Severe Mucocutaneous Necrotizing Vasculitis Associated with the Combination of Chloroquine and Proguanil

Minh Son Luong[1], Didier Bessis[1], Nadia Raison-Peyron[1], Véronique Pinzani[2], Jean-Jacques Guilhou[1] and Bernard Guillot[1]

Departments of [1]Dermatology-Phlebology and [2]Pharmacovigilance, CHU Montpellier, Hôpital Saint-Eloi, 80 avenue Augustin Fliche, 34295 Montpellier cedex 5, France. E-mail: d-bessis@chu-montpellier.fr

Accepted September 10, 2002.

Sir,

The combination of chloroquine, an amino-4-quinoleine, and proguanil, a biguanide derivative, is widely used for antimalarial prophylaxis by travellers in countries of high endemic prevalence of *Plasmodium falciparum* chloroquino-resistance (1).

Among numerous adverse effects of these two drugs, vascular purpura due to chloroquine has been mentioned only once (2). Since then, no case report of vasculitis induced by proguanil or chloroquine has ever been published. We report a case of severe cutaneous necrotizing vasculitis induced by Savarine®, (AstraZeneca, Rueil-Malmaison, France) a combination of chloroquine and proguanil.

CASE REPORT AND DISCUSSION

A 49-year-old man, with no notable medical history, was referred because of a generalized eruption occurring after 13 days of treatment with Savarine®, 200 mg of proguanil and 100 mg of chloroquine daily. The patient denied intake of any other medication. Clinical examination showed diffuse painful purpuric and extensive necrotizing plaques, localized mainly on the upper and lower limbs, with a particular acral distribution involving the hands and feet. Purpuric petechial macules were present on the hard palate associated with an aphthoid ulcer of the tip of the tongue. Widespread maculo-papular erythema on the trunk was also noted. General condition was conserved, with no fever or organomegaly. Laboratory investigations disclosed hypereosinophilia ($0.720 \times 10^9\ l^{-1}$), a high rate of C–reactive protein ($133\ mg\ l^{-1}$). Routine coagulation investigations, antithrombin III, protein C and protein S levels, activated protein C resistance, factor V Leiden, prothrombin 20210A allele, anti-nuclear antibody, anti-neutrophilic cytoplasmic antibody, rheumatoid factor, complement, cryoglobulinaemia, lupic anticoagulant, anticardiolipines and anti-beta 2 glycoprotein 1 IgG and IgM were normal or absent. Hepatitis B and C serologies were negative, whereas Epstein-Barr virus, cytomegalovirus and parvovirus B19 serologies demonstrated a former immunization. Renal and hepatic function, and serumcalcium and phosphor were normal. A skin biopsy showed normal epidermis and dermal leucocytoclasic vasculitis with erythrocyte extravasation. Direct immunofluorescence of a purpuric lesion was negative. Three weeks after withdrawal of Savarine®, the cutaneous lesions resolved dramatically, marked by post-necrotizing ulceration followed by complete re-epithelialization under topical treatment including sulfadiazine (Flammazine®, Solvay Pharma, Suresnes, France).

Epicutaneous tests were performed 3 months later, with Savarine®, chloroquine (Nivaquine®, Laboratoire Aventis, Paris, France), quinine, proguanil (Paludrine®, AstraZeneca, Rueil-Malmaison, France) and metformine (Stagid®, Lipha Santé, Lyon, France), another biguanide derivative. These molecules were tested directly and diluted at 10% and 30% in vaseline. Chloroquine and Savarine® at 30% concentration induced local erythemato-vesiculous lesions at 48 h and 72 h, respectively. Tests with quinine, proguanil and metformine remained negative. Skin biopsies of two positive test sites showed eczematous features.

We postulate that this case of necrotizing vasculitis was induced by Savarine® prophylaxis because of the chronology, the semiology and the lack of other causes of necrotizing vasculitis. The causative drug is most likely chloroquine according to the epicutaneous tests result, even though it did not show the same histologic pattern of vasculitis. An interaction between the two drugs in the preparation of Savarine® could also be possible. Numerous side effects of chloroquine and proguanil associated or each one alone has already been reported: pruritus, urticaria, angioneurotic oedema, multiforme erythema, Stevens-Johnson syndrome and, more recently, acute generalized exanthematous pustulosis (3, 4). Exfoliative dermatitis has been described with these two drugs used alone but not with the association. Moreover, chloroquine is a well-known inducer of mucous and nail pigmentation, psoriasis exacerbation and photosensitivity. Our observation reports the first case of severe mucocutaneous necrotizing vasculitis after antimalarial prophylaxis by Savarine.

REFERENCES

1. Bradley DJ, Warhurst DC. Malaria prophylaxis: guidelines for travellers from Britain. BMJ 1995; 310: 709–714.
2. Schindel L. Antiprotozoal drugs. In: Meyer L, Herxheimer A, editors. Side effects of drugs, 6th edn. Amsterdam: Excerpta Medica, 1968: 320–326.
3. Janier M, Froidevaux D, Lons-Danic D, Daniel F. Acute generalized exanthematous pustulosis due to the combination of chloroquine and proguanil. Dermatology 1998; 196: 271.
4. Cipriano G, Djossou F, Sibaud V, Geniaux M, Malvy D, Le Bras M, Taieb A. Severe skin disease induced by a chloroquine-proguanil combination. Thérapie 2001; 56: 59–61.

 ISSN 0001-5555