Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2015;28:369-373
DOI: 10.5350/DAJPN2015280409

Case Report / Olgu Sunumu

Hydroxychloraquine-Induced Acute Psychotic Disorder in a Female Patient with Rheumatoid Arthritis: a Case Report

Ebru Altintas[1]

[1]Psychiatrist, Baskent University, Faculty of Medicine, Department of Psychiatry, Adana - Turkey

ABSTRACT

Hydroxychloraquine-induced acute psychotic disorder in a female patient with rheumatoid arthritis: a case report

Chloroquine and its derivative hydroxychloroquine (HCQ) have been used for acute and prophilactic treatment of malaria for most of the last century. HCQ has anti-inflammatory, antilipidemic and antithrombotic effects and in recent years has become an important drug for treating rheumatoid arthritis (RA). In the literature, antimalarial-induced psychosis has been reported in a small number of cases; however, we did not find any case related with HCQ-induced psychosis in rheumatoid arthritis. We want to report a 73-year-old female RA patient without a previous history of psychosis who developed psychosis after use of HCQ. HCQ is being increasingly prescribed in autoimmune diseases. Clinicians need to be aware of psychosis as a rare but debilitating side effect.

Keywords: Hydroxychloroquine, psychosis, side-effect

ÖZET

Romatoid artriti olan kadın hastada hidroksiklorokin kullanımına bağlı gelişen akut psikotik bozukluk: Olgu sunumu

Klorokin ve ondan sentez edilen hidroksiklorokin (HCQ) sıtmanın akut ve idame tedavisinde son yüzyılda yaygın olarak kullanılmaktadır. HCQ'nin antiinflamatuvar, antilipidemik ve antitrombotik etkileri vardır ve son yıllarda romatoid artrit tedavisinde önemli hale gelmiştir. Yazında antimalaryal kullanımına bağlı psikoz birkaç vaka sunumunda bildirilmiş fakat romatoid artritte HCQ kullanımına bağlı bir olguya rastlanmamıştır. Bu olgu sunumunda psikoz öyküsü olmayan 73 yaşında RA'i olan yaşlı kadın hastada HCQ kullanımına bağlı gelişen psikoz vakasını sunduk. HCQ otoimmün hastalıkların tedavisinde yaygın olarak reçete edilmeye başlanmıştır. Klinisyenlerin nadir ancak işlevselliği bozan bir yan etki olan psikoz konusunda uyanık olmaları gerekmektedir.

Anahtar kelimeler: Hidroksiklorokin, psikoz, yan etki

Address reprint requests to / Yazışma adresi:
Psychiatrist Ebru Altintas,
Baskent University, Faculty of Medicine,
Department of Psychiatry, Dadaloglu Mahallesi, Serinevler Sokak, No: 4/A, 01250 Yuregir/Adana, Turkey

Phone / Telefon: +90-322-327-2727

Fax / Faks: +90-322-327-1274

E-mail address / Elektronik posta adresi:
yurdagulebru@hotmail.com

Date of receipt / Geliş tarihi:
December 17, 2014 / 17 Aralık 2014

Date of acceptance / Kabul tarihi:
February 24, 2015 / 24 Şubat 2015

INTRODUCTION

Besides acute and maintenance treatment of malaria, 4-Aminoquinolones (chloroquine and hydroxychloroquine) are also frequently used for the treatment of immune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), as well as extraintestinal amebiasis. Absence of serious adverse events other than on the field of vision, presence of antithrombic and antilipidemic efficacy in addition to anti-inflammatory efficacy, being cheap and well tolerated compared to the other drugs, and a fast onset of action are the main reasons for preferring these drugs (1,2). Despite widespread usage in regions where malaria is endemic, toxic dose range and mental and behavioral side effects of these drugs are not known definitely.

