Hydroxychloroquine, a potentially lethal drug

La hidroxiclороquina, un fármaco potencialmente letal

Dear Editor,

Although hydroxychloroquine is widely used in Spain, mainly in application to rheumatological disorders, very few cases of intoxication caused by this drug have been reported to date. The present clinical case describes the basic characteristics of hydroxychloroquine intoxication, and provides a review of the guidelines for using the drug.

A 29-year-old woman presented with a history of one normal pregnancy and no known allergies or substance abuse. She was undergoing follow-up in another center due to non-specified connective tissue disease, and had not received treatment for months.

The out-hospital emergency service was alerted from the home. The patient had been asymptomatic when a relative heard her fall to the floor. She was found to be unconscious, without abnormal movements. Upon arrival of the ambulance, the patient presented a Glasgow coma score of 3, with anisocoria (left-eye mydriasis) and a blood pressure of 40/28 mmHg. Orotracheal intubation was performed in the home, with volume replacement measures. She presented sudden ventricular tachycardia (VT) requiring 6 min of advanced cardiopulmonary resuscitation (CPR) manoeuvring to resolve the situation. The patient subsequently suffered cardiorespiratory arrest in VT rhythm during 5 min, receiving a total of three defibrillations and 5 mg of adrenalin.

Upon arrival in the emergency service, the patient presented low level of consciousness but was able to mobilize all four extremities without apparent paresis. The mentioned anisocoria was confirmed, with bilaterally responsive pupils.

She was initially hemodynamically stable, though with rapid progression to hypotension requiring the start of vasoactive support with noradrenalin. The initial electrocardiogram (ECG) revealed sinus rhythm at 75 bpm, with no other alterations. The laboratory tests showed plasma potassium 1.5 mEq/l, pH 7.01, lactic acid 11 mmol/l and bicarbonate 12 mEq/l. The brain computed axial tomographic (CAT) findings were normal, and thoracic angioCAT for the evaluation of other possible causes of cardiac arrest discarded the presence of pulmonary thromboembolism.

During the first hours of admission to the Intensive Care Unit (ICU), hypopotassemia was seen to persist despite intravenous corrective measures. Eight hours after admission the patient developed self-limiting bursts of polymorphic/monomorphic and torsades de pointes type VT, with prolongation of the QT interval on the basal ECG tracing between bursts. The condition subsequently evolved toward sustained VT requiring repeat electrical shock and the start of isoproterenol infusion—followed by shortening of the QT interval and disappearance of the ventricular arrhythmias.

The initial case history compiled from information supplied by the relatives was unremarkable. The patient was receiving no medication on a regular basis and had not consumed toxic substances in the last few hours, though she was described as having emotional problems.

Following the difficult diagnostic orientation at the start, given the incomplete anamnèsis in the context of the situation, we suspected a possible toxic origin—in this case represented by hydroxychloroquine, which the patient had been prescribed months ago for her connective tissue disease. A review of the literature confirmed that her symptoms were consistent with hydroxychloroquine intoxication. Since there were limitations in confirming the diagnosis due to the lack of available serum drug levels determined by the laboratory, we asked the relatives to conduct a search in the home, which yielded several empty blister strips of the medication. This supported our initial suspicion: the patient had consumed 42 tablets of 200 mg of hydroxychloroquine each, in the context of attempted suicide.

After the first 48 h, protocolized extubation could be performed, with a good clinical course, no neurological defects, and no further cardiovascular alterations. The patient admitted having attempted suicide, and subsequent psychiatric care was indicated. It should be mentioned that at the time when hydroxychloroquine intoxication...
was suspected, we also administered benzodiazepines on
the basis of the data found in the literature (commented
below) (initially diazepam 10 mg as a bolus dose, followed
by sedation with midazolam in continuous perfusion for a
maximum dose of 11 mg/h).

