Hypotension and Seizure in a Healthy Young Woman

An otherwise healthy young woman is convulsing, diaphoretic, and unresponsive when she is brought to the ED. Her ECG demonstrates cardiotoxicity, and it is known that she took her own medication. The authors discuss the clues used to identify the precipitating agent, as well as considerations in case management.

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Case

A 23-year-old African woman with no significant medical or psychiatric history presents to the ED 1 hour after she ingested her own medication following an argument with her boyfriend. Her roommate found her convulsing and called EMS. EMS personnel note that the patient was minimally responsive and they administered naloxone and dextrose without noticeable clinical improvement. They also note that the patient exhibited signs of convulsive activity.

Upon arrival to the ED, the patient has the following vital signs: blood pressure, 50/20 mm Hg; heart rate, 103 beats/min; respiratory rate, 30 breaths/min; temperature, 37.4°C; oxygen saturation, 100% on a nonrebreather mask. In the ED, she has frequent episodes of generalized convulsions lasting less than 30 seconds. Though the patient is unconscious and unresponsive, her pupils are at midposition and sluggishly reactive. Her skin is diaphoretic, her lungs are clear to auscultation, and her bowel sounds are normoactive.

An ECG obtained shortly after arrival demonstrates a heart rate of 150 beats/min, a QRS complex duration of 200 ms, and a QT interval of 525 ms (Figure 1).

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The patient receives a 2-mEq/kg bolus of sodium bicarbonate (3 x 50 mEq ampoules), and shortly thereafter a repeat ECG demonstrates a heart rate of 145 beats/min with dramatically improving intervals. The QRS complex is 110 ms, and the QT interval is 414 ms (Figure 2, page 16).

What class of agent most likely produced this patient's hemodynamic and ECG findings?

The findings on the ECG raise concern for exposure to an agent that either (1) antagonizes the myocardial sodium channel, slowing depolarization and prolonging the QRS complex (which increases the QT interval duration), or (2) antagonizes both the myocardial sodium and potassium channels, with direct simultaneous effect on depolarization (QRS complex) and repolarization (QT interval). The vital signs also suggest the possibility of exposure to an agent from one of these classes. Blockade of the myocardial sodium channel slows impulse conduction through the His-Purkinje system, slowing the rate of depolarization of the myocardial tissue and thus the force of contraction. This effect alone may lead to hypotension, change in mental status, and seizures due to diminished cerebral perfusion. The Table (page 17) lists available medications that are sodium channel antagonists in overdose.

The medications that prolong the QT interval duration through potassium channel blockade are numerous and are comprehensively outlined on various Web sites, such as qtdrugs.org. Antimalarials, bupropion, cyclic antidepressants, diphenhydramine, and propoxyphene are associated with seizures as well, independently of the myocardial sodium channel blockade.

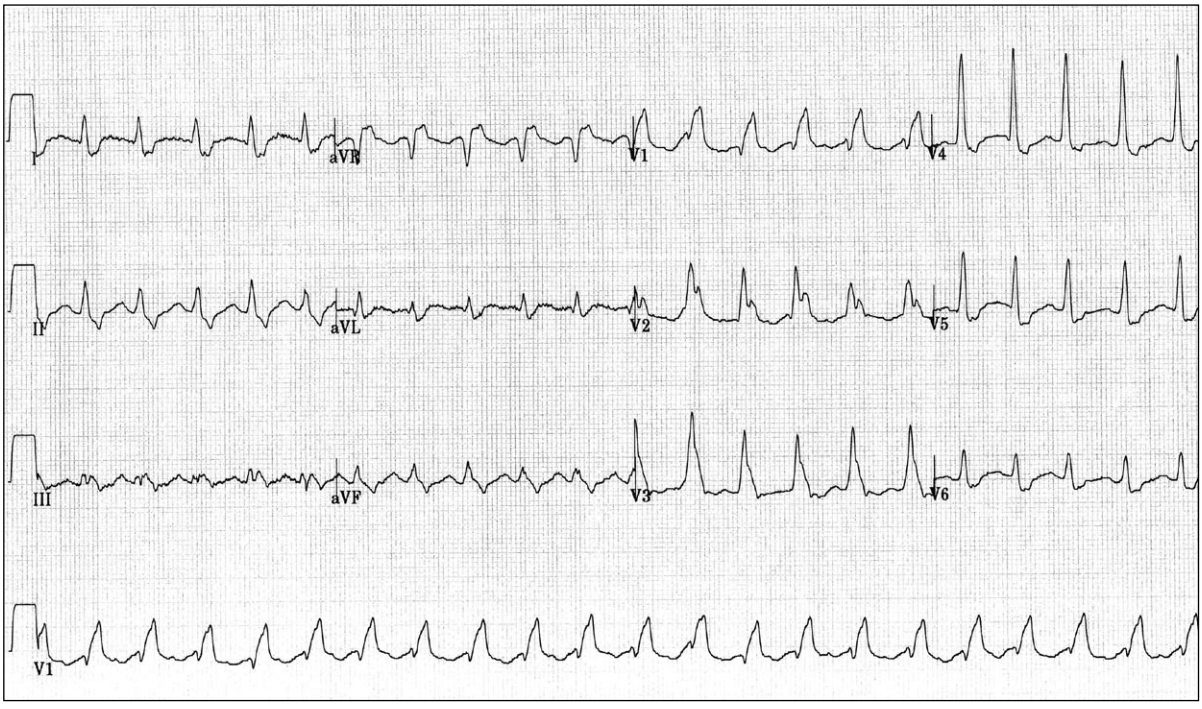

FIGURE 1. Initial ECG.

