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Digoxin Toxicity in a 9 Year Old Girl: A Case Report

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Abstract: Digoxin toxicity is still a possibility in any child on the medication. Therefore, a higher index of suspicion, with regular serum level estimations and possible dose readjustment should be considered in every child using the drug. Digoxin is no longer commonly used in the treatment of non-anaemic heart failure in children due to its toxicity. It is presently giving way to newer drugs like Angiotensin converting enzyme and Beta-adrenergic inhibitors in the management of congestive cardiac failure (CCF). The narrow margin between the therapeutic and toxic doses of digoxin remains a cause for concern. Female sex, lean body mass, extremes of age and renal insufficiency contribute to an increase in serum levels and toxicity. Reports in the literature of digoxin toxicity in children are very limited compared to adult cases, and any such case in a child ought to be documented to add to the sparse reviews. A 9-year-old girl with chronic kidney disease stage 5 (CKD-5) and heart failure developed digoxin toxicity recently. This manifested with bradycardia, prolonged PR interval, and 3rd degree heart block. Her serum digoxin level was 6.4ng/ml (normal reference is 0.8-2.0 ng/ml) at the time of the crises. She was managed with discontinuation of digoxin, intranasal oxygen, constant cardiac monitoring, haemodialysis and symptomatic treatment of electrolyte disturbances until the toxic crises resolved.

Keywords: Children, Digoxin, Toxicity, Heart Failure, CKD-5

1. Introduction

The use of Digoxin is now uncommon due to its toxicity, which in the past has caused a significant level of iatrogenic morbidity and mortality [1-4]. When given over a period of time, the trough value can exceed toxic levels especially in renal insufficiency [5, 6]. Digoxin is absorbed in the intestines and also reabsorbed in the renal tubules. The bioavailability of digoxin is 70-80% for oral intake, and 100% for intravenous administration [7, 8]. It is widely distributed in the tissues with only a small fraction bound to serum albumin [7, 8]. Majority of the drug is stored in the heart and kidneys [7].

Cardiac glycosides are exponentially excreted via the kidneys, although a minor portion is eliminated via enterohepatic circulation [7, 9]. Digoxin has an elimination half-life of 26-45 hours in normal individuals. This is increased to 4-6 days in patients with renal failure [7, 8]. After initiating a maintenance regimen, it takes 7-10 days (normal renal status) and 15-20 days (renal insufficiency) to achieve steady state concentration of the drug [8].

Digoxin has a positive inotropic effect on the heart. This is due to its inhibition effect on the membrane bound Na-K ATPase (sodium pump) [10, 11]. This action causes an increased intracellular concentration of sodium and Calcium, with a decreased intracellular potassium concentration, and subsequent serum hyperkalemia [10]. Again, digoxin has a negative chronotropic effect on the heart by slowing down the electrical conduction between the atria and the ventricles [10, 11]. This pharmacologically decreases the heart rate.

The normal therapeutic range of digoxin is 0.5-2ng/ml. This is a very narrow therapeutic index that can easily lead to toxicity [12].

Digoxin toxicity can be acute or chronic. Cardiac effects are of greater concern in both cases, and include bradycardia and different forms of arrhythmias. The resultant hyperkalemia during digoxin toxicity contributes to the vicious effect on the heart. Gastrointestinal symptoms are

prominent in acute cases, while signs and symptoms tend to be non-specific in chronic toxicity [13]. In any case of suspected toxicity, serum digoxin concentrations, serum potassium, serial electrocardiograms, and renal function tests must be done [11].

ECG changes appear when supra-therapeutic levels occur. Common toxicity changes include sinus bradycardia, premature ventricular complexes, and different degrees of atrioventricular blocks with prolonged PR intervals. Arrhythmias are caused by slowing of conduction velocity and increased ectopic activities [10]. A classical sign of digoxin toxicity is "the reverse tick sign" which appears as a down sloping ST segment depression on ECG [14].

Regular measurements of the serum levels of digoxin is crucial in preventing its toxicity in children [15]. Samples for serum level estimations must be collected only when the drug has reached its steady state concentration.

Reduced usage of digoxin in modern times has decreased the number of recorded toxicities. Furthermore, the modern clinician's index of suspicion of digoxin toxicity in the few patients using the drug is reduced [1]. A recent case of digoxin toxicity stressed the need for a high index of suspicion for its toxicity in children. Again, there is need for regular monitoring of serum digoxin levels with the adjustment of therapeutic doses when required.

