

7. Guerrero HA, Briones-Vega CG, Díaz de León-Ponce M, Briones-Garduño JC. Cuidados intensivos en ginecología y obstetricia en el Hospital General de México. *Rev Asoc Mex Med Crit Ter Int.* 2011;XXV:211–7.
8. Prakash J, Niwas SS, Parekh A, Pandey LK, Sharatchandra L, Arora P, et al. Acute kidney injury in late pregnancy in developing countries. *Renal Fail.* 2010;32:309–13.
9. Bentata Y, Housni B, Mimouni A, Azzouzi A, Abouqal R. Acute kidney injury related to pregnancy in developing countries: etiology and risk factors in an intensive care unit. *J Nephrol.* 2012;25:764–75.
10. Aggarwal RS, Mishra VV, Jasani AF, Gumber M. Acute renal failure in pregnancy: our experience. *Saudi J Kidney Dis Transpl.* 2014;25:450–5.

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## Hydroxychloroquine, a potentially lethal drug<sup>☆</sup>



## 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) maneuvering 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 anamnesis 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

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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 disorders. 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.<sup>1</sup> The structural similarity between the two molecules, and the analogies of the clinical course of intoxication with both substances, has caused the management measures in cases of chloroquine 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.<sup>1,9</sup>

The respiratory manifestations of chloroquine intoxication 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 extraocular muscles, resulting in accommodation alterations. Our patient initially presented anisocoria, followed by spontaneous resolution, and which may have been a consequence of such disorders.

Hypokalemia is observed in 85% of all cases of chloroquine intoxication, and is secondary to intracellular potassium transport rather than to genuine potassium deficiency.<sup>2,4</sup>

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 hydroxychloroquine is potentially fatal in adults.<sup>3,8</sup> The onset of action is rapid, in the same way as in the case of chloroquine: severe cases manifest within the first two hours after ingestion of the drug, with coma and hypotension, while stability of the hemodynamic and electrocardiographic parameters, and of patient level of consciousness within the first 5 hours after hydroxychloroquine overdose makes later complications less likely.<sup>3</sup>

As has been commented, the management of hydroxychloroquine 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.<sup>1,5,7</sup> Chloroquine is quickly distributed within the intracellular compartment; extrarenal filtration measures are therefore ineffective. Furthermore, high-dose diazepam is recommended<sup>5</sup> in the case of crises, arrhythmias, wide QRS tracings, hypotension and circulatory collapse. Early orotracheal intubation may be required, with the administration of vasoactive drugs (adrenalin, noradrenalin). Isoproterenol has been suggested in the event of hypotension and bradycardia induced by hydroxychloroquine.<sup>10</sup> Type I antiarrhythmic drugs can

further prolong the QT interval, and therefore should be avoided. The correction of hypokalemia is to be closely monitored,<sup>6</sup> without exceeding 10–15 mEq KCl/h, since there is no genuine potassium deficit in these cases: potassium undergoes intracellular redistribution that tends to correct itself as intoxication is gradually resolved. Serum and urine alkalinization has been proposed in some studies as an adjuvant to increase excretion of the drug, but there are no conclusive benefits from such measures,<sup>1,7</sup> and hypokalemia moreover could be worsened. Other management 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.<sup>5</sup> We can also resort to extracorporeal circulatory support or extracorporeal membrane oxygenation (ECMO) in cases of severe cardiotoxicity with circulatory collapse and cardiac arrest.<sup>11,12</sup> There have been reports of the use of such measures in intoxication caused by chloroquine and hydroxychloroquine.<sup>5,13,14</sup>

In sum, hydroxychloroquine intoxication is infrequent but potentially fatal, and should be suspected in cases of severe hypokalemia 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 hypokalemia in these cases reflects altered distribution of the ion rather than a genuine deficit; an excessive supply of potassium therefore could lead to iatrogenic hyperkalemia if the plasma levels are not closely monitored.

## References

1. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. *Am J Emerg Med.* 2001;19:420–4.
2. Smith ER, Klein-Schwartz W. Are 1-2 dangerous? Chloroquine and hydroxychloroquine exposure in toddlers. *J Emerg Med.* 2005;28:437–43.
3. Isbister GK, Dawson A, Whyte IM. Hydroxychloroquine overdose: a prospective case series. *Am J Emerg Med.* 2002;20:377–8.
4. Gunja N, Roberts D, McCoubrie D, Lamberth P, Jan A, Simer DC, et al. Survival after massive hydroxychloroquine overdose. *Anaesth Intensive Care.* 2009;37:130–3.
5. McBeth PB, Missirlis PI, Brar H, Dhingra V. Novel therapies for myocardial irritability following extreme hydroxychloroquine toxicity. *Case Rep Emerg Med.* 2015;2015:692948.
6. Mégarbane B, Résière D, Sonnevile R, Guerrier G, Deye N, Baud F. Acute hydroxychloroquine poisoning: the danger of rapid or excessive correction of initial hypokalemia. *Presse Med.* 2005;34:933–4 [article in French].
7. Mongenot F, Tessier Gonthier Y, Derderian F, Durand M, Blin D. Treatment of hydroxychloroquine poisoning with extracorporeal circulation. *Ann Fr Anesth Reanim.* 2007;26:164–7.
8. Messant I, Jérémie N, Lenfant F, Freysz M. Massive chloroquine intoxication: importance of early treatment and pre-hospital treatment. *Resuscitation.* 2004;60:343–6.
9. White NJ. Cardiotoxicity of antimalarial drugs. *Lancet Infect Dis.* 2007;7:549–58.
10. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila).* 2006;44:173–5.

11. Mégarbane B, Deye N, Baud FJ. Extracorporeal life support for poisonings with cardiotoxicants. *Rev Prat.* 2008;58:855–60.
12. St-Onge M, Fan E, Mégarbane B, Hancock-Howard R, Coyte PC. Venoarterial extracorporeal membrane oxygenation for patients in shock or cardiac arrest secondary to cardiotoxicant poisoning: a cost-effectiveness analysis. *J Crit Care.* 2015;30:437, e14.
13. Champion S, Malisin I, Cleophax C, Vodovar D, Deye N, Mégarbane B, et al. Chloroquine poisoning-associated inverted Tako-tsubo cardiomyopathy. *Clin Toxicol (Phila).* 2012;50:721–2.
14. Mongenot F, Tessier Gonthier Y, Derderian F, Durand M, Blin D. Treatment of hydroxychloroquine poisoning with extracorporeal circulation. *Ann Fr Anesth Reanim.* 2007;26:164–7 [article in French].

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