What did the patient ingest?

The patient's ethnicity and unremarkable psychiatric history (ie, no antidepressants available) point to the likelihood of exposure to an antimalarial. The patient later admitted to ingesting 6 g of chloroquine. She had the medication available from a previous prescription for malaria prophylaxis.

Chloroquine was discovered in 1934 in Germany and rapidly gained recognition as an effective antimalarial agent.[1] Due to the development of resistance, chloroquine is not as widely used for malaria prophylaxis as it had been, and chloroquine toxicity in the US is no longer a frequent phenomenon.

Chloroquine shares many similarities with quinine. Both are cardiotoxic, as well as ototoxic and oculotoxic. Both potentiate the release of insulin from pancreatic islet cells, resulting in hypoglycemia. Although perhaps more cardiotoxic than quinine, chloroquine is much less toxic to the ear, eye, and islet cell. The clinical effects of quinine overdose are commonly referred to as *cinchonism*, a term derived from the name of quinine's source: the Cinchona tree. Cinchonism is characterized by decreased hearing acuity, tinnitus, vertigo, headache, nausea, vomiting, abdominal pain, tachycardia, dystonia, and skin flushing. These effects are much less prominent with chloroquine overdose. Neurologic manifestations of chloroquine overdose include sedation, dizziness, headache, and seizures.

It is commonly accepted that acute ingestion of more than 5 g of chloroquine (>30 to 50 mg/kg) is associated with life-threatening cardiotoxicity. Clinical effects following overdose occur rapidly, generally within 1 to 3 hours. Oral chloroquine is rapidly absorbed and has a very high volume of distribution (>100 L/kg), suggesting that hemodialysis to enhance its clearance has limited utility. Chloroquine toxicity may be associated with hemolysis due to oxidative stress in people with glucose-6-phosphate dehydrogenase deficiency.

How should this toxicity be managed?

Severe chloroquine toxicity marked by ECG and/or hemodynamic changes with CNS depression should be aggressively treated to maximize survival. The majority of the data for management of chloroquine toxicity comes from France and dates to the 1980s. The data suggest that early intubation and ventilation, high-dose diazepam, and administration of epinephrine are associated with reductions in mortality.[2,3]

IV diazepam at 2 mg/kg should be administered over 30 minutes followed by 1 to 2 mg/kg/day for

