
Letters to the editor

COMPARISON OF EBASTINE WITH CETIRIZINE

To the Editor:

In the recently published comparison of ebastine with cetirizine¹ the investigators did not include a placebo group, raising questions about the conclusions. The average differences from baseline between the treatments are very small. The Student's *t* test may result in type I error (rejecting the null hypothesis when it is true).

The authors are selective in their discussion when they only mention results from the study of Ramaekers et al to show that a single dose of cetirizine, 10 mg, impaired car driving. Using the same car driving test Volkerts et al showed that multiple doses of cetirizine 10 mg did not impair driving performance.²

Regarding QTc, in the discussion the authors attempted to illustrate the cardiac safety of ebastine by referring to results from a study of Connell et al that showed none of the patients experienced a QTc interval greater than 500 msec. It is important to emphasize that the generally accepted normal range for QTc interval is between 360 msec and 420 msec,³ and the highest value considered normal is 440 msec.⁴

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Response:

The design of the study did not include a placebo group, because the aim of the study was a comparison between ebastine given at the two recommended dosages and a second generation reference treatment (cetirizine at the 10 mg once daily recommended dosage) and not the demonstration of the efficacy of ebastine and cetirizine, knowing that both products have already shown efficacy in seasonal allergic rhinitis.

The conclusion of the study is that, globally, ebastine 10 mg and cetirizine 10 mg appear to possess similar efficacy with a 50% decrease of total symptoms scores between baseline and end-of-treatment assessment in both groups. We agree with Dr. Volkerts that the difference between groups is not clear-cut when assessed by global symptomatic scores or VAS. A statistically and clinically significant difference, however, is that 84% of patients improved in the 20-mg ebastine group versus 78% in the 10-mg ebastine group and 73% in the 10 mg cetirizine group. This 11% increase in the number of patients with a good clinical response is of clinical significance.

Dr. Volkerts criticizes the use of the Student's *t* test, arguing that this test increases the type I error (rejecting statistically the null hypothesis when it is true). This is false. The use of the Student's *t* test doesn't lead to falsely statistical significant differences. This test has been shown to be the asymptotically most efficient test. It can therefore reject the null hypothesis, even if the difference is small. Using the Student's *t* test tends to decrease type II error (accepting the null hy-

pothesis when the alternative hypothesis is in reality true) rather than to increase type I error.

It was not the aim of our study to assess drug safety or to discuss the effect of cetirizine on standard deviation of lateral position (SDLP) as primary criteria for evaluating driving performance.

If the effects of 10 mg cetirizine on SDLP are questionable (one significant result after a single dose in one study; nonsignificant results after multiple doses in the other study) it is clear that ebastine, at both 10 and 20 mg daily dosages, is devoid of effects both after single doses and at steady state (day 5) in the same test.¹ Furthermore, a recent publication by Simons et al² shows that subjective somnolence is significantly greater than baseline and placebo after cetirizine, 10 mg, once daily (change in visual analogue scale for somnolence two and one-half hours after ingestion). These published data are in favor of a mild but definite effect of cetirizine on the central nervous system.

Regarding effects on the QTc interval, a major reference for the much quoted 440 ms as the upper limit of normal appears to be a textbook published some 40 years ago, and subsequent studies using data from many thousands of healthy subjects have shown that this figure is too low^{3,4} especially because of circadian QTc variability in normal subjects.⁵

In any event the findings of Connell⁶ confirm the favorable cardiac safety of ebastine at therapeutic dosage whatever the criteria of evaluation. The maximum observed QTc values (mean $\pm$ SD) demonstrated no statistically significant difference between placebo (411 ± 1.2 ms), ebastine 10 mg (405.9 ± 1.3 ms), and ebastine 20 mg (411.6 ± 1.1 ms) and unpublished data from the same study demonstrated no statistical difference between ebastine 10 and 20 mg groups and placebo,

when comparing the number of patients with QTc > 444 ms.

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HEPATITIS C AFTER INTRAVENOUS IMMUNOGLOBULIN

To the Editor:

Flora et al¹ report an outbreak of hepatitis C virus (HCV) infection in a cohort of patients exposed to a contaminated batch of immunoglobulin (Gammagard, Baxter Healthcare, Ltd). We would like to contrast this report with our larger group of patients² exposed to a different but HCV-contaminated batch, and raise several concerns with Flora's report.

