

Clofazimine induced cardiotoxicity—a case report

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Summary A 66-year-old Indian male who had been treated for recurrent erythema nodosum leprosum with 300 mg of clofazimine per day for 11 months presented to hospital with a 4 week history of severe gastrointestinal upset. Soon after admission he developed several short runs of ventricular tachycardia with a morphology suggestive of torsade de pointe. The patient had a slightly low magnesium level which was corrected within 2 days; however, his rhythm disturbance persisted for 5 days despite management with intravenous lidocaine. His gastrointestinal symptoms abated 2 weeks after clofazimine was discontinued.

Subsequent investigations showed that the patient had a keratopathy and myelin-type figures in his polymorphonuclear white cells similar to that seen with the cardiotoxic drugs chloroquine and amiodarone. It is postulated that clofazimine alone or in conjunction with electrolyte disturbance was responsible for the patient's cardiac arrhythmia.

Introduction

Clofazimine has been used in the treatment of leprosy since 1962.¹ Chronic clofazimine use can cause accumulation of the drug in various tissues where it can persist for some time due to its long half-life. Tissue deposition of clofazimine also results in the well-described adverse effects of skin discoloration and gastrointestinal toxicity. Other side-effects include the production of anticholinergic symptoms and, in rare cases, phototoxicity.² We describe here the first known case of clofazimine-induced cardiotoxicity and speculate on the possible pathophysiological mechanisms.

Case Report

The patient was a 66-year-old Indian male who emigrated to Canada in May 1986. Lepromatous leprosy was diagnosed 1 month before the patient's arrival in Canada and treatment with dapsone, rifampicin and clofazimine was begun. After 2 weeks of the commencement of therapy, the patient developed erythema nodosum leprosum (ENL) which was managed with chloroquine and subsequently with corticosteroids. Rifampicin was discontinued at this point because of abnormal liver function tests. Over the next 14 months he had recurrent flares of ENL whenever an attempt to taper the corticosteroid dose was made.

On 17 October 1987 the patient was admitted to hospital with a 4-week history of generalized abdominal pain, nausea and vomiting. He had been taking 100 mg of clofazimine tid since November 1986, but this was stopped 1 week before admission due to suspected gastrointestinal (GI) toxicity. Despite this, his GI symptoms continued to worsen with increasing abdominal pain and vomiting. Medications at the time of admission consisted of: dapsone 100 mg od; azathioprine 100 mg od; prednisone 27.5 mg od; sucralfate 1 g qid; warfarin 5 mg od; hydrochlorothiazide 50 mg od; buscopan 10 mg AC meals and at HS, fluoride 20 mg BID, 32 units of NPH and 10 units of regular humulin insulin in the morning, thalidomide 100 mg od and bid on alternate days, as well as vitamin D supplements and an antacid on a prn basis.

Past medical history revealed that the patient had a 10-year history of adult-onset diabetes which had been managed with diet alone. He required insulin when corticosteroid therapy was begun. The patient suffered from chest pain at rest during his initial hospital admission in May 1986 but a graded exercise stress test and a stress-Thalium test were negative. Ventriculography revealed some mild anteroapical hypokinesis with normal left ventricular ejection fraction while coronary angiography showed insignificant coronary artery disease. Other studies showed oesophageal dysmotility as well as gastroesophageal reflux. On the basis of these studies, the chest pain was felt to be of gastroesophageal origin. His course was also complicated by ENL induced femoral vein phlebitis complicated by recurrent pulmonary emboli which were diagnosed by a pulmonary arteriogram in October 1986. The patient was a nonsmoker and denied any ethanol use. There was no history of drug allergies. The family history was noncontributory.

On admission, the patient looked ill and complained of periumbilical and epigastric abdominal pain. The blood pressure was 110/56, pulse 72, respiratory rate 18, and the temperature 36.7°C. Pertinent physical findings included a soft, diffusely tender abdomen, marked tenderness in the epigastric area and mild rebound tenderness. There was no guarding. Bowel sounds were infrequent. On cardiovascular examination, there was no evidence of heart failure. A previously-documented grade II/VI systolic ejection murmur was present at the apex. Pitting oedema was present in both lower limbs up to the knees.

