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Case Report

Acute Rapid QTc Changes Following Chloroquine Overdose With No Suicidal Intent

Ogunmodede J.A.¹, Ogunmodede A.J.², Dele-Ojo B.F.³, Buhari O.N.²

¹ Department of Medicine, University of Ilorin Teaching Hospital, Ilorin, Kwara state, Nigeria

² Department of Behavioural Sciences, University of Ilorin Teaching Hospital, Ilorin. Kwara State, Nigeria

³ Department of Medicine, Ekiti state University, Ado-Ekiti, Ekiti State, Nigeria

ABSTRACT

We report a 39 year-old male with unintentional chloroquine overdose without any suicidal intention. Marked QTc prolongation of 0.508sec was observed acutely though patient's total ingested dose was lower than most fatal doses reported in literature. This range of QTc carries a predisposition to potentially fatal ventricular arrhythmias. Serial electrocardiograms (ECGs) demonstrated gradual return of QTc towards normal while patient was on observation without any indication for active intervention. We recommend that in the event of chloroquine overdose, close monitoring of the cardiovascular system should be done even in apparently stable individuals.

Keywords: Chloroquine. Acute QTc changes, overdose, suicidal intent

*Author for correspondence: Email: ayodeleogunmodede@yahoo.com; Tel: +2348052081183

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INTRODUCTION

Despite being potentially cardiotoxic in high doses, chloroquine was the first line treatment for malaria fever for many decades in most parts of the world's malaria-endemic regions. Expanding patterns of resistance in many countries have seen the drug being replaced by Artemisinin-based combination therapy (ACT) as the first line treatment for uncomplicated malaria 15 years ago. (FMOH, 2005; Smith *et al*, 2005) It is however still available over the counter in most of these countries and still used by many as second-line agents when ACT fails or for malaria prophylaxis in travellers to malaria endemic zones. The use of chloroquine in rheumatoid diseases and amoebic dysentery are other non-malarial uses of the drug. Though at therapeutic doses chloroquine use is fraught with several discomforting side-effects such as pruritus, blurred vision, nausea, vomiting and abdominal cramps, the drug is usually safe and serious life-threatening side effects such as allergic reactions are rare.

The routine prescription of chloroquine doses higher than the World Health Organisation (WHO) recommendation in children with no commensurate increase in the incidence of side-effects has been reported some African

communities. (Ursing *et al*, 2009) Most cases of chloroquine overdose reported in literature in adults are of very large doses of the drug and usually with suicidal intent. (Wilkey, 1973; Clemmesy *et al*, 1996; Meeran & Jacobs, 1993) Conversely, reports of large doses of the medication by children are usually accidental. (Smith & Klein-Schwartz, 2005; Collee *et al*, 1992) Accidental overdose without suicidal intent in adults has not been often reported in literature, especially in a malaria-endemic environment such as ours. We report the case of an adult who presented with accidental overdose of chloroquine and specifically highlight the evolution of QTc changes observed during his evaluation.

CASE PRESENTATION

A 39 year-old man presented with one hour history of dizziness and occasional palpitations following accidental ingestion of 1.5g of chloroquine phosphate "double strength" tablets. Chloroquine phosphate in Nigeria is usually dispensed in tablets each containing 150mg of chloroquine base each and packaged in satchets of 10 tablets which is the complete adult dose of 1.5g usually taken over a three day period. However, the patient did not notice that he was dispensed with "double strength" chloroquine tablets of 300mg chloroquine

base each. For ease of compliance, he planned to take five tablets of chloroquine on each of two days instead of spreading the treatment over the usual three days. Hence he took 1500mg of chloroquine base stat and only observed that something was amiss when he discovered that the drug packet contained only one sachet of five tablets instead of the expected ten. It was on closer scrutiny at that point that he found that the pack contained “double strength” tablets commercially branded in Nigeria as “2-2-1” and that he had swallowed the entire full dosage of medication at once. He denied any history of prior mental illness, no family history of mental illness, no suicidal ideation or hallucinations and family members attested that he had not manifested any odd behaviour recently.

