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Digoxin for atrial fibrillation: good, but not too good: a case report

Digoxina para fibrilação atrial: boa, mas não muito: relato de caso

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ABSTRACT: Digoxin is a cardiotonic glycoside that is traditionally used for the treatment of heart failure and atrial fibrillation in humans and animals. However, the use of digoxin is still a challenge in clinical practice due to its narrow therapeutic range and its potential interaction with several drugs, which could facilitate the development of toxicity. A 12-year-old Labrador retriever was referred with a clinical diagnosis of heart failure and atrial fibrillation, anorexia, vomiting, and diarrhea. He had been medicated with digoxin, furosemide, lisinopril, and amiodarone. The patient also showed clinical signs of hip osteoarthritis and received firocoxib for four days. He additionally received drugs for gastrointeritis. The electrocardiogram demonstrated atrial fibrillation and signs of digitalis toxicity. Laboratory examination showed a high concentration of plasma digoxin, and 5 days after withdrawal of the drugs, the symptoms disappeared, as did the digitalis effects seen in the previous electrocardiogram.

KEYWORDS: cardiotonic glycosides; digitalis; atrial fibrillation; digoxin intoxication.

RESUMO: A digoxina é um glicosídeo cardiotônico tradicionalmente utilizado no tratamento de insuficiência cardíaca e fibrilação atrial em humanos e animais. Porém, o uso da digoxina continua sendo um desafio na prática clínica devido a sua estreita faixa terapêutica, bem como a sua potencial interação com diversos fármacos, facilitando o desenvolvimento de toxicidade. Um Labrador Retriever de 12 anos de idade foi encaminhado com diagnóstico clinico de insuficiência cardíaca, apresentando fibrilação atrial, anorexia, vômitos e diarreia. Ele vinha sendo medicado com digoxina, furosemida, lisinopril e amiodarona. Ele havia sido concomitantemente medicado com firocoxibe por quatro dias para tratamento de osteoartrite coxo-femoral, além de medicamentos para gastroenterite. O eletrocardiograma demonstrou fibrilação atrial e sinais de toxicidade digitalica. O exame laboratorial revelou alta concentração de digoxina plasmática sendo que, cinco dias após a suspensão dos medicamentos, o paciente já apresentava melhora clinica acentuada, enquanto os efeitos digitálicos observados no eletrocardiograma anterior desapareceram.

PALAVRAS-CHAVES: glicosídeos cardiotônicos; digital; fibrilação atrial; intoxicação por digoxina.

INTRODUCTION

Digoxin is a cardiotonic glycoside that is obtained from the foxglove, an herbal remedy popularized by Sir William Withering after the publication of his memorable monography on the treatment of dropsy in humans (WITHERING,1875). The genus name *Digitalis* comes from the Latin for "finger" since the foxglove flower resembles a glove's finger. From a chemical point of view, cardiac glycosides are part of a family of almost 300 *digitalis* compounds, but only two pharmaceutical formulations are actually marketed: digitoxin and digoxin, which are obtained from *Digitalis purpurea* and *Digitalis lanata* (WALLACE, 2006; BENOWITZ, 2014). In veterinary medicine, Blaine (1841) first recommended foxglove as a therapeutic remedy for dropsy in dogs when he published his historical book, "Canine Pathology; or A Full Description of the Diseases of Dogs".

After more than two centuries, digoxin is still considered a useful drug for people with heart failure (HF) or atrial fibrillation (AF) (ZIFF; KOTECHA, 2016; RHODE et al. 2018). For domestic animals, it is indicated for HF or AF caused by degenerative mitral valve disease and dilated cardiomyopathy (KEENE et al., 2019; STEAGALL et al., 2020). Digoxin acts on the sodium/potassium pump of the cardiomyocytes, thereby increasing the concentration of calcium influx and producing

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positive inotropism, while the heart rate is reduced by the vagal effect (BENOWITZ, 2014; WALLACE, 2006). This action improves diastolic filling, increases ventricular output, improves glomerular filtration, and decreases edema by improving diuresis.

Despite its worldwide usage, digoxin is a critical drug due to its low therapeutic index; i.e., there is a small difference between the therapeutic and toxic ratios, which facilitates the development of adverse effects. Furthermore, digoxin's pharmacokinetics and pharmacodynamics are complex and influenced by several factors, particularly dosing; old age; glomerular filtration; comorbidities; and interaction or interference with several medications, including furosemide, amiodarone, dronedarone, macrolide antibiotics, benzodiazepines, indomethacin, propafenone, quinidine, verapamil, and spironolactone, which can lead to the development of toxicity (BENOWITZ, 2014; DIFRUSCIA, 1984; WALLACE, 2006). Thus, the aim of this report is to discuss the clinical, electrocardiographic, echocardiographic, and laboratory results observed in a case of *Digitalis* intoxication in a dog treated for HF and AF.