2. Case Presentation

Our case report is on a 9 yr old girl who was being managed for immune complex (IgG) mediated focal segmental glomerulosclerosis (FSGS) with hypertension. She later developed End Stage Renal Disease (ESRD) and was referred to our out-patient transplant clinic for regular review and transplant work-up. Part of her treatment for the ESRD was 5 times a day home automated peritoneal dialysis (PD) using 1.5% diaoneal.

This therapy was complicated with recurrent peritonitis (3x in 6 months). Two months after first attending our transplant clinic, she was admitted to the referral hospital with her 3rd episode of peritonitis and had cardiac failure with anaemia. She was treated with a blood transfusion and intravenous and intraperitoneal antibiotics. During this admission, a cardiac ECHO revealed mild left ventricular (LV) dysfunction with an ejection fraction (EF) of 47%. Digoxin, 0.1mg BD was started. *Candida parapsylosis* was identified as the cause for the peritonitis. Her PD was stopped due to a deteriorating clinical condition with severe anorexia and a serum albumin of 13mg/dl. At this point she was transferred to us due to failed PD requiring haemodialysis (HD), fungal peritonitis and cardiac failure.

At presentation, she weighed 15kg and was already on Intravenous (IV) Fluconazole (100mg daily) and Cefotaxime (650mg daily), plus oral "slow K" (K+ =2 mmol/l). Two stat doses of Vancomycin and Amikacin had been given prior to the transfer to our hospital. She was also on the following maintenance drugs for her primary pathologies: prednisolone, oral calcium, mist potassium chloride (KCL), a multivitamin, folate, antacid suspension, erythropoietin, amlodipine, MMF and thiamine.

On admission, her current medications were continued. Intravenous KCL (as K+ was still <3) and albumin infusion were added. After bringing her serum K+ up to 3.9mmol/L, the PD Tenckoff catheter was removed while a permanent central catheter was surgically inserted. HD was commenced with series of intradialysis red cell transfusions to improve her haemoglobin. Potassium supplements continued until her serum K+ was 5.3.

Within a week of starting HD, she became moody and started complaining of anorexia, nausea and moderate abdominal pain. There was subsequent abdominal distension with mild to moderate tenderness but no fever. The liver was moderately enlarged with a lower abdominal fullness. There was mild splenomegaly. Bowel sounds remained normal. Abdominal ultrasound revealed resolving peritonitis with a pelvic mass. An abdominal CT showed a pelvic mass suggesting organized haematoma, to rule out a fungal ball.

She was commenced on IV Ertapenem. A surgical consult resulted in the decision to perform an exploratory laparotomy. The electrolytes measured a few hours prior to taking her to the theatre were normal, including K+ which was 3.8mmol/l.

While on the operating table, during pre-medication, the anesthetist recorded a heart rate of 48beats/min, and subsequent persistent drop in heart rate. Blood pressure (BP) remained normal (100/70mmHg). The doctor was advised to stop the surgery. An immediate ECG showed sinus bradycardia (30b/min), 3rd degree heart block with prolonged PR interval (Figure 1).

A diagnosis of digoxin toxicity was made. Digoxin and amlodipine were stopped immediately. She was placed on a cardiac monitor and given intranasal oxygen. The paediatric cardiologists were consulted. Their plan was to start a dobutamine infusion (10ug/kg/hr) if the HR remained <50b/min, and cardiac pacing if HR remained <45b/min. An urgent serum digoxin level and repeat electrolytes and venous blood gases were ordered.

The available results, 2hours later, showed: PH=7.35, PCO2=40.3, PO2=31.9, Na=138, Cl=105, K+=3.3, Ca=1.21; and a digoxin level of 6.4 (normal reference is 0.5-2.0 ng/ml). She was hemodialysed immediately, and the plan was to continue daily HD until serum digoxin level normalized. K+ supplementation was re-started.

Twelve hours overnight HR recording showed a fluctuation of the HR between 52-64beats/min. By 24 hours later, she was still bradycardic (56b/min) but now with a high BP, most likely due to the discontinuation of amlodipine. A repeat serum digoxin level was 5.4. Albumin infusion was stopped at this point, while intensive care of the patient continued. At 48 hours, repeat serum digoxin level was 2.4, BP was 146/110mmHg, and the HR was improving with rates between 62 and 68 beats/min. Another antihypertensive medication, Cardura (Doxazosin) was now added to replace amlodipine. On the 4th day, her digoxin level came down to 1.8ng/dl, and the heart rate normalized. Regular close monitoring and dialysis continued.

