Correspondence

Seretide meta-analysis missed important features and overstates any advantages over concurrent LABA/ICS devices

To the Editor:

The recent meta-analysis comparing Seretide fixed combination long-acting β-agonist/inhaled corticosteroid devices (LABA/ICSs) with concurrent salmeterol and fluticasone inhalers[1] has important limitations in its data and interpretation, which may affect the key findings.

We are concerned that there was no reporting of withdrawals and adverse events (where rates of reported adverse events with Seretide were significantly higher). Reporting focused on and overstated the magnitude of physiologic effects, when there was no difference in clinically relevant outcomes. Also, Seretide's improvements seem comparatively low.

Despite withdrawals and adverse events being reported for all the individual randomized controlled trials, these were not reported in the meta-analysis. From the original studies, we calculate that rates of total withdrawals and withdrawals due to adverse effects were higher in Seretide users, and there were significantly more (26%) reported adverse events (289 in patients taking Seretide [59%] versus 263 in concurrent LABA/ICS users [47%]; relative risk [RR], 1.26; 95% CI, 1.09 to 1.44).

Withdrawals affect analysis of physiologic and clinical outcomes and are themselves clinical outcomes and should have been reported (as in the Cochrane review of fluticasone).

Reporting of odds ratios (ORs) overstated the magnitude of PEFR improvement; RR should have been used. If the OR is interpreted as RR, it will always appear larger—particularly when baseline risk is high.[2] Recalculating relative risks (using published ORs, calculating baseline risks) gives a lower (11%) likelihood of patients improving by ≥15 L/min in morning PEFR (RR, 1.11; 95% CI, 1.03 to 1.18). This would mean treating 14 patients to have 1 patient gain 15+ L/min (65% improvement in concurrent users; RR, 1.11; hence, number needed to treat = 14).

There were apparently no significant differences in more clinically relevant outcomes in which reductions in days or nights without symptoms or the use of reliever drugs were low (0.0% to 1.1% reductions). This is consistent with the low impact on PEFR of approximately 1.4% ([5.4 L/min added PEFR increase with Seretide]/[344 L/min mean baseline PEFR]).

Contextually, the physiologic and clinical improvements with Seretide were low relative to those seen in other relevant ICS/LABA meta-analyses, in which all meta-analyses showed lesser clinical than physiologic improvements. Seretide's above 5.4 L/min morning PEFR improvement was less than salmeterol's 22.4 L/min improvement in MIASMA (68% relative improvement in PEFR) but had a lower 5% to 20% relative reduction in days or nights without symptoms or use of reliever drugs.[3] Fluticasone had an estimated 13.3 L/min improvement but approximately a 3% reduction in exacerbations and 6% improvement in symptom/reliever-free days (neither statistically significant). Likewise, Seretide had both the lower 5.4 L/min added PEFR improvement (16% RRI) but no significant clinical impact. Of salmeterol, fluticasone and Seretide, only salmeterol has demonstrated significant clinical improvements.

Further details are available on the PHARMAC website at http://www.pharmac.govt.nz/economic_analysis.asp, including tables and analysis of withdrawals/adverse events and the quality of individual RCTs and the meta-analysis.

We believe that the advice from the BTS/SIGN, GINA, and New Zealand asthma guidelines still applies, namely that there is no difference in clinical efficacy between combination and concurrent LABA/ICS treatment.

Scott Metcalfe, MBChB, FAFPHM(RACP)
Peter Moodie, MBChB, FRNZCGP
PHARMAC
Wellington
New Zealand

Scott Metcalfe is externally contracted to the New Zealand Pharmaceutical Management Agency (PHARMAC) for consultant public health medicine advice. PHARMAC is the government agency responsible for funding community pharmaceuticals. PHARMAC is currently involved in litigation with Glaxo Smith Kline (suppliers of Seretide, salmeterol and fluticasone) relating to an advertising campaign for Flixotide.

doi:10.1016/j.jaci.2003.12.005

REFERENCES

1. Nelson HS, Chapman KR, Pyke SD, Johnson 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. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316:989-91.
3. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320:1368-73.