Sultan Qaboos University Med J, August 2013, Vol. 13, Iss. 3, pp. E476-478, Epub. 25th Jun 13
Submitted 4th May 12
Revision Req 25th Nov 12; Revision Recd. 22nd Dec 12
Accepted 21st Jan 13

ONLINE CASE REPORT

Chloroquine-induced Acute Dystonic Reactions after a Standard Therapeutic Dose for Uncomplicated Malaria

*Olusegun A. Busari,[1] Joseph Fadare,[1] Segun Agboola,[2] Olusegun Gabriel,[2] Olayide Elegbede,[2] Yusuf Oladosu[2]

تفاعل خلل التوتُّر العضلي الحاد بعد جرعة قياسية للكلوروكين لعلاج الملاريا غير المعقدة

أولوسيجون بوساري، جوزيف فادير، سيغان اجبولا، اولوسيجون جبرائيل، أولايد اليجبيد، يوسف أولادوسو

الملخص: تفاعل خلل التوتُّر العضلي الحاد هو من الآثار خارج الهرمية التي تحدث عادة بعد استخدام مجموعة متنوعة من الأدوية أو العوامل المثيرة للتوتر غير أدوية الذهان.هنا نعرض حالة رجل يبلغ من العمر 54 عاما نقل إلى المستشفى بعد 10 ساعات من ارتعاش العضلات حول العينين والوجه والرقبة بعد تناول الجرعة الأولى عن طريق الفم من فوسفات الكلوروكين (1 غم [600 ملغ]) وصفت لعلاج الملاريا الغير معقدة. أعطي المريض الديازيبام في الوريد (10 ملغ) تلتها 10 ملغ من الديازيبام عن طريق الفم 3 مرات في اليوم. تحسّنت الأعراض في غضون 30 دقيقة من العلاج، وخرج المريض بعد 14 ساعة بعد الشفاء الكامل.

مفتاح الكلمات: رد فعل؛ خلل التوتُّر العضلي الحاد؛ الملا ريا؛ الكلوروكين؛ التناول عن طريق الفم؛ تقرير حالة؛ نيجيريا.

ABSTRACT: Acute dystonic reactions (ADR) are extrapyramidal effects that usually occur after the initiation of a wide variety of drugs or triggering factors besides neuroleptics. We report the case of a 54-year-old man who was admitted with an approximately 10-hour history of muscle twitching around the eyes, face and neck after he took the first dose of oral chloroquine phosphate (1 g [600 mg base]) prescribed for uncomplicated malaria. He was given intravenous diazepam (10 mg statum) followed by 10 mg of oral diazepam 3 times a day. The symptoms improved within 30 minutes of treatment, and he was discharged 14 hours later after a complete recovery.

Keywords: Dystonia; Reactions, acute; Malaria; Chloroquine; Administration, Oral; Case Report; Nigeria.

Acute dystonic reactions (ADR) are extrapyramidal side effects (EPSE) that usually occur after the initiation or a rapid increase in the dose of neuroleptic drugs.[1] However, the reactions may occur with a wide variety of drugs or triggering factors besides neuroleptics.[2,3] ADRs are characterised by the intermittent spasmodic or sustained involuntary contractions of muscles in the face, neck, trunk, pelvis and extremities.[4] They are often not life-threatening, but can cause great discomfort, producing significant anxiety and distress for patients, and may seriously disturb the relationship between the doctor and the patient.[5]

Chloroquine (CQ), a 4-aminoquinoline drug used for both the prevention and treatment of malaria, was discovered in 1934 and introduced into clinical practice in 1947.[5] It has been largely replaced by the newer artemisinin-based combination therapy (ACT) as the first line of treatment for uncomplicated malaria due to *Plasmodium falciparum*. This is because of the emergence and spread of resistant strains through East and West Africa, Southeast Asia, and South America.[5–8] However, in some African countries there have been reports of a rapid decline in the frequency of resistance to CQ after its withdrawal, to the point where the drug is now once again considered to be effective.[9–11] Thus, CQ still remains a frequently used drug in the treatment of uncomplicated malaria in sub-Saharan Africa. Given its low cost and wide availability, its occasional use in some autoimmune disorders, and current evaluation for new potential utilisations, CQ may remain in clinical use for a long time.[12–14]

Extrapyramidal syndrome (EPS) following CQ therapy has been reported in the past.[15,16] However,

Departments of [1]Internal Medicine and [2]Family Medicine, Federal Medical Centre, Ido-Ekiti, Nigeria
**Corresponding Author e-mail: olubusari@yahoo.com*

in our setting, CQ-induced ADR is very rare. This case report describes an occurrence of ADR in a middle-aged man after commencing a standard dose of oral CQ phosphate for parasitologically-confirmed uncomplicated malaria.

