

Psychomotor Agitation Following Treatment with Hydroxychloroquine

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Abstract We describe the case of an elderly woman with elderly-onset rheumatoid arthritis, where the use of 4 mg/kg/day of hydroxychloroquine (HCQ) was followed by the onset of psychomotor agitation with marked physical and verbal violence towards her partner, including throwing objects at her partner. No disturbance in sleep and no anxiety, nervousness, or irritability had emerged before the onset of her psychomotor agitation. The disappearance of agitation following targeted pharmacologic intervention and HCQ interruption, its re-onset after reintroduction of the drug, and the high score (9) of Naranjo's algorithm are surely linked to the existence of a causal relationship between HCQ and psychomotor agitation. HCQ may produce undesirable effects on the central nervous system, mainly irritability, nervousness, emotional changes, and nightmares. To the best of our knowledge, there are only a few case reports of psychosis due to HCQ. No favoring condition such as pharmacokinetic interactions or a personal and family psychiatric history was present in our patient. The neuropsychiatric manifestations we observed could be considered a bizarre-type adverse drug reaction linked to an individual's hypersensitivity.

Key Points

Hydroxychloroquine can induce adverse effects on the central nervous system, from irritability, nervousness, and emotional changes to true psychoses.

Doses greater than 6 mg/kg/day, pharmacokinetic interactions, a personal or family psychiatric history and the disease per se for which HCQ is used can represent important favoring conditions.

In susceptible individuals, hydroxychloroquine can exert a stimulant effect on the central nervous system in the absence of these favoring conditions, probably as a consequence of an individual's hypersensitivity.

Introduction

Hydroxychloroquine (HCQ) is a synthetic antimalarial drug derived from 4-aminoquinoline; it has been used for several decades for the treatment of some rheumatic diseases such as rheumatoid arthritis (RA). A dosage between 3 and 6 mg/bodyweight/day is considered therapeutic. In obese individuals, the dosage must be assessed considering the patient's ideal bodyweight [1, 2]. Hydroxychloroquine may potentially result in adverse effects on the central nervous system, mainly irritability, nervousness, emotional changes, nightmares, and even true psychoses [3, 4]. We describe the case of an elderly person with elderly-onset rheumatoid arthritis (RA), where the use of therapeutic doses of HCQ was followed by the appearance of psychomotor agitation.

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Case Report

EDC was an 80-year-old Caucasian woman affected with RA since 78 years of age. She was receiving pharmacologic treatment with methotrexate (MTX 10 mg weekly subcutaneously), oral folate supplementation (folic acid 5 mg, 24 h after MTX), and low doses of oral corticosteroids (6-methylprednisolone 8 mg/day in the first 2 weeks, then 4 mg/day for a further 2 weeks; and then administered during exacerbations only for a short time). Her comorbidities were: (1) familiar hypercholesterolemia (she used pravastatin 20 mg after dinner); (2) high blood pressure (she used amlodipine 5 mg daily); and (3) non-hemodynamically significant carotid atheromasia (she used acetylsalicylic acid 100 mg at lunchtime). She had no psychiatric history and no family history of psychiatric problems. After 2 years, RA was stable with an overall minimal disease activity, with a 28-item Disease Activity Score of 2.6 and a Clinical Disease Activity Index of 3.1 [5]. The patient asked the rheumatologist to stop MTX because she complained of general malaise and fatigue, which significantly affected her quality of life. These effects were not improved by switching to oral administration of MTX. It was proposed to take one tablet of HCQ/day (HCQ 200 mg; 4 mg/kg/day); her weight was 52 kg and her body mass index was 20.06 kg/m². No over-the-counter or herbal supplements were used by the patient. Ten days later she developed, while she was healthy, significant psychomotor agitation [6] with marked physical and verbal violence towards her partner, including throwing objects at her partner. No disturbance in sleep and no anxiety, nervousness, or irritability had emerged prior to the onset of her psychomotor agitation. It was necessary to transport EDC to the hospital's emergency room in her city, where she was administered half a vial of intramuscular promazine (equal to 25 mg). The agitation ceased in less than 1 h and there were no relapses or sequelae. Brain magnetic resonance imaging plus contrast medium was performed; it was negative for vascular lesions or neoplastic diseases and only a mild age-related atrophy was found. Laboratory tests were normal. Because no other potential triggers were identified, HCQ administration was interrupted. At a consultation 2 week later, we did not attribute the agitation to HCQ use and advised to introduce it again. However, following two tablets of HCQ, the agitation appeared again.

The patient was treated with promazine drops (15 drops equal to 30 mg) and HCQ was stopped again—the agitation disappeared. The administration of a placebo did not cause the onset of agitation to the patient. When we applied the Naranjo scale [7] to our patient, she had a score of 9 and

this authorized the diagnosis of a defined (and not random) adverse drug reaction. One year later, the patient presented with neither cognitive impairment nor psychosis, with no further episodes of agitation. The patient's cognition, in particular, was assessed using the Mini-Mental State Examination by Folstein et al. [8] in the Italian version validated by Magni et al. [9]; her score was equal to 26. At present, she is taking pravastatin, amlodipine, and acetylsalicylic acid with small doses of corticosteroids (4 mg of 6-methylprednisolone or 5 mg of prednisone) as needed. The RA is stable and well controlled (28-item Disease Activity Score of 2.8; Clinical Disease Activity Index score of 3.1).