Maximum plasma concentration after single dose is reached in one to two hours, its half-life being as much as 3-6 days (average five days). High concentration occurs in the liver, spleen, kidneys, lungs, and brain and spinal cord. Elimination half-life ranges between 2 and 3 days in plasma to over 300 hours in tissues (3,4). Potential side effects include central nervous system

involvement, such as headache, neuropathy, vertigo, depression, psychosis and mania, neuromuscular system-related symptoms such as myopathy, loss of sensation and atrophy in the proximal muscles, and dermatological reactions such as hair loss, pruritus, pigmentation and skin rashes (2). Although the incidence of serious neuropsychiatric adverse events has not been definitely established, they have been reported to occur at a rate of approximately 1:136005. It is thought that these adverse events result from idiosyncratic drug reactions (6,7), and female gender is stated to be a risk factor (8).

Neuropsychiatric adverse events reported in the literature are generally those associated with the use of antimalarial drugs in malaria. However, we encountered no study highlighting side effects of these drugs when used in the treatment of RA, for which they recently have been widely used because of their anti-inflammatory efficacy.

With this case report, we aimed to discuss a psychotic disorder due to hydroxychloroquine-use in a geriatric patient who was being followed for rheumatoid arthritis, as well as to attract the clinicians' attention to this subject by scrutinizing side effects of chloroquine in this context.

CASE

We present the case of a 73-year-old illiterate woman with five children. She consulted an internal medicine-rheumatology specialist approximately a month ago for joint pain in wrist and knee; she was diagnosed with RA attack and recommended to receive hydroxychloroquine at a dose of 400mg/day. She was brought to our psychiatry policlinic by her relatives due to the development of symptoms such as repeating the same sentences, meaningless speech, hearing voices, seeing things, not recognizing the people around her, crying for no reason, contraction in the body, inability to swallow solid/fluid foods, inability of speaking, and sometimes shouting. Symptoms had developed after the 5th day of treatment. Her history revealed that she had been treated for RA for about 25 years, receiving various medications such as sulfasalazine, methotrexate, and corticosteroids, and had had no psychiatric complaints during that period. On mental examination of the patient, who was brought in a wheelchair because of difficulty in walking, her appearance was consistent with her age but self-care was decreased, and she was awake with somewhat retarded association of ideas. Thought content and memory could not be evaluated. Her mood was agitated. Her perception included visual and auditory hallucinations. Orientation to place, time and person was correct. Expressed behaviors included meaningless shouting, fearful facial expression and looking at different sides of the room with sudden reactions. No mental disorder was determined in personal and family histories. Her medical history is significant for diabetes mellitus, and insulin was used for treatment. In her neurologic examination, no focal changes or motor or sensory symptoms were found.

Dementia, delirium and central involvement of RA were considered in differential diagnosis of the patient. Psychiatric side effects in RA patients are also associated with increased functional disability, drugs or pain. Therefore, central involvement due to RA were excluded. The presentation of delirium was considered in differential diagnosis but excluded because of the absence of any reason that might explain this situation in organic examination, complete orientation, and absence of diurnal rhythm. Alzheimer dementia was also excluded based on her relative's anamnesis revealing that her cognitive functions were normal before the onset of these complaints. Vascular dementia can occur suddenly after a stroke, and symptoms can vary widely, depending on the severity of the blood vessel damage and the part of the brain affected. The core features of dementia with Lewy bodies are behavioral disturbances, detailed recurrent and well-formed visual hallucinations, fluctuations in cognitive performance, motor Parkinsonism, and the presence of Lewy bodies in the brain. Frontotemporal dementia was excluded because of the absence of dramatic changes of personality, impulsiveness or emotional indifference, progressive aphasia, or social withdrawal. Mini Mental Test could not be performed

because of limited communication with the patient.

