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Psychiatric adverse effects of chloroquine

Psychiatryczne działania niepożądane chlorochiny

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Abstract

Chloroquine is a prototype antimalarial drug, widely used in several branches of medicine. Antimalarial drugs are used in the treatment of various dermatological, immunological, rheumatological and infectious diseases. Examples of off-labelled indications for chloroquine analogues use include dermatomyositis, sarcoidosis, polymorphous light eruption, disseminated granuloma annulare and porfiria cutanea tarda. There is a relatively small number of adverse effects related to chloroquine analogues used in standard doses, such as gastrointestinal disturbances, headaches, skin reactions, hypotension, convulsions, extrapyramidal symptoms and visual disturbances. Psychiatric side effects of chloroquine seem to be rare, but may manifest in a wide range of symptoms, such as confusion, disorientation, ideas of persecution, agitation, outbursts of violence, loss of interest, feeling sad, suicidal ideas and impaired insight. There is also a report of a manic episode with psychotic features in the course of bipolar disorder, and another case report of persecutory delusions, anxiety, derealisation and visual illusions triggered by chloroquine. The duration of psychiatric symptoms usually ranges from one to two weeks, and symptoms usually disappear within several days following cessation of chloroquine usage and starting psychiatric treatment where indicated. This article reviews the case studies of patients diagnosed with mental disorders resulting from the use of chloroquine, and discusses the management in such cases.

Keywords: chloroquine, antimalarial drugs, mental disorders, adverse effects, side effects

Streszczenie

Chlorochina jest prototypowym lekiem przeciwmalarycznym, szeroko stosowanym w kilku gałęziach medycyny. Leki przeciwmalaryczne wykorzystuje się w leczeniu różnych chorób dermatologicznych, immunologicznych, reumatologicznych i chorób zakaźnych. Przykłady pozarejestracyjnych wskazań użycia analogów chlorochiny obejmują zapalenie skórno-mięśniowe, sarkoidozę, wielopostaciowe osutki świetlne, rozsiany ziarniniak obrączkowaty i porfirię skórną późną. W standardowych dawkach chlorochina powoduje stosunkowo niewielką liczbę działań niepożądanych, takich jak zaburzenia żołądkowo-jelitowe, bóle głowy, reakcje skórne, obniżone ciśnienie, drgawki, objawy pozapiramidowe i zaburzenia widzenia. Wydaje się, iż psychiatryczne objawy niepożądane chlorochiny występują rzadko, ale w szerokim zakresie możliwości – od splątania, dezorientacji, urojeń prześladowczych, pobudzenia i zachowań agresywnych po utratę zainteresowań, uczucie smutku, myśli samobójcze oraz zaburzenie wglądu. Istnieje również doniesienie, w którym opisuje się epizod manii z cechami psychotycznymi w przebiegu choroby afektywnej dwubiegunowej, a także opis przypadku z urojeniami prześladowczymi, niepokojem, derealizacją i iluzjami wzrokowymi wywołanymi zastosowaniem chlorochiny. Czas trwania objawów psychiatrycznych zazwyczaj zawiera się w przedziale od jednego do dwóch tygodni, a objawy zazwyczaj ustępują w ciągu kilku dni po zaprzestaniu przyjmowania chlorochiny oraz po włączeniu leczenia psychiatrycznego, jeżeli istnieją do tego wskazania. W artykule przedstawiono opisy przypadków pacjentów z rozpoznaniem zaburzeń psychicznych wynikających z zastosowania chlorochiny, a także przedstawiono zastosowane postępowanie w takich przypadkach.

Słowa kluczowe: chlorochina, leki przeciwmalaryczne, zaburzenia psychiczne, objawy niepożądane, działania uboczne

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INTRODUCTION

Chloroquine is widely used in medicine. Its registered indications include chemoprophylaxis and treatment of malaria, rheumatoid arthritis and lupus erythematosus (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2014). However, its off-labelled use is wider. Chloroquine, a 4-aminoquinoline, was synthesised in the 1930s by German scientists, who named it resochin (Nevin and Croft, 2016). In the 1940s chloroquine was valuated as an antimalarial drug with activity against *Plasmodium vivax* and *falciparum* infections in humans (Loeb, 1946). The first discovered natural antimalarial drug was quinine, which was isolated from the bark of the cinchona tree in the 1920s and made it possible to live in tropical countries despite lethal tropical malaria (Chen *et al.*, 2006). However, chemical synthesis of antimalarial drugs and chloroquine analogues started earlier, in 1891, when Paul Ehrlich's group developed methylene blue (Al-Bari, 2015). After that pamaquine, quinacrine, sontoquine, primaquine and hydroxychloroquine were discovered (Al-Bari, 2015). During the World War II it was found that taking antimalarial prophylaxis improved soldiers' rashes and inflammatory arthritis (Al-Bari, 2015). Nowadays, antimalarial drugs are beneficial for many dermatological, immunological, rheumatological and infectious diseases (Al-Bari, 2015).