Of 34 patients in the UK exposed to one common contaminated batch (Gammagard, Baxter), 30 developed HCV infection. None had other risk

factors for HCV infection. Diagnoses included common variable immunodeficiency (n = 18), IgG subclass deficiency (8), chronic lymphocytic leukemia (3), myeloma (2), X-linked agammaglobulinemia (1), drug-induced hypogammaglobulinemia (1), and intestinal lymphangiectasia (1). Twenty-eight of these were HCV positive by the polymerase chain reaction (PCR), and two were PCR negative but anti-HCV antibody-positive with abnormal liver function tests.

Nine of 24 patients developed jaundice and 27 had abnormal aminotransferase levels within four months of exposure. Eighteen became symptomatic, with malaise, dark urine, pruritus, food intolerance, or nausea. Two have died of liver failure and eight of unrelated causes. Nine have become HCV-PCR negative within 1 year of exposure; three without treatment, and six following a 6-month course of interferon-alpha (IFN α). Ten patients have still not cleared the virus. Five of these are receiving no further treatment, two are receiving further courses of IFN α and two are receiving ribavirin and IFN α . Two patients await liver transplantation.

Flora et al¹ conclude that the initial sequelae of HCV infection are mild; however many of our patients were antibody deficient and developed sequelae, including transaminitis (79%), symptoms (53%) and two patients progressed to liver failure. Previous authors of reports of IVIG associated non-A non-B hepatitis^{3–5} have been unable to identify the genotypes of the viral strains transmitted, which may be multiple. In our cohort only one genotype, 1a, was detected. It is unclear whether this discrepancy in outcome severity is related to viral genotype or pre-existing morbidity.

Flora et al also highlight the high success and low side effect rate of IFN α . Even in immunocompetent patients, however, interferon therapy is limited by poor efficacy, high relapse rates and significant side effects.⁵ Also, of our 12 patients who did not receive IFN α , five are alive at 2 years and two of these remain PCR-negative

indicating that some patients may spontaneously clear the virus.

Finally, serologic screening for HCV infection is inadequate, as many immunodeficient patients do not mount an antibody response. Conversely, an effective antibody response may render HCV-PCR falsely negative. These tests should be used in combination, in conjunction with careful clinical and biochemical monitoring.

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Response:

To my knowledge, the patients reported by Dr Sewell, et al represent the largest and best described group of individuals contracting acute hepatitis C from intravenous immunoglobulin (IVIG). We were aware of their experience¹ as we were identifying similar patients within our own practice,² and it is true, Dr. Sewell's patients did have a more severe presentation of their illness. We also wondered whether this might have been due to their underlying immune deficiencies.

Among our ten patients who had received contaminated IVIG and subsequently contracted hepatitis C only, one had an underlying immune disorder. This patient had no symptoms at presentation and had a moderate elevation in her AST level at 443 U/L. Percutaneous liver biopsy, however, revealed cirrhosis. She had received a variety of immunoglobulin preparations over an 8-year period but even if she had contracted the virus earlier in her course of IVIG therapy this represented a rapid histologic progression. We did not perform genotyping on our patients and it remains unclear whether genotype I is associated with a more aggressive or more symptomatic course than genotypes II or III.

While interferon treatment for patients with hepatitis C of many years' duration with standard therapy has sustained response rates in the 15% to 20% range, we agree with the observations of Dr. Chapel and others that therapy of 'recent onset' hepatitis C has resulted in long term response rates as high as 60%.^{1,3,4} These trials had involved immunocompetent individuals, however, and it remains to be seen whether similar favorable response rates occur in recently infected immunodeficient patients.

Interferon therapy is not devoid of side effects. Our patients have voiced complaints ranging from flu-like symptoms to hair loss, rashes, and thrombocytopenia at rates similar to those described in the literature. We have been able to alleviate many of these symptoms by using a combina-

tion of diphenhydramine and anti-inflammatory medications, but few patients "feel better" while on interferon therapy.

