Letters to the Editors

Angioedema and cough in Nigerian patients receiving ACE inhibitors

We read with interest the article of Gibbs *et al*. [1] published in the British Journal of Clinical Pharmacology, indicating a higher incidence of the potentially fatal angioedema in patients of black or Afro-Carribean descent in the Birmingham University teaching hospital. This report is in accord with an earlier finding of a high relative risk of 4.5 for angioedema, among African–Americans in comparison with white patients in the United States [2]. If a racially determined risk is being proposed, then the incidence of angioedema in a homogenously negroid population needs be determined. However, little information is available in indigenous Africans about these adverse effects.

We have employed ACE inhibitors, captopril, enalapril and lisinopril in the treatment of cardiovascular and renal diseases and monitored adverse reactions to the agents since 1988, and our experience in this predominantly indigenous negroid population, is somewhat different from the earlier reports [1, 2]. At the Obafemi Awolowo University Teaching hospitals complex, Ile-Ife, Nigeria, adverse drug reactions are routinely monitored, reported and recorded. In a prospective study of adverse reactions to ACE inhibitors, captopril and enalapril in 100 patients receiving the medications, the incidence of ACE-inhibitor induced cough was 27%, exhibited a significant ($P < 0.001$) 3:1 female preponderance (48% in females and 16% in males), but no cases of angioedema were found [3]. A similarly high incidence of cough of 27–30%, was found in other controlled studies [4]. The most severe coughing requiring drug withdrawal was seen in four post menopausal women aged 60 ± 4 years, leading to a 4% drug-withdrawal rate [3]. In a 10-year review of 369 in-patients and ambulatory patients treated between 1989 and 1998, with a calculated 1200 patient-years of ACE inhibitor use, two cases of angioedema were seen. This represents an 0.54% incidence rate. One case was an 18-year-old boy with congestive heart failure, secondary to endomyocardial fibrosis who developed palmo-plantar blisters and pruritus, but no laryngospasm, after 3 months of enalapril 5 mg daily. He responded to a dose reduction to 2.5 mg daily, but was lost to follow up. The other case was a postmenopausal woman, who developed severe cough, wheezing, tongue and lip swelling, following 4 weeks of captopril 25 mg daily for hypertensive heart failure. Neither of the cases was life-threatening, and the woman responded to temporary captopril withdrawal and to nightly, oral hyoscine butylbromide [5].

Thus, the incidence of cough of 27% in black Africans [3, 4] is somewhat higher than the rates of 5–16% reported in Caucasians [6].The incidence of two proven cases of nonfatal angioedema in our cohort with 1,200 patient-years of ACE inhibitor use, represents a prevalence of 1.6/1000 patient-years which is lower than the expected 5–7 cases/1000 patient-years predictable from the American data indicating increased risks in African-Americans [2]. Although angioedema may be clinically unrecognized, we are unlikely to have missed any important or life-threatening cases on our service. However, with both the cough and angioedema, no clear dose or time-dependency was noticed. Generally, low doses of ACE inhibitors, about 50% of the recommended doses (captopril 12.5–50 mg enalapril 2.5–10 mg, lisinopril 2.5–5 mg) have been used, in order to minimize cost to our mostly poor patients. These low doses have led to substantial reduction in intrahospital mortality in heart failure in Nigerians [7]. It is not clear if the incidence of angioedema in our cohorts would be higher if the standard doses of ACE inhibitors used in Western practice or recommended in clinical trials were employed. The incidence of ACE inhibitor induced cough is reportedly higher among a Chinese cohort (44%) than in Caucasians [8]. Since the polymorphism of the ACE–gene and D genotype frequency is similar among Nigerians, Europeans and black Americans [9], it is unlikely to be a marker for the susceptibility to cough or angioedema. The racially related increase in cough and angioedema in the negroid race raises the possibility of ethnic and gender differences in bradykinin metabolism or receptor density/and or affinity, which requires further elucidation and enquiry.

In conclusion, the use of low doses of ACE inhibitors in African patients appears associated with a lower than expected frequency and/or severity of angioedema, than is predictable from their reported heightened racial susceptibility.

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Received 13 January 2000, accepted 4 February 2000.

References

1 Gibbs CR, Lip GY, Beevers DG. Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Clin Pharmacol* 1999; **411**: 861–865.

2 Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor induced angioedema. *Clin Pharmacol Ther* 1996; **60**: 8–13.