Significant findings on examination were of a pulse rate of 98 beats per minute (bpm) regular and of full volume, (since he checked his blood pressure (BP) regularly with a friend’s digital sphygmomanometer, he claimed his usual pulse rate ranged between 76 to 82 bpm and he was not hypertensive). His blood pressure was 130/78mmHg, heart sounds were S1 and S2 only. He was fully conscious, alert, oriented in time, place and person. His respiratory rate was 18 cycles per minute, and he did not have any respiratory system or gastrointestinal tract system abnormalities.

Because of complaints of palpitations an urgent ECG was done on him. The first ECG done on him revealed heart rate of 96 bpm and normal sinus rhythm. This was done about 65 minutes after the drug was ingested. The QTc was measured

in Lead II using the cycle with the highest QT interval after evaluating successive beats and using the maximum slope intercept method to define the end of the T wave as described by Vink *et al* (2018) and other authors (Burns, 2019). He was observed to have QTc prolongation of 0.508sec using the cardiac cycle with the longest QT interval in Lead II (QT interval- 0.4sec, RR interval- 0.62sec; Fig 1a and b). A previous routine ECG done by him about three months earlier was found in his medical records and the QTc at that time was 0.413sec.

The prolonged QTc of 0.508sec prompted serial repeat ECGs while the patient was admitted. The first which was done 5 minutes after the first one revealed a QTc of 0.5sec (QT interval- 0.4sec, RR interval- 0.64sec; Fig 2a and b). A repeat ECG about one hour twenty minutes after the first one showed a significant reduction in heart rate to 85 bpm a near normalization of QTc at 0.45sec (QT interval- 0.38sec, RR interval- 0.7sec; Fig 3a and b). The patient by this time felt a significant improvement in symptoms, declined further evaluation and treatment and requested for discharge before activated charcoal became available. He declined his blood samples being taken for serum electrolytes, and serum chloroquine levels could also not be offered to him for reason of unavailability of the test in our laboratory. A follow-up encounter in the out-patient clinic a day after revealed that he remained asymptomatic and stable.

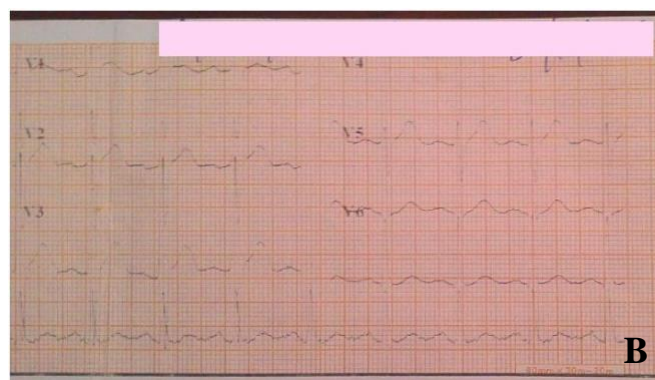
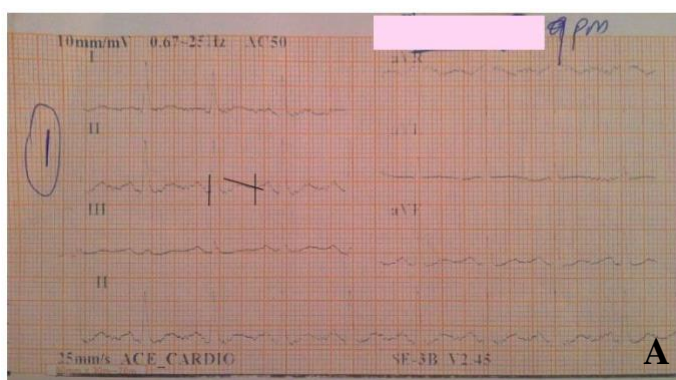


