Although digoxin toxicity has been documented in childhood, reports describing such toxicity and treatment with digoxin-specific antibody Fab fragments (DigiFab®) in neonates are limited.³⁻⁶ This study describes the clinical symptoms, electrocardiographic features, blood digoxin and electrolyte levels, and treatment of neonates with toxic digoxin levels.

Material and Methods

This retrospective study was conducted in neonates with toxic levels of digoxin at the Karadeniz Technical University Faculty of Medicine, Department of Pediatrics, Division of Neonatology between 2007 and 2017. The study protocol was approved by the Institutional Ethics Committee of Karadeniz Technical University (File number: 2017/24237859-555). Neonates received maintenance doses of digoxin (5-6 µg/kg/day p.o. for premature neonates and 5 µg/kg every 12 h p.o. for full-term subjects) without a loading dose. The immunoassay method was used to determine serum digoxin concentrations.

Neonates using digoxin due to CHF or arrhythmias and with serum digoxin levels greater than 2 ng/ml were included in the study, and those with serum digoxin levels below 2 ng/ml were excluded.

Medical reports were reviewed in terms of patient demographics, serum digoxin concentrations, signs and symptoms of digoxin toxicity, serum digoxin and electrolyte levels, renal function tests, electrocardiograms, echocardiography, and treatments applied. Mean serum digoxin concentrations were compared between symptomatic and asymptomatic patients.

DigiFab® was used in the presence of any of the following conditions: Life-threatening cardiac dysrhythmias, hyperkalemia (>6mmol/L), significantly altered mental status, renal failure, or a serum digoxin level greater than 10 ng/ml.^{7,8} If an indication for digoxin Immune Fab was determined, the following formula was used: number of vials containing Fab=serum digoxin concentration (ng/ml) x weight (kg)/100.⁹ Each vial of DigiFab® contains 40 mg of purified digoxin-specific Fab.⁹ DigiFab® was administered slowly in the form of intravenous infusion over at least 30 min.⁹

Results

Serum digoxin levels were measured in 119 neonates followed-up in our neonatal intensive care unit during the study period, and these exceeded >2 ng/ml in 13 (10.9%). Nine (69%) of the 13 neonates with toxic digoxin levels were term, and eight (62%) were female. Mean gestational age was 34.8±5.4 (27-42) weeks, birth weight 2460±1286 (580-4050) grams,

and postnatal age 29±17 (8-64) days. Eleven neonates with signs of CHF and two with life-threatening supraventricular tachyarrhythmia were treated with digoxin. Signs and symptoms of digoxin toxicity, serum digoxin levels, serum electrolyte levels, renal function tests, and electrocardiographic and echocardiographic findings are shown in Table I. High digoxin levels were detected during routine follow-up in 10 asymptomatic neonates. Twenty-three percent (3/13) of newborn infants were symptomatic. Vomiting was the most common symptom (3/3), followed by lethargy, apnea (2/3) and sinus bradycardia (1/3). Serum digoxin levels in the symptomatic neonates were >5 ng/ml (Table I). Symptomatic patients had statistically significantly higher serum digoxin levels, at 7.76±2.76 (5.4-10.8) ng/ml, than asymptomatic patients, at 3.31±1.09 (2.02-4.95) (p=0.036). Despite high digoxin levels, no electrocardiographic abnormalities were observed in any patients except for one neonate with sinus bradycardia. The highest serum digoxin, potassium, calcium, magnesium, blood urea nitrogen (BUN), and creatinine levels (mean±standard deviation [minimum-maximum]) were 4.34±2.45 (2.02-10.8) ng/ml, 4.96±0.5 (3.9-5.82) mmol/L, 9.5±1.06 (7.6-10.7) mg/dl, 2.22±0.42 (1.77-3.26) mg/dl, 18.8±17.4 (5-54) mg/dl, and 0.59±0.7 (0.1-2.7) mg/dl, respectively. No patients had hypokalemia, hypomagnesemia, or hypercalcemia when high digoxin concentrations were measured. Serum BUN levels and creatinine levels were high in three and two neonates, respectively.

Two symptomatic premature neonates received DigiFab®. Hypokalemia was detected in the neonates who received DigiFab® therapy (Fig.1). Serum digoxin levels temporarily increased from 10.8 ng/ml to 11 ng/ml and from 7.1 ng/ml to 11.6 ng/ml after DigiFab® therapy in these cases, and then decreased (Fig. 1). No mortality was observed in the neonates with toxic digoxin levels.

Discussion

This study describes 13 neonates with toxic digoxin levels. Digoxin is widely used in the treatment of CHF and some arrhythmias. In our study, 11 neonates with signs of CHF and two with arrhythmias were treated with

Table I. Clinical and Laboratory Findings of the Neonates with Digoxin Toxic Level.

