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Digital is toxicity during acute renal failure associated with multiple myeloma: A considerable risk

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ABSTRACT

Digitalis (cardiac glycosides) is a naturally occurring substance in various plants (digitalis, squill). They are mainly used in the treatment of heart failure and cardiac rhythm disorders. They induce a positive inotropic effect by inhibiting NA^+/K^+-ATPase which results in an increase in the amount of calcium released from the sarcoplasmic reticulum in each cycle of contractions. Digitalis toxicity is a rare drug complication, but potentially serious. This is rare when good rules of drug prescription are respected, though this is not often the case. This highlights on the need for further information to physicians and their patients about the risk involved, including renal failure and electrolyte imbalance (hypercalcemia, hyperperkalemia, hypokalemia etc.).

Introduction

Digitalis medicines are substances found in pharmacopoeia that have been used for a long time. Acute digitalis toxicity (digoxin, digitoxin and deslanoside) is rare but potentially serious. Hypercalcemia increases myocardial digitalis toxicity while renal failure can lead to an accumulation of digoxin. We report a case of acute digitalis toxicity associated with acute renal failure and hypercalcaemia.

Case presentation

A 46 year old female patient with a family history of breast cancer is being monitored for congestive heart failure due to a dilated-hypokinetic cardiomyopathy with a 57 % ejection fraction. She was put on: Digoxin 0.25 mg daily, Valsartan 80 mg daily, aspirin 160 mg daily, Aldactone 100 mg daily and Furosemide 40 mg daily.

The patient's general condition significantly deteriorated with a 30 Kg weight loss. The patient was hospitalized at the department of nephrology after her blood test revealed hypercalcemia associated with kidney failure. Physical examination at admission found a patient with an altered general condition; a heart rate of 90 beats per minute,signs of right heart failure (jugular venous distension, ascites and leg edema) and oliguria(200ml per day) .Urine Dipstick tested positive for proteins, blood and a pH of 6.

Blood tests at admission revealed renal failure (creatinine = 59mg / L and urea= 1.68 g / L), associated with hypoproteinemia (117g / L), hypercalcemia (147 mg / L); anemia (5.2 g / dL) and thrombocytopenia (60,000 cells / mm^3). Further investigation on the cause of hypercalcemia in the patient revealed a monoclonal spike in gamma globulin(Fig.1). The serum and urine immunoelectrophoresis revealed the presence of kappa light chain (Fig.2 and 3). Plain X rays showed lytic bone lesions (Figure 4).

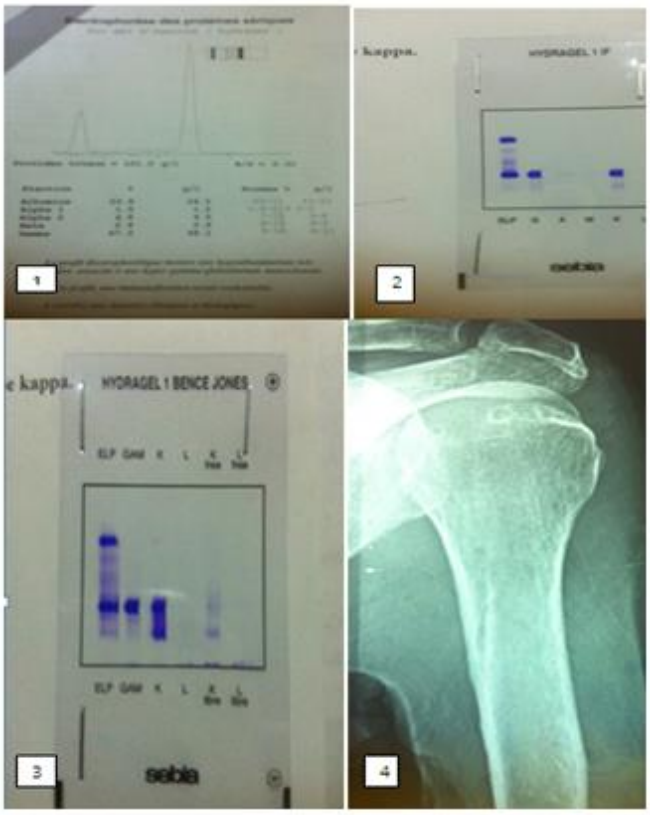

Figure 1. Serum Electrophoresis showing a monoclonal peak in gamma zone.

