IJMS
Vol 34, No 1, March 2009

Case Report

Sulfasalazine plus Chloroquine-Induced Mood Disorder in a Patient with Rheumatoid Arthritis

Gulcan Gulec[1], Cinar Yenilmez[1], Unal Ayranci[2]

Abstract
Rheumatoid arthritis is a chronic systemic inflammatory disease that affects approximately 0.5-1% of the world population. The current approach to this disease is to start an intensive treatment without delay once the disease has developed. Various studies in the literature have shown that combination of disease modifying antirheumatic drugs such as sulfasalazine and chloroquine offers a more advantageous treatment. Although these drugs may cause central nervous system adverse effects such as serious psychiatric problems including mania and psychosis, these symptoms have been reported to occur only infrequently. The present case study reports a female patient who was hospitalized due to bipolar affective disorder-mixed episode. She had been receiving 250 mg/day chloroquine for 9 months for rheumatoid arthritis without exhibiting any adverse psychiatric effects. However, upon receiving a combination of 250 mg/day chloroquine and 2 gr/day sulfasalazine, she developed serious psychiatric symptoms.
Iran J Med Sci 2009; 34(1): 72-75.

Keywords ● Chloroquine ● sulfasalazine ● affective disorders ● mood disorder ● rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a disease that leads to damage and loss of function of the joints. Most authorities believe that RA should be treated in the vast majority of patients by at least one specific anti-rheumatic medication, also called disease modifying antirheumatic drug (DMARD). These medications include azathioprine, cyclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine (SSZ), to which other medications and non-medical interventions can be added as needed.[1,2] Various studies have shown that the combination of DMARDs such as hydroxychloroquine and SSZ is far more advantageous.[3]

Hydroxychloroquine may cause ocular toxicity, although this side effect is rare. Because hydroxychloroquine does not affect the bone marrow or liver, it is often considered to be the DMARD with minimum toxicity.[1,4] Unfortunately, hydroxychloroquine is not very potent, and its use as monotherapy is insufficient to control symptoms for most patients.[5]

SSZ is composed of sulphapyridine linked to 5-aminosalicylic acid (5-ASA) by an azo-band.[6] Whilst the mechanism of the effect of SSZ remains obscure, some studies have reported this drug to affect cell activity by changing folate metabolism.[1,4] 5-ASA provides the anti-inflammatory

[1]Department of Psychiatry, Medical Faculty,
[2]Medico-Social Center, Osmangazi University, Meselik-Eskisehir, Turkey.

Correspondence:
Unal Ayranci MD,
Medico-Social Center,
Osmangazi University,
Meselik-Eskisehir, Turkey
Tel: +90 222 2401817
Fax: +90 222 2370978
Email: unalayrancioglu@yahoo.com
Submitted: 29 March 2008
Revised: 26 July 2008
Accepted: 7 September 2008

properties of the drug. It exhibits a specific anti-rheumatoid effect that begins in such a relatively short time as 4 weeks in RA. No death or late adverse effects have been reported for this drug when used as an anti-rheumatoid agent. Although adverse reactions are seen mostly during the first 2 to 3 months, the unwanted effects may arise any time during the treatment.[4,6]

Chloroquine is a drug derived from quinine used commonly since World War II for the prophylaxis of malaria. In addition to being used for malaria, chloroquine is also used as a safe, inexpensive and well-tolerated agent in the treatment of chronic inflammatory diseases.[7] Adverse effects include gastrointestinal problems and less commonly, dermatologic reactions, blood dyscrasis, myopathy, neuropathy, cramp, anaphylactic shock, and central nerve system symptoms such as headache, vertigo, tinnitus, extrapyramidal syndrome.[7,8] Serious adverse effects such as acute psychosis have been reported to occur less commonly when the drug is used in standard anti-malarial doses.[7] To the best of our knowledge, recurrent psychosis due to chloroquine use has been reported only twice, in 1996 and 2007.[9,10]

The present case study reports a female patient diagnosed as having bipolar affective disorder (mixed episode). She had been prescribed chloroquine for 9 months. After being switched to combined chloroquine and SSZ, she began to develop serious adverse psychiatric reactions. Assuming that her psychiatric symptoms could be related with this combination therapy, the present study discusses this relationship in the frame of the medical literature.

Case Report

The patient was a 39-year-old female, married with two children, housewife, with education level of elementary school. The patient was referred to our University Emergency Clinic from the State Hospital Psychiatry Polyclinic due to psychiatric symptoms such as insomnia, increased energy, suicidal tendency, nervousness, feeling of lightning in the eyes, crying, feeling of sexual intercourse with someone while hearing the voice of this person, behavioral changes, mistaking people for each other, growing suspicious of others and excessive touchiness. Her psychiatric examination revealed that she was wide-awake and that her orientation and cooperation were good, though she spoke much faster than she was used to. Her affect was anxious. She had audial hallucinations and delusions of grandiose, persecutive, reference, and also erotomanic.