CASE REPORT

In July 2020, a 12-year-old, 40-kg, male Labrador retriever was referred for second opinion due to a five-month history of AF and a clinical diagnosis of HF. The patient had been receiving digoxin (0.25 mg, 1.4 tablets BID), furosemide (40 mg, one tablet TID), amiodarone (200 mg, one tablet SID), and lisinopril (5 mg, one tablet BID). He also received oral firocoxib (57 mg/day/4 days) for hip osteoarthritis and subsequently developed anorexia, vomiting, diarrhea, and weight loss. He was then medicated with omeprazole (one tablet 20 mg/SID), maropitant (one tablet 16 mg/SID), famotidine (one tablet 20 mg/SID), ondansetrone (one tablet 4 mg/TID), and domperidone (one tablet 10 mg/BID) to control the gastrointestinal manifestations.

Taking into account the scenario of polypharmacy and the appearance of gastrointestinal disturbances, a trigger tool system for the detection of adverse drug events was applied (FONSECA et al., 2020), which led to high suspicion of drug toxicity. On physical examination, the patient presented mild dehydration and weakness. Cardiac auscultation revealed irregular cardiac rhythm, variable first heart sound, heart rate of 64–100 bpm, no murmur, and no third heart sound. Palpation revealed femoral pulse deficit and irregular rhythm. Systolic arterial blood pressure was measured by Doppler sphygmomanometry as 100 mmHg. A six-lead computed electrocardiogram showed AF and changes consistent with the effects of *Digitalis* (Fig. 1).

The clinical and electrocardiographic data strongly suggested *Digitalis* toxicity. After recommendations for measuring digoxinemia in dogs (NAKASHIMA et al., 2001), a blood sample was collected at 10–12 h after the last dose of digoxin and sent for laboratory analysis. The chemiluminescence immunoassay test demonstrated a digoxin plasma concentration of 5.67 ng/ml, which is consistent with the toxic level of the drug. The hemogram showed leukocytosis, while the blood chemistry demonstrated increased levels of cholesterol, glucose, alkaline phosphatase, and urea, as well as decreased sodium and potassium (Table 1).

Five days after discontinuing the medications (except antibiotic and hydration), the patient ameliorated rapidly, and a repeat electrocardiogram demonstrated AF but no *Digitalis* effect (Fig. 2). On the same day as the second electrocardiogram, a transthoracic bidimensional echocardiography examination revealed no structural cardiac abnormalities (Fig. 3). The M-mode cross-sectional study (Fig. 4) revealed measurements within the normal reference ranges published for dogs based on body weight, as shown in Table 2 (CORNELL et al., 2004).

With hydration, nutrition, and antibiotic therapy, the patient presented continuous clinical amelioration. The systolic arterial blood pressure rose to 140 mmHg, and in the next 3 weeks, the patient did well clinically. The aim of this report is to discuss the results of clinical, laboratory, echocardiographic, and electrocardiographic findings consistent with