Figure 2.Serum immunoelectrophoresis reveals the presence of a kappa chain.

Figure 3. Bence Jones urinary Immunoelectrophoresis revealing the presence of a kappa chain.

Figure 4. Plain Xray of the humerus showing geodes.

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The diagnosis of IgG kappa multiple myeloma staged IIIB according to Durie- Salmon staging system was retained. At admission, the patient had multiple hemodialysis due to hypercalcemia and was put on a dose of zoledronate.

Despite dialysis and bisphosphonate administration, the patient presented signs of digitalis toxicity (nausea and vomiting) a few days after admission. Laboratory tests revealed hypokalemia(3,1 mEq / l).A complete sinoatrial block was observed on her electrocardiogram (Fig.5). Digoxin was stopped and the patient was put on symptomatic treatment with correction of serum potassium and cardiac monitoring.

A normal ECG was observed (Figure 6) after several days of symptomatic treatment. The evolution was marked by an improvement in renal function, serum calcium within normal limits and an improvement in general health.

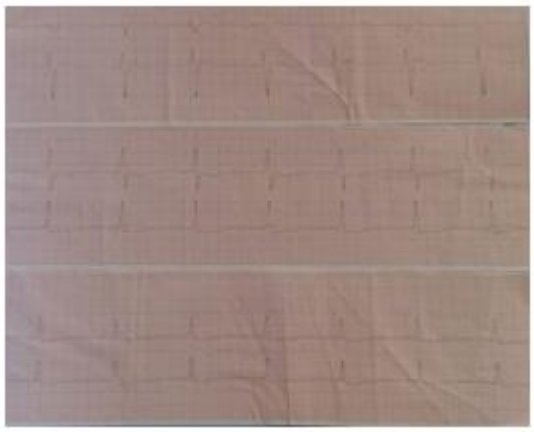

Figure 5 . ECG objectivant la présence d'un bloc sino-auriculaire.

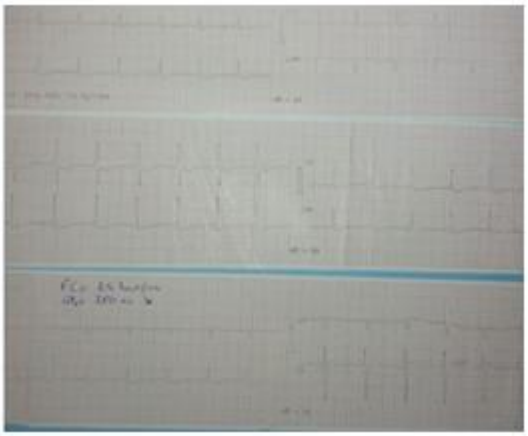

Figure 6.ECG de contrôle après arrêt des digitaliques avec un retour à un rythme sinusal suggérant l'origine iatrogène du bloc sino-auriculaire.

Discussion

Digitalis a homogeneous group of cardiac glycosides (extract from the Digitalis plant, structure composed of a saccharide part and a genin part, and similar pharmacodynamic action) that simply have different pharmacokinetic properties.

They all have the property of significantly increasing cardiac contractile force (by increasing the amount of cytosolic calcium ions). [1] Pure inotropic concentrations of these drugs are very close to its toxic concentrations. Digitalis drugs are among drugs with narrow therapeutic ranges.

Digitalis toxicity is relatively rare but can be potentially severe. Hypercalcemia and renal failure increases this severity. Thus,the need to be careful in risky situations similar to that of our patient.

Digitalis toxicity can be acute or chronic, voluntary or involuntary. Chronic toxicity is by far the most common.

