Hydroxychloroquine, a potentially lethal drug³

La hidroxicloroquina, 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-specific 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.

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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. 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.\(^1\, \text{,}^{19}\)

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 extracircular 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.\(^1,\, \text{4}\)

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 hydroxychloroquine is potentially fatal in adults.\(^1,\, \text{8}\) 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.\(^3\)

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.\(^1,\, \text{5,}^{17}\) Chloroquine is quickly distributed within the intracellular compartment; extrarenal filtration measures are therefore ineffective. Furthermore, high-dose diazepam is recommended 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). Isoprotenerol has been suggested 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 hypokalemia is to be closely monitored,\(^6\) 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,\(^1,\, \text{17}\) 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.\(^5\) We can also resort to extracorporeal circulatory support or extracorporeal membrane oxygenation (ECMO) in cases of severe cardiotoxicity with circulatory collapse and cardiac arrest.\(^11,\, \text{12}\) There have been reports of the use of such measures in intoxication caused by chloroquine and hydroxychloroquine.\(^2,\, \text{5,}^{13,\text{14}}\)

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


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