INDICATIONS FOR CHLOROQUINE USAGE

A typical indication for chloroquine (base) usage is prophylaxis of malaria, where chloroquine is administered 1 week before entering an endemic area and continued for 4 weeks after leaving it, at a dosage of 310 mg once weekly (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2014). It is also used with proguanil where chloroquine-resistant falciparum malaria is present (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2014).

Another indication is the treatment of rheumatoid arthritis and lupus erythematosus, where chloroquine (base) is used at a dosage of 150 mg daily (max. 2.5 mg/kg daily) based on ideal body weight. In the treatment of rheumatoid arthritis and lupus erythematosus chloroquine sulfate is used at a daily dosage of 200 mg, and chloroquine phosphate at 250 mg (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2014).

Despite a relatively small number of registered indications of chloroquine usage, there are numerous off-labelled indications, such as dermatomyositis, sarcoidosis, polymorphous light eruption, disseminated granuloma annulare and porfiria cutanea tarda (Al-Bari, 2015).

MECHANISM OF ACTION

It was shown that chloroquine absorption from the gastrointestinal tract is complete or nearly complete, and considerable amounts of chloroquine are deposited in tissues and nucleated cells, especially in those of the liver, spleen, kidneys and lungs, and these organs contain the highest concentrations, from 200 to 500 times the amount found in the plasma (Loeb, 1946). Antimalarials accumulate in different concentrations in various body tissues and organs. Fat, bone, tendon and brain contain relatively small amounts, close to the plasma level of the drug, in contrast to higher concentrations in kidney, bone marrow, spleen, lungs, adrenal glands and liver, where the concentration may be higher than the plasma level (Wozniacka and McCauliffe, 2005). Within the cell, chloroquine is accumulated in lysosomes, therefore chloroquine analogues are known as lysosomotropic agents (Al-Bari, 2015). Chloroquine analogues interfere with lysosomal acidification, which in turn inhibits proteolysis, chemotaxis, phagocytosis and the process of antigen presentation by decreasing the number of autoantigenic peptides appearing on the cell surface. Thus, the synthesis of cytokines by both T cells and antigen-presenting cells also decreases (Al-Bari, 2015).

SIDE EFFECTS

Taking into account how widely chloroquine analogues are used, there is a relatively small number of side effects at the standard doses of chloroquine analogues. Side effects include gastrointestinal disturbances, headaches, skin reactions (rashes, pruritus), hypotension, convulsions, extrapyramidal symptoms, visual disturbances, depigmentation and loss of hair, and more rarely bone marrow suppression or hypersensitivity reactions such as urticaria and angioedema (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2014). Chloroquine has been found to cause deposits in the corneal epithelium and to cause retinopathy (Hobbs *et al.*, 1961), and its retinal toxicity is a serious adverse effect (Geamănu Pancă *et al.*, 2014). Other serious adverse effects include cardiomyopathy characterised by concentric hypertrophy and conduction abnormalities (Yogasundaram *et al.*, 2014), QT prolongation and refractory ventricular arrhythmia (Chen *et al.*, 2006).

PSYCHIATRIC SIDE EFFECTS

In contrast to the numerous reports of psychiatric side effects of other antimalarial drugs, the reports regarding chloroquine seem to be rare. Nevertheless, the list of described psychiatric side effects induced by chloroquine represents a wide range of symptoms. Rab (1963) described lightheadedness, confusion, disorientation, ideas of persecution, agitation and outbursts of violence. A confused state was reported by Brookes (1966). Das and Mohan (1981) described loss of interest, feeling sad, suicidal ideas, a weeping spell, and impaired insight. Overactivity, irritability, talkativeness, experiencing racing thoughts, expressing delusions of reference and grandeur were reported by Lovestone (1991).

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Collins and McAllister (2008) presented a case of female patient with irritability, confusion, and paranoia associated with delusions and visual hallucinations progressing to a catatonic state caused by chloroquine. There are also reports of a manic episode with psychotic features in the course of bipolar disorder (Bogaczewicz *et al.*, 2014) and feelings of lightheadedness and derealisation, persecutory delusions, anxiety, and visual illusions triggered by chloroquine (Bogaczewicz *et al.*, 2016).

