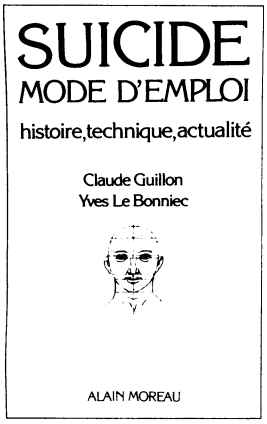
Chloroquine poisoning

Rapidly fatal without treatment



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BMJ 1993;307:49-50

Chloroquine overdose is advocated as a means of suicide in a French book *Suicide Mode d'Emploi*.[1] The toxicity of this drug in overdose is often underestimated by doctors and patients. We describe three cases of deliberate self-harm with chloroquine and discuss its toxic effects and recent advances in management of these cases.

Case histories

Case 1—A 45 year old Asian woman ingested at least 30 tablets of chloroquine sulphate (total dose chloroquine base at least 4·5 g) at home. She did not ingest any other drugs concurrently. Some time later she collapsed and was found to be asystolic on arrival at hospital. She was impossible to resuscitate by all conventional means.

Case 2—A 23 year old Asian man ingested 13 tablets of chloroquine sulphate (total dose chloroquine base 1·95 g) together with an unknown quantity of alcohol. The chloroquine tablets had been prescribed as malaria prophylaxis for members of his family, who frequently travelled to India. On assessment 45 minutes after ingestion he showed no features of serious suicidal intent; there was no history of a previous overdose. His blood pressure was 130/80 mm Hg and his electrocardiogram was normal, with a QRS duration of 110 ms. His stomach was washed out and activated charcoal (50 g) instilled through the orogastric tube. One hour later his blood pressure had fallen to 95/70 mm Hg. He recovered spontaneously without complications. An electrocardiogram taken while he was convalescent showed a QRS duration of 71 ms.

Case 3—A few days after returning from her country of origin, a 24 year old Madagascan woman ingested 30 tablets of chloroquine sulphate (total dose chloroquine base 4·5 g). She had been prescribed these tablets as malaria prophylaxis for her visit to Madagascar, but was advised locally that they were ineffective and did not take them while abroad. On arrival in accident and emergency three hours after ingestion she was profoundly shocked with an unrecordable blood pressure. Electrocardiography showed normal sinus rhythm with a rate of 70 beats per minute but her QRS duration was at the upper limit of 120 ms (figure (top)). A high dose adrenaline infusion was started (starting dose 2·5 μg/kg/min followed by increments of 2·5 μg/kg/min until an adequate blood pressure was achieved). She was given a large dose of intravenous diazepam (2 mg/kg), which necessitated intubation and assisted ventilation, followed by an infusion of diazepam (2 mg/kg/day). Her stomach was washed out and activated charcoal (50 g) was instilled through the orogastric tube. Her blood pressure steadily improved and her QRS duration fell to 90 ms within two hours (figure (bottom)). She was extubated after 12 hours and subsequently recovered without complications. Psychiatric assessment showed no features of serious suicidal intent.

