Clarithromycin induced digoxin toxicity

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Abstract

A case of digoxin poisoning following the co-administration of digoxin and clarithromycin in a 28 year old male is described. Since the aetiology of chronic digoxin poisoning is often unclear, clinicians should be aware of the potential drug-drug interaction between digoxin and clarithromycin.

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Digoxin remains a popular drug, particularly in the treatment of congestive heart failure and atrial fibrillation. Improvements in critical care medicine and immunotherapy have decreased the morbidity and mortality associated with digoxin toxicity. However, this still remains a common problem. We present a case of digoxin poisoning following an interaction between digoxin and the macrolide antibiotic clarithromycin.

Case report

A 28 year old male presented to the emergency department with three days of anorexia and vomiting. Past medical history included tetralogy of Fallot and pulmonary atresia. Drug treatment before admission included clarithromycin, captopril, frusemide, and digoxin. Six years previously a pacemaker was installed without difficulties. Twelve days earlier he was admitted for a community acquired pneumonia and placed on clarithromycin. He was discharged four days afterwards to complete the course at home. Four days after discharge he began vomiting. He was noted to be confused and complained of visual disturbances. A physical examination revealed decreased breath sounds bilaterally and an irregular pulse. He was haemodynamically stable.

An electrocardiogram showed a paced rhythm with frequent premature ventricular beats. Episodes of ventricular couplets and runs of non-sustained ventricular tachycardia were seen on continuous monitoring. Blood

analysis showed potassium 4.8 mmol/l, blood urea nitrogen 10.1 mmol/l, creatinine 106.1 µmol/l, digoxin 5.0 ng/ml (normal therapeutic range 0.5 to 1.2 ng/ml). His last digoxin dose had been 20 hours before presenting to the emergency department.

He was rehydrated and placed on telemetry. Digoxin specific Fab fragments were available at the bedside. Clarithromycin was withheld along with digoxin. His renal function remained unchanged during his admission and his digoxin level fell steadily to 3.4 ng/ml the following day, reaching a nadir of 1.2 ng/ml six days after admission. He was treated with sulphamethoxazole-trimethoprim for his pneumonia without adverse effects, and was discharged six days after admission on digoxin, frusemide, and captopril. Subsequent follow up visits revealed normal digoxin levels.

Discussion

Digoxin poisoning remains a common occurrence. The chronicity of digoxin toxicity should be addressed, as acute poisonings differ from chronic poisonings. A classification is given in table 1. Acute poisonings are generally seen in younger, suicidal patients who have ingested someone else's drugs.¹ These patients are usually in good health and mortality is low so long as supportive management is adequate and treatment with digoxin specific Fab fragments is readily available. Unlike acute digoxin poisoning, the onset of chronic poisoning is more insidious. Hyperkalaemia is the hallmark of acute digoxin poisoning, owing to massive blockade of sodium-potassium ATPase pumps throughout the body.^{2,3} Acute digoxin toxicity should be considered as a possible cause of unexplained hyperkalaemia. Conversely, in chronic digoxin poisoning, hypokalaemia is more common, for two main reasons. Firstly, the blockade of sodium-potassium pumps occurs gradually over a period of time, allowing the excess extracellular potassium to be excreted in the urine. Secondly, many patients chronically receiving digoxin are on potassium wasting diuretics.

Table 1 Classification and presentation of digoxin poisoning

Acute	Gastrointestinal symptoms	Nausea and vomiting
	Hyperkalaemia	Massive release of intracellular potassium from sodium-potassium ATPase blockade
	Cardiovascular symptoms	Any arrhythmia possible <i>except</i> a rapidly conducted supraventricular rhythm
Chronic	Central nervous system symptoms	Headache, visual changes (haloes),* confusion
	Raised serum digoxin concentration	
	Gastrointestinal symptoms	Nausea and vomiting, anorexia†
Chronic	Hypokalaemia (or eukalaemia)	Patients are often on diuretics predisposing to hypokalaemia
	Central nervous system symptoms	Headache, visual changes (haloes),* confusion,† malaise, seizures‡
	Normal or raised serum digoxin concentration	

*Not always seen.

†Often the chief complaint (particularly in elderly patients).

‡Rare.

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Table 2 Factors predisposing to digoxin toxicity

Decreased renal function	Impaired renal clearance of digoxin
Electrolyte imbalances	Hypokalaemia, hypomagnesaemia, and hypercalcaemia may all increase the effect of digoxin
Decreased lean body mass	
Cardiovascular	Acute myocardial infarction
Drug interactions	Diuretics, quinidine, verapamil, amiodarone, erythromycin, clarithromycin

Table 3 Treatment of digoxin poisoning

Gastrointestinal decontamination	Activated charcoal (1 g/kg body weight)
Symptomatic bradycardia	Atropine Digoxin specific Fab fragments*
Hyperkalaemia	Digoxin specific Fab fragments* Insulin and dextrose or sodium bicarbonate may be used Avoid calcium if digoxin poisoning is known or suspected
Severe or life threatening arrhythmias	Digoxin specific Fab fragments*

*Preferred method of treatment if available. Caution with use as it will reverse digoxin effects (may unmask congestive heart failure, atrial fibrillation, or atrial flutter. Serum digoxin concentrations cannot be followed after use of Fab fragments.

Digoxin is primarily excreted by the kidneys; therefore decreased renal function predisposes to digoxin toxicity.¹ The main predisposing factors to digoxin toxicity are given in table 2. Our patient was clinically dehydrated owing to excessive vomiting and decreased oral intake, which contributed to the decreased clearance of digoxin.

Chronic digoxin toxicity often presents with anorexia, nausea, vomiting, altered mental state, and arrhythmias.¹ Our patient's main symptoms were anorexia, visual disturbances, and altered mental state. Visual disturbances, classically described as blue-green halos around lights, are not always seen and their absence does not rule out toxicity. Seizures have also been reported, although these are seen less often.¹

Another factor precipitating increased digoxin levels is interaction between digoxin and other drugs. There are several clinically important interactions. These include potassium wasting diuretics, which decrease the serum potassium and thereby increasing the pharmacological effects of digoxin.⁴ Amiodarone, quinidine, and verapamil all decrease the clearance of digoxin from the body, thereby greatly increasing its half life.⁴ Our patient had been uneventfully maintained on digoxin for several years. It was not until clarithromycin was

added to his regimen for the treatment of a community acquired pneumonia that clinical effects consistent with chronic digoxin poisoning were seen.

Erythromycin and other macrolides have been shown to sterilise the gut of its normal flora, thereby increasing the bioavailability of digoxin.⁵⁻⁶ Approximately 10% of the population maintained on digoxin inactivate a portion of digoxin in the gut to inactive metabolites.⁷ This is performed by *Eubacterium lentum*, an enteric Gram positive rod in the gut flora.⁸ We suspected our patient was experiencing a drug-drug interaction. He improved over time with the discontinuation of clarithromycin and digoxin. Digoxin specific Fab fragments were not given, as he was haemodynamically stable. Digoxin specific Fab fragments completely reverse the effects of digoxin within 30 to 240 minutes.¹ There is concern over reversing these effects in patients who require the pharmacological effects of digoxin, as acute reversal can result in acute congestive heart failure or pulmonary oedema, or unmask atrial fibrillation.⁹ The treatment of digoxin poisoning is summarised in table 3.

Digoxin was restarted in our patient without event. Subsequent serum digoxin concentrations have been in the therapeutic range. Since the aetiology of chronic digoxin poisoning is often unclear, clinicians should be aware of the potential drug-drug interaction between digoxin and clarithromycin.

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