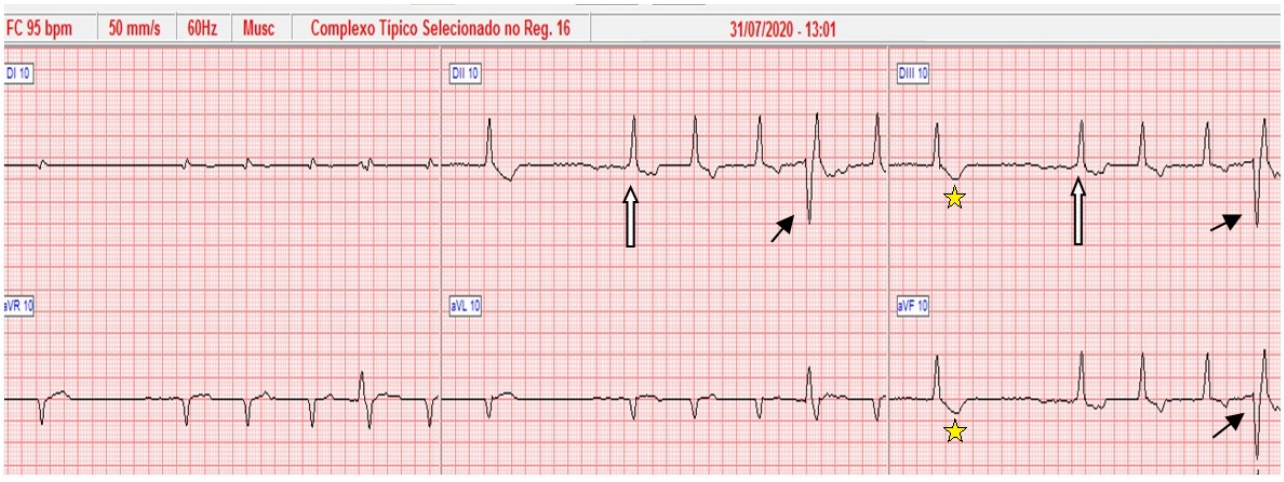

Figure 1. Six-lead electrocardiogram presenting AF, junctional escape beat (open arrow), and ventricular ectopic complex (black arrow). The mean heart rate is 95 bpm. Note the distinct Digitalis effect: secondary repolarization abnormality (S-T segment down-up sloping), also termed "hammock shaped" or "Salvador Dali's mustache" appearance (yellow star). Calibration 10 mm=1 mv, velocity 50 mm/s.

Digitalis toxicity observed in a dog on treatment for HF and AF, as well as to call attention to the potential of side effects whenever using *Digitalis* glycosides.

DISCUSSION

After more than two centuries, digoxin remains a mainstay drug in the treatment of HF and AF in humans and domestic animals, despite the historical controversies about its indications, dosing, and results (RAMIREZ, 2005; ZIFF; KOTECHA, 2016). For dogs with systolic HF or AF caused by myxomatous mitral valve disease or dilated cardiomyopathy, the recommended maintenance dosage of digoxin is 0.22 mg/m^2 BID for large and giant dogs (>20 kg) and 0.011 mg/kg BID for small dogs (WILLIS, 2018). Thus, for a 40-kg dog, the daily dose should be 0.025 mg/BID or 0.05 mg/day instead of the dose of 0.62 mg/day given.

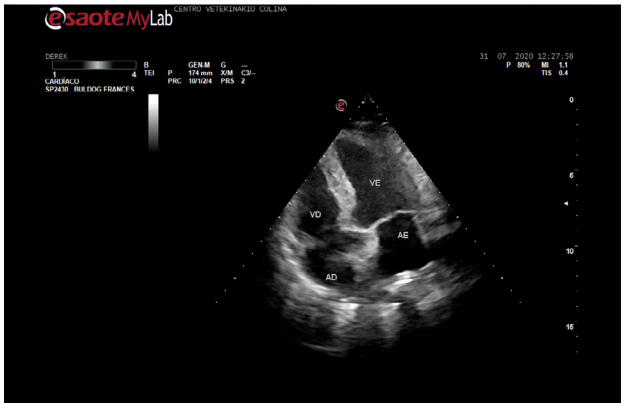

Figure 3. B-mode echocardiography, left apical four-chamber view, showing no morphological changes. VD=right ventricle; AD= right atrium; VE=left ventricle; AE=left atrium

Table 1. Laboratory results.

Blood chemistry	Results	Reference range
Alanine transaminase (ALT)	46.8 U/L	10.0–102.0 U/L
Cholesterol	263.7 mg/dL	120–250 mg/dL
Triglycerides	87.8 mg/dL	60–118 mg/dL
Glucose	141.4 md/dL	60–118 mg/dL
Sodium	136 mmol/L	141–152 mmol/L
Potassium	4 mmol/L	4.3–5.4 mmol/L
Albumin	2.85 mg/dL	2.8–4.0 mg/dL
Urea	70 mg/dL	10.0–60.0 mg/dL
Creatinine	1.3 mg/dL	0.5–1.5 mg/dL
Alkaline phosphatase	280 U/L	12.0–121.0 U/L
Digoxin	5.67 ng/mL	1.0–2.5 ng/mL