Comment

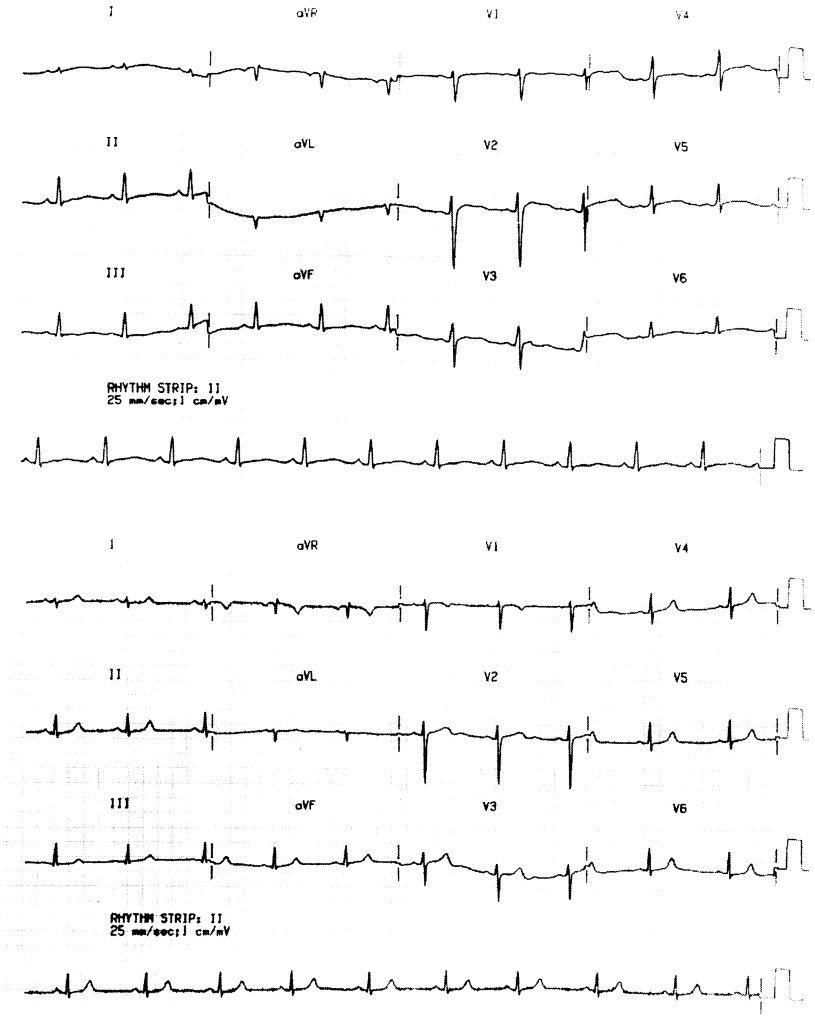
These cases show the toxicity of chloroquine in overdose. This drug is often prescribed for malaria prophylaxis and treatment, as well as having several uses in rheumatological practice. Patients are often given potentially fatal quantities of the drug and few doctors are aware of the danger of misuse of chloroquine.

Chloroquine exerts its toxicity by quinidine-like mechanisms: it is a profound negative inotrope and slows intraventricular conduction[2]; it is also a vasodilator. Oral chloroquine is rapidly and almost completely absorbed, resulting in transiently high blood concentrations early in the distribution phase that are potentially cardiotoxic.[3] As a result ingestion of surprisingly small amounts of chloroquine may have severe adverse effects. In retrospective studies ingestion of 5 g of chloroquine (33 tablets of chloroquine sulphate) by adults was found to be almost inevitably fatal within four hours if no treatment was given,[4] and as little as 2 g may be lethal.[5] Most deaths occur one to three hours after ingestion. Because chloroquine is redistributed into tissues toxic effects rarely last beyond 24 hours despite a terminal elimination half life for chloroquine of six to 14 days.

Our third case shows recent advances in the management of severe chloroquine intoxication. In addition to steps to limit absorption of chloroquine and appropriate supportive measures, high dose intravenous adrenaline and diazepam are used for specific therapy.

The use of diazepam in treating chloroquine toxicity originates from a fortuitous observation in Africa in the 1970s. Several large series of cases of chloroquine intoxication found that patients seemed more likely to survive if they had taken a large amount of diazepam concurrently.[6] Subsequent animal experiments confirmed that diazepam has a protective effect in experimental chloroquine poisoning.[7] A recent prospective trial confirmed the potential therapeutic value of giving high dose diazepam to patients with severe chloroquine poisoning.[4] Eleven patients who had each ingested 5 g or more of chloroquine were treated with high dose intravenous adrenaline and diazepam in Paris by mobile intensive care teams. Ten of the 11 patients survived compared with only one survivor in comparable (but historical) controls.