A week after the onset of the digoxin crises, patient became weak with apex beat now at the 6LICS-MCL, the HR was 83beats/min with a gallop rhythm and there was a grade 2 pan-systolic murmur. JVP was raised, RR was 28cycles/min, SpO2 was 100%, (on intranasal O2), BP was 158/111mmHg, and repeat ECG showed a sinus rhythm with prolonged P-R interval (Figure 2). Repeat ECHO showed worsening LV function with EF of 22-28%. There were also blood clots inside the LV. The cardiac team added aspirin, 150mg daily, while restarting amlodipine (5mg) and digoxin (0.125mg stat, then 2x per week). Digoxin level was ordered at 6 hours after re-introduction of digoxin and then daily in order to monitor and adjust dose as needed.

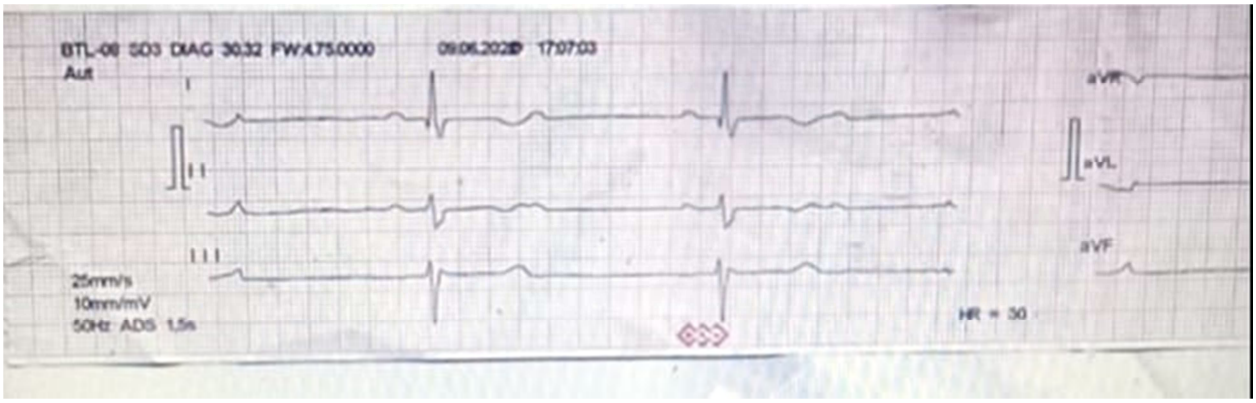

Figure 1. *Sinus Bradycardia (30b/min), 3rd degree Heart Block with prolonged PR interval.*

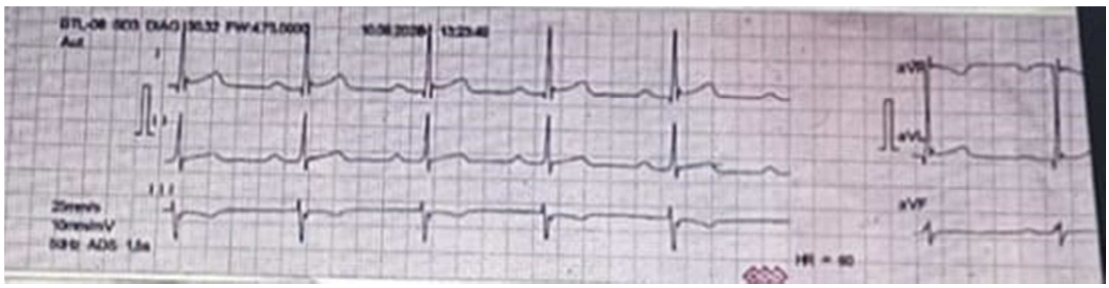

Figure 2. *Sinus Rhythm with Prolonged P-R Interval.*

One week after recommencing digoxin, her LV function continued to deteriorate (EF=11-17%) despite correction of anaemia and daily dialysis. The elevated BP persisted with amlodipine, so Prazocin and Lisinopril were added. Digoxin level was now 1.3ng/ml. The cardiac team increased the digoxin dosage to 0.125mg on alternate days. This led to improvement in her cardiac function with resolution of her CCF. The pelvic mass also resolved with both IV antibiotic and antifungal medications. Her digoxin level was monitored weekly, and it remained normal thereafter.

3. Discussion

The patient reviewed was an ESRD patient and started digoxin because of CCF. In patients with renal failure, the volume of distribution of digoxin is decreased [7, 8]. This necessitates reduction in the loading, as well as maintenance doses [5, 6, 9].