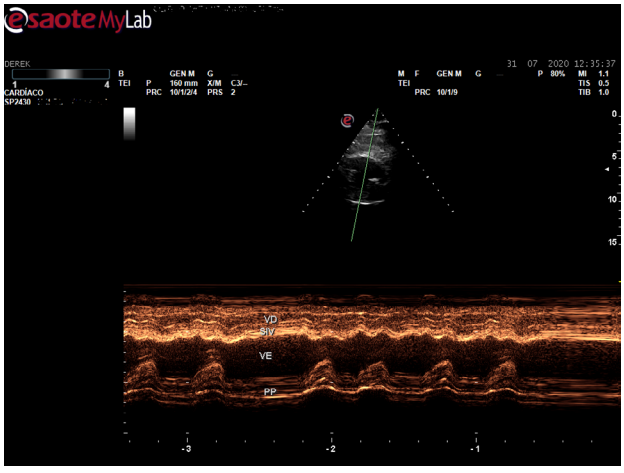

Figure 4. Left ventricular M-mode dimensional echocardiogram, right parasternal short axis view. VD: right ventricle; SIV: interventricular septum; VE: left ventricle cavity; PP: left ventricle posterior wall.

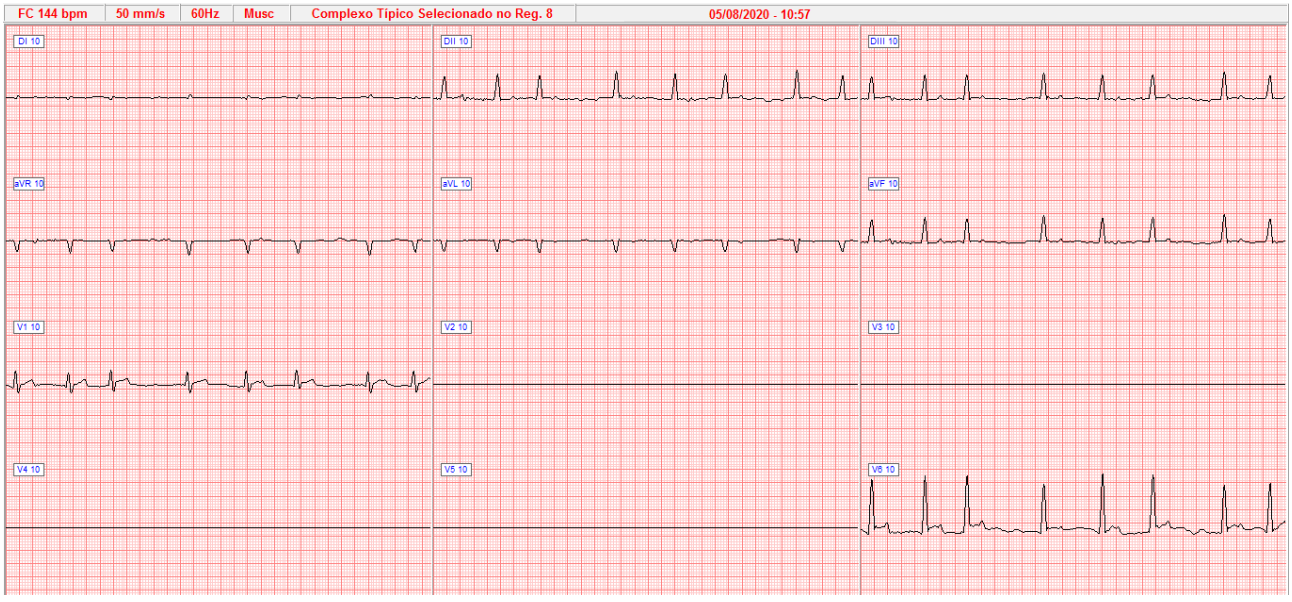

Figure 2. Atrial fibrillation is still present; mean heart rate is 144 bpm, but there are no more effects of Digitalis. Calibration: 10 mm=1 mv, velocity = 50 mm/s.

Table 2. M-mode measured values.

Parameter	Result (cm)	Ref. Range (cm)
LA	3.5	2.1 – 3.5
Ao	3.2	2.2 – 3.4
LVIDd	5.1	3.8 – 5.5
LVIDs	32.6	23 – 40
IVSTd	1.3	0.7 – 1.4
LVWd	1.3	0.7 – 1.4

LA= left atrial diameter; A= aortic root diameter; LVIDd= left ventricular end diastolic diameter; LVIDs= left ventricular end systolic diameter; IVSTd= interventricular septal thickness in diastole; LVWd= left ventricular free wall thickness in diastole.

Furthermore, a significant aspect to take into consideration is that unlike certain drugs that accumulate in the adipose tissue, digoxin concentrates more in muscle and reaches higher levels in the heart muscle, facilitating cardiac toxicity (COLTART et al., 1972). It is also important to remember that when gastrointestinal signs of digoxin toxicity appear, myocardial toxicity is already present and may even be fatal (RAMIREZ, 2005). For these reasons, when digoxin is used, it is recommended that the dosage be adjusted according to the patient's lean body mass, and it is advisable to reduce the total daily quantity to 85% of the initial calculated dose (DIFRUSCIA, 1984).