Computed tomography of the brain and laboratory analyses were within the normal ranges. A Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) was performed with the patient after recovery from agitation on the 3rd day of psychiatric treatment (9,10). She was diagnosed with drug-induced psychotic disorder. Her Clinical Global Impressions-Severity of Illness Scale (CGI-S) (11) score at baseline was 6 (severely ill). Hydroxychloroquine was discontinued and the already restricted fluid intake was supported with intravenous fluid replacement. Intramuscular diazepam was injected for the contractions in her body and olanzapine was commenced at a dose of 5mg/day via oral route. On the 3rd day of treatment, the patient's stabilized emotional state was observed, as aggression and uneasiness disappeared. On the 5th day of treatment, restored sleep and appetite and good insight were observed, The psychotic picture completely improved approximately one week after discontinuation of hydroxychloroquine. Her CGI-S score at this point was 1 (normal, not at all ill), CGI-Improvement Scale score was 1 (very much improved). The score of the Mini Mental Test performed in that period was 27/30. Olanzapine therapy was discontinued. Her symptoms did not recur within a 2-month follow-up period.

DISCUSSION

Psychotic signs and symptoms may appear not only in schizophrenia and similar disorders, but also over the course of other psychiatric and neurological disorders. In addition, drugs such as glucocorticoids and other steroids, anticholinergic drugs, L-Dopa, H_2 receptor blockers, digitalis, antabuse, quinolones, selegiline, isoniazid and topiramate, toxins, and substances such as LSD and cocaine may lead to a similar picture (12).

Chloroquine and hydroxychloroquine were developed in 1934 by German scientists and have been used in the treatment of inflammatory diseases such as malaria, RA and SLE since 1944 (13). The most common side effects of hydroxyquinolines are encountered in the field of vision. However, drug-related neuropsychiatric adverse events are rare (1:13600) (5). Although the mechanisms of such adverse events are not clear, some hypotheses have been suggested. It is thought that chloroquine enhances turnover of dopamine transporter protein, inhibits dopaminergic and muscarinic-cholinergic receptors by decreasing the number of postsynaptic dopamine receptors, and thereby shows anticholinergic efficacy. Another hypothesis states that chloroquine behaves as a strong serotonin reuptake inhibitor, inhibiting serotonin transporter protein. Telgt et al. (14) suggested another explanation, according to which antimalarials may have the same pathologic activity as quinolines in acting as N-methyl-d-aspartate agonists and gamma-aminobutyric acid antagonists. Another mechanism considered for the explanation of neuropsychiatric adverse events is the drug's probability of decreasing the cortical flow of information by inhibiting P glycoprotein (7).

A great variety of psychiatric side effects, such as mania, depression, visual and auditory hallucinations, delusions of persecution/grandiosity, agitation, suicidal ideation/suicide, and insomnia have been reported due to chloroquine use. These adverse events are dose-independent and may appear approximately within 2 hours or 40 days. They generally disappear within one week following discontinuation of the drug (6,15-17). In their review, Mohan et al. reported chloroquine-induced psychiatric adverse events in at least 10 cases between 1978 and 1980. The mentioned symptoms appeared between the third and 10th day after starting chloroquine use and disappeared within 1-2 weeks following discontinuation of drug (6). Bhatia et al. (16) used chloroquine and evaluated six cases that developed psychiatric adverse events. They reported that 70% of the patients were female and that adverse events appeared between the 2nd and 7th day after the onset of treatment independently of the dose and the way of its administration (before/after meals). They determined organic psychosis in 32, schizophrenia-like disorder in 12, mania in four, and anxiety or depressive disorder in eight cases (16). Using a database, Meier et al. (15) reviewed 35370 patients that had used antimalarial

drug between 1990 and 1999 in England and determined that 45.2% of the cases were male and 505 patients had depression, 16 patients had psychosis, and 57 patients had panic attack. They emphasized that the risk of psychosis and panic attack due to overall antimalarial drugs (mefloquine, chloroquine, proguanil, and doxycycline) is significantly lower compared to other psychiatric disorders (15).

In the present case, which had no personal or family history of psychiatric disorder, agitation, auditory and visual hallucinations, perseveration, and impairment of the eating routine appeared on the 5th day after chloroquine use, which is consistent with the literature. She was diagnosed with hydroxychloroquine-induced psychotic disorder, and drug therapy was discontinued. It was observed that the symptoms improved approximately one week later and did not recur subsequently. Because of the absorption, metabolism, and excretion features of HCQ, the patient's symptoms may occur after 5 days of treatment and disappear one week after discontinuation of the treatment.