A chest radiograph obtained upon admission was normal. Flat plate examination of the abdomen was unremarkable apart from the presence of large amounts of stool in the descending colon. The leucocyte count was $8.9 \times 10^9/l$ with 89% granulocytes. Haemoglobin was 103 g/l and the platelet count was $147 \times 10^9/l$. Erythrocyte sedimentation rate was 57 mm. Serum electrolytes were normal on admission with the exception of the serum magnesium level which was 0.68 mmol/l (normal rate 0.8–1.20 mmol/l) and the

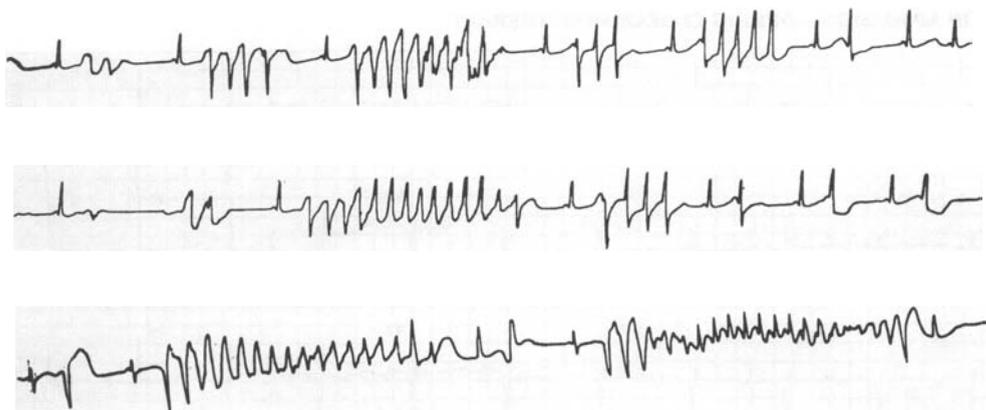


Figure 1. Continuous electrocardiographic recording obtained on admission to hospital. This reveals frequent self-terminating salvos of polymorphic ventricular tachycardia in the setting of marked QT prolongation. The runs of tachycardia are consistent with the diagnosis of torsade de pointes.

serum phosphate which was 0.83 mmol/l (normal range 0.70–1.30 mmol/l). The urea, creatinine, and cardiac enzyme levels were normal.

Soon after admission, the patient developed several short runs of ventricular tachycardia with a morphology suggestive of torsade de pointe (Figure 1). These were managed with intravenous lidocaine and intravenous magnesium sulphate. An electrocardiogram obtained at the time of the torsade revealed a prolonged QT interval of 0.60 s and repolarization abnormalities (Figure 2).

The patient was transferred to the coronary care unit and intravenous lidocaine as well as intravenous magnesium supplementation were continued. Serial assays of cardiac enzymes were obtained and these remained within the normal range throughout his hospital stay. Intermittent runs of ventricular tachycardia continued over the next 5 days. QT prolongation and T-wave changes persisted despite normalization of the magnesium and phosphate levels 2 days after admission. No further arrhythmias were observed after 5 days and lidocaine was discontinued. The electrocardiogram reverted to normal 9 days after admission. At this time the QT interval was 0.44 s and the T-wave changes had resolved (Figure 3). A MUGA scan obtained during the patient's hospital stay showed normal left ventricular function with an ejection fraction of 50%.

Abdominal ultrasound examination was normal apart from the finding of dilated small bowel loops. A subsequent small bowel barium enema showed jejunal oedema, consistent with a picture of clofazimine toxicity. The gastrointestinal symptoms, managed conservatively with nasogastric suction, resolved 1 week after admission.

Several additional investigations were carried out in an attempt to elucidate the mechanisms behind the cardiac toxicity. An ophthalmologic examination revealed a keratopathy with corneal deposits similar to those seen with chronic chloroquine or amiodarone administration. On examination of a buffy coat preparation, the polymorphonuclear cells were found to contain increased amounts of glycogen and occasional myelin-type figures. A skin biopsy, when examined by electron microscopy, revealed irregular electron dense granules in the cytoplasm of epithelial cells.