Another aspect to consider is that interference in the pharmacokinetics of digoxin occurs in cases of concomitant administration of agents that slow peristalsis, thus prolonging the contact time of the drug during bowel transit and increasing its absorption. This probably occurred with our patient since various drugs for vomiting and diarrhea were used simultaneously. Thus, in this case report, it is presumed that several factors acted together to cause toxicity, particularly the high drug burden, old age, hypokalemia, hyponatremia, dehydration, and interaction or interference among medications. The concentration digoxin in serum and thus its toxicity are increased by concomitant use of some antiarrhythmics (such as quinidine, calcium channel blockers (especially verapamil and diltiazem), amiodarone, spironolactone, and propafenone). Adjunct digoxin and betablockers may be useful but may also cause or accentuate previous bradycardia (PATOCKA et al., 2010), as well as adverse events, especially in patients with systolic dysfunction (SAUNDERS ET AL, 2006).

This patient was receiving amiodarone at a maintenance dose of 5 mg/kg/day, which is lower than the median dosing of 9 mg/kg/day used in a study on dogs with AF (SAUNDERS et. al, 2006). That study reported that adverse effects associated with amiodarone included bradycardia and augmented ALT activity, which ranged from 1.1 to 1.8 times the upper limit of normal. Furthermore, some dogs presented anorexia, vomiting, and diarrhea. In the case of our patient, ALT was 46.8 UL, which is within the normal reference range (Table 1).

In another study using client-owned dogs with supraventricular tachyarrhythmia, uncommon gastrointestinal side effects were attributed to oral amiodarone, and the clinical signals improved after the does was reduced to 5 to 7.5 mg/day. The conclusion was that amiodarone could be a safe and effective alternative for the treatment of arrhythmias that are not controlled with other anti-arrhythmic drugs (PEDRO et al., 2012).

Since the patient in this case report was receiving a low dose of amiodarone, it is doubtful that it caused the gastrointestinal signs by itself. However, investigations of humans and experimental pigs demonstrate that amiodarone-digoxin interaction increases the plasma digoxin concentration and thus the risk for digoxin toxicity. The mechanism of this interaction is that amiodarone increases digoxin concentrations by inhibiting the P-glycoprotein-mediated efflux transporter of the intestinal cells, biliary canalicular membrane, and renal tubular cells, which facilitate the elimination of digoxin from the organism. Moreover, amiodarone also acts by changing the concentration and distribution of digoxin across the tissues through interference in gastrointestinal and renal elimination (BUSTI, 2021).

In dogs with AF, heart disease is usually present as well (WILLIS, 2018), affecting mostly large and giant breeds. However, this arrhythmia is occasionally found in dogs with demonstrably structurally normal hearts (MENAUT et al., 2005; PEDRO et al., 2020), as observed in this case report. This condition is called lone AF. In the veterinary literature, there are exceedingly rare reports describing the clinical and electrocardiographic manifestations of digoxin toxicity in dogs (MALMASI et al., 2009). The clinical signs of *Digitalis* intoxication are unspecific and vary among patients. They include anorexia, which is the first complaint, but also common are vomiting, dehydration, diarrhea, and several types of arrhythmias (KEENE, 1983).

The hallmark of cardiotoxicity of cardiac glycosides is increased automaticity and electric conduction delay. As a consequence, it can produce electrocardiographic aberrations (i.e., different types of ectopy, such as premature ventricular depolarizations, atrioventricular escape beats, and primary changes of ventricular repolarization). In this situation, changes in ventricular repolarization are manifested by the classic sagging or "scooped" appearance of repolarization with simultaneous ST-segment depression (BRADY et al., 2001; AGARWAL and AMSTERDAM, 2015), as documented in this case study.

CONCLUSION

The aim of this case presentation was to describe the clinical, laboratory, echocardiographic, and electrocardiographic manifestations of *Digitalis* toxicity in a dog treated for AF. The focus was on directing clinicians' attention to the use of digoxin and the value of interpretation of clinical manifestations, laboratory examination, and serial electrocardiograms to identify the presence of *Digitalis* toxicity. Early suspicion and recognition of *Digitalis* toxicity are crucial for the proper treatment of this potentially lethal condition.

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