Figure 1(A & B)
First ECG done by the patient with Prolonged QTc of 0.508sec. Patient’s personal details are covered

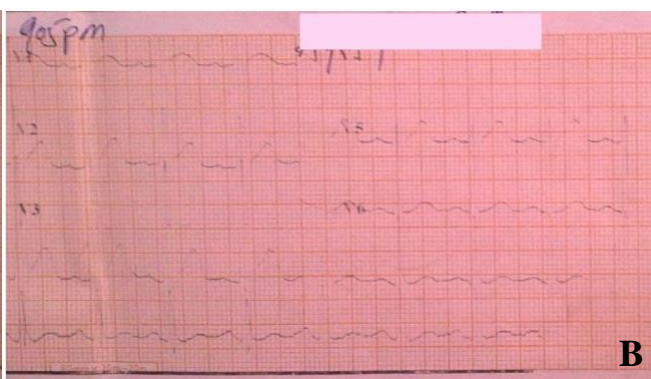
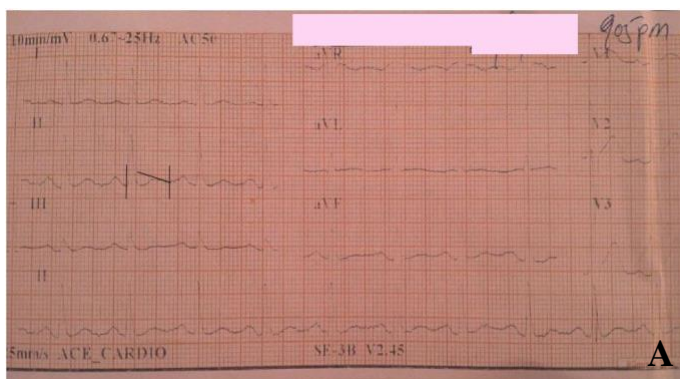


Figure 2 (A&B):
The second ECG done by the patient with Prolonged QTc of 0.5sec. Patient’s personal details are covered

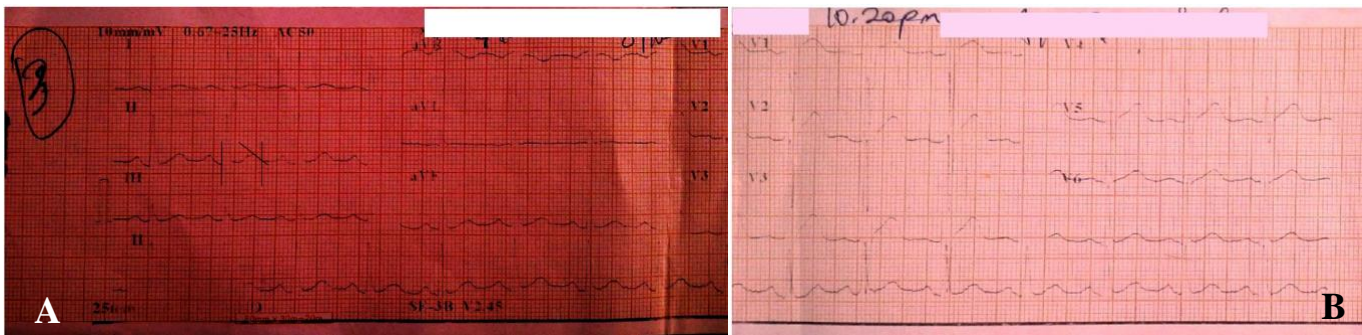


Figure 3 (A&B):

The third ECG done 80 minutes after admission with QTc of 0.45sec. Patient's personal details are covered

DISCUSSION

Chloroquine overdose as reported in our patient is purely accidental overdose arising out of an error of judgement though in an individual who was used to taking higher than the recommended dosages, though within the limits of the total recommended dose for treatment. Chloroquine overdose is not uncommon in Africa and some series have reported up to 280 cases (N'Dri, 1976). Toxic effects are thought to be dose-related and doses greater than 5g are usually fatal without intervention.

