Ventolin remains a breath of fresh air for asthma sufferers, after 40 years

In the first article in a series on landmark drugs, Jenny Bryan retells the history of Ventolin and explains why it still plays a major role in the treatment of asthma

When Allen & Hanburys launched the first selective β_2-receptor agonist, Ventolin (salbutamol), in 1968, the drug was an instant success. With asthma mortality peaking at over 2,000 deaths per year in the mid 1960s, an effective bronchodilator that specifically targeted the β_2-receptors of the lungs was immediately seen as an important advance.

"There was precious little before Ventolin for routine bronchodilation," recalls Tim Clark, professor of pulmonary medicine at the National Heart and Lung Institute, Imperial College, London. "We used isoprenaline, but its lack of selectivity for bronchial smooth muscle meant that it caused tachycardia and there was concern that it could be linked with the asthma deaths.

"The only other drugs we had to treat asthma symptoms were adrenaline and aminophylline for severe asthma, and theophylline and ephedrine for chronic asthma. Other preparations for chronic asthma included sedatives such as barbiturates," he explains. "So there were great expectations for Ventolin because it was a good bronchodilator, it lasted longer than isoprenaline and it didn't have the cardiac side effects. It was hoped that Ventolin would be of great use for both acute and chronic asthma."

Development of salbutamol

The development of salbutamol followed the discovery in the early 1960s that beta adrenoceptors had two subtypes — β_1 found predominantly in the heart and β_2 in smooth muscle such as that in the lungs.[1] Allen & Hanburys chemists therefore set to work to make analogues of isoprenaline which were more specific to the β_2-receptor. They were rewarded with salbutamol, which was over 500 times more potent at the β_2- than the β_1-receptor.[2]

Activation of the β_2-receptor is understood to relax the airways by increasing intracellular cyclic adenosine monosphosphate (cAMP), which leads to phosphorylation of regulatory proteins that control muscle tone, reduction in the release of intracellular calcium and reduced sensitivity of contractile proteins.[3] The β_2-receptor straddles the cell membrane in a series of seven loops and becomes activated when it is coupled with the Gs protein and guanine triphosphate. It is thought that β_2-agonists work by stabilising β_2-receptors in their activated form, so that the bronchial smooth muscle is relaxed and the airways dilated.[3]

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Ventolin lived up to expectations and it was not long before it had almost replaced isoprenaline and become the mainstay of asthma treatment with a liquid formulation suitable for nebulisation, as well as oral preparations added to the range. Other short acting β_2-agonists followed, such as Astra's terbutaline (Bricanyl) and Boehringer Ingelheim's fenoterol (Berotec). But Ventolin cornered the market; not only was it first, it was British.

Race for a long-acting β_2-agonist

The new race was to develop a long-acting β_2-agonist which would be as selective and free of cardiac side effects as salbutamol and provide symptom relief well beyond the four hours achieved with the first generation, short-acting drugs. At Allen & Hanburys, the aim was to find a way to anchor a selective β_2-agonist to its receptor for prolonged periods, thus extending its activity. The solution proved to be salmeterol (Serevent) — the first long-acting β_2-agonist (LABA). Launched in 1990, it was subsequently shown to achieve its 12-hour duration of action by binding to the β_2-receptor at the active site and at a second "exosite" on the receptor at a point close to the junction of the cell membrane and the cytoplasm.[4]

But, just as Ventolin had been launched against a backdrop of rising asthma mortality in the mid 1960s, salmeterol and its rival formoterol (Oxis) made by Astra, came onto the market with asthma deaths on the rise.

Increase in death of asthma patients

During the 1980s, an increase in asthma deaths in New Zealand was linked to the over use of fenoterol, a short-acting β–agonist marketed in a high-dose preparation with β_1-agonist activity comparable to that of isoprenaline and with similar accompanying cardiac side effects.[5] The rise in asthma deaths in New Zealand started in 1976, the year of fenoterol's highly successful introduction. In response to epidemiological evidence of a link between fenoterol and asthma deaths, three case-control studies were carried out, all showing a link between fenoterol use and asthma deaths.[5] The product was removed from the New Zealand drug tariff in 1989 and then withdrawn from the market. Asthma deaths subsequently fell back to pre-fenoterol levels. British rates never reached those seen in New Zealand and fenoterol was not widely used in the UK, but mortality did rise again through the late 1980s to peak once more at nearly 2,000 deaths per year. Although the rise occurred before the introduction of salmeterol, there were concerns that LABAs could exacerbate the problem and the finger of suspicion was soon pointing in their direction.

"The problem will always be that severe asthma is associated with deaths and the more severe a person's asthma, the more they use their bronchodilator, so it's always going to be difficult to unravel the link," explains Professor Clark. "I used to liken it to finding a person dead in the desert grasping an empty water bottle. Would you assume that it was the water which had killed him?"

A recent contributor to the controversy — the Salmeterol Multicenter Asthma Research Trial (SMART) — showed small, statistically significant increases in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in asthma patients who took salmeterol in addition to their usual treatment, compared with placebo.[6] Subgroup analyses suggested that the risk was greater in African Americans compared with Caucasian subjects and in those not taking inhaled corticosteroids.

Both UK and US guidance now stress the importance of only using LABAs in combination with inhaled steroids. But, with mortality rates in the UK back down to about 1,300 in 2005, it may be time for a short pause in the long-running debate.

Whatever the eventual conclusions, Ventolin has remained free of the claims and counter-claims which have left question-marks over the LABAs. Indeed, as Professor Clark points out, it is now used not only to relieve the symptoms of asthma, but as a measure of asthma control. Patients who need more than a few puffs per week of their Ventolin do not have full control of their asthma and probably need to step up their other treatment.

"Ventolin has undoubtedly stood the test of time for relief of symptoms and measuring asthma control and, although most people are now prescribed generic salbutamol, people still call it Ventolin and a surprising number do still get the original brand," Professor Clark said.

After nearly 40 years and many millions of blue puffers since its launch, the name Ventolin has become to asthma what Hoover is to housework.

References

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