Discussion

Hydroxychloroquine includes the vast majority of prescriptions for RA. It is an alkylated 4-aminoquinoline. It is more polar, less lipophilic, and has more difficulty in diffusing across cell membranes compared with chloroquine. Near-complete absorption following an oral dose occurs within 2–4 h and is relatively unaffected by concomitant ingestion of food [10]. Variability in the extent of absorption leads to differences in steady-state HCQ concentrations among patients, potentially contributing to the variability in response observed in clinical practice [11]. Hydroxychloroquine has a large volume of distribution owing to extensive sequestration of the drug by tissues. In particular, a plasma volume of distribution up to 44,257 L for HCQ has been reported [12, 13]. Drug disposition proceeds in three phases: distribution from blood to tissues, equilibration between blood and tissues, and release from tissues back into blood [11, 13, 14]. These phases have half-lives of 3–8, 40–216 h, and 30–60 days, respectively. The most commonly quoted median value for the terminal elimination half-life is 40 days [15]. Metabolism of HCQ occurs by dealkylation in the liver; the two most important metabolites are desethyl chloroquine and bisdesethyl chloroquine, both of which have pharmacologic activity and are thought to be approximately as toxic as the parent compounds [11]. Thirty to 79% of an oral dose of HCQ is metabolized and 21–70% is excreted without metabolism [15]. At steady state, the ratio of HCQ to desethyl hydroxychloroquine was 1.75 ± 0.37 [10]. Cytochrome P450 3A4 inhibitors such as ketoconazole, cimetidine, and ciprofloxacin may increase the half-lives of HCQ [16, 17, 18]. The possible HCQ-induced neuropsychiatric side effects depend on its ability to cross the blood–brain barrier. In the brain, HCQ can have a tissue concentration 10–20 times higher than a plasma concentration [2, 14].

There are several possible mechanisms hypothesized for the onset of HCQ-induced psychosis. For example, the induction of a cholinergic imbalance with acetylcholine reduction, probably mediated by prostaglandin E and interleukin-1; the accumulation of metabolic and toxic wastes as a result of lysosome dysfunction, where HCQ accumulates; the down-regulation of P-glycoprotein at the level of the blood–brain barrier. Drug interactions (as already mentioned) may represent an additional mechanism. Finally, the possibility that it may be an idiosyncratic or bizarre-type adverse drug reaction [19] must be considered. Other antimalarial drugs such as chloroquine and mefloquine can cause neuropsychiatric side effects [20–24]. There are only a few case reports of psychosis due to HCQ [3, 18, 25, 26]. Our patient used a dose of HCQ equal to 4 mg/bodyweight/day; this dosage is within the therapeutic range. None of the three molecules taken from our patient was within the categories of drugs causing interaction with HCQ. Psychomotor agitation cannot be considered a manifestation of elderly-onset RA; neurological and psychiatric manifestations in the course of RA mostly depend on vasculitis, opportunistic infections, and accelerated atherosclerosis [27], all conditions excluded in our patient. Therefore, the RA was (at the time of the introduction of HCQ) in a minimal activity and typically there is a close relationship between disease activity and RA extra-articular manifestations. Our patient was not receiving corticosteroid treatment and this aspect needs to be highlighted.

In other case reports regarding the relationship between neuropsychiatric manifestations and therapy with HCQ, some important biases were present, such as important pharmacokinetic interactions (18), a potential effect of the rheumatic disease on the neuropsychiatric manifestations (3), and a personal and/or family history of psychiatric disorders (25, 26). Furthermore, the bodyweight (real or ideal) of the patient was not always reported or properly assessed in other case reports.

Conclusions

Hydroxychloroquine may produce undesirable effects on the central nervous system. These side effects usually appear with high doses of the drug (>6 mg/bodyweight/day) or in the presence of favoring elements (pharmacokinetic interactions, personal and family psychiatric history, the disease for which HCQ is used). To our knowledge, the possibility that HCQ may cause psychomotor agitation in the absence of such favoring elements has not been reported. The disappearance of agitation after targeted pharmacologic intervention and

HCQ interruption, its reonset following reintroduction of the drug and the score of Naranjo's algorithm are surely linked to the existence of a causal relationship between HCQ and psychomotor agitation. Furthermore, 1 year after the discontinuation of HCQ, our patient presented with no further episodes of psychomotor agitation or other psychotic manifestations and she had good cognitive performance.

We can hypothesize that in susceptible people, for unknown reasons, HCQ might exert a stimulant effect on the central nervous system resulting in agitation onset that disappears on drug interruption and is responsive to sedative treatments. The neuropsychiatric manifestations described in our patient could be considered a bizarre-type adverse drug reaction linked to an individual's hypersensitivity.

Compliance with Ethical Standards

Funding No financial support was received for the conduct and preparation of this case report.

Conflict of interest Ciro Manzo, Pietro Gareri, and Alberto Castagna declare they have no conflicts of interest directly relevant to the content of this case report.

Consent for publication Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent may be requested from the corresponding author.

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