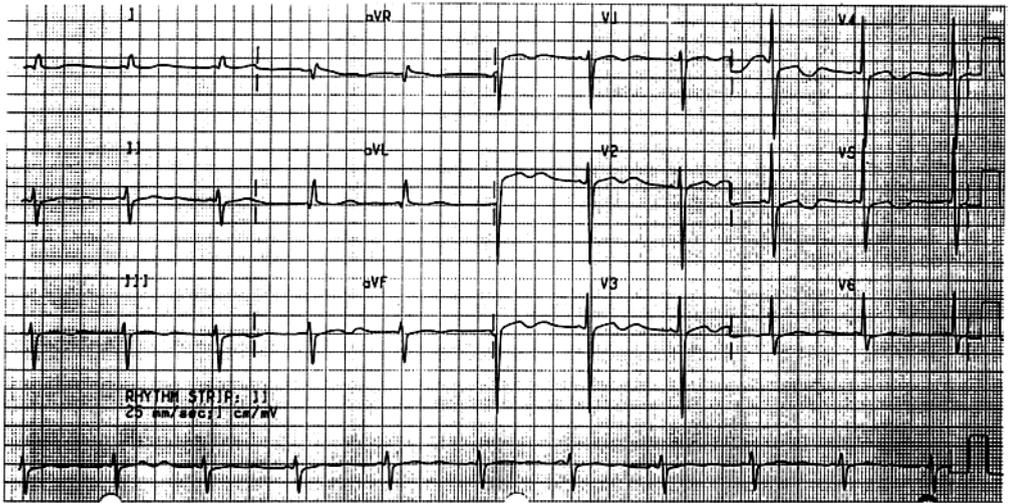
ON ADMISSION - DURING CLOFAZIMINE THERAPY

Figure 2. A 12-lead electrocardiogram obtained upon the patient's admission to hospital. Marked repolarization abnormalities with QT prolongation are evident on this electrocardiogram and most pronounced in the precordial leads.

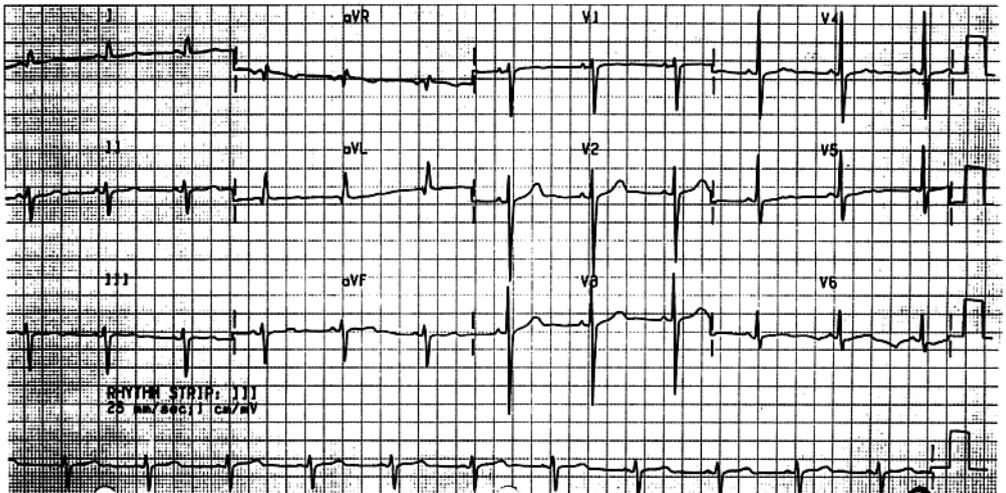
FOLLOWING CLOFAZIMINE WITHDRAWAL (ONE WEEK OFF THERAPY)

Figure 3. A 12-lead electrocardiogram from the same patient 1 week after drug withdrawal. Following drug withdrawal, the QT interval has returned to normal.

