

Safety of long-acting β_2 -agonists: current state of knowledge

Dr. Paul O'Byrne in an interview with Dr. Roman Jaeschke: part 2

There was a new paper, published very recently, regarding the concern of safety of long-acting β_2 -agonists (LABAs). Again, we have reviewed already the role of inhaled corticosteroids and the history of β_2 -agonists. And what is the current knowledge about the dangers or safety of β_2 -agonists?

The issue about the safety of the LABA never really went away. As you know, Professor Jaeschke, because you published the most important meta-analysis of the safety of the variety of LABAs that we currently have, there are actually 2 main ones, which is salmeterol and formoterol. When used together with inhaled corticosteroids (ICSs), not as a monotherapy, a new meta-analysis was very reassuring that in fact there was not a significantly increased risk of an untoward event, such as death or intubation because of acute severe asthma, in patients treated with LABA compared to placebo.

While on corticosteroids...

While on corticosteroids. However, the U.S. Food and Drug Administration once again mandated a series of studies to be done, where the use of a LABA together with an inhaled steroid in a single device—so that you cannot take the LABA without taking the steroid at the same time—was compared to the steroid alone, with regards to safety. There were 3 large studies designed. One with salmeterol and fluticasone, which is a LABA plus a steroid, compared to fluticasone alone, which is the study we are going to talk about now; it has just been published in the *New England Journal of Medicine*. A study in a little under 12 000 patients over 6 months. Again with the primary outcome variable: a composite of asthma death or intubation, intensive care management, or admission to hospital because of acute severe asthma.

The study demonstrated quite clearly no increased risk when the LABA was added to fluticasone, a steroid, when compared to the steroid alone, but a significant reduction in the risk of a severe asthma exacerbation in

the LABA-ICS-treated population compared to the steroid-treated population. Again, that is consistent with what we have known previously, that when you do add a LABA to an ICS—in fact, when they are given together, ideally using the same device—you get a reduction in severe exacerbations, not an increase. That study was very reassuring that in fact there was absolutely no safety signal at all.

There are 2 further large safety studies that are just about to be completed and to be hopefully soon published: One comparing budesonide/formoterol, which is again in the same device, to budesonide alone, and the third one, an inhaled steroid mometasone and formoterol compared to mometasone alone. Each of those other 2 studies again, about close to 12 000 individuals for 6 months, exactly the same design. So when the 3 studies are published, we are going to have a cohort of patients of roughly 35 000 to 40 000, followed over 6 months, and that should I think finally put this issue to rest.

Nice opportunity for another meta-analysis.

Indeed....

If that is the case and if that is the safety concern, is there a place for LABAs as a single drug in a single inhaler?

That is an excellent question. And the answer in asthma is: "Absolutely not." LABAs should never ever be used as a monotherapy, or indeed short-acting β_2 -agonists, in my view, as a monotherapy used regularly to manage patients with asthma. However, there is a place for LABAs as a monotherapy or combined with another bronchodilator, a long-acting muscarinic antagonist (LAMA), for the management of chronic obstructive pulmonary disease (COPD). In fact, the COPD treatment recommendations are fairly consistent that the first treatment approaches for COPD should be optimizing bronchodilation with either a LABA alone or LABA and a LAMA combination. Only in

patients who are having exacerbations in COPD should an inhaled steroid be added. So that is why there are still going to be, for the foreseeable future, LABAs or a LABA together with a LAMA in the same device available.

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