The patient's medical history showed that she had been diagnosed as having RA. She had the symptoms such as pain, edema, arthralgia, swelling, and burning 2 years before she developed the psychiatric symptoms. She had been prescribed 250 mg/day chloroquine for 9 months during which her RA complaints had disappeared without causing the psychiatric adverse effects. Once her symptoms had improved chloroquine was discontinued. After 3 months, the patient's RA related symptoms again had commenced, she applied to another rheumatologist and was prescribed methotrexate (MTX) 7.5 mg/week. After the patient had had the complaints of edema and swelling, the same rheumatologist assumed that MTX could have caused massive edema and discontinued the drug. The rheumatologist had taken into account that RA complaints include arthralgia and nodule subsided, and proposed that the patient should take a non-steroidal anti-inflammatory drug (NSAID) when she suffered from the pain. The patient was followed with the NSAID for a certain while. However, she was admitted to the rheumatology clinic about 2 months ago once her arthritis, artralgia and nodule complaints relapsed. Having already benefited from chloroquine, she was given chloroquine 250 mg/day in addition to SSZ 2 gr/day. After she was prescribed SSZ in addition to chloroquine, her complaint increased. The patient had not had any mood disorder upon giving births to her children.

The patient had never experienced any psychiatric disorder before her psychiatric complaints arose. Also no family history of psychiatric disorders was found. She had not experienced medical conditions that might have caused psychiatric disorders. She had not used any steroids. Other systemic diseases, which could be related to psychiatric problems such as lupus, had been rule out before the diagnosis of RA was performed.

She had visited her rheumatologist 3 days after the emergence of her psychiatric symptoms. The rheumatologist had discontinued her RA drugs and referred her to our emergency department.

Her psychiatric examination and evaluation showed that inpatient treatment was necessary, although her family refused to authorize her being hospitalized in our inpatient clinic. For this reason, we started an outpatient treatment by prescribing Risperidone 2 mg/day and Ketiapin 200 mg/day, and asked her come to our clinic in 2 days for follow up. On follow up examination we realized that she had started using the drugs she was prescribed and her complaints were diminished significantly.

Interestingly, the patient and her family consented to her being hospitalized in our inpatient clinic, as both sides had become concerned about her health.

All laboratory tests, electroencephalogram (EEG) and brain computed tomography (CT) performed at the admission were normal. It was concluded that the anti-rheumatic drugs the patient was receiving, could be responsible for the psychiatric symptoms, since they disappeared upon the discontinuation of these drugs. By the 4th day of her inpatient treatment, symptoms had totally disappeared and she was discharged with the diagnosis of 'substance-induced mood disorder' according to DSM IV-TR.[11] She was visited at 15 days, 1 month, and 3 months during the follow-up period. It has been 6 months since she was discharged from our inpatient clinic and she has exhibited no psychiatric symptoms so far.

Discussion

After the patient started taking antipsychotic drugs, a rapid disappearance of severe psychiatric symptoms led us to conclude that this improvement might not be simply related to use of antipsychotic drugs upon the discontinuation of anti-rheumatic drugs. Also, neither the patient nor her family members had a history of psychiatric disorder. For these reasons, we considered a correlation between this interesting occasion and the anti-rheumatic drugs she used. With this in mind, we browsed through the literature and found two psychiatric cases in association with sulfaperason,[12,13] although the number of the psychiatric cases associated with chloroquine was much more.[7,8,14,15]

Most cases developing psychiatric symptoms have been reported to develop the symptoms 2 or 4 days after taking chloroquine between 2 and 6 gr. Such patients have been reported not to have had a psychiatric history before taking chloroquine, and their symptoms disappeared once the drug was discontinued.[15] No correlation has been found between the psychosis development and the age of the patients, nor has gender been shown to play a role in the development of psychiatric symptoms.[8] Whether toxic central nervous system effect is related to the dose and duration of treatment with chloroquine has yet to be determined. Toxic symptoms have been reported both with normal and high dosages.[8,14] Behavioral symptoms are observed approximately in 1-7 days. The shortest period reported is 2 hours and the longest period has been 40 days.[8] Duration of psychiatric disorder is variable and its relationship with blood/urine level of the drug is not yet ascertained.[8,14] Recuperation period of the reported cases has been shown to range between 3 days to a few months.[8,15] The reason for this, could be the slow elimination of chloroquine from the body through the urinary system in such a long period as 2 months.[8] Therapeutic index of chloroquine is narrow and its plasma concentration may fail to reflect brain concentration that is 10-30 times higher than that of plasma. This high concentration may cause adverse effects including psychiatric symptoms. The drug half-life can also account for the long-term psychiatric symptoms.[7]