Our patient began to experience symptoms of overdose within one hour of ingestion of the drug. Chloroquine is rapidly and almost completely absorbed orally and its peak concentration is obtained 1 to 3 h after oral intake, 50 to 65% of it is protein bound in plasma. (Ursing *et al*, 2009) Following absorption, chloroquine is distributed throughout the body, accumulating in tissues, especially the liver, lungs, spleen, and kidneys and its volume of distribution is very large – up to 100 liters/kg. (Krishna & White, 1996) Clinical features of toxicity usually onset within one to two hours and include dizziness (which our patient had), nausea and vomiting and more severe features such as hypotension, cardiac conduction defects manifesting as QRS and QTc prolongation. In its most severe manifestations, altered consciousness, seizures and cardiac arrest can occur.

The QTc prolongation observed in our patient was an early manifestation of the large dose of chloroquine he ingested though individual peculiarities with drug metabolism also play a role. A 23 year-old patient who was reported by Meeran *et al* (1993) with accidental ingestion of 1.95g (larger than our patient's intake) of chloroquine base had a normal ECG without QTc prolongation. Most reports of QTc prolongation following chloroquine overdose occurred with large doses of the drug and doses greater than 5g in adults has been found to predict a fatal outcome, almost inevitably within four hours if no treatment was given, (Riou *et al*, 1988; Long, 2019) but doses as low as 2g may also be lethal. (Weniger, 1979) The QT interval is the time from the start of the Q wave to the end of the T wave and it represents the time taken for ventricular depolarisation and repolarisation. It is effectively the period of ventricular systole from ventricular isovolumic contraction to isovolumic relaxation. An abnormally prolonged QTc in the range of our patient's is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The effect of Chloroquine on the QTc may be related to its effect on serum potassium levels. (Collee *et al*, 1992; Clemessy *et*

al, 1995; Bethlehem *et al*, 2019) The hypokalemia is thought to be from potassium-channel blockade causing excess intracellular potassium distribution. (Phipps *et al*, 2011; Lofaso *et al*, 1987) One of the manifestations of hypokalemia is QTc prolongation. Chloroquine also has a negative inotropic effect and this contributes to QRS interval prolongation and QT interval prolongation. (Phipps *et al*, 2011)

The availability of the patient's previous ECG and a normal QTc on it supports the fact that the dynamic ECG changes observed in our patient were due to effects of chloroquine overdose. Strategies employed to treat Chloroquine toxicity include early mechanical ventilation, and a high dose of diazepam and norepinephrine (Riou *et al*, 1988; Clemessy *et al*, 1996) usually following administration of activated charcoal since chloroquine is a carbon-absorbable molecule. (Marquadt & Albertson, 2001) Other strategies reported by Bethlehem *et al* include the use of sodium bicarbonate and intravenous lipid emulsion. These are used in very ill patients who present with marked clinical instability. Our patient remained clinically and acute changes in cardiovascular system did not worsen.

The serum level of chloroquine was not assayed in our patient due to unavailability of laboratory facilities for doing this. This is one of the identified barriers to conducting toxicology studies in the developing world (Queen *et al*, 1999) including others such as withdrawal of patient's consent due to religious or cultural beliefs and inadequate medical records. However, it has been reported that patients do not need to have a high serum level of chloroquine to develop cardiovascular effects of drug toxicity and findings on clinical evaluation will still guide definitive management strategies. (Collee *et al*, 1992)

In conclusion, Chloroquine overdose can occur in dramatic circumstances and without suicidal intent such as occurred in our patient. Even at lower doses than largely reported in literature, cardiovascular effects of the drug are detectable and all patients with any level of overdose should have thorough cardiovascular evaluation and monitoring

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