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Correspondence

Comparative trial of two non-sedative H_1 antihistamines, terfenadine and astemizole, for hay fever

SIR—Dr MB Emanuel (November 1985;**40**:799) has misinterpreted our work[1] in an attempt to explain the surprising inability of Drs PH Howarth and ST Holgate to find an effect of terfenadine (September 1984;**39**:668–72).

The quotation selected by Dr Emanuel in fact came from a report of a study comparing chlorpheniramine with astemizole,[2] and the phrase "suggests tolerance" referred to tachyphylaxis with chlorpheniramine. I now appreciate the unfortunate ambiguity introduced by its context and wish therefore to make it quite clear that we have not demonstrated tachyphylaxis with terfenadine. In fact, we found that with the recommended dose of 60 mg twice daily terfenadine "was still clinically effective [in chronic dermographic urticaria] after 47–84 days' treatment"; there was a slight, insignificant change in the linear part of the weal force-response curve with continued treatment but no change in the clinically more relevant weal threshold force. We have since found no pharmacological evidence of tachyphylaxis using full histamine weal dose-response curves before and after administration of 60 mg twice daily terfenadine for six weeks[3]; nor was there any greater effect from doubling the dose, which would have been expected had there been tachyphylaxis.

The apparent ineffectiveness of terfenadine in the study of Drs Howarth and Holgate cannot therefore be explained by tachyphylaxis or use of too low a dose (see letter by Dr B Freedman, May 1985;**40**:399); but it can be explained, at least in part, by reduced bioavailability. Thus, although the recommended dose of terfenadine was used, it was incorporated into a capsule to make it indistinguishable in appearance from astemizole. Desirable though that may have been for the execution of a double blind trial, it appears to have had an adverse effect on bioavailability because histamine wealing was impaired much less by terfenadine 60 mg twice daily in the particular preparations they used than by the astemizole 10 mg daily; whereas it is clear from full histamine weal dose-response curves with regular terfenadine and astemizole that these doses are approximately equiactive.[3–5]

In terfenadine and astemizole we have two interesting, still comparatively new, H_1 receptor antagonists, and with few exceptions the evidence indicates that their maximal therapeutical effect is comparable to and no greater than that of the old H_1 antihistamines despite much greater inhibition of histamine wealing, presumably because only part of the various disease processes is due to histamine.[3 4] Their main advantage lies in a greater therapeutic ratio because of the absence of unwanted effects such as drowsiness, although this does preclude their use for itch other than that due to peripheral histamine release.[6] Nevertheless, our own studies show that their different biokinetic effects on histamine wealing corresponds to their different therapeutic properties. Thus astemizole has a slow onset of effect (days), which can be overcome only in part by use of a loading dose, and a very slow offset, weal inhibition still being apparent as much as a month after the drug has been stopped; whereas the onset of effect of terfenadine was apparent by 2–4 hours and its offset by 24 hours.

The disadvantage of a slow onset is obvious for initial treatment, but is less well recognised for long term administration. Thus when prolonged symptomatic treatment is required until there is spontaneous remission it is desirable to ask patients to stop the drug from time to time to see whether they still need it, and this is more easily done when recurrence can rapidly be brought under control by a drug with a quick onset of effect. The advantage of a once daily, weekly, or fortnightly dosage is considerable for some patients but has to be balanced against the unknown risk of drug persistence if toxicity occurs; and in the case of these new drugs it is far too soon to be sure that it won't. For these reasons I believe that clinicians and clinical pharmacologists should themselves consider the desirability or otherwise of possible manipulation of speed of binding and dissociation of drugs such as histamine receptor antagonists before they are presented with new hybrids and "act-alikes." Meanwhile it is the clearcut biokinetic differences between terfenadine and astemizole which should dictate their clinical use.

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2 Krause LB, Shuster S. A comparison of astemizole and chlorpheniramine in dermographic urticaria. *Br J Dermatol* 1985;**112**:447–53.
3 Krause LB, Shuster S. Recent studies with terfenadine. *Ann Allergy* 1985;**55**:284.
4 Krause LB, Shuster S. H_1 receptor-active histamine not sole cause of chronic idiopathic urticaria. *Lancet* 1984;ii:929–30.
5 Sorkin EM, Heel RC. Terfenadine: a review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 1985;**29**: 34–56.
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**This letter was sent to Dr Emanuel, whose reply appears below.

SIR,—I am surprised at Professor Shuster's claim that his statement concerning tachyphylaxis was ambiguous and related only to chlorpheniramine. Let me restate his quote: "The displacement of the weal response curve was maximal at 2 weeks with chlorpheniramine and somewhat less at 4 weeks. This is similar to that previously found with terfenadine and suggests tolerance."

The bioavailability of terfenadine in the study by Drs Howarth and Holgate was sufficient to produce almost a 70% suppression of histamine skin reactivity. Dissolution studies showed no difference between the encapsulated form and terfenadine tablets. Tachyphylaxis to antihistamines may be important and merits further investigation. Professor Shuster's approach to this problem seems to be nihilistic and may lead to inappropriate drug usage within this class of drugs.

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