Discontinuation of chloroquine during the treatment, initiation of antipsychotic drugs, and acidification of the urine by using vitamin C are among methods recently applied.[8] Sedatives including promethazine and diazepam have also been used in similar cases.[16]

Some manic episodes related to chloroquine have also reported, although small in number. Akhtar and Mukherjee reported long-term bipolar affective disorders and manic episodes.[15] These authors described the two sub-types of chloroquine-induced mania and reported that one of these sub-types matched with the criteria for substance-induced psychosis. They also added that this only persisted for a short time and disappeared once the drug was discontinued. On the other hand, they stated that the symptoms would relapse if the same drugs were used again. As to the other sub-type of mania, they suggested that mania was triggered by chloroquine and that it behaves as an ordinary emotional state disorder, and added that psychiatric symptoms not necessarily relapsed upon a second exposure to the drug.

Our literature review showed that only few cases have been reported to have developed psychotic symptoms or manic adverse effects due to SSZ, one of them developed depression while receiving SSZ for non-specific ulcerative colitis.[12] Another patient was a female patient who developed an acute psychosis while she was on SSZ for only 1 month due to psoriatic arthritis.[13]

Some cases of psychiatric disorder resulting from high doses of chloroquine (2-6 gr/day) have been previously reported.[9] Although some cases developed chloroquine-induced psychiatric symptoms for the first time they were given chloroquine, chloroquine-induced psychiatric symptoms did not develop when chloroquine was started again.[15] Our case is one of its kinds that developed psychiatric symptoms upon using chloroquine for the second time after having used it for a long time previously. It should be considered that the half-life of chloroquine and the long period necessary to disappear its

effects can decrease the possibility of causing mood disorder by chloroquine.

Regarding our case, we concluded that her psychiatric symptoms could well be due to SSZ, given that emergence of the symptoms consistent with the data on the adverse effects of SSZ are seen in the first 2-3 months. However, the simultaneous withdrawal of the drugs makes it hard for us to decide which one could have induced the symptoms. Another possibility seems to be that the combination of chloroquine and SSZ could account for the emergence of psychiatric symptoms. However, further case studies are needed to confirm our conclusions as well as to identify the exact mechanism of chloroquine plus sulfasalazine-induced psychiatric symptoms.

Conflict of Interest: None declared

References

1 Simon LS. The Treatment of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2004; 18: 507-38.

2 Guidelines for the management of rheumatoid arthritis: 2002 update. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. *Arthritis Rheum* 2002; 46: 328-46.

3 Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2005; 19: 163-77.

4 Gul A. Sulfasalazine. In: Karaaslan Y, editor. Klinik Romatoloji. Ankara: Hekimler Yayin Birligi, 1996. p. 334-5.

5 Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 1449-61.

6 Russinko PJ, Agarwal S, Choi MJ, Kelty PJ. Obstructive nephropaty secondary to sulfasalazine calculi. *Urology* 2003; 62: 748.

7 Telgt DS, van der Ven AJ, Schimmer B, et al. Serious psychiatrric symptoms after chloroquine treatment following experimental malaria infection. *Ann Pharmacother* 2005; 39: 551-4.

8 Garg P, Mody P, Lall KB. Toxic psychosis due to chloroquine-not uncommon in children. *Clin Pediatr (Phila)* 1990; 29: 448-50.

9 Bhatia MS. Chloroquine-induced recurrent psychosis (brief report). *Indian J Med Sci* 1996; 50: 302-4.

10 Sahoo S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. *Am J Ther* 2007; 14: 406-7.

11 Akiskal HS. Mood Disorders. Clinical Features. In: Sadock BJ, Sadock VA, editors. Comprehensive Texbook of Psychiatry. Philadelphia: Lippincott Williams & Wilkins, 2005. p. 1627.

12 Rebrov VG, Lukomskiĭ MI. A case of depression in the treatment of nonspecific ulcerative colitis with sulfasalazine. *Klin Med (Mosk)* 1989; 67: 106.

13 Jajić Z, Jajić I. Acute psychoses in patients with psoriatic arthritis during treatment with sulfasalazine. *Reumatizam* 1998; 46: 43-4.

14 Garg P, Mody P, Lall KB. Toxic psychosis due to chloroquine. *Indian J Pediatr* 1990; 57: 133-4.

15 Akhtar S, Mukherjee S. Chloroquine induced mania. *Int J Psychiatry Med* 1993; 23: 349-56.

16 Halder D, Nagpaul I, Patwari AK, Mullick DN. Chloroquine psychosis. *Indian J Pediatr* 1988; 55: 983-5.