Discussion

Clofazimine, a substitute phenazine dye, is used extensively for the treatment of leprosy. Due to its highly lipophilic nature and prolonged half-life of 70 days, extensive tissue deposition of the drug occurs in patients who are on prolonged clofazimine therapy.² Autopsy series have shown that drug accumulation occurs in skin, subcutaneous fat, gall bladder, spleen, mesenteric lymph nodes, small intestine, kidneys, adrenals, heart, pancreas, muscle and bone.⁴ Tissue deposition leads to the well-known adverse effects of altered skin pigmentation and small bowel toxicity. Clofazimine induced cardiotoxicity has, however, not been documented.⁴

Our patient had cardiotoxicity as manifested by nonspecific ST and T wave changes and ventricular arrhythmias (torsade de pointe) on electrocardiography. Although the patient was on multiple medications, none of these are known to cause cardiac toxicity, aside from the diuretics which may initiate or aggravate an arrhythmia by producing electrolyte disturbances. While an ischaemic event may produce similar changes, this was excluded by serial assays of the cardiac enzymes.

Torsade de pointe, first described by Stratmann & Kennedy,⁷ is a ventricular arrhythmia in which the QRS complexes are seen to twist about the isoelectric line of the electrocardiogram. The QT interval is characteristically prolonged. A wide variety of drugs and toxins are known to cause torsade, including the anti-arrhythmic drug amiodarone, and antimalarials such as chloroquine. Torsade is also associated with various electrolyte abnormalities.⁷ Amongst electrolyte abnormalities, hypomagnesemia is a known cause of 'torsade'⁷ and magnesium is a recommended therapy for this arrhythmia.^{8,3} Our patient's magnesium level was only moderately low and was quickly corrected into the normal range by intravenous magnesium supplementation. The electrocardiographic changes and recurrent episodes of arrhythmia persisted even after this correction, suggesting that the cardiotoxicity was not due to electrolyte abnormalities alone. However, since tissue levels of magnesium may take longer to correct than serum levels, we cannot rule out the possibility that hypomagnesemia was a substantial contributing cause to our patient's arrhythmia.

Although cardiotoxicity has not been seen with clofazimine in the past,⁴⁻⁶ we believe that it did play a role in producing the electrocardiographic abnormalities and arrhythmias seen in this patient. The cardiotoxicity was first noted after the patient presented with clofazimine-induced GI toxicity and resolved when the patient's GI symptoms resolved 2 weeks after the drug was stopped. Correction of the patient's electrolyte abnormalities did not alter the course of the arrhythmias or normalize the electrocardiographic abnormalities. This patient had a keratopathy similar to that seen with chloroquine or amiodarone. In particular, the myelin-type figures seen in the patient's polymorphonuclear cells and the electrondense granules in the cytoplasm of his epithelial cells are similar to those seen with amiodarone and chloroquine therapy. In both instances, they are felt to be layers of phospholipid which accumulate within lysosomes due to inhibition of phospholipase. Taken together, these findings suggest that clofazimine may have produced torsade de pointe in this patient via a mechanism similar to that seen with chloroquine or amiodarone.

The accumulated literature on clofazimine-induced adverse effects does not contain any reference to cardiotoxicity,⁴⁻⁶ implying that this is a rare side-effect. While clofazimine may accumulate in the heart, other predisposing factors may be required for

the full syndrome of cardiotoxicity to develop. In this patient, hypomagnesemia secondary to the thiazide diuretics and clofazimine induced small bowel toxicity, may have served this role. Conceivably, subclinical cardiotoxicity was present for some time but only became significant when the patient developed electrolyte abnormalities. Interestingly, in the largest review of clofazimine-induced side-effects, the incidence of gastrointestinal toxicity was only 0.04% and none of these patients had electrolyte abnormalities.⁴ This may explain why cardiotoxicity was not seen in this large case series.

In summary, we have described the case of a patient with no underlying heart disease who we believe presented with clofazimine-induced cardiotoxicity. This side-effect has not been described before in the literature, possibly because it may manifest itself only when additional provoking factors such as electrolyte disturbances are present. We would recommend that patients on clofazimine who develop electrolyte abnormalities be screened with an electrocardiogram to rule out the presence of co-existing cardiotoxicity. An electrocardiogram should also be obtained whenever other signs of clofazimine toxicity are present. With confirmation of our findings, clofazimine may soon join the growing list of drugs and toxins that are known to cause torsade de pointe. Additional studies are needed to further elucidate the pathophysiology of clofazimine-induced cardiotoxicity and to determine what critical tissue load, if any, is required before cardiotoxicity becomes a problem.

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