inhibitor-based HAART until more data are available.

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QT lengthening and arrhythmias associated with fexofenadine

Sir—Additional data should be mentioned with regard to the case reported by Yigal Pinto and colleagues (March 20, p 980) of QT lengthening and life-threatening arrhythmias associated with use of fexofenadine.[1] These data were provided to us by Pinto and colleagues during two site visits, the last one on March 17, 1999.

The patient has several risk factors for ischaemic heart diease which is the most frequent cause of ventricular arrhythmia (age >65 years, familial history of ischaemic heart disease, current smoking, and hypertension with left-ventricular hypertrophy). In addition, a coronary angiography in 1997 showed no coronary artery stenosis and a myocardial scintingraphy in 1998 showed an interoposterior defect (judged as false positive). A coronary angiogram done after the arrhythmic episodes revealed a long stenosis of the circumflex artery (although it was deemed not significant 40%), and myocardial perfusion imaging by a single photon emission computed tomography showed a large defect from the apex to the basal wall. These elements indicate that this patient had progression of coronary artery disease with a possible inferior myocardial infarction.

Carvedilol, known to protect the heart via its β-blocking properties, had been discontinued. The first recorded episode of ventricular tachycardia occurred during a fexofenadine-free interval, 4 days after withdrawal of fexofenadine (mean terminal elimination half-life 11–16 h). The patient was advised to receive an internal cardioverter defibrillator, usually indicated for treatment of recurrent ventricular tachycardia. He was ultimately treated with a β-blocker and an inhibitor of angiotensin-converting enzyme before discharge.

The QTc time was increased at baseline, a condition known to predispose to serious ventricular arrhythmias at any time. Subsequent electrocardiograms showed that the QTc time remained abnormally long without fexofenadine. The QTc intervals were calculated with the Bazett formula. The use of more up-to-date methods of QT adjustment[2,3] might be more appropriate in this case. For example, the highest reported QTc value during fexofenadine treatment (532 ms, heart rate 95 beats per min), when recalculated with the two other methods[2,3] (477 and 475 ms, respectively), is similar to the intervals reported at baseline or after the events. This result indicates no positive dechallenge or positive rechallenge with regard to QTc intervals in this case.

It is also noteworthy that fexofenadine has undergone rigorous preclinical and clinical testing for cardiac events and was shown to have no significant QT lengthening effect, even at doses much higher than those prescribed. Although a causal relation can be rarely entirely excluded in such cases, we believe the multiple confounding factors in this case offer alternative explanations of the observed events, independently of fexofenadine administration.

Thierry Giraud

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3 Sagie A, Larson MG, Goldberg RJ, Bengston JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 1992; **70:** 797–801.

Authors' reply

Sir—Thierry Giraud's statement that the "patient was advised to receive an internal cardioverter defibrillator" is incorrect. As stated explicitly in the clinical discharge letter, we judged the chances of a recurrence to be unlikely if the patient refrained from fexofenadine or QT-lengthening factors. Therefore, we did not advise use of an internal cardioverter defibrillator. Giraud also suggests the presence of a previous myocardial infarction in our patient, which again is incorrect. The perfusion defects seen twice in our patient had not changed in 2 years, and were not accompanied by any sign of hypokinesia or akinesia on echocardiography or ventricular angiogram. Thanks to the consent of our patient and the hospital, Giraud was well aware of all the above clinical data, which were discussed with him during his site visit.

We stated in our report that our patient had a long QTc time in the absence of fexofenadine. Giraud adds to this observation by suggesting that the patient had risk factors for arrhythmias. He then states that the presence of these risk factors explains the two collapses of our patient. This conclusion is difficult to defend since our patient was exposed to these risk factors for a long time and is still exposed to them, but collapsed only when he was exposed to fexofenadine. He has not collapsed again since he discontinued fexofenadine. Therefore, our conclusion that the events in our patient were associated with the use of fexofenadine is justified.

Giraud criticises the use of the Bazett formula for calculation of QTc time, but only recalculates one measurement, and subsequently compares this value with our measurements calculated with a different method. When all the measurements are recalculated by the method proposed by Giraud, the association as we reported is confirmed, albeit at lower absolute QTc times: after the first discontinuation of fexofenadine QTc shortens from 477 ms to 467 ms, to increase again at rechallenge to 476 ms; hereafter QTc shortens again to 453 ms after the second discontinuation. Thus, our conclusion of a positive dechallenge and rechallenge is fully supported. There are many more ways to calculate QTc time, and each will yield different numbers, but there is no consensus about the most appropriate method.

Giraud notes the safety of fexofenadine. Although the drug was tested in clinical trials, it is important to note that rare adverse drug reactions are not likely to be detected during such clinical trials. The number of patients included in the clinical trials is small, compared with the use of the drug after marketing, and so it is hazardous to disregard the possibility of rare adverse reactions. Such adverse reactions can be detected only during use in clinical practice. Therefore, publication of case reports, spontaneous reporting systems, and other pharmacoepidemiological approaches are important.

