

NEUROPSYCHIATRIC CLINICAL MANIFESTATIONS IN ELDERLY PATIENTS TREATED WITH HYDROXYCHLOROQUINE: A REVIEW ARTICLE

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Introduction: Little is known about the development of psychosis during hydroxychloroquine (HCQ) treatment, especially in elderly patients affected by rheumatic diseases, with multiple comorbidities and treatments. HCQ could be used both as antimalarial or anti-rheumatic agent although its use as antimalarial requires higher doses. Over the years, some studies were published about the risk of neuropsychiatric clinical manifestations during HCQ treatment for rheumatic diseases, but few of them were related to elderly patients. To summarize the available evidence on HCQ-induced psychosis in elders, we performed a literature review. Moreover, to take stock of the available evidence on HCQ-induced psychosis in elderly patients, we also analyzed the European Pharmacovigilance Database (Eudravigilance).

Material and methods: We performed a detailed analysis of evidence from the scientific literature of the role of HCQ in inducing neuropsychiatric disorders. Furthermore, since 2012, the European Medicines Agency (EMA) has made publically available data on suspected adverse drug reactions for authorized medicines in the European Economic Area. From this database, which is named Eudravigilance it is possible to obtain information for drug-event couples in an aggregate manner. In particular, it is possible to aggregate information on sex, age, adverse events, and source of the report for each drug-event couple. Therefore we analyzed all individual case safety reports (ICSR) collected from the Eudravigilance up to September 2017.

Results: From literature data in seven case reports HCQ was identified as a possible cause of neuropsychiatric clinical manifestations. Three of seven cases were related to the development of psychiatric events in elderly patients (age greater than 65 years old). From the date of the establishment of 'Eudravigilance' to September 2017, a total of 5550 ICSR with HCQ as a suspected drug were identified, of which 406 (7%) were associated with the System Organ Class 'Psychiatric disorders'. Two out of 406 cases were related to patients with an age greater than 85 years, 73 cases were related to patients aged 65–85 years, 269 cases were related to patients aged 18–64 years, 12 cases were related to patients aged 12–17 years, 1 case was related to a patient aged 2 months–2 years, and 49 cases had an age not specified. Considering that in each ICSR could be reported more than one adverse drug reactions (ADRs), a total of 646 suspected ADR were identified. The most reported ADR was depression (N = 70), followed by insomnia (N = 59), completed suicide (N = 53), sleep disorder (N = 33), and anxiety (N = 32). A total of 71 out of 646 reported reactions were fatal, 138 were resolved, and 116 were not resolved at the time of the report.

Discussion and conclusions: Neuropsychiatric clinical manifestations are reported in the summary of product characteristics of medicinal products containing HCQ. Over the years, different predisposing factors, such as family history, female gender, and co-administration of CYP3A4 inhibitors, which can prolong the HCQ half-life, or co-administration of low-dose glucocorticoids, alcohol intake, and low body weight, were identified. It is important to consider that the rheumatic disease and malaria in itself can cause neuropsychiatric disorders. Moreover, neuropsychiatric adverse events could occur in the absence of predisposing risk factors. This review showed that HCQ-induced psychiatric manifestations such as depression, anxiety, and even suicide ideation may differ among elderly patients with rheumatic diseases and may precipitate according to the presence of risk factors, serving as an alert for the management of this risk. A limitation of this descriptive analysis is our inability to correlate the number of neuropsychiatric adverse events occurred in all treated elders.