In a recent study in 24 French hospitals that included a total of 838 patients identified from digitalis assays performed by laboratories, chronic digitalis toxicity was found in 96% of cases [2]. This result is likely understated as digitalis overdose is not always reported [3]. The frequency of overdoses is due to the narrow therapeutic index of digitalis.

In the study of Lapostolle [2]) which included 722 patients, digitalis toxicity is favored by errors of dosage which is common in elderly patients with a median age of 83 years (76-88 years) , pharmacokinetic changes related to age,

concomitant disease or drug interactions. [4] In our patient, digitalis toxicity was not related to age but rather to kidney failure and electrolyte imbalances induced by multiple myeloma.

Digitalis stimulates a vagal response and inhibits Na K-ATPase membrane pump [5,6]. Toxic dose of this drug induces sympathetic nervous system stimulation responsible for an increase in ectopic foci activity. This results in positive inotropic and bathmotropic effects and negative chronotropic and dromotropic effects. Clinical manifestations of digitalis toxicity regroups digestive, neurosensory and cardiac disorders [7,8]. The latter is responsible for the severity of digitalis toxicity.

Clinical manifestations of digitalis toxicity are identical, whether caused by digoxin or digitoxin. Kidney failure is common. F. LAPOSTOLLE and Al studies on 722 patients, found a median creatinine=122 mmol / L. 70% of the patients had a serum creatinine > 100 mmol / L whilst 25% had a higher creatinine>180 mmol / L [2].

Kidney failure is thus involved in the genesis of overdose and perpetuation of this disorder. Kidney failure accentuates the digitalis toxicity as this reduces its urine elimination. For example, the half-life of digoxin reaches 57 hours when the creatinine clearance is reduced by half and increases to 84 hours when it drops to 8 ml / min). Hypercalcemia increases myocardial digitalis toxicity. Hypokalemia increases the glycoside - Na / K-ATPase pump bond and thus potentialises the toxic effects of digitalis. [9]

According to current recommendations, gastric lavage and activated charcoal are not indicated for chronic overdose. [10] Hemodialysis and hemoperfusion have no clinical relevance. The introduction of antidigitalis antibody as an alternative treatment has changed the management of digitalis poisoning. [11]

The purpose of symptomatic treatment is essentially to prevent and correct hydro -electrolyte imbalances and other aggravating factors of toxicity. Hyperkalemia, which is real factor of severity of digitalis toxicity, should be distinguished from hypokalemia, which is an aggravating factor. Hypokalemia probably promotes the binding of digitalis on myocardial receptors. The existence or occurrence of hypokalaemia requires intravenous correction.

This correction should be with caution in order not to cause hyperkalemia. Hyperkalemia contra indicates any potassium intake. It is effectively treated by the antibody. Hypercalcemia must be also corrected as it has a synergic effect with digitalis in the myocardium, especially on cardiac automatism. On the other hand, hypocalcemia significantlyreduces the toxic effects of cardiac glycosides.

Magnesium, sodium or phosphorus imbalances potentialise digitalis toxicity and must be corrected. In our case, digitalis toxicity was mainly due to overdose secondary to advanced renal failure and exacerbated by hypokalemia and hypercalcemia caused by multiple myeloma.

Early diagnosis of this toxicity allowed early and effective therapeutic management that improved the prognosis of our patient as well as the correction of other aggravating electrolyte disorders, including hypercalcemia and hypokalemia. On the other hand, it also helped to establish the diagnosis of multiple myeloma, for which the patient is undergoing chemotherapy. Hence the interest to look for risk factors for digitalis toxicity, by performing blood test for renal function, blood electrolytes including potassium and calcium levels before any prescription of digitalis drugs.

Conclusion

Digitalis drugs are effective in advanced heart disease; especially ischemic heart diseases. However, they must be handled with caution, especially in the elderly, patients with renal insufficiency, and patients with hypokalemia and hypercalcemia. The adaptation of the therapeutic dosage and monitoring of patient are essential.

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