It is our opinion that patients identified as contracting acute hepatitis C from exposure to contaminated intravenous immunoglobulin, as with any other patient with suspected 'recent onset' of infection, should be considered for early interferon therapy, because infection of short duration is associated with an increased response as noted by Dr. Chapel.¹

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LACK OF RAGWEED IN NORTHWESTERN US

To the Editor:

David Frenz et al¹ have performed yeoman service, gathering pollen data from 23 locations. Their data reflect many measurements and undoubtedly will be noted in future allergy publications dealing with ragweed prevalence and pollination.

Their study is also important for the negative data reported by pollen collecting sites in the Seattle, Portland

and South Central Idaho pollen reporting stations and for the fact that there is indeed no ragweed pollen present in these areas. This is in contradistinction to previously published literature, including maps, showing prevalence of ragweed pollen.² Drug companies have copied the maps and literature from this reference and other works and would seemingly be in error.

We have entertained expert biologists in our area who have assured us that there is no ragweed present in South Central Idaho. In seventeen years of pollen counting we have rarely identified any pollen that can be mistaken for ragweed.

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To the Editor:

I wish to clarify some points made by Richard C. Ahrens in his guest editorial¹ in which he commented on an article.² He claims the study suggests the DeVilbiss Aerosonic Ultrasonic nebulizer delivers a higher percentage of 2.5 mg albuterol to the lung than the jet nebulizer. What we concluded was that both the ultrasonic and the jet nebulizer produce comparable increases in FEV₁ after albuterol. There was no statistically significant difference between nebulizers with respect to increases in FEV₁ and FVC after albuterol in patients with moderate to severe asthma (Table 3²). The results of the mean daily symptom scores only showed a statistical difference with respect to activity level (Table 4²). None of the other symptoms evaluated showed a statistical difference.

He states there needed to be a dose-response relationship between devices. The purpose of the study was to compare bronchodilator responses to standard doses of albuterol (2.5 mg) used in everyday practice in patients with moderate to severe asthma. Certainly there may be inter-individual variation in response to albuterol. The study was not designed to detect those differences. Nonetheless, the spirometry data did not demonstrate a difference between devices after 2.5 mg albuterol. Peak evening expiratory flow rates, however, were increased more with the ultrasonic nebulizer.

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Response:

I am in agreement with the facts that Dr. Pallares lists in his letter regarding his recent publication in the *Annals*.¹ My difference of opinion with the authors lies not with the results presented, but in their interpretation. Dr. Pallares objects to my statement that the data "suggest" that the ultrasonic nebulizer is more effective than the jet. Perhaps this is too strong a statement for me to have made based on the fact

that the only significant difference between nebulizers identified in the study was in favor of greater potency for the ultrasonic. My point, however, was that clinically important differences in efficacy between these nebulizers could, in truth, exist and yet not have been identified by the study Pallares et al performed. A basic premise of statistical hypothesis testing (eg, t-testing and analysis of variance [ANOVA] used by these authors) is that failure to show a significant difference is *not* the same as demonstrating that effects of the compared treatments are, in truth, comparable or equivalent.^{2,3} If a study lacks sufficient statistical power due to too small sample size and/or highly variable outcome responses, the study may miss even large true differences between treatments. For example, Pallares et al indicate that percent increase in FEV₁ 30 minutes following dosing was 35.5 for the jet and 25.3 for the ultrasonic (a difference of +10.2% in favor of the jet, which is not significant). Using data presented by the authors and standard statistical procedures,⁴ I calculated that 95% confidence interval (CI) for this difference runs from -21% to +41%. The 95% CIs for differences at other time points are similarly large. In other words, true, clinically important differences in favor of either the ultrasonic or the jet are both quite possible based on these results. Consequently, the fact that most of the differences between the nebulizers were nonsignificant provides no clinically useful information.

The idea of including more than one dose from at least one delivery device in the study design has been discussed

elsewhere.⁵ In brief, this characterizes the dose-response relationship present in the study and it permits translation of a difference in response such as that noted above into a difference in dose delivered to the lung by the two nebulizers. It also allows for validation of the study by showing that it is adequate to detect clinically important differences in dose delivery. Studies of the type done by Pallares et al are commonly unable to detect several-fold difference in dose delivered even when sample size is large.⁴

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