3 Adigun AQ, Ajayi AA. ACE inhibitor induced cough in Nigerians: A prospective study of 100 patients. *Proceedings of the 25th Annual Scientific Conference of the Nigerian Cardiac Society*, Lagos, 1996; p 24.

4 Ajayi AA, Oyewo EA, Ladipo GOA, Akinsola A. Enalapril and hydrochlorothiazide in hypertensive Africans. *Eur J Clin Pharmacol* 1989; **36**: 229–234.

5 Adigun AQ, Ajayi AA. Muscarinic blockade with oral hyoscine palliates angiotensin converting enzyme inhibitor induced cough. *Afr J Med Med Sci* 1998; **27**: 139.

6 Yeo WW, Foster G, Ramsay LE. Prevalence of persistent cough during long term enalapril treatment: controlled study versus nifedipine. *Q J Med* 1991; **80**: 763.

7 Adewole AD, Ikem RT, Adigun AQ, Akintomide AO, Balogun MO, Ajayi AA. A 3 year clinical review of the impact of ACE, inhibitors on the intrahospital mortality of congestive heart failure in Nigerians. *Cent Afr J Med* 1996; **42**: 253–255.

8 Chan WK, Chan TY, Luk WK, Leung VK, Li TH, Critchley JA. A high incidence of cough in Chinese subjects treated with angiotensin converting enzyme inhibitors. *Eur J Clin Pharmacol* 1993; **44**: 299–300.

9 Rotimi C, Puras A, Cooper R, *et al*. Polymorphisms of renin angiotensin – genes among Nigerians Jamaicans, and African-Americans. *Hypertension* 1996; **27**: 63.

A drug interaction between fusidic acid and a combination of ritonavir and saquinavir

A 32-year-old male infected with the human immunodeficiency virus (HIV) was seen for acute onset of nausea, fatigue, arthralgias, vertigo and jaundice. At that time, he was being treated twice daily with ritonavir 400 mg, saquinavir 400 mg and stavudine 40 mg for 3 months. Fusidic acid (Fucidin®) 500 mg three times daily had been started 1 week earlier for a scalp furuncle.

On examination he was ill-appearing but was afebrile with stable vital signs. Examination was significant only for jaundice. Figure 1 indicates the patient's laboratory values, plasma drug concentrations, and time courses of drug therapy. The patient was admitted to hospital with a possible diagnosis of fusidic acid toxicity. Fusidic acid therapy was stopped and hydration was initiated.

While in hospital viral causes of hepatitis were excluded. His plasma concentration of fusidic acid 16 h after his last dose was 195 $\mu g\ ml^{-1}$ (expected level $< 100\ \mu g\ ml^{-1}$ [1]), and ritonavir and saquinavir plasma concentrations were 19.3 and 11.2 $\mu g\ ml^{-1}$, respectively, between 5 and 10 h after the doses (observed range of maximum concentrations [2, 3]: ritonavir: 4–12 $\mu g\ ml^{-1}$, saquinavir: 1–4 $\mu g\ ml^{-1}$). The patient improved after 24 h and was discharged. Four days later he returned with nausea, weakness, jaundice and a further increase in liver function tests. All medications were discontinued and his liver function tests improved. Drug analysis revealed a fusidic acid concentration of 132 $\mu g\ ml^{-1}$ (6 days post), and ritonavir and saquinavir levels of 43.4 and 16.3 $\mu g\ ml^{-1}$, respectively, between 3 and 10 h after the doses. On day 45 (39 days since starting fusidic acid), ritonavir, saquinavir and stavudine were restarted. The following month, his liver function tests were normal and his plasma viral load was suppressed (Figure 1). A follow-up plasma analysis (day 122) demonstrated no fusidic acid present, and ritonavir and saquinavir plasma concentrations were within the expected ranges.

Oral administration of standard doses of fusidic acid, 500 mg three times daily, is well tolerated, but adverse reactions to the drug include gastrointestinal upset, reversible jaundice, anorexia, lethargy, vertigo and arthralgias. Maximum plasma concentrations occur 2–3 h after the dose in healthy volunteers. Fusidic acid is eliminated primarily by biliary excretion of various conjugative and cytochrome P450 (CYP) oxidative metabolites [4]. Fusidic acid has demonstrated inhibition of CYP3A4 isoforms *in vitro* [unpublished data]. Fusidic acid displays nonlinear pharmacokinetics with an elimination half-life ranging from 6–14 h [4, 5].