Patient no	Digoxin indication	Clinic	ECG	ECHO	Digoxin level (ng/ml)	Potassium (mmol/L)	Calcium (mg/dl)	Magnesium (mg/dl)	BUN (mg/dl)	Cr (mg/dl)
1	CHF	Asymptomatic	NSR	-	3.36	3.9	9.9	2.5	10	0.1
2	SVT	Asymptomatic	NSR	ASD	3.18	5.2	7.6	2.5	45	0.6
3	CHF	Asymptomatic	NSR	CoA+ PDA	4.8	4.6	8	3.26	54	1.3
4	CHF	Vomiting, lethargy, apnea	NSR	VSD	10.8	5.82	10.53	2.46	9.3	0.43
5	CHF	Asymptomatic	NSR	Normal	4.6	5.1	10	2	5	0.2
6	Atrial flutter	Asymptomatic	NSR	Normal	2.02	-	-	-	10	0.4
7	CHF	Vomiting	NSR	VSD+Truncus arteriosus	5.4	5.1	8.9	1.9	16	0.5
8	CHF	Asymptomatic	NSR	ASD	2.61	5.4	10	1.9	47	2.7
9	CHF	Asymptomatic	NSR	ASD+ PS	4.95	4.5	9.9	2.07	13	0.34
10	CHF	Asymptomatic	NSR	VSD	2.47	4.9	10.1	1.98	7	0.18
11	CHF	Asymptomatic	NSR	VSD	2.72	4.6	10.2	1.77	5	0.33
12	CHF	Vomiting, lethargy, apnea	Sinus bradycardia	VSD	7.1	5.3	8.1	2.39	12	0.2
13	CHF	Asymptomatic	NSR	VSD	2.36	5.2	10.7	1.88	11	0.43

ASD: Atrial septal defect, BUN: Blood urea nitrogen, CoA: Coarctation of the aorta, CHF: Congestive heart failure, Cr: Creatinine ECHO: Echocardiography, ECG: Electrocardiography, NSR: Normal sinus rhythm, PDA: Patent ductus arteriosus, PS: Pulmonic stenosis, SVT: Supraventricular tachycardia VSD: Ventricular septal defect,

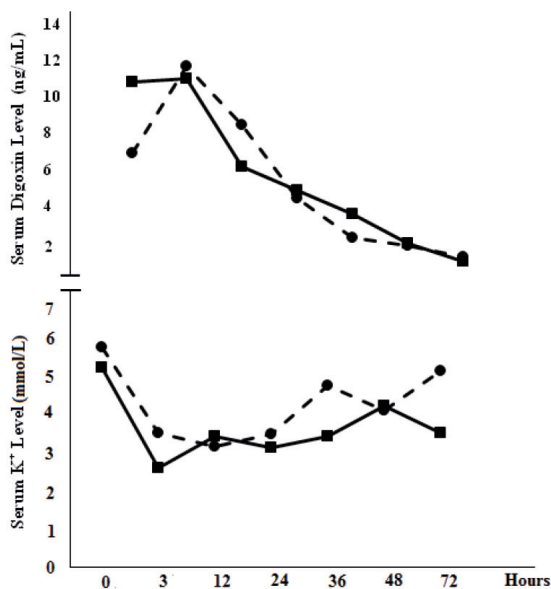


Fig. 1. Serum digoxin and potassium levels in the neonates who received DigiFab®,
 •— shows case 1, —• shows case 2

digoxin due to failure to respond to other medical treatments. The most common cause of CHF was ventricular septal defect. Moderate to large ventricular septal defects with signs of CHF require treatment in the neonatal period.¹⁰ Although most children with isolated atrial septal defects are free of symptoms and require no medication, neonates with significant a large left-to-right shunt causing heart failure symptoms require treatment, although this is rare. Diuretics, afterload reducing agents, and digoxin have been used to treat CHF.¹⁰

Digoxin toxicity occurs more commonly in neonates and infants.¹¹ Toxic digoxin levels can cause extracardiac and life-threatening cardiac effects. Clinical and electrocardiographic features of digoxin intoxication are frequently nonspecific in the neonatal period.¹² Electrocardiographic evaluation should comprise part of the evaluation for digoxin toxicity. Life-threatening arrhythmias may be seen at electrocardiography in neonates with toxic digoxin levels.⁶ Digoxin-related side-effects may also be seen in infants without toxic levels.¹³ The cardiovascular manifestations of digitalis toxicity include sinoatrial and atrioventricular blocks, extrasystole, asystole, atrial tachycardia with atrioventricular block, ventricular tachycardia, and ventricular fibrillation.^{6,14} Bradyarrhythmias and atrioventricular block

associated with digoxin toxicity are more common in children.^{6,11,14} Woolf et al.⁶ reported life-threatening cardiac effects in 10 neonates with serum digoxin levels of >5-17.9 ng/ml and treated with DigiFab®. Atrioventricular block was the most common sign of toxicity, and four neonates died.⁶ In our study; despite high digoxin levels, no digoxin-related arrhythmia was observed on electrocardiography, other than sinus bradycardia. Sinus bradycardia was treated with atropine. No mortality occurred in our study.

