Bronchodilators:Past,Present and Future.

Malcolm Johnson

Bronchodilators have been used as a mainstay treatment for asthma and COPD for over 35 years.

Selective beta-2-agonists,such as salbutamol, were first developed in the 1960's.Although highly efficacious and safe, their major drawback was that they had a duration of action of only 4-6 hours. Advances were made in the 1980's with the development of the long-acting beta-2-agonists(LABAs), salmeterol and formoterol, with 12-hour bronchodilator activity, allowing twice-daily dosing. However, there are now several compounds such as indacaterol, vilanterol trifenatate, olodaterol and abediterol undergoing clinical evaluation as once-daily, ultra-long acting agents, producing significant increases in lung function in asthmatic and COPD patients over 24-hours.This third generation of beta-2-agonist bronchodilators will also be administered as the more potent single R-enantiomer, whereby a smaller dose can be used, minimising systemic side effects. In the future, in asthma, these new beta-2-agonists are likely to be combined with other drugs, such as inhaled corticosteroids, rather than being used as monotherapy. Combinations such as indacaterol/mometasone and vilanterol trifenatate/fluticasone furoate are in development.

An alternative approach to bronchodilatation in COPD is through antagonists of the airway muscarinic receptors. The original short-acting compounds, such as ipratropium bromide, have now been improved with the development of tiotropium bromide, the first long-acting "M-3-selective" muscarinic antagonist (LAMA),with a duration of action of 24-hours.Other compounds currently in Phase III development include:NVA-237,aclidinium bromide and umeclidinium. These agents may be used as monotherapy or combined with LABAs to promote a dual-bronchodilator mechanism eg. NVA-237/indacaterol,umeclidinium/vilanterol trifenatate,aclidinium bromide/formoterol and tiotropium bromide/olodaterol.

Finally, it is now possible to combine beta-agonist and muscarinic antagonist bronchodilator activity in a single ,dual-pharmacophore molecule (MABA).GSK 961081 is currently in Phase II development for COPD.