Another point worth mentioning is that the patient, while having used antimalarial medication previously, had not developed any psychiatric disorder so far. Many factors such as age, multiple health problems requiring polypharmacy as well as changes in pharmacokinetics and pharmacodynamics in elderly patients may result in an increased incidence of drug toxicity and adverse drug reactions. In elderly people, due to the amount of water in the body decreasing and fat tissue increasing, lipophilic drugs such as HCQ are more easily stored in fat tissues. In addition, elderly arthritic patients may have raised levels of HCQ due to reduced renal clearance (18). Because of all these age-related changes, age may have been responsible for psychiatric side effects in this patient.

It is important to question the psychiatric history of the patient in detail, keeping a record of the psychiatric disorders that might develop with chloroquine use in the treatment of compelling diseases such as RA, SLE and malaria, to be alert for potential adverse events particularly in old and female patients, and to adjust the dose slowly and gradually. Considering that 4-Aminoquinolones are frequently being used in regions where malaria is endemic, while at the same time offering a good therapeutic option in some other diseases and have a low cost, it is obvious that these drugs should be known better. Scientific studies and case reports are needed particularly on their usage in extra-malarial diseases.

REFERENCES

1. Blyth C, Lane C. Hydroxychloroquine retinopathy: is screening necessary? BMJ 1998; 316:716-717. **[CrossRef]**

2. Weniger H. Review of side effects and toxicity of chloroquine. Bulletin World Health Organization 1979; 906:1-26.

3. Sahoo S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. Am J Ther 2007; 14: 406-407. **[CrossRef]**

4. Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxy-chloroquine following intravenous administration to healthy volunteers. Br J Clin Pharmacol 1988; 26:303-313. **[CrossRef]**

5. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? Drug Saf 1995; 12:370-383. **[CrossRef]**

6. Mohan D, Mohandas E, Rajat R. Chloroquine psychosis: a chemical psychosis? J Natl Med Assoc 1981; 73:1073-1076.

7. Alisky JM, Chertkova EL, Iczkowski KA. Drug interactions and pharmacogenetic reactions are the basis for chloroquine and mefloquine-induced psychosis. Med Hypotheses 2006; 67:1090-1094. **[CrossRef]**

8. Schneider C, Adamcova M, Jick SS, Schlagenhauf P, Miller MK, Rhein HG, Meier CR. Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. Travel Med Infect Dis 2013; 11:71-80. **[CrossRef]**

9. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Clinical Version (SCID-I/CV, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute, 1997.

10. Corapcioglu A, Aydemir O, Yildiz M, Esen A, Koroglu E. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinical Version. Hekimler Yayin Birligi, Ankara, 1999. (Turkish)

11. Guy W. CGI: Clinical Global Impressions. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept of Health, Education, and Welfare publication (ADM) 76-338. Rockville; National Institute of Mental Health 1976:218-222.

12. Sadock BJ, Sadock VA. Kaplan&Sadock's Comprehensive Textbook of Psychiatry. Aydin H, Bozkurt A (Translation Editors), Eight Edition, Günes Kitabevi, Ankara; 2007:1423-1424.

13. Ochsendorf FR, Runne U. Chloroquine and hydroxychloroquine: side effect profile of important therapeutic drugs. Hautarzt 1991; 42:140-146.

14. Telgt DS, van der Ven AJ, Schimmer B, Droogleever-Fortuyn HA, Sauerwein RW. Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann Pharmacother 2005; 39:551-554. **[CrossRef]**

15. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf 2004; 27:203-213. **[CrossRef]**

16. Bhatia MS, Malik SC. Psychiatric complications of chloroquine. Indian J Psychiatry 1994; 36:85-87.

17. Das P, Rai A, Chopra A, Philbrick K. Psychosis likely induced by hydroxychloroquine in a patient with chronic Q fever: a case report and clinically relevant review of pharmacology. Psychosomatics 2014; 55:409-413. **[CrossRef]**

18. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009; 41:67-76. **[CrossRef]**