FDA alerts asthmatics to drug safety risk

The US FDA has changed the label for the long-acting β_2-agonist salmeterol, warning users of an increased risk of death associated with its use.

Clare Ellis

In August this year, the US FDA added a new warning to drug products containing GlaxoSmithKline's long-acting β_2-agonist salmeterol (Serevent). It alerted users to a small increased risk of death observed in a large-scale trial in asthma patients. The FDA stressed that the benefits of salmeterol continue to outweigh the risks, but asthma researchers say the question of why some patients are dying is one that cannot be ignored.

Asthma is a chronic inflammatory disorder of the lungs that affects nearly 150 million people worldwide and causes more than 180,000 deaths each year. The standard 'quick-relief' cure for asthma attacks is short-acting β_2-agonists. These bronchodilating drugs bind to β_2-adrenoceptors dotted along the surface of the smooth muscle cells lining the bronchial tubes. Agonist binding elicits a complex signalling cascade that results ultimately in a reduction in intracellular calcium levels and subsequent smooth muscle relaxation, opening up the airways and protecting against contraction.

For persistent sufferers, who struggle frequently with laboured breathing, the introduction in the early 1990s of long-acting β_2-agonists such as salmeterol was a saviour. Like its short-acting predecessors, salmeterol stimulates β_2-adrenoceptors, but the presence of a lipophilic side chain in salmeterol means that it latches onto its target receptors for longer, providing prolonged relief.

But ten years ago, results from a large-scale post-marketing trial — the Serevent Nationwide Surveillance Study — hinted at a small, although statistically insignificant, increase in asthma-related deaths in patients taking salmeterol. Concerns about the long-term safety of β_2-agonists led GSK to initiate the Salmeterol Multi-Centre Asthma Research Trial (SMART). SMART was halted pre-maturely in January this year after an interim analysis of around 26,000 patients alerted investigators to a small, but significant, risk of asthma-related deaths or life-threatening episodes in patients taking salmeterol. This risk was significantly greater in African-Americans, and among patients who were not taking inhaled corticosteroids, which tackle the underlying inflammation that causes asthma.

As the FDA and GSK discuss the next steps, experts in the field are attempting to explain the apparent paradox of how a drug designed to relieve symptoms can, in some instances, make them worse.

Professor Peter Barnes of the National Heart and Lung Institute at Imperial College, London, says that people in the asthma community have long been advocating the use of salmeterol as an 'add-on' therapy for asthmatic patients who are not well controlled on inhaled corticosteroids. "Patient use of inhaled corticosteroids should have been a prerequisite for SMART," says Barnes. He believes that long-acting agonists should never be used alone in patients with asthma, and is a firm advocate of combination inhalers, in which a corticosteroid and a long-acting agonist are administered together. These include GSK's Seretide (fluticasone/salmeterol) and AstraZeneca's Symbicort (budesonide/formoterol), which is currently only approved for use in Europe.

"There is no question that using long-acting β_2-agonists alone without inhaled corticosteroids is risky and may give a false sense of control to patients," agrees Nick Hanania, Principal Investigator of the Asthma Clinical Research Center at Baylor College of Medicine, Texas. It could be that when used alone, β_2-agonists lull patients into a false sense of security by making them feel better, but might actually mask deteriorating condition, thereby increasing the risk of death.

But Hanania and others stress that this is not the whole story. Although no one denies the immense benefits of salmeterol, they all agree that some questions regarding the safety of the chronic use of long-acting β_2-agonists in the treatment of asthma remain to be answered.

"The problem is that 24/7 occupancy of β_2-adrenoceptors gives no chance for the system to recover," says Professor Brian Lipworth of Dundee University. "The receptors reduce in number, or downregulate, and become uncoupled from their downstream signalling pathways. This desensitizes the system so that it doesn't respond as well to agonist." This 'desensitization' not only reduces the body's response to long-term β_2-agonists, but could also have serious consequences in the event of a severe attack if patients fail to respond to the short-acting agonist treatments that are

Salmeterol, the active ingredient of Serevent, has been linked with a small, but significant, risk of asthma-related death.

the only way of opening the airways and providing relief.

Professor Stephen Liggett of the University of Cincinnati, Ohio, thinks that prolonged use of β_2-agonists could also promote hyper-sensitivity to asthmatic triggers. "It seems the body counter-regulates chronic opening of the airways by increasing the restrictive component," he suggests. "β_2-adrenoceptor activation may initiate crosstalk with pathways in the cell involving contractile receptors, leading to heightened airway contraction in response to certain stimuli."

One thing most people agree on is that genetics could help to clarify what's going on. Several papers have identified polymorphisms in the genes encoding β_2-adrenoceptors that might effect their response to β_2-agonists. "There is absolutely no question that the frequencies of several β_2-adrenoceptor polymorphisms differ between Caucasians and African-Americans," says John Lima, Principal Investigator of the American Lung Association Asthma Clinical Research Center at the Nemours Children's Clinic in Jacksonville, Florida. "That the SMART results could reflect genetic differences between ethnic groups should not be ignored." Stephen Liggett agrees, adding that "DNA should be collected in all drug trials. It's an issue that regulatory bodies cannot ignore."