Relationship between blood hydroxychloroquine and desethylchloroquine concentrations and cigarette smoking in treated patients with connective tissue diseases

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Ann Rheum Dis 2007;**66**:1547–1548. doi: 10.1136/ard.2007.072587

Cigarette smoking has been suspected to increase the risk and the activity of systemic lupus erythematosus (SLE)[1 2] and cutaneous lupus.[3 4] Some data indicate that cigarette smoking might interfere with the effectiveness of hydroxychloroquine and chloroquine in cutaneous lupus.[3 4] As these antimalarial agents are partly metabolised via the cytochrome P450 enzyme system and as the constituents of cigarette smoke are known potent inducers of cytochrome P450, it has been hypothesised that the resistance of cutaneous lupus might be explained by a modification of the metabolism of these drugs.[3 4]

Hydroxychloroquine levels can be quantified by high-performance liquid chromatography. We have recently established that low blood hydroxychloroquine concentrations are associated with SLE disease activity, are a strong predictor of exacerbations,[5] and may help to diagnose poor adherence.[6] We investigated for the first time the relationship between cigarette smoking and blood hydroxychloroquine and desethylchloroquine (hydroxychloroquine metabolite) concentrations.

The study included 223 unselected, non-pregnant patients, routinely followed in Pitié-Salpêtrière Hospital, treated with 400 mg/day hydroxychloroquine sulphate (Plaquenil; Sanofi-Aventis, France) for at least six months. The indication for treatment with hydroxychloroquine was SLE (n = 176) or other connective tissue disease (n = 47). All patients provided written informed consent. Patients with a history of non-compliance were excluded.[6] Hydroxychloroquine and desethylchloroquine concentrations were measured in whole blood by high-performance liquid chromatography with fluorometric detection.[6] Smokers and non-smokers were compared by Student's *t*-test for continuous variables and chi-square test for categorical variables.

Fifty-four patients (24%) were active smokers with a mean number of 13 ± 8 cigarettes per day and 169 had not smoked for at least six months. Table 1 reports their characteristics. The mean blood hydroxychloroquine concentration was very similar between active smokers (1109 ± 511 ng/ml) and non-smokers (1064 ± 464 ng/ml; p = 0.55). No differences were seen between both groups for the mean blood desethylchloroquine concentration and the mean hydroxychloroquine/desethylchloroquine ratio. When heavy smokers (⩾10 cigarettes/day) were compared with non-smokers, we found a slightly higher desethylchloroquine level in heavy smokers, but hydroxychloroquine and the hydroxychloroquine/desethylchloroquine ratio remained similar between both groups (data not shown). Among smokers, no

Table 1 Demographic and clinical characteristics of the patients, according to smoking status

	Active smokers	Non-smokers	p
No. of patients (%)	54 (24)	169 (76)	
Age (years)	37.3 (9.8)	37.8 (12.9)	0.81
Female, n (%)	47 (87)	153 (90)	0.46
Mean number of cigarettes/day [range]	13 (8 (3–40))	0	
Mean body weight (kg)	62 (14)	64 (12)	0.52
Estimated creatinine clearance (ml/min)	86 (28)	88 (25)	0.69
Connective tissue diseases, n (%)			
SLE (%)	38 (70)	138 (82)	
Other (%)	16 (30)	31 (18)	0.11
Treatments			
Mean daily dose of hydroxychloroquine (mg/kg a day)	6.69 (1.43)	6.48 (1.16)	0.27
Prednisone therapy			
No. of patients (%)	26 (48)	116 (69)	0.06
Dose (mg/day)*	12 (10)	11 (9)	0.57
Immunosuppressive treatment (%)†	3 (6)	25 (15)	0.10
Use of known inhibitor of CYP (%)‡	11 (20)	36 (21)	0.99
Use of known inducer of CYP (%)§	1 (2)	1 (1)	0.43
Mean hydroxychloroquine concentration (ng/ml)	1109 (511)	1064 (464)	0.55
(range)	(299–2512)	(205–2629)	
Mean desethylchloroquine concentration (ng/ml)	175 (78)	155 (66)	0.06
(range)	(38–380)	(17–404)	
Ratio (hydroxychloroquine/desethylchloroquine)	6.75 (2.5)	7.2 (2.5)	0.25

CYP, cytochrome P450; SLE, systemic lupus erythematosus.
*Mean ± SD doses of steroids calculated among patients taking steroids.
†For non-smokers, immunosuppressive treatments were azathioprine (n = 14), cyclophosphamide (n = 8), mycophenolate mofetil (n = 3). For smokers, immunosuppressive treatments were azathioprine (n = 1) and cyclophosphamide (n = 2).
‡Known inhibitors of cytochrome P450 were calcium antagonists, serotonin re-uptake inhibitors, fluconazole.
§Known inducers of cytochrome P450 were carbamazepine and rifampicin.
Creatinine clearance was estimated using the Cockcroft–Gault formula. Plus–minus values are mean ± SD.

correlation was found between the number of cigarettes and the blood hydroxychloroquine concentrations ($R^2 = 0.09$). Finally, no more differences were observed between smokers and non-smokers when the analyses were restricted to SLE patients.

Our results regarding blood hydroxychloroquine and desethylchloroquine concentrations in 223 treated patients did not show any significant relationship between cigarette smoking and hydroxychloroquine or desethylchloroquine concentrations. This is a strong argument against a direct effect of smoking on hydroxychloroquine metabolism. Another mechanism of interaction (as a modification of the lysosomal accumulation of antimalarial agents) or a direct deleterious effect of smoking on cutaneous lesions seems more likely.

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Accepted 30 April 2007

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CORRECTIONS

doi: 10.1136/ard.2006.062760.corr1

The affiliation of Tore Saxne was inadvertently omitted from an article in the October issue (Askling J, Fored CM, Brandt L, *et* al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis* 2007;**66**:1339–44). He is affiliated to the Department of Rheumatology, Lund University, Lund, Sweden.

doi: 10.1136/ard.2006.063230.corr1

The affiliations of Karina de Leeuw, Miek van Leeuwen and Marc Bijl were inadvertently omitted from an article in the October issue (van Rossum AP, Huitema MG, Limburg PC, Stegeman CA, de Leeuw K, van Leeuwen. MA, Bijl M, Kallenberg CGM. Standardised assessment of membrane proteinase 3 expression. Analysis in ANCA-associated vasculitis and controls. *Ann Rheum Dis* 2007;**66**:1350–5). They are all affiliated to the Department of Rheumatology and Clinical Immunology, Groningen University Medial Centre, University of Groningen, The Netherlands.