Patients with a long QTc interval are at increased risk of drug-induced arrhythmias. Therefore, the presence of a long QTc interval in the absence

of any drug in our patient does not argue against, but rather favours the possibility that fexofenadine lengthens QTc and induces arrhythmias. The observation of a positive dechallenge and rechallenge strengthens this hypothesis. Thus, our observations indicate that fexofenadine may increase QTc time and induce ventricular arrhythmias in susceptible patients.

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CYP2A6 polymorphism, nicotine, and environmental nitrosamines

Sir—We reported (S J London and colleagues, March 13, p 898)[1] that polymorphism in the *CYP2A6* gene, which codes for a cytochrome P450 isozyme that metabolises both nicotine and nitrosamines, seemed to have little influence on the propensity either to smoke cigarettes or to develop lung cancer. I have two differences of opinion with my co-authors that were not debated before submission of this research letter.

First, ours was a genetic epidemiological investigation of risk factors for lung cancer and was not designed to detect factors that might affect acceptability of, or aversion, to nicotine in tobacco products. However, we did undertake *CYP2A6* genotyping of lung cancer cases and controls, with known smoking histories. Unfortunately, our definition of an ever smoker was someone with a lifetime smoking history of 100 cigarettes or more. Our first hypothesis, and that of a group from Toronto,[2] was that people with one or two inactivating *CYP2A6* alleles, who would have a lowered capacity to detoxicate metabolically the nicotine absorbed during cigarette smoking, might have an aversion to nicotine, and thus choose not to smoke. I judge that our classification of ever smokers and never smokers has insufficient capability to detect people who might have a genetic and metabolically based intolerability to cigarettes.

Second, we designed the study to examine the potential relation between *CYP2A6* genotypes and lung cancer causation. Two (1%) of 182 cases and 11 (2%) of 460 controls had the metabolically compromised genotype (two inactivating alleles), generating a non-significant odds ratio for lung cancer of 0·5 in the combined smokers and non-smokers and 0·4 for smokers alone, a finding which, if statistically significant, would have been commensurate with the second hypothesis that CYP2A6-deficient individuals have an impaired metabolic activation of nitrosamines. The question is which nitrosamines? There is little reason to suppose that these must be the so-called tobacco-specific nitrosamines (TSN). Orally administered diethylnitrosamine (not a TSN), for example, which caused tracheobronchial tumours in hamsters[3] is abundant in bacon, cheese, and fish, and microgram amounts of such dietary nitrosamines are much greater than those obtainable from cigarette smoking. I have yet to see the experimental evidence that smoking is the major cause of lung cancer and I am not aware that the burden of epidemiological evidence can refute an important role of diet.

We can now formulate a new pharmacogenetic hypothesis for lung cancer: that persons who inherit the greatest CYP2A6 metabolic capacity will be those with the fastest metabolism of nicotine, and therefore those most likely to smoke cigarettes, those most likely to activate environmental nitrosamines, particularly from the diet, and, those most likely to develop lung cancer, not contingent on them being an ever smoker. As with traditional epidemiology, the pitfalls of confounders will need to be avoided (other genotypes and environmental and lifestyle factors). Finally, when a metabolic phenotype is a causative factor, misclassification of individuals by incomplete genotyping will drive the odds ratio towards unity. As yet undiscovered *CYP2A6* inactivating alleles probably exist in certain human populations.[4]

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Betamethasone and placental vascular resistance

Sir—Euan Wallace and Lesleigh Baker (April 23, p 1404)[1] suggest that administration of maternal betamethasone improves placental vascular resistance. The effects of betamethasone on fetal dynamics, including heart rate, have been previously reported and explained by the same underlying mechanism.[2]

Despite Wallace and Baker's cautious words about the potential harmful effect to the fetus of such treatment, their results should also be interpreted in conjunction with past evidence of the pathophysiological background of absent end-diastolic flow (AEDF) in umbilical arteries.

Cumulative therapy was used in 21 patients, the interval between diagnosis and therapy was inconsistent, no data on blood-flow in other fetal vessels, such as the cerebral arteries, are provided, and the longitudinal umbilical blood-flow assessment should raise some doubts on the real meaning of the improvement in placental vascular resistance as shown in their figure.

When relying on longitudinal monitoring of AEDF with subsequent follow-up,[3] the interval from diagnosis to delivery is one of the main factors that can determine the perinatal outcome, and different longitudinal haemodynamic behaviours are enough to justify the transient changes in blood-flow patterns. Furthermore, to arrive at Wallace and Baker's conclusions about these transient changes, we should be sure that the same umbilical artery has been explored at all timepoints.

Our data on placental morphological findings in cases of AEDF[4] also raise the question of whether the lesions encountered definitively compromise the villi capillaries, and impede the potential improvement of vascular resistance and subsequently of umbilical blood flow to the placenta. Moreover, data on short-term maternal oxygen administration in cases of AEDF, provide some evidence of eventual deleterious effects on fetal condition despite transient improvements in haemodynamic status.[5]

Finally, we speculate that once AEDF is established, a transient increase in blood flow to the placenta can represent a reperfusion and reoxygenation process of adaptation, or even decompensation, with enhanced oxidative stress and