

Causality assessment of adverse drug effects: when is rechallenge ethically acceptable?

Sir—One of the most difficult tasks in the assessment of adverse reactions is causality assessment. The gold standard for establishing cause and effect is dechallenge followed by rechallenge. Unfortunately, this approach is rarely practical for safety and ethical reasons. Y Pinto and colleagues (March 20, p 980)¹ describe rechallenge with fexofenadine.

Fexofenadine is the active metabolite of terfenadine, a non-sedative antihistamine compound whose high-dose formulation was withdrawn in October, 1998, because of its arrhythmogenic potential, particularly when given with other cardiotoxic drugs or with drugs that inhibit its oxidative metabolism. Simons and colleagues² claimed that fexofenadine did not have an arrhythmogenic effect. The patients in Pinto and colleagues' study had taken 180 mg daily fexofenadine and had an abnormally long QTc interval, which shortened on withdrawal of the antihistamine. On day 6, fexofenadine was reintroduced and the QTc time increased. For unclear reasons, fexofenadine was not discontinued and on day 11, the patient developed ventricular tachycardia, which rapidly progressed to ventricular fibrillation.

Was the rechallenge acceptable? We would argue that it was not. Although the results with volunteers indicate that the drug was safe, it is well recognised that such studies are insufficient for establishing drug safety. Only extensive safe use of the drug can provide the necessary reassurance.³ Although increased attention was paid to screening for the cardiotoxic effects of fexofenadine relative to terfenadine, such screening does not provide adequate protection against the inherent weakness of this approach—namely the exclusion of patients with concurrent disease, concomitant medication, and genetic predisposition to particular adverse effects or interactions. Given that withdrawal of fexofenadine led to normalisation of the lengthened QTc time and the history of the cardiotoxic effects of terfenadine, a reasonable hypothesis was that fexofenadine was causally related. The likelihood of harm from re-exposure outweighed the potential benefit given that the consequences were potentially serious and safe alternative antihistamines were readily available.

A redeeming feature of Pinto and colleagues' study is that if one were to adopt a societal perspective, rather than that of the individual patient, the investigators' actions seem more defensible. Without the rechallenge, a substantial number of readers would no doubt have argued that the case against fexofenadine was weak. The response to rechallenge would have persuaded most, though apparently not the manufacturers,⁴ that the drug had a causal effect. Therefore, in the long run fewer patients would be put at risk by being prescribed the drug inappropriately. Social benefits therefore outweigh the risks. Is it ethical to adopt this perspective? Wide acceptance of the concept of cost-effectiveness within health care suggests that it is. The good of the many overrides the good of the individual patient. Perhaps we are too strongly anchored to the rule of rescue,⁵ but we would still argue it was unethical to expose the patient to fexofenadine. At the very least, he should have been asked to give informed consent.

*Alain Li Wan Po, Martin J Kendall

*Centre for Evidence-Based Pharmacotherapy, School of Life and Health Sciences, Aston University, Birmingham B4 7ET, UK; and Department of Medicine, Birmingham Medical School Birmingham (e-mail: a.liwanpo@aston.ac.uk)

- 1 Pinto YM, van Gelder IC, Heerings M, Crijns HJGM. QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; **353**: 980.
- 2 Simons FE, Bergma NJ, Watson WT, Simons KJ. The clinical pharmacology of fexofenadine in children. *J Allergy Clin Immunol* 1996; **98**: 1062-64.
- 3 Li Wan Po A, Zhang WY. What lessons can we learn from the withdrawal of mebifradil from the market? *Lancet* 1998; **351**: 1829-30.
- 4 Giraud T. QT lengthening and arrhythmias associated with fexofenadine. *Lancet* 1999; **353**: 2072.
- 5 Hadorn DC. Setting health priorities in Oregon: cost-effectiveness meets the rule of rescue. *JAMA* 1991; **265**: 2218-25.

Authors' reply

Sir—Alain Li Wan Po and Martin Kendall question the ethics of rechallenge. Although not described in our report, we did obtain explicit informed consent from our patient, as is mandatory under Dutch law for any medical intervention, including changes in drug treatment. Li Wan Po and Kendall's argument is based on the assumption that fexofenadine as the active metabolite of terfenadine (which is known to lengthen QTc time) was, a priori, a likely cause. However, there were no published

reports available on QT-lengthening or sustained ventricular tachycardias related to fexofenadine, whereas there are such reports on alternative antihistamines. This point was of particular importance for our patient, since fexofenadine relieved his severe itching and urtica. Therefore, in this case, the rechallenge was not only to confirm our suspicion under controlled circumstances, but also to answer the question of the patient who wanted absolute certainty about whether or not he could safely re-use fexofenadine.

Since we did not set out to find out whether fexofenadine lengthens QTc time, we did not stop treatment as soon as we observed a longer QTc time during rechallenge. The clinical debate about whether or not he could re-use fexofenadine continues, and obviously ended as soon as he had a polymorphic tachycardia, which necessitated defibrillation. Unfortunately, the patient's symptoms are not relieved by other antihistamines, so he continues to suffer from itching.

We agree with Li Wan Po and Kendall that even an intensive screening for cardiotoxic effects does not provide adequate protection against the risk to which those rare susceptible patients are subjected. We made a similar point in our earlier reply to your correspondents (July 12, p 2072).¹ We also agree that rechallenge with a potentially harmful substance needs to be carefully weighed. The Oregon Health Services Commission² has found that cold cost-effectiveness reasoning will not be accepted by society.

We believe that the ethics of rechallenge should be mainly guided by the needs of the individual at risk. Thus, the valuable remarks by Li Wan Po and Kendall allow us to underline that we rechallenged in the patient's own interest and after his explicit informed consent. Unfortunately and unexpectedly, we had to use the rule-of-rescue. We hope our report will contribute to a safe use of this antihistamine.

*Yigal M Pinto, Isabelle C van Gelder, Harry J G M Crijns, Maarten Heeringa

*Department of Cardiology, University of Groningen, PO Box 30001, 971392 Groningen, Netherlands; and Pharmacovigilance Foundation LAREB, Netherlands.

- 1 Pinto YM, van Gelder IC, Heeringa M, Crijns HJGM. QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; **353**: 2072.
- 2 Hadorn DC. Setting health priorities in Oregon: cost-effectiveness meets the rule of rescue. *JAMA* 1991; **265**: 2218-25.