Beneficial Antiinflammatory Effects of Leukotriene Receptor Antagonists in Asthma

To the Editor:

The recent study by Perng et al in CHEST (May 2004)4 provides valuable insight into the comparative effects of therapy with zafirlukast (20 mg bid) plus low-dose budesonide (400 μg/d) vs high-dose budesonide alone (1,200 μg/d) in terms of airway hyperresponsiveness to methacholine.2 Indeed, both randomized treatments conferred improvements in lung function, suggesting that the observed reduction in airway hyperresponsiveness may have been in part due to a greater airway diameter. In contrast, the use of an indirect stimulus such as adenosine monophosphate, which causes the release of proinflammatory mediators, would have provided greater insight into the antiinflammatory effects of leukotriene receptor antagonists and inhaled corticosteroids. For example, the shift in adenosine monophosphate threshold is closely correlated to the degree of sputum eosinophilia and has been shown to be a more sensitive indicator of allergic airway inflammation than methacholine.3,4

It would have been of interest if the authors had measured the time taken to recover following bronchial challenge, as it is likely that a further useful effect of leukotriene antagonism in asthma would have demonstrated. Previous data5,6 have shown that montelukast (another leukotriene receptor antagonist) quickens the time taken to recover following bronchial challenge compared to placebo. This in turn suggests that cysteinyl leukotrienes are important mediators in sustaining the bronchoconstrictor response. Indeed, the “real-life” implication of this was observed in a randomized controlled study that evaluated 194 patients admitted to the hospital with acute asthma.2 It was demonstrated that therapy with IV montelukast, in addition to standard therapy, conferred a more rapid recovery in FEV1 over a 2-h period compared to therapy with placebo.

In conclusion, this study serves as an important reminder of the beneficial effects of administering leukotriene receptor antagonists as add-on therapy to inhaled corticosteroids in terms of the integral components of the asthmatic inflammatory process. However, assessing shifts in airway hyperresponsiveness with an indirect bronchoconstrictor stimulus such as adenosine monophosphate would have provided a more robust surrogate marker of antiinflammatory activity than the use of a direct agent such as methacholine.

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Right Ventricular Dysfunction

To the Editor:

In his article (April 2004)1 concerning the impact of right ventricular (RV) dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism (PE), Dr. Kreit concludes, as have other recent reviewers,2,3 that thrombolytic...
therapy is not indicated for individuals who have echocardiographic evidence of RV dysfunction without hypotension or shock. Dr. Kreit may even have overestimated the mortality in this group of patients, as his Table 1 includes two studies in which there is no indication that hypotensive patients were excluded. When these studies are not considered, the average mortality falls from the quoted 9.3% for the four studies in the Table 1, to 4.5% for the remaining two studies. Additionally, Dr. Kreit does not comment on the 10-year retrospective study by Vieillard-Baron et al. in which 32 subjects with massive PE and echocardiographic RV dysfunction without frank shock had only a 3% mortality.

Dr. Kreit suggests that hypotensive patients have a higher mortality and quotes the 14% mortality in 43 such patients in a large registry. However, in the study by Grifoni et al., included in Table 1, 19 patients were prospectively identified who had echocardiographic evidence of RV dysfunction and hypotension without shock. The mortality in this group was only 5%, identical to that in the normotensive patients in the study. Furthermore, in the study by Vieillard-Baron et al. in 32 patients with echocardiographic RV dysfunction and hypotension requiring vasopressor support but without metabolic acidosis, the mortality rate was 3% and no different than the in group without hypotension. In sharp contrast, 34 patients who were hypotensive with a metabolic acidosis despite intravascular volume expansion and vasopressor support had a 59% mortality rate. Although not randomized, it is notable that the mortality in these 34 patients was the same in the 14 patients receiving thrombolytics (57%) as in the 20 patients receiving only heparin (60%).

It is important to be fully aware of several limitations in the study by Jerjes-Sanchez et al., which Dr. Kreit cites, the only randomized prospective study to claim a survival advantage in patients in shock receiving thrombolytic and heparin therapy rather than heparin alone. The groups differed substantially with respect to the time of onset of symptoms of PE to onset of shock. The patients randomized to streptokinase presented quickly and directly to the study hospital, while those randomized to heparin were all transferred to the study hospital after sudden deterioration on heparin at another institution. This suggests a different pathophysiology between the groups, such as recurrent PE prior to randomization in the heparin only group. The patients in this study were very unusual. The patients were much younger than in most series of patients with PE (mean age, 51 years and 47 years in the two groups, respectively) and had extremely high estimated pulmonary artery systolic pressure (97 mm Hg and 94 mm Hg, respectively). Angina was reported in all patients, and three of the four patients who died and underwent autopsy all had grossly visible RV infarctions. Finally, the termination of the study after enrollment of only 8 of the intended 40 patients is problematic for two reasons. First, the small sample size lowers the confidence in the p value. That is, if a ninth patient had been enrolled and had a different outcome from the previous eight patients, the p value would be markedly higher. Second, the analysis of the data “as it accumulated” rather than at the intended end point of 40 patients requires the application of “sequential methods” to the statistical analysis in order for it to be valid; it is far from clear that this was done.

It appears that what Dr. Dalan stated in an editorial in 2002 remains true today: “Despite > 3 decades of experience with thrombolytic agents, their role in the treatment of PE remains uncertain and controversial.” In making treatment decisions on individual patients with PE, however, the physician must bear in mind that the sharp rise in mortality from PE may not occur until patients are vasopressor dependent and exhibit a metabolic acidosis. Even in this latter group, solid evidence that thrombolysis confer a survival advantage is lacking.

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Interpretation of Transpulmonary Thermodilution Curves

To the Editor:

Michard recently reported a possible artifact that appeared to mimic the biphasic thermodilution display of temperature vs time of an intracardiac right-to-left shunt after injection of cold indicator via a femoral vein catheter and temperature measurement using a thermistor placed via the femoral artery. It was thus stated to be similar to transpulmonary thermodilution curves observed with this technique in the presence of right-to-left intracardiac shunts with early temperature change from rapid transit of indicator through the shunt followed later by temper-