H_1-Antihistamines and Aircrew

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For many years it was accepted that antihistamines were among the safest medications in the world, and this reputation was enhanced by the development of the so-called second generation compounds, which were largely free of adverse effects on vigilance and performance. It was against this background that there was wide agreement that they could be used safely by aircrew. However, cardiotoxicity has now become an issue with these antihistamines,[1] and the confidence which was once placed in their use for aircrew requires re-examination.

With certain antihistamines, plasma concentrations of the parent compound, caused by overdosage, inhibition of metabolism, or hepatic insufficiency, may lead to prolongation of the QT_c interval, and thus to ventricular dysrhythmias similar to those seen with quinidine. Such dysrhythmias are likely due to blockade of the rapidly activating component (I_{Kr}) of the delayed rectifier potassium channel, since inhibition of this channel is common to virtually all drugs that prolong the QT interval.[2] There is no evidence of any correlation between I_{Kr} inhibition and antihistamine potency or H_1 receptor blockade.

Inhibition of metabolism is a particularly important issue and some individuals may even be poor metabolisers. Antihistamines such as terfenadine and astemizole are metabolised by the P400 enzyme CYP3A4 to compounds which have little or negligible cardiac effects. The enzyme may be inhibited by anti-fungals such as ketoconazole, itraconazole and terbinafine, the macrolide antibiotics erythromycin, clarithromycin and troleandomycin, the azalide antibiotic azithromycin, 6,7-dihydroxybergamottin (an active principle of the flavonoids of grapefruit juice), and ethinylestradiol. Cimetidine and ranitidine are H_2-antihistamines which also inhibit CYP3A4. Caution must be exercised with any coadministered drug which inhibits the enzyme, and thus may raise the plasma concentration of the parent antihistamine or its metabolite.

Caution must also be exercised with the use of antihistamines in individuals with congenital prolongation of the QT_c interval, bradycardia, ischemic heart disease, congestive cardiac failure, electrolyte changes (especially hypokalemia) and drugs that prolong the QT_c interval such as quinidine. All potential H_1-antihistamines must be screened for cardiac toxicity, as some individuals may be susceptible to plasma concentrations near the therapeutic range.

At the time of writing, there are two antihistamines which may be considered for use by aircrew. These are fexofenadine, the metabolite of terfenadine, and loratadine. The metabolite of loratadine, desloratadine, is under clinical development. Fexofenadine and loratadine have been shown to be clinically effective, are believed to be free of central effects, and have low, if any, cardiotoxic effects.

Cetirizine has sedative activity, and is therefore not suitable for use by aircrew.[3]

LORATADINE

Loratadine is rapidly and completely absorbed, reaching peak plasma levels within 1 to 2 hours after ingestion. The elimination half-lives of loratadine and its metabolite (descarboethoxy-loratadine) are 8 to 14 hours and 17 to 24 hours respectively.[4,5] This elimination rate allows loratadine to remain active over 24 hours, enabling once daily dosing.

Performance studies have shown that loratadine (10mg) is free of effects on performance and sedation and so is suitable for those involved in skilled work or driving.[6,7] Loratadine has no effect on a wide variety of psychomotor skills including reaction time, vigilance, visuomotor coordination, visual acuity or digit symbol substitution. Studies using subjective and objective (daytime sleep latencies) measures of sleepiness have also shown no sedative effect. Further, the lack of any sedative effect of loratadine has also been shown in driving tests.[8]

In contrast with terfenadine and astemizole, loratadine is believed to be free of adverse cardiac effects in humans. However, there are reports which suggest it may be associated with atrial arrhythmias,[9,10] and studies have shown that loratadine in therapeutic concentrations[4] can modulate potassium currents in isolated human atrial myocytes.[11] The analysis of Lindquist & Edwards,[9] however, has been questioned.[12,13] The study by Crumb[11] evaluated the effect of loratadine on different potassium channels; studies using isolated ventricular myocytes have shown only a 10-15% suppression of the I_{Kr} channel at a loratadine concentration of 2.5 μM, a level which is probably clinically unachievable.[14] There is little, if any, firm evidence from clinical studies to support an increased risk of arrhythmias from loratadine. Co-administration of agents known to inhibit the metabolism of loratadine with high plasma concentrations have not led to changes in the QTc interval. Further, exposure to four times the recommended daily dose of loratadine, i.e., 40mg once daily, for 13 weeks has failed to show changes from baseline in any electrocardiographic parameter, and there was no evidence in any individual of prolongation of the QTc interval.[15]

FEXOFENADINE

Fexofenadine is a racemic mixture of two pharmacologically active isomers. It is the active metabolite of terfenadine, and is a highly specific H_1-receptor antagonist free of anticholinergic and antiadrenergic activity. It is rapidly absorbed by the oral route, reaching peak plasma levels within 1 to 3 hours. It is excreted unchanged by the biliary and renal routes and has an elimination half life of 11 to 15 hours.

In a study carried out at the UK Defence Evaluation and Research Agency Centre for Human Sciences, digit symbol substitution, tracking and vigilance tasks, as well as objective (daytime sleep latencies) and subjective measures of sleepiness, were studied in healthy volunteers from one hour to eight hours post-ingestion using 120, 180 and 240mg. There were no changes in performance or sleepiness with any dose of fexofenadine at any time compared with placebo.[16]

The effects of fexofenadine in doses up to 240mg daily have also been studied on driving and on psychomotor performance.[17] Volunteers were treated for five days with each of four different doses of fexofenadine (60mg twice daily, 120mg twice daily, 120mg once daily, 240mg once daily). On days one, four, and five of each treatment period the subjects underwent a highway driving test and a battery of psychomotor performance tests. The results for all fexofenadine doses were not significantly different from placebo.