The value of adrenaline is not surprising: it reverses the cardiotoxic effects of chloroquine by reducing intraventricular conduction time.[2] Adrenaline is also a positive inotrope and vasoconstrictor. The therapeutic mechanism of diazepam, however, is poorly understood. Small studies have found that diazepam increases urinary excretion of chloroquine and improves the haemodynamics of experimentally poisoned animals.[8] The action of diazepam at central nervous system receptors may contribute to its beneficial effects in chloroquine poisoning, but there is increasing evidence that a specific action of diazepam at binding sites on heart muscle is important. These putative receptors on cardiac myocytes are quite distinct from diazepam receptors in the central nervous system, being γ-aminobutyric acid independent, and until recently had no known function. Benzodiazepine analogues at these receptors have been shown to shorten the duration of intracellular action potential in animal myocardium[9] and may have anti-arrhythmic properties. Moreover, diazepam has been reported to reduce the concentration of chloroquine in rat cardiac muscle despite increasing blood concentrations.[10] The



Electrocardiograms of 24 year old women with chloroquine poisoning (top) on admission; (bottom) two hours later

importance of these observations in relation to the clinical use of diazepam remains unclear, and novel actions of benzodiazepines on cardiac muscle are the subject of continuing research.

Discussion

NIMcN: These three patients presented to us within four weeks, and gave us an unusual insight into the manifestations and management of chloroquine overdose. In Africa chloroquine overdose is much more common, and large series of up to 280 cases have been reported; the dangers of chloroquine in overdose are more widely appreciated. Children who have ingested twice the recommended dose have died. It is remarkable that until a few years ago chloroquine was available over the counter in Britain.

KM: Our catchment area incorporates a large number of patients of Asian origin who travel to countries where malaria is endemic. Chloroquine is readily available within this community.

JS: Had any of your patients read the book about commiting suicide? Presumably it is not available here.

KM: None of these patients had read the book and the two survivors had not appreciated the danger of chloroquine in overdose.

WAL: This book was translated into English and released in the United States recently, amid much controversy. It is not published in Britain.

JC: On what basis should the aggressive treatment regimen with adrenaline and diazepam be started? Do you need to measure plasma chloroquine concentration to decide?

KM: Poor prognostic indicators are ingestion of more than 5 g of chloroquine; fall in systolic blood pressure to below 80 mm Hg; and QRS duration greater than 120 ms. Patients with any of these features should receive high dose intravenous adrenaline and diazepam immediately. Death may be very rapid without treatment and chloroquine concentration usually has no role in this decision.

CDP: Unfortunately neither haemodialysis nor peritoneal dialysis has been found to be effective in treating chloroquine overdose.

JAP: Might smaller doses of diazepam be effective? Most cases of chloroquine poisoning occur in countries where mechanical ventilation is not readily available.

KM: In animal studies diazepam produced a dose dependent reduction in death from chloroquine poisoning. The dose used in humans was extrapolated from these studies and whether less would suffice remains unknown.

SCW: A better understanding of the protective mechanism of diazepam would be invaluable. Benzodiazepine analogues may exist which, for example, selectively bind myocardial receptors and cause less effect in the central nervous system. It would also be interesting to study the efficacy of glucagon, which has many similar actions to adrenaline at a cellular level and is potentially much less dangerous.

KAAD: Are hydroxychloroquine and quinine toxicity treated in the same way as chloroquine toxicity?

KM: Hydroxychloroquine in overdose may have potentially fatal depressant effects on the myocardium, similar to those caused by chloroquine. The recommended management is the same for both drugs. Quinine has the potential to cause disturbance of cardiac conduction and arrhythmias, but unfortunately no specific antidote is known. It is important to remember that quinine may cause life threatening hypoglycaemia.

We thank Dr John Henry for his advice during the preparation of the manuscript.

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