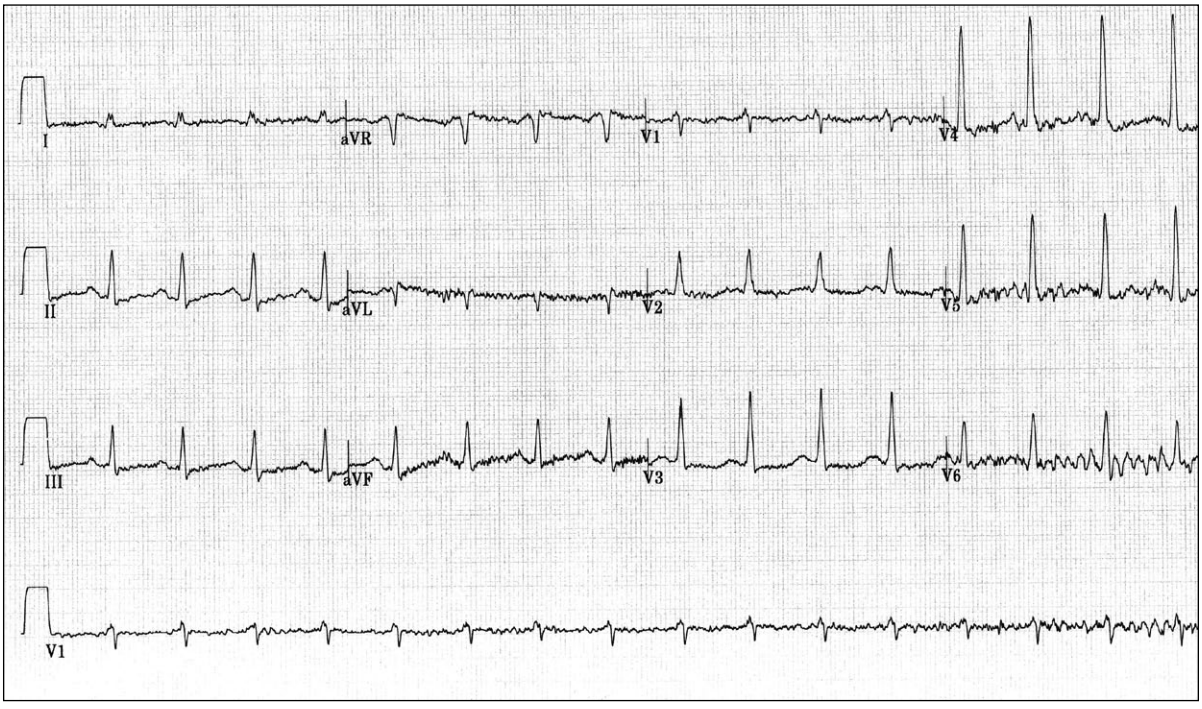

FIGURE 2. ECG obtained after initiation of treatment.

2 to 4 days. Isolated animal studies suggest that diazepam improves hemodynamic function and reduces mortality following chloroquine poisoning.[3] It is possible that the effects of diazepam on cardiac function are due to its beneficial effects on myocardial benzodiazepine receptors.[4] It is unknown whether other benzodiazepines are as effective as diazepam, though there is little reason to suspect they are not.

Epinephrine at 0.25 µg/kg/min should be administered intravenously and titrated until a systolic blood pressure of 100 mm Hg is attained. Its β_1-adrenergic effects increase inotropy, improving myocardial function. Although other catecholamines, such as norepinephrine, may be as efficacious as epinephrine, the latter is more physiologically logical. That is, the β_1-receptor agonist activity of epinephrine raises the blood pressure through enhanced inotropy, while the α-receptor agonist activity of norepinephrine increases it by causing peripheral vasoconstriction. This latter effect may be detrimental in the setting of a poorly contractile ventricle.

Given the potential for morbidity and mortality, orogastric lavage should be considered in patients presenting with a recent potentially toxic ingestion of chloroquine. Activated charcoal should be administered in patients with adequate protective airway reflexes or following intubation.

Sodium bicarbonate should be administered in the setting of QRS complex prolongation, whether the ingestant is identified or unknown, with a goal of reducing the duration to less than 100 ms.[5] Although sodium bicarbonate would be expected to counteract the sodium channel antagonism and narrow the QRS complex, it also leads to hypokalemia and subsequent lengthening of the QT interval. The use of sodium bicarbonate has been described as beneficial in the management of chloroquine overdose in case reports. However, no clinical trials have been performed. Patients who receive sodium bicarbonate for a wide QRS complex in chloroquine overdose should undergo close monitoring of the QT intervals and repletion of serum potassium.

Although more information could be gained from prospective observational studies, the likelihood of carrying out such studies is low, given the relative rarity of chloroquine poisoning. There may be ethical concerns over withholding the "standard of care" treatment of epinephrine and diazepam and administering a "novel" treatment, without any support for clinical equipoise, to a very ill person. Therefore, the

TABLE. Sodium Channel Antagonists

Class	Examples	QRS Widening
Class IA antidysrhythmics	Disopyramide, procainamide, quinidine	Therapeutic effect
Class IB antidysrhythmics	Lidocaine, phenytoin, mexiletine	Therapeutic effect
Class IC antidysrhythmics	Flecainide, propafenone	Therapeutic effect
Cyclic antidepressants	Amitriptyline, imipramine	Toxic effect
Opioids	Propoxyphene	Toxic effect
Antihistamines	Diphenhydramine	Toxic effect
Antidepressants	Bupropion, venlafaxine	Toxic effect
Antimalarials	Quinine, chloroquine	Toxic effect
Local anesthetics	Bupivacaine, lidocaine, mepivacaine prilocaine, cocaine, benzocaine, procaine, tetracaine	Toxic effect

question of efficacy of other vasopressors and benzodiazepines remains unanswered.

What did management for this patient entail?

The patient received 1 to 2 mEq/kg of sodium bicarbonate, with marked improvement in QRS complex duration. The sodium bicarbonate infusion was administered with a goal pH of 7.45 to 7.50. Her serum potassium level and QT interval duration were monitored closely.

She received IV volume resuscitation with normal saline. Despite adequate volume resuscitation and a markedly narrowed QRS complex, the patient continued to be hypotensive. Norepinephrine infusion was subsequently administered and titrated to a mean arterial pressure greater than 65 mm Hg. Norepinephrine infusion was chosen likely because it was easily accessible and more familiar to the staff in the adult ED where the patient was treated. Interestingly, epinephrine infusion may be more readily available in a pediatric ED, as hypotension in children may be more commonly of cardiogenic origin. The patient received a lorazepam infusion for both sedation and management of frequent convulsions. Lorazepam was chosen because diazepam was not commonly used at this particular hospital.

Case Resolution

The patient improved clinically by hospital day 3 and was ultimately extubated with no adverse residual neurologic sequelae. She was evaluated by a psychiatrist and, after recovery from the ingestion, was transferred to a psychiatric ward for further treatment. □

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