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## Vitamin C and exercise-induced bronchoconstriction in athletes : [Letter]

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The section on urticaria and angioedema mentions case reports on the use of omalizumab in idiopathic angioedema.<sup>2</sup> We published 3 earlier case reports on the efficacy of omalizumab in intractable chronic urticaria.<sup>3</sup> We reported on 3 patients with refractory chronic urticaria who had marked improvement with omalizumab. Two of the patients showed evidence of increased anti-FcεRI antibody levels, and 1 did not. We postulated that the possible mechanisms included the downregulation of IgE receptors, providing fewer targets for IgE or anti-FcεRI antibodies.

All our patients were started on injections every 2 weeks (based on weight and IgE level) but are currently still doing well with increasing the intervals between injections to every 4 weeks. We have also started 2 additional patients on omalizumab, with similar significant clearing of urticaria within 1 week.

Successful treatment of urticaria with anti-IgE therapy has also been reported by other authors.<sup>4,5</sup> Omalizumab appears to be a very promising therapeutic alternative for refractory urticaria and angioedema.

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*Editor's note:* There is no accompanying reply to this correspondence.

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## Vitamin C and exercise-induced bronchoconstriction in athletes

*To the Editor:*

Anderson and Kippelen<sup>1</sup> reviewed the mechanisms of and therapeutic approaches to exercise-induced bronchoconstriction (EIB) in athletes. In addition to the treatments they discussed, vitamin C can also affect EIB.

We carried out a systematic review of the effect of vitamin C supplementation on the common cold.<sup>2,3</sup> Vitamin C consistently reduced the duration of common cold symptoms, but the effect on common cold incidence was significantly heterogeneous. In the general population, vitamin C supplementation had no preventive effect; however, the supplements halved the incidence of colds in 6 placebo-controlled trials with participants under heavy acute physical stress: pooled relative risk, 0.50 (95% CI, 0.38-0.66; total, n = 642). Four of these trials were with marathon runners,

1 was with Canadian soldiers in a northern training exercise, and 1 was with schoolchildren in a skiing camp in the Swiss Alps.<sup>2,3</sup>

In the general community the acute symptoms of cough, sore throat, and runny nose usually have a viral cause. However, it is not obvious that similar symptoms occurring after a marathon run are caused by a viral infection because they can result from an injury to runners' airways caused by their hours of exceptional ventilatory exertion.<sup>1</sup> Thus the common cold studies of marathon runners might have been measuring, at least in part, the effects of vitamin C on the physical injury to their airways instead of viral infections.

In their trial with marathon runners, Peters et al<sup>4</sup> recorded the "self-reported symptoms including a running nose, sneezing, sore throat, cough, and fever" during a 2-week posttrace period. The incidence of posttrace cough was significantly reduced in the vitamin C group compared with the placebo group: relative risk, 0.29 (95% CI, 0.10-0.83; 4/43 vs 13/41). The incidence of sore throat was also reduced by vitamin C: relative risk, 0.33 (95% CI, 0.16-0.66; 8/43 vs 23/41). In contrast, vitamin C had no significant effect on the incidence of runny nose (*P* = .2). Peters did not carry out virologic or pulmonary function tests before or after the race, and thus the cause of the symptoms is uncertain, yet there is no strong basis to assume viruses caused the symptoms. Furthermore, a few studies have directly measured the effect of vitamin C supplementation on bronchial responsiveness.

Ogilvy et al<sup>5</sup> reported that vitamin C reduced the duration and intensity of bronchoconstriction induced by methacholine. The action of vitamin C was abolished by indomethacin, indicating that the effect was mediated through the prostaglandin metabolism. Direct evidence indicating that vitamin C affects EIB was found in 3 small (n ≤ 20) laboratory studies in which the decrease of FEV<sub>1</sub> after exercise was attenuated by vitamin C supplementation.<sup>6-8</sup> Tecklenburg et al<sup>8</sup> also reported that vitamin C decreased the levels of proinflammatory eicosanoids in urine. These 3 laboratory studies do not, however, define the clinical importance of vitamin C for athletes. On the other hand, the 6 trials with participants under heavy acute physical stress<sup>2,3</sup> indicate that vitamin C has clinically important effects on the respiratory symptoms of some athletes, although it is not clear to what degree that effect is directed at their viral infections and the physical injury to their airways. This means that more trials that examine the mechanisms and therapeutic effects of vitamin C on the respiratory symptoms of athletes are warranted.

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## Levalbuterol kinetics

### To the Editor:

We read with interest the results of Tripp et al,<sup>1</sup> who used a cumulative dose-response protocol to compare hydrofluoroalkane (HFA) formulations of either levalbuterol or racemic albuterol in asthmatic subjects. They found that plasma levels of R-albuterol were lower after levalbuterol (ie, R-enantiomer) than after racemic (ie, RS) albuterol in conjunction with reduced heart rate but not potassium response when levalbuterol was administered at a 1:2  $\mu\text{g}$  dose ratio.

These results are contrary to previous observations with nebulized administration, in which plasma levels of R-albuterol were higher after levalbuterol than after racemic albuterol in either healthy volunteers or asthmatic subjects, with no difference in extrapulmonary  $\beta_2$ -mediated responses, such as heart rate and potassium level.<sup>2,3</sup> It is known that the S-enantiomer of albuterol is inactive on extrapulmonary  $\beta_2$ -adrenoceptors, whereas plasma levels of S-albuterol are higher after administration of the S-enantiomer than after the equivalent dose of the racemate, as is the case with the R-enantiomer.<sup>2</sup> It would be hard to explain why heart rate but not potassium response was attenuated with levalbuterol in the study of Tripp et al<sup>1</sup> when both are mediated by the same systemic  $\beta_2$ -adrenoceptor and are dependent on peak albuterol plasma levels.<sup>4</sup> Perhaps one explanation for the results of Tripp et al<sup>1</sup> might be that the particular kinetics of HFA levalbuterol are different from those of HFA racemic albuterol in terms of

delivering a relatively lower fine-particle dose, resulting in lower plasma R-albuterol levels. This hypothesis could easily be verified by providing supporting data with these formulations on the overall *in vitro* fine-particle dose ( $<4.7 \mu\text{g}$ ) with an Anderson Cascade Impactor over stages 3 to 7 because the *in vitro* fine-particle dose determines the *in vivo* early lung bioavailability and associated peak systemic  $\beta_2$  adverse effects.<sup>5</sup>

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*Editor's note:* There is no accompanying reply to this correspondence.

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