Case Report

A 54-year old man was brought to the emergency room (ER) of the Federal Medical Centre, Ido-Ekiti, Nigeria, with a complaint of involuntary muscle twitching around the eyes, face and neck which had started approximately 10 hours prior to presentation. He was experiencing difficulty in speaking and an abnormal posturing of the neck. There was no fever, dizziness, altered consciousness, photophobia or weakness of the limbs. He had been diagnosed with parasitologically-confirmed uncomplicated malaria about 18 hours previously and had immediately been given oral CQ phosphate BP (1 g CQ phosphate [600 mg base]) to be followed by 500 mg (300 mg base) at 6, 24 and 48 hours. The presenting complaint had started within 8 hours of the first dose of CQ. He was not on any other drugs, food or herbal preparations. There was no past history of similar complaints or of any transient ischaemic attack, and he had neither a family history of dystonia nor a history of alcohol ingestion, cigarette smoking or use of illicit drugs such as cocaine.

A general examination revealed an anxious middle-aged man with facial muscle twitching and facial grimace. Other aspects of the general examination were unremarkable. A central nervous system examination showed a fully-conscious man who was well-oriented in time, place and person. There were neither signs of meningeal irritation nor asterixis. There was no cognitive impairment and no cranial nerve palsy. Deep tendon reflexes and tones were also normal. All other systems were grossly normal. All baseline investigations, which included complete blood counts, serum electrolytes, urea and basic urea nitrogen, liver enzymes and function tests, random and fasting blood glucose, and a serum lipid profile, were within normal limits. His resting electrocardiogram was also normal. A peripheral blood smear study for malaria parasites by light microscopy of thick and thin stained blood showed trophozoite and schizont forms of *P. falciparum*.

A clinical diagnosis of ADR secondary to CQ was made. The drug was discontinued and the patient was treated with intravenous diazepam (10 mg statum followed by 10 mg oral diazepam three times a day). An intravenous access line was also secured and a maintenance dose of an intravenous infusion of isotonic saline was administered. The symptoms improved rapidly within 30 minutes of commencing treatment and the patient was discharged after about 14 hours of admission with complete recovery. He remained well at follow-up one week later.

Discussion

The therapeutic index for CQ is small.[17] However, at a standard dose for malaria treatment, the common adverse effects include gastrointestinal problems, headaches, nightmares, blurring of vision and itching. An ADR due to the use of CQ is very rare and there is a paucity of data on it in the literature.[18] Achumba *et al.* reported a case of ADR after a single dose of CQ in a postoperative patient and in the presence of metronidazole.[19] The reported case suggested that the ADR might have been an idiosyncratic reaction and probably potentiated by the metronidazole. In our case, the ADR also occurred after a single dose of CQ but in the absence of any other medications. Although ADRs occasionally are dose-related, they are more often idiosyncratic and unpredictable.[19]

For most drugs that often cause ADR, particularly the neuroleptics, the pathophysiology is a drug-induced alteration of dopaminergic-cholinergic balance in the *nigrostriatum*. They produce ADR by a nigrostriatal dopamine D2 receptor blockade, which results in an excess of striatal cholinergic output.[20] The pathophysiological mechanism underlying CQ-associated ADR is not well-known. However, it has been linked to a reduction in forebrain catecholamine levels and an inhibition of neuronal calcium uptake.[19] This hypothesis could be supported in part by the effectiveness of benzodiazepines in the reversal of CQ-associated ADR. A normal balance between dopamine and acetylcholine in the basal ganglia involves modulation from gamma aminobutyric acid (GABA)-containing striatonigral neurons. GABA-ergic neurons are inhibitory and antagonise excitatory dopaminergic neurons. Stimulation of

the benzodiazepine receptors coupled to GABA receptors via the chloride ion channel in the central nervous system facilitate GABA transmission with a consequent inhibitory effect of muscle hypertonia and tremors.[19–22]

