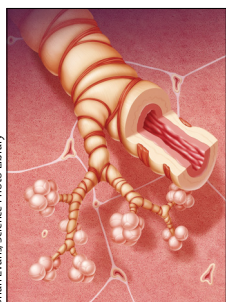


Safety of long-acting β 2-agonists in asthma



Brian Evans/Science Photo Library

Patients with persistent asthma can be given long-acting β 2-agonists (LABAs) alongside inhaled glucocorticoids (ICS) without increased risk of serious asthma-related events, according to a US randomised trial published in *The New England Journal of Medicine*.

In 2009, concerns about a possible increase in deaths in LABA treatment arms of trials led the US Food and Drug Administration (FDA) to request that manufacturers do post-marketing safety studies to assess the incidence of serious asthma-related events (including hospitalisation, intubation, or death) when the drugs are added to ICS.

In the AstraZeneca-sponsored, multicentre, non-inferiority study, patients who reported one to four asthma exacerbations in the previous year were randomly assigned to receive the LABA formoterol

plus the ICS budesonide ($n=5846$; two actuations of $4.5\ \mu\text{g}/80\ \mu\text{g}$ or $4.5\ \mu\text{g}/160\ \mu\text{g}$) or budesonide alone ($n=5847$; two actuations of $80\ \mu\text{g}$ or $160\ \mu\text{g}$) twice a day for 26 weeks.

43 patients assigned to budesonide plus formoterol had a serious asthma-related event compared with 40 assigned to budesonide (hazard ratio [HR] 1.07; 95% CI 0.70–1.65), which was within the margin for non-inferiority. In an efficacy analysis, the risk of an asthma exacerbation was lower with budesonide and formoterol than with budesonide alone (0.84, 0.74–0.94; $p=0.002$).

Coauthor Stephen Peters from Wake Forest School of Medicine (Winston-Salem, NC, USA) told *The Lancet Respiratory Medicine* that although patients with severe asthma were excluded because they “could not be ethically randomised to monotherapy”, the results should

reassure clinicians. “This article adds further evidence to support the safety of LABAs in combination with ICS in the treatment of patients not well controlled on an ICS alone.”

However, the FDA-mandated trials have proven controversial. Ian Pavord from the Nuffield Department of Medicine at the University of Oxford, UK, commented that it was “a positive result, but [it is] a shame that money was spent on this large trial when we already knew these drugs were safe and effective.”

Another of the FDA-mandated studies, the AUSTRI trial, has now been published and showed similar results for the safety of salmeterol added to fluticasone therapy. Results will need to be pooled from all trials before data for asthma deaths are adequately powered.

Louise Rishton

SAVE trial: no cardiovascular benefits for CPAP in OSA



Chassene/BSIP/Science Photo Library

Continuous positive airway pressure (CPAP) therapy did not significantly reduce cardiovascular events among patients with obstructive sleep apnoea (OSA) and cardiovascular disease, according to controversial findings from the Sleep Apnea Cardiovascular Endpoints (SAVE) trial.

“I think most experts in the field anticipated that the SAVE trial would identify a benefit of CPAP therapy on cardiovascular events”, said Sanjay Patel (University of Pittsburgh, Pittsburgh, PA, USA). “That no such effect was identified was a big surprise.”

SAVE enrolled 2717 adults aged 45–75 years who had been diagnosed with moderate-to-severe OSA and coronary or cerebrovascular disease. Participants were randomly assigned to receive usual care with or without CPAP. The primary study endpoint was a composite measure

of cardiovascular events, including deaths, myocardial infarctions, strokes, and hospitalisations for heart failure, unstable angina, or transient ischaemic attack.

At a mean follow-up of 3.7 years, CPAP was associated with significantly improved health-related quality of life and daytime sleepiness and mood. But no significant differences were found in cardiovascular event incidence among the intention-to-treat populations (17.0% of the CPAP group vs 15.4% of the control group; hazard ratio 1.10; 95% CI 0.91–1.32, $p=0.34$). However, a prespecified propensity-score-matched analysis of the 561 patients who used CPAP for more than 4 h per night found that the cerebrovascular event risk was significantly reduced in the CPAP group (0.52; 0.30–0.90, $p=0.02$).

These findings might reflect insufficient durations of CPAP use or

its timing within the sleep cycle; mean duration of CPAP use was only 3.3 h per night. “Previous studies have demonstrated dose-response relationships between CPAP use and many surrogate endpoints as well as on cardiovascular events”, noted Lee Brown (University of New Mexico Health Sciences Center, Albuquerque, NM, USA).

The single-blind study design without the use of a placebo (eg, sham CPAP) meant the control-group patients might have changed their lifestyles or better adhered to medication, Brown said, adding that he would not recommend any change in current practice based on SAVE.

“Given the serious methodological flaws inherent to the SAVE study, it is imperative that additional clinical trials be pursued”, Brown said.

Bryant Furlow

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For the **study** see *N Engl J Med*

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For more on the **controversy**

about the FDA-mandated

studies see *Thorax* 2013;

68: 195–98

For the **AUSTRI trial** see

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For the **SAVE trial findings** see

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