The initial plasma sample in this patient was collected during the elimination phase of fusidic acid, and the concentration (195 $\mu g\ ml^{-1}$) was about twice the peak levels observed in patients with cholestasis who had received fusidic acid 500 mg three times daily intravenously over 2 h for 4 days [1]. In our patient, the fusidic acid concentration decreased only 32% over 4.5 days, suggesting a first order elimination half-life of 8 days. The high concentrations and prolonged elimination of fusidic acid may have been caused by ritonavir and saquinavir inhibiting fusidic acid metabolism through CYP [6] or Phase II conjugation.

Concurrently, fusidic acid appears to have inhibited the metabolism of both ritonavir and saquinavir as suggested by their elevated concentrations (43.2 and 16.3 $\mu g\ ml^{-1}$) during fusidic acid administration, which normalized after fusidic acid was discontinued. Ritonavir and saquinavir are common causes of gastrointestinal upset, and have also been responsible for cases of hepatitis [7]. In the current case, ritonavir and saquinavir were previously well-tolerated, but vertigo, anorexia, jaundice and paresthesias were observed after addition of fusidic acid. These effects may have resulted from protease inhibitor or fusidic acid administration.

		Day	–65	0	6	7	8	12	13	17	45	75	98	122
Laboratory parameter	Reference units:													
Aspartate aminotransferase (IUl^{-1})	8-30		54			51	53	80	82	57	35	20		
Alanine aminotransferase (IUl^{-1})	8-40		85			78	77	143	149	125	68	33		
Alkaline phosphatase (IUl^{-1})	42-110		183			205	169	202	194	163	113	127		
Total bilirubin ($\mu mol l^{-1}$)	4-24					114	98	147	122	28	28	25		
CD3+/CD4+ T cell count ($cells\mu l^{-1}$)	626-1698		386										507	
Plasma viral load (copies per ml)	<500		<500										<500	
Fusidic acid, Fucidin® ($\mu g ml^{-1}$)	<100					195		132						0
Ritonavir, Norvir® ($\mu g ml^{-1}$)	<12					19.3		43.2						3.7
Saquinavir, Invirase® ($\mu g ml^{-1}$)	<4					11.2		16.3						0.38

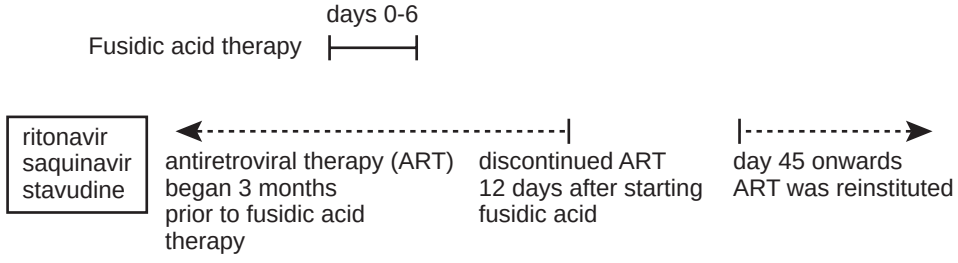

Figure 1 Plasma drug concentrations, laboratory values and time course of drug therapy.

This case demonstrates that plasma concentrations of both protease inhibitors, ritonavir and saquinavir, as well as fusidic acid, may be significantly elevated when these agents are administered in combination, possibly from mutual inhibition of metabolism. Therefore we recommend that coadministration of fusidic acid with either of these two drugs be avoided.

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Received 13 January 2000, accepted 18 April 2000.

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References

1 Peter JD, Jehl F, Pottecher T, Dupeyron JP, Monteil H. Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. *Antimicrob Agents Chemother* 1993; **37**: 501–506.

2 Cameron DW, Japour AJ, Xu Y, *et al*. Ritonavir and saquinavir combination therapy for the treatment of HIV infection. *AIDS* 1999; **13**: 213–224.

3 Danner SA, Carr A, Leonard JM, *et al*. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. *N Engl J Med* 1995; **333**: 1528–1533.

4 Fucidin® (fusidic acid) product monograph. Leo Laboratories Canada Ltd. September. 1993.

5 Reeves DS. The pharmacokinetics of fusidic acid. *J Antimicrob Chemother* 1987; **20**: 467–476.

6 Hsu A, Granneman R, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35**: 275–291.

7 Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B infection. *JAMA* 2000; **283**: 74–80.