In the aforementioned cases chloroquine was used due to various indications, such as amoebic hepatitis, discoid lupus erythematosus, malaria, antimalarial prophylaxis and systemic lupus erythematosus. The onset of chloroquine-induced psychiatric side effects may vary largely in terms of time. Biswas *et al.* (2014) reported the latency between chloroquine usage and the onset of psychosis to be within a range of 6 to 432 hours, with mean and standard deviation equal to 100.08 ± 96.00 hours. Mohan *et al.* (1981) indicated that the symptoms were not dose-related. Similarly, Biswas *et al.* (2014) found no linear relationship between the amount of consumed chloroquine and the severity of psychosis. The duration of psychiatric symptoms usually ranges from one to two weeks, with symptoms typically disappearing within two days to one week following the cessation of chloroquine usage and onset of the psychiatric treatment where indicated (Mohan *et al.*, 1981; Rab, 1963). During the differential diagnosis of psychiatric side effects following chloroquine usage, many more common comorbidities should be excluded, such as metabolic disorders, primary mental disorders, neuropsychiatric lupus, and a glucocorticoid-induced psychotic disorder. As a method of estimating the likelihood of adverse drug reactions the algorithm by Naranjo *et al.* (1981) can be used.

MOLECULAR MECHANISMS INVOLVED IN CHLOROQUINE-INDUCED PSYCHIATRIC SIDE EFFECTS

The molecular mechanisms responsible for the psychiatric complications following chloroquine use are not fully understood, and when initial reports appeared the mode of action on the brain was a matter of speculation (Rab, 1963). Interference of chloroquine with the muscarinic cholinergic systems was revealed 30 years ago, when Schmidt and Oettling (1987), using a chick embryo, found that chloroquine displaced a specific muscarinic ligand from its receptor and acted as a muscarinic antagonist. In another animal study, in which chloroquine increased the locomotion of rats and elicited their stereotyped behaviour, it was concluded that chloroquine produces excitatory effects via dopaminergic mechanisms and that it may be involved in the observed effects of chloroquine (Amabeoku, 1994). However, it would be an oversimplification to search for mechanisms responsible for chloroquine-induced psychiatric side effects only in muscarinic and dopaminergic pathways. In a recent study by Thompson and Lummis (2008) chloroquine was found to be an antagonist for both 5-HT_{3A} and 5-HT_{3AB} receptors, yet it is not known whether 5-HT_3 receptors are inhibited in patients taking chloroquine, even though blood and its tissue concentrations indicate that it is possible. Thompson and Lummis (2008) suggested that nausea, a reported side effects of chloroquine, could be caused by $5HT_3$-mediated effects. Interestingly, $GABA_A$ receptors were also inhibited by chloroquine, but at higher concentrations, whereas no inhibition was observed at $GABA_C$ receptors (Thompson and Lummis, 2008). In the view of neuropsychiatric side effects of chloroquine usage, its impact on the nervous system seems to be underestimated. Hirata *et al.* (2011) revealed that chloroquine protected mouse hippocampal HT22 cells from glutamate-induced oxidative stress by attenuating production of excess reactive oxygen species, and suggested that chloroquine could be a neuroprotective agent against oxidative stress that seems to occur in a variety of neurodegenerative diseases.

MANAGEMENT

When diagnosis of a chloroquine-induced psychiatric side effect is made, the best solution is to discontinue chloroquine. The next steps depend on the clinical manifestation of the psychiatric disorders. In one report, when a diagnosis of toxic psychosis was made, chloroquine was discontinued and chlorpromazine administered, with the patient's mental status reverting to normal within three days (Rab, 1963). In the case of a confused state, reported by Brookes (1966), when chloroquine was discontinued, during the following week the patient became quite well. In chloroquine-induced subacute paranoid-like disorder, all the symptoms resolved two days after chloroquine discontinuation (Bogaczewicz *et al.*, 2016). In the case of moderate to severe depression with suicidal ideas and weeping spells with impaired insight, amitriptyline 100 mg per day improved the patient's condition after 4 days (Das and Mohan, 1981). In hypomania, a single dose of 5 mg of haloperidol returned the mental state to normal within three days (Lovestone, 1991). More problematic are situations where chloroquine exacerbates the primary psychiatric disorder.

In a case of the patient with exacerbations of bipolar disorder triggered by chloroquine used to treat systemic lupus erythematosus, where the patient suffered from a severe depressive episode with psychiatric features, perazine, mirtazapine, sertraline and hydroxyzine were administered, while during the manic episode with psychotic features quetiapine and lamotrigine were used (Bogaczewicz *et al.*, 2014).

Conflict of interest

The authors have no conflicts of interest to declare.

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