In view of the clear cut cardiotoxic effects of terfenadine, careful attention has been given to the possibility that its metabolite, fexofenadine, might also modulate cardiac conduction. However, animal studies and human studies specifically designed to examine the effect of repeated doses of fexofenadine on the electrocardiogram have failed to show any changes of significance in the QT_c interval.

In a letter to the Lancet,[18] Pinto et al raised the possibility of QT lengthening from fexofenadine in a cardiac patient, which in turn led to correspondence with the manufacturer, Hoechst-Marion-Roussel. Giraud[19] pointed out that the patient reported by Pinto *et al* had several risk factors for ischemic heart disease, with evidence of progressive coronary artery disease and a

possible inferior infarction. Of even greater significance, there was evidence of QTc prolongation before the initiation of therapy with fexofenadine, and the first documented episode of ventricular tachycardia occurred during a drug-free interval, four days after discontinuing fexofenadine. Pinto *et al*[20] disputed the importance of the coronary disease, noting that the coronary lesion documented at follow-up angiography would not likely have been of hemodynamic significance; however, they did not dispute the other two points. Review of the original report by Pinto *et al*[18] also shows that the subject had pre-existing left ventricular hypertrophy, likely due to hypertension. Furthermore, the reported fluctuations in the measured QTc interval fell within the range of expected variability. Pratt *et al*[21] found, when comparing single tracings before and after exposure to a drug, that an increase in QTc of at least 60 msec was necessary before one could reasonably ascribe the difference to the medication. In essence, then, this was a report of questionable cardiotoxicity from fexofenadine, in one individual with numerous confounding factors, against a background of preclinical and clinical evidence that fexofenadine has no significant QT lengthening effect.

CONCLUSION

At the time of writing there would appear to be two antihistamines which could be used by aircrew. Both loratadine (10mg daily) and fexofenadine (120-180mg daily) are free of adverse effects on vigilance and performance. Though it is not possible in all circumstances to exclude an adverse effect on cardiac conduction, the considered evidence is that both loratadine and fexofenadine are acceptable for aircrew, and that it is not possible to state a preference for one drug over the other.

REFERENCES

1. Nicholson A.N. Antihistamine (H_1-receptor antagonists), Side Effects of Drugs Annuals, 23, 1999, Elsevier.

2. Haverkamp W, Breithardt G, Camm AJ, *et al.* The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report of a policy conference of the European Society of Cardiology. Eur Heart J 2000;21:1216-31.

3. Nicholson AN, Turner C. Central effects of the H_1-antihistamine, cetirizine. Aviat Space Environ Med 1999;69:166-71.

4. Hilbert J, Radwanski E, Weglein R, *et al.* Pharmacokinetics and dose proportionality of loratadine. J Clin Pharmacol 1987;27:694-8.

5. Radwanski E, Hilbert J, Symchowics S, Zampaglione N. Loratadine: multiple-dose pharmacokinetics. J Clin Pharmacol 1987; 27:530-3.

6. Roth T, Roehrs T, Koshorek G, *et al.* Sedative effects of antihistamines. J Allergy Clin Immunol 1987;80:94-8.

7. Bradley CM, Nicholson AN. Studies on the central effects of the H_1-antagonist, loratadine. Eur J Clin Pharmacol 1987;32:419-21.

8. Betts T, Wild J, Ross C, Kenwood C, Thirtle-Watts R. A double-blind, single-dose study of the effects of loratadine on driving skills in normal volunteers. In: *Management of Allergy in the 1990s.* Hans Huber, Editor M Kaliner; 1990, p 71-8.

9. Lindquist M, Edwards IR. Risk of non-sedating antihistamines. Lancet 1997;349:1322.

10. Haria M, Fitton A, Peters DH. Loratadine: a reappraisal of the its pharmacological properties and therapeutic use in allergic disorders. Drugs 1994; 48:617-37.

11. Crumb WJ. Rate-dependent blockade of a potassium current in human atrium by the antihistamine loratadine. Br J Pharmacol 1999; 126:575-80.

12. Cohen AT. Dangers of non-sedating antihistamines. Lancet 1997;350:369.

13. Himmel MH, Honig PK, Worobec AJ. Dangers of non-sedating antihistamines. Lancet 1997; 350:369.

14. Barbey J-T, Anderson M, Ciprandi G, Frew AJ, Morad M, Priori SG, Ongini E, Affrime MB. Cardiovascular safety of second-generation antihistamines. Am J Rhinol 1999;13:235-43.

15. Affrime MB, Brannan MD, Lorber RR, Danzig MR, Cuss F. A 3-month evaluation of

electrocardiographic effects of loratadine in healthy individuals. Advances in Therapy 1999;16:149-57.

16. Nicholson AN, Stone BM, Turner C, Mills S. Antihistamines and aircrew: Usefulness of aircrew. Aviat Space Environ Med 2000;71:2-6.

17. Vermeeren J, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol on actual driving and psychomotor performance. J Allergy Clin Immunol 1998;101:306-11.

18. Pinto YM, van Gelder IC, Heeringa M, Crijns HJGM. QT lengthening and life threatening arrhythmias associated with fexofenadine. Lancet 1999a;353:980.

19. Giraud T. QT lengthening and life threatening arrhythmias associated with fexofenadine. Lancet 1999;353:2072.

20. Pinto YM, van Gelder IC, Heeringa M, Crijns HJGM. Authors Reply. Lancet 1999b;353:2072-73.

21. Pratt CM, Ruberg S, Morganroth J, McNutt B, Woodward J, Harris S, Ruskin J, Moyé L. Dose-response relation between terfenadine (Seldane) and the QTc interval on the scalar electrocardiogram: distinguishing a drug effect from spontaneous variability. Am Heart J 1996;131: 472-80.