

Correspondence

Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers

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To the Editor:

We read with interest the recent meta-analysis of Nelson et al suggesting enhanced synergy between fluticasone and salmeterol delivered from a single inhaler versus separate combination inhalers.¹ The basis for this conclusion was from the primary outcome variable for all four studies, which was the change in baseline from morning peak flow over 12 weeks. Pointedly, in all four studies, for the primary outcome, the confidence intervals for the difference between combination versus concurrent therapy included zero, while the mean value for the pooled estimate amounted to a difference of 5.4 L/min (95% CI, 1.5 to 9.2). The clinical relevance of such a small difference has to be questioned, particularly as most peak flow meters are only calibrated to within 10 L/min. Likewise, for the secondary outcome of FEV₁, the confidence intervals for the difference in all four studies included zero, as did the confidence interval for the pooled estimate with a mean difference of only 40 mL.

When interpreting a meta-analysis, one always has to be careful to distinguish between results that may be statistically significant but are clinically irrelevant, and the study of Nelson is a good example of this. Glaxo-SmithKline continues to perpetuate the myth that there is an enhanced synergistic property between fluticasone and salmeterol when given in a combination inhaler, which, presumably is driven by the impending patent expiry for fluticasone.

In a recent ex vivo study from Usmani et al,² the degree of glucocorticoid receptor activation was measured in induced sputum of asthmatic patients, showing 31% for placebo, 47% fluticasone 100 µg alone, 61% for fluticasone 500 µg alone, 43% for salmeterol 50 µg alone, and 54% for fluticasone 100 µg with salmeterol 50 µg in combination. There was no significant difference between the combination inhaler and fluticasone 100 µg alone. We have recently shown in vivo in asthmatic patients, using adenosine monophosphate challenge as an inflammatory surrogate, that there is no difference in response to fluticasone 250 µg bid alone versus fluticasone 250 µg/salmeterol 50 µg bid combination inhaler, also suggesting a lack of any glucocorticoid receptor potentiation.³

Most of the clinical evidence would point to additive rather than synergistic effects with fluticasone and salmeterol in combination, due to their known separate activities on inflammatory and smooth muscle pathways. No one would doubt that fluticasone/salmeterol combination is more effective than fluticasone alone on clinical outcome measures, but this type of data torturing by Nelson et al should not be used as evidence-based medicine to support synergy for the fluticasone/salmeterol combination inhaler.

REFERENCES

1. Nelson HS, Chapman KR, Pike SD, Johnston M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *J Allergy Clin Immunol* 2003;112:29-36.
2. Usmani OS, Maneechotesuwan K, Adcock IM, Barnes PJ. Glucocorticoid receptor activation in induced sputum following inhaled long acting beta 2 agonist and glucocorticoid treatment. *Thorax* 2002;57(Suppl 3):10.
3. Currie GP, Lee DKC, Haggart K, Bates CM, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid patients with asthma. *Am J Respir Crit Care Med* 2003;167:1232-8.
doi:10.1016/j.jaci.2003.10.035