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Use of anti-malarial drugs and the risk of developing eye disorders☆

Cornelia Schneider [a], Miriam Adamcova [b], Susan S. Jick [c], Patricia Schlagenhauf [d], Mary K. Miller [e], Hans-Georg Rhein [b], Christoph R. Meier [a,c,f,*]

[a] *Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University Basel, Basel, Switzerland*
[b] *Safety Risk Management, F. Hoffmann-La Roche Ltd., Basel, Switzerland*
[c] *Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA, USA*
[d] *University of Zuerich Centre for Travel Medicine, Institute for Social and Preventive Medicine, Zuerich, Switzerland*
[e] *Department of Epidemiology, Genentech Inc., South San Francisco, USA*
[f] *Hospital Pharmacy, University Hospital Basel, Basel, Switzerland*

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Summary *Background:* Ocular toxicity was described in the late 1950s for some anti-malarial drugs, but only limited information is available on the comparison of ocular toxicity of different anti-malarials.
Methods: We conducted a follow-up study with a nested case-control analysis using the General Practice Research Database to compare the risk of developing a first-time diagnosis of an eye disorder during exposure of mefloquine, chloroquine and/or proguanil or atovaquone/proguanil use to non-users. We calculated incidence rates with 95% confidence intervals (CI) and odds ratios using multivariate conditional logistic regression analyses.
Results: We included 83,148 patients and identified 652 cases with an incident eye disorder. The incidence rates with 95% CI of all eye disorders combined in users of mefloquine, chloroquine and/or proguanil, atovaquone/proguanil or travellers not using anti-malarials were 5.3 (4.3–6.5), 7.1 (5.0–9.9), 6.3 (5.6–7.2) and 5.1 (4.6–5.7), per 1000 person-years, respectively. As compared to non-users of anti-malarials, the adjusted odds ratio with 95% CI in the nested

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* Corresponding author. Basel Pharmacoepidemiology Unit, Hospital Pharmacy, University Hospital Basel, Spitalstrasse 26, CH-4031 Basel, Switzerland. Tel.: +41 61 556 53 69; fax: +41 61 265 88 70.
E-mail addresses: schneiderc@uhbs.ch (C. Schneider), miriam.adamcova@roche.com (M. Adamcova), sjick@bu.edu (S.S. Jick), pat@ifspm.uzh.ch (P. Schlagenhauf), miller.katie@gene.com (M.K. Miller), hans-georg.rhein@roche.com (H.-G. Rhein), meierch@uhbs.ch, christoph.meier@usb.ch (C.R. Meier).

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case-control analysis for users of mefloquine, chloroquine and/or proguanil, or atovaquone/proguanil were 1.33 (1.01—1.75), 1.61 (1.06—2.45), and 1.25 (1.03—1.52), respectively.
Conclusions: The study provides evidence that there was an increased risk of eye disorders in users of all anti-malarials compared to non-users of anti-malarials.

Malaria is still an important cause of morbidity and mortality worldwide; the greatest burden is in children in sub-Saharan Africa [1,2]. It is, however, also an important cause of serious illness in returning travellers [3—6]. Most travellers develop clinical malaria because they did not adhere to personal protection measures and/or chemoprophylactic regimens [3]. Experience with, or fear of, adverse events are possible reasons why patients do not adhere to chemoprophylaxis [7]. Adverse events associated with the use of anti-malarials include (but are not limited to) nausea, pruritus, cardiac arrhythmias, anaemia, ocular disorders and psychogenic effects [8,9]. The adverse event profile varies for different anti-malarial drugs and is influenced by factors such as comorbidities, gender, dosage and duration of use.

Ocular toxicity was described as early as the 1950s for some anti-malarial drugs [10]. In users of chloroquine or hydroxychloroquine early retinopathy was estimated to occur in 10% or 2.7% of users, respectively [8,11]. The mechanism of anti-malarial drug associated ocular toxicity is not well understood. Anti-malarials seem to accumulate in the retina and in melanin-rich tissues. They may also have an effect on the metabolism of retinal cells. Photochemical activation at different wavelengths may explain some of the toxic variability of anti-malarial drugs. In contrast to amodiaquine, quinacrine or primaquine, mefloquine does not absorb wavelengths greater than 400 nm, which is the shortest wavelength transmitted through the cornea of adult eyes [12].

Eye disorders during or after use of mefloquine, which shares some structural similarities with other anti-malarials, have been reported. Mefloquine use has been associated with the occurrence of isolated cases of bilateral pigment changes in the retinal pigment epithelium of the macula [13] and bilateral enlarged blind spots [14]. In a study evaluating the safety of mefloquine malaria prophylaxis in 1876 Japanese soldiers, there was one report of optic neuritis [15]. It is unclear whether this case report referred to a causal association or not. Formal studies investigating this association are lacking.

This study aims to assess the risk of developing a first-time diagnosis of any eye disorder (including blindness) affecting the cornea, lens, uvea, iris, retina (mainly the macula and the optic nerve) or other parts of the eye, or the risk of developing a first-time diagnosis of glaucoma associated with use of mefloquine for malaria prophylaxis, and to compare this risk to users of chloroquine and/or proguanil, atovaquone/proguanil, as well as to a comparison group of patients not exposed to anti-malarial drugs.

Methods

Data source

We conducted a follow-up study with a person-time analysis and a nested case-control analysis using data from the General Practice Research Database (GPRD). The GPRD is a large UK-based database which encompasses some seven million people who are enrolled with selected general practitioners (GPs), as described in detail elsewhere [16—18]. GPs record medical information in a standard manner and supply it anonymously. The recorded information includes age and sex, year of birth and practice location, medical diagnoses (based on 'Read' codes), and all drug prescriptions, containing the name of the preparation, route of administration, dose, and number of tablets for each prescription. The recorded information on drug exposure and diagnoses in the GPRD has been validated and proven to be of high quality [19]. For confidentiality reasons, the information is strictly anonymous. This study was approved by ISAC, the Independent Scientific Advisory Committee for the GPRD.

Study design

Definition of the study population

We identified in the GPRD all patients who had one or more prescriptions recorded for mefloquine, chloroquine and/or proguanil or atovaquone/proguanil at some time between January 1, 2001 and October 1, 2009 and who had in addition a pre-travel consultation within 1 week of the prescription. The start of follow-up for our analyses was the date when the patient received the first prescription. In addition we identified at random a comparison group of patients who had not been exposed to any anti-malarial drug but had a pre-travel consultation. Their start of follow-up was the date when they had their first pre-travel consultation during the study period. One such non-user was matched to one user on age, sex, and general practice.

As anti-malarial drugs can be used for malaria prophylaxis, for the treatment of an acute malaria infection, or for stand-by emergency treatment (i.e. the patient gets a prescription but takes the drug only in case high fever of unknown origin develops at the travel destination), we identified those subjects who received a prescription for one or more of these anti-malarial drugs of interest for malaria prophylaxis as the most likely indication. We did this by requiring that the GP recorded — within a week of the prescription for the anti-malarial drug — a specific code indicating that the person received the prescription most likely for malaria prophylaxis, such as "travel advice" or "prophylactic drug use". Furthermore, individuals had to have at least 12 months of information on drugs prescribed and medical diagnoses recorded on computer by their GP before the date of first prescription for a study drug. In addition, subjects had to have some recorded activity (diagnoses or drug prescriptions) at any time after the prescription for an anti-malarial drug to make sure that we only included subjects whose outcome events would be captured in the patients' medical records because they returned to the UK.