Extracardiac symptoms associated with digoxin intoxication include gastrointestinal, neurological, and visual manifestations. Gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal pain are predominant and frequently observed in infants.¹⁵ The most common symptoms in this study were vomiting, lethargy, and apnea.

Measurement of serum digoxin levels can be useful in clinical practice in terms of efficacy as well as in order to avoid digoxin toxicity, to determine patient compliance, to detect abnormalities in absorption and excretion, and for managing accidental overdoses.¹ Serum digoxin levels in children are not strongly associated with the classic signs and symptoms of digoxin toxicity.¹³ Routine serum digoxin level monitoring is therefore neither useful nor indicated.¹¹ In our study, three newborns (23%) with serum digoxin levels >5ng/ml, showed signs and symptoms of digoxin toxicity. Diagnosis of digoxin toxicity should be made clinically, and levels should be determined for confirmation.

The immunoassay method is commonly used in clinical laboratories to determine serum digoxin concentrations. This method is affected by endogenous compounds known as "digoxin-like immunoreactive substances" (DLIS), which have been isolated in volume-expanded patients.¹⁶ Falsely elevated serum digoxin levels secondary to DLIS may be observed.¹⁷ DLIS levels of 0.20-1.00 ng/mL have been reported in neonates.¹⁷ DLIS levels may be much higher in preterm infants than in other pediatric age groups.¹⁸ In our study, the immunoassay method was also used to determine serum digoxin concentrations. This may have been contributed to the higher digoxin levels in the some neonates, especially in premature infants.

Lang et al.¹² reported a high probability of digoxin intoxication with plasma digoxin concentrations in neonates of 5 ng/ml or more, but not with concentrations below 3 ng/ml. In agreement with that study, we also observed symptoms related to toxic digoxin levels in the three neonates with plasma digoxin levels >5 ng/ml.

Dehydration and elevated renal function tests were identified as predisposing factors for toxic digoxin levels in three neonates. Serum digoxin levels improved rapidly with hydration and withdrawal of the drug in those neonates who did not receive DigiFab®.

DigiFab® has a very high affinity for digoxin, greater than that of digoxin for its sodium-potassium ATPase pump. DigiFab® is not indicated for asymptomatic patients with high serum digoxin concentrations.⁸ Two symptomatic premature neonates in our study were treated with DigiFab®. Both of these had significantly altered mental status, and one had a serum digoxin level of 10.8 ng/ml. Serum digoxin levels in the other neonates improved rapidly with hydration and withdrawal of the drug.

DigiFab® binds free digoxin in both the intravascular and interstitial spaces, and facilitates its renal excretion. Decreased extracellular free digoxin concentrations result in the removal of digoxin from tissue stores into the extracellular fluid, and it is also rapidly bound. Total serum digoxin concentrations may therefore increase following administration of DigiFab®.^{9,19} In our two patients, serum digoxin levels temporarily increased from 10.8 ng/ml to 11 ng/ml and from 7.1 ng/ml to 11.6 ng/ml.

Extracellular potassium levels can be raised through inhibition of the enzyme sodium potassium ATPase by digoxin. Hyperkalemia causes increased urinary excretion of potassium. As a result, despite the presence of a hyperkalemic state in the vascular area, whole body potassium decreases. When DigiFab® is infused into the patient, potassium shifts back into the cell. Serum potassium levels may decrease rapidly after DigiFab® administration. Antman et al.¹⁹ reported that hypokalemia developed in 4% of patients with life-threatening digoxin toxicity following the administration of DigiFab®. Our patients who received DigiFab®

were closely monitored in terms of serum digoxin levels, body temperature, blood pressure, electrocardiogram, and potassium concentrations, during and after administration. Serum potassium levels decreased after the administration of DigiFab® in both of the premature infants.

Our study has a number of limitations. First, it was a retrospective study with a small group with toxic serum digoxin concentrations, and with too few symptomatic neonates to permit definite conclusions. Second, levels of DLIS capable of contributing to high digoxin concentrations were not measured. Despite these limitations, since there is limited data concerning digoxin intoxication in the neonatal period, and although clinical symptoms and electrocardiographic features of toxic digoxin levels may be different in neonates, we believe that our study will contribute valuable additional information to the existing literature.

Toxic digoxin levels can easily occur in the neonatal period. Despite high digoxin levels, digoxin-induced arrhythmia was not observed in any of our patients. However, gastrointestinal, and neurological symptoms were common. Diagnosis of digoxin toxicity should be made clinically, and levels should be measured for confirmation. Serum digoxin levels should be measured in case of signs and symptoms of digoxin toxicity or risk factors for such toxicity. Serum electrolytes should be closely monitored in patients treated with digoxin or requiring DigiFab®. Further prospective studies involving patients with digoxin intoxication are now needed to be able to make definite recommendations.

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