Hydroxychloroquine intoxication is infrequent, despite
common use of the drug in different rheumatological dis-
orders. There is much greater toxicological experience with
chloroquine, and although cases of overdose are infrequent
in Europe, there have been reports of suicide attempts with
the latter drug in Africa and France. The structural sim-
ilarity between the two molecules, and the analogies of the
clinical course of intoxication with both substances, has
carried the management measures in cases of chloro-
quine intoxication to be extrapolated to hydroxychloroquine
intoxication. Both drugs exert toxic effects upon the cardiac
conduction system and myocardium, with negative inotropic
action, prolongation of the QRS complex and QT interval,
	
torsades de pointes

and ventricular ectopic rhythms.1,9

The respiratory manifestations of chloroquine intoxica-
tion comprise lung edema and respiratory arrest between 1
and 3 hours after ingestion of the drug, secondary to both
direct action upon the lung tissues and effects at respiratory
center level. The actions upon the central nervous system
comprise excitability, irritability, seizures and coma. The
drug can also induce hepatitis as a result of direct toxic
action upon the liver parenchyma.

At ocular level, a number of retinal disorders have been
reported, as well as paralysis of the ciliary or extracoc-
mular muscles, resulting in accommodation alterations. Our
patient initially presented anisocoria, followed by sponta-
neous resolution, and which may have been a consequence
of such disorders.

Hypokatemia is observed in 85% of all cases of
chloroquine intoxication, and is secondary to intracellular
potassium transport rather than to genuine potassium
deficiency.1,4

The toxic dose of chloroquine has been defined as
20 mg/kg. Although the lethal dose has not been well
established, the clinical series suggest that 4 g of hydroxy-
chloroquine is potentially fatal in adults.1,8 The onset of
action is rapid, in the same way as in the case of chloro-
quine: severe cases manifest within the first two hours
after ingestion of the drug, with coma and hypotension,
while stability of the hemodynamic and electrocardio-
graphic parameters, and of patient level of consciousness
within the first 5 hours after hydroxychloroquine overdose
makes later complications less likely.2

As has been commented, the management of hydroxy-
chloroquine intoxication is modeled upon the management
of chloroquine intoxication. Gastric lavage (pumping) and
the administration of activated charcoal are advised in the
first hour after ingestion of the drug.1,5,7 Chloroquine is
quickly distributed within the intracellular compartment;
extrenal filtration measures are therefore ineffective.
Furthermore, high-dose diazepam is recommended2 in the
case of crises, arrhythmias, wide QRS tracings, hypoten-
sion and circulatory collapse. Early orotracheal intubation
may be required, with the administration of vasoactive
drugs (adrenalin, noradrenalin). Isoproterenol has been sug-
gested in the event of hypotension and bradycardia induced
by hydroxychloroquine.10 Type I antiarrhythmic drugs can
further prolong the QT interval, and therefore should be
avoided. The correction of hypokatemia is to be closely
monitored,6 without exceeding 10–15 mEq KCl/h, since
there is no genuine potassium deficit in these cases: potas-
sium undergoes intracellular redistribution that tends to
correct itself as intoxication is gradually resolved. Serum
and urine alkalization has been proposed in some stud-
ies as an adjuvant to increase excretion of the drug, but
there are no conclusive benefits from such measures,1,10 and
hypokatemia moreover could be worsened. Other man-
agement options have been postulated, such as the use of
intravenous lipid emulsions. The combination of such
emulsions with intermittent hemodialysis (not hemodialysis
alone, which has not been found to be effective) might offer
benefit in intoxications of this kind.5 We can also resort to
extracorporeal circulatory support or extracorporeal mem-
bane oxygenation (ECMO) in cases of severe cardiotoxicity
with circulatory collapse and cardiac arrest.11,12 There have
been reports of the use of such measures in intoxication
caused by chloroquine and hydroxychloroquine.2,5,13,14

In sum, hydroxychloroquine intoxication is infrequent
but potentially fatal, and should be suspected in cases of
severe hypokatemia associated to shock, ventricular
arrhythmias or cardiopulmonary arrest of uncertain origin.
Normalization of the potassium levels is essential for the
favorable evolution of hydroxychloroquine intoxication.
Furthermore, it must be remembered that hypokatemia in
these cases reflects altered distribution of the ion rather
than a genuine deficit; an excessive supply of potassium
therefore could lead to iatrogenic hyperpotassemia if the
plasma levels are not closely monitored.

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