This patient was started on a maintenance dose initially (with no loading dose) which was with full consideration of her renal status. However, because of the circumstance surrounding her admission into our unit, with major emphasis on fixing her mode of dialysis and her surmounting peritonitis, monitoring of her serum digoxin level was mistakenly forgotten. This was remembered when symptoms of drug toxicity occurred.

Female sex, lean body mass, and renal insufficiency have all been implicated as risk factors for enhanced digoxin toxicity [8]. This is because they contribute to higher serum levels of the drug [8]. The index patient is a female, was underweight (15kg) and also had ESRD. Children with severe heart disease are also more prone to digoxin toxicity [16]. This is because of the altered characteristics of the myocardium, loss of contractile tissue mass, and a low cardiac output state with the accumulation of the glycoside in the body [16]. All of these factors may have contributed to her digoxin toxicity after only 4 weeks of medication.

Normal therapeutic serum range for digoxin is 0.5–2 ng/ml, and toxicity is usually seen at serum level > 2 ng/ml [10-12]. The patient had digoxin level of 6.4ng/ml at the time of toxicity. Most infants and younger children tend not to show any symptoms until the level of digoxin has reached 4ng/mL [10]. The more common cardiac symptoms of digoxin toxicity in young children are bradycardia, atrioventricular blocks and increased PR intervals [10, 11, 17]. The index patient had bradycardia, a prolonged PR interval and 3rd degree AV block.

Extra-cardiac symptoms of toxicity include nausea, anorexia, vomiting, abdominal pain, diarrhoea, cold sweats, lethargy, confusion, vertigo, delirium, blurred vision, diplopia, tinnitus, convulsions and syncope [10, 11, 17]. The patient in addition to the resolving peritonitis, had frequent complaints of anorexia, epigastric pain, nausea and occasional vomiting prior to the diagnosis of digoxin toxicity. These abdominal symptoms may have been early signs pointing to the increasing levels of serum digoxin.

This patient remained clinically stable physically but for the aforementioned cardiac symptoms during the whole period of toxicity. This could be explained by the fact that younger children (excluding infants/neonates) can tolerate higher levels of digoxin better than teenagers/adults [11]. Also, we were not sure at what point her serum digoxin level exceeded the normal serum therapeutic range since it was not initially monitored. This case could also have been a state of chronic toxicity compounded by an acute episode.

Depending on the severity of digoxin toxicity in children, treatment may include discontinuation of digoxin, correction of electrolyte imbalance, use of drugs like atropine and dobutamine, digoxin-specific antibody fragments (Fab) and cardiac pacing [10, 11]. Patients should be placed on a continuous cardiac monitor with oxygen and intravenous fluid support. Gastrointestinal cathartic treatment using activated charcoal can be given in an awake and alert patient [10].

This patient was placed on continuous cardiac monitoring with oxygen, potassium correction and haemodialysis, after discontinuation of digoxin. Eyanet al [18], successfully treated a 12-weeks old female baby with digoxin toxicity using Fab. Shadel [11] and Husby [19] also reported the use of Fab in treating children with digoxin poisoning. Although Fab is safe in patients with ESRD [20], it was not available in our centre as at the time of the crises, and we did not source for it as other modalities of treatment were available.

Although our index patient survived digoxin toxicity, several observational and retrospective studies and meta-analysis have shown an association between the use of digoxin and increased mortality to about 20% [21]. This brings to question whether digoxin should be scrapped as a treatment option for heart failure, especially in children. However, this is beyond the scope of this case report.

Digoxin therapy and anti-hypertensives were re-commenced on the index patient following worsening cardiac failure and elevated blood pressure respectively. Digoxin was cautiously re-introduced with regular serum level immunoassays, enabling us to keep the patient's serum digoxin at therapeutic levels.

The patient has remained stable on 0.125mg of alternate day digoxin, and is currently undergoing renal replacement therapy normally. Her digoxin level continues to be monitored weekly to avoid toxicity as long as she is on the medication.

This case report adds to the scarce literature [10, 19, 22] on digoxin toxicity in children.

4. Conclusion

Digoxin toxicity is still a possibility in any child on the medication. Therefore, a higher index of suspicion, with regular serum level estimations and possible dose readjustment should be considered in every child using the drug. This is very important, especially in patients with renal insufficiency.

Conflict of Interest

The authors declare that they have no competing interests.

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