Conclusion

Although CQ-induced ADR is a very rare adverse effect, it can be confused with other medical conditions in the ER such as a seizure disorder or a transient ischaemic attack. A detailed history-taking remains pivotal, particularly the medication history, which should be obtained from others if the patient is not able to speak. ADRs occur very rarely in CQ use; thus, its prophylaxis is unnecessary and also not feasible. However, the treatment is usually straightforward and nearly always effective.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 9th ed. Washington, DC: American Psychiatric Association, 1991.
2. Oo MT. Acute dystonic reactions in a lady presenting with repetitive involuntary muscle twitching: A case report. Cases J 2009; 2:186.
3. Fadare JO, Owolabi LF. Carbamazepine-induced dystonia. A case report. Neurol Asia 2009; 14:160–5.
4. Fahn S. The varied clinical expression of dystonia. Neurol Clin 1984; 2:541–54.
5. Casey DE. Neuroleptic induced acute dystonia. In: Lang AE, Weiner WJ, Eds. Drug-Induced Movement Disorder. Mount Kisco, New York: Futura Pub. Co., 1992. Pp. 21–40.
6. Centre for Disease Control and Prevention. Malaria. From: www.cdc.gov/malaria Accessed: Aug 2011.
7. Martin RE, Marchetti RV, Cowan AL, Howitt SM, Broer SA, Kirk K. Chloroquine transport via the malaria parasite's chloroquine resistance transporter. Science 2009; 325:1680–2.
8. Tripathi KD. Essentials of Medical Pharmacology. 5th ed. Delhi: Jaypee Medical Publishers, 2003. Pp. 739–40.
9. Mwai L, Ochong E, Abdirahman A, Kiara SM, Ward S, Kokwaro G, et al. Chloroquine resistance before and after its withdrawal in Kenya. Malaria J 2009; 8:106.
10. Kublin JG, Cortese JF, Njunju EM, Mukadam RA, Wirima JJ, Kazembe PN, et al. Re-emergence of chloroquine sensitive Plasmodium falciparum malaria after cessation of chloroquine use in Malawi. J Infect Dis 2003; 187:1870–5.
11. Lacifer MK, Thesing PC, Eddington NO, Masonga R, Dzinjalamala FK, Takala SL, et al. Return of chloroquine antimalaria efficacy in Malawi. N Engl J Med 2006; 355:1959–66.
12. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases? Lancet Infect Dis 2003; 3:722–7.
13. Savarino A, Lucia MB, Giordano F, Cauda R. Risks and benefits of chloroquine use in anticancer strategies. Lancet Oncol 2006; 7:792–3.
14. Sotelo J, Briceno E, Lopez-Gonzalez MA. Adding chloroquine to conventional treatment for glioblastoma multiforme: A randomised, double blind, placebo controlled trial. Ann Intern Med 2006; 144:337–43.
15. Singhi S, Singhi P, Singhi M. Extrapyramidal syndrome following chloroquine therapy. Indian J Paediatr 1979; 46:58–60.
16. Joseph V, Varma M, Vidhyasagar S, Mathew A. Comparison of the clinical profile and complications of mixed malarial infections of Plasmodium falciparum and Plasmodium vivax versus Plasmodium falciparum mono-infection. Sultan Qaboos Univ Med J 2011; 11:377–82.
17. Cann HM, Verhulst HL. Fatal acute chloroquine poisoning in children. Paediatrics 1961; 27:95–102.
18. Lange AE. Miscellaneous drug induced movement disorders. In: Lange AE, Weiner WJ, Eds. Drug-induced Movement Disorders. Mount Kisco, New York: Futura Pub. Co., 1992. Pp. 339–81.
19. Achumba JI, Ette EI, Thomas WO, Essien EE. Chloroquine-induced acute dystonic reactions in the presence of metronidazole. Drug Intell Pharma 1988; 22:308–10.
20. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side effects of neuroleptic drugs. Psychol Med 1980; 10:55–72.
21. Adjei GO, Goka BQ, Rodrigues OP, Hoegberg LCG, Alifrangis M, Kurtzhals JAL. Amodiaquine-associated adverse effects after inadvertent overdose and after a standard therapeutic dose. Ghana Med J 2009; 43:135–8.
22. McCormick MA, Manoguerra AS. Dystonic reaction. In: Harwood-Nuss A, Linden CH, Luten RC, et al, Eds. Clinical Practice of Emergency Medicine. Philadelphia: Lippincott Williams & Wilkins, 1991. Pp. 510–11.