WHAT YOU SHOULD KNOW ABOUT ASTHMA MEDICATIONS

Main points

- Historically asthma was not associated with mortality.
- Deaths from asthma first appeared in the 1930s when the first drug treatments became available.
- Overuse of bronchodilator treatments in the 1960s-70s were found to increase asthma mortality.
- Asthma was re-classified as an inflammatory disorder in the 1980s and steroids become the first line of treatment.
- Long-acting beta 2 adrenergic agonists (LABAs) when used alone, without concomitant inhaled steroids, increase the risk of asthma-related death.
- You should not make any changes to prescribed medication without first consulting your prescribing doctor/specialist.

A brief history of asthma

Asthma is first described in Homer's Iliad. The word asthma comes from the ancient Greek aazein, meaning to exhale with open mouth, to pant.[1]

Fast forward to the early 20th century and a review of classical textbooks. **Nowhere is death from asthma mentioned prior to the 1930s.** All physicians writing at that time are adamant that asthma is not a lethal disease.[2] Sir William Osler (1882) states that the asthmatic will "pant unto old age" and "The outcome is not unfavourable even if left untreated."

Advent of drug treatments and asthma mortality

The original concept of asthma being primarily a disease of airway smooth muscle drove the development of bronchodilator drugs. The earliest treatments in the 1930s delivered adrenalin intravenously. Deaths from asthma are first reported in the 1930s coinciding with these treatments. Modern aerosol metered inhalers (blue puffers) that administer adrenaline-like micro droplets first appeared in the late 1950s. Increasing availability of "blue puffers" in the 1960s was also marked by a corresponding increase in asthma deaths. Several physicians at that time started to suspect that increased asthma mortality might be linked to the introduction of bronchodilators (blue inhalers).[3 4]

Asthma was treated largely a disease of "bronchospasm". Bronchodilators included theophylline, ephedrine, adrenaline and, by the first half of the 20th century, isoprenaline to be followed by the selective β2-adrenoceptor agonists, salbutamol, terbutaline, remiterol and fenoterol by inhalation and as oral medications. However, their very effectiveness in reversing bronchospasm and their initial apparent safety led to their unrestricted use as over-the-counter medications.

Over-reliance on bronchodilators was thought to underlie the epidemic of asthma death reported in Australia, the US and the UK that peaked in the mid-1960s (isoprenaline-related).[5] [6] A second peak in New Zealand in the mid-1980s was linked to a popular bronchodilator (fenoterol). [7] Fenoterol was found to be responsible for 600 asthma deaths and was subsequently withdrawn from sale in New Zealand.[8]

What we have learned since the 1970s

These asthma death epidemics led to a realisation that airway inflammation underpinned the disordered airway function. This led to the development of controller therapies such as inhaled cromones and corticosteroids. These medications are now the first line of drug treatment in asthma.[5]

Studies since the 1970s have identified the dangers of overuse of beta agonist reliever medications.[4] [7] They have also highlighted the risks from the use of long acting beta agonists (LABAs).[9] The research has shown beta agonist tolerance is possible even with normal use of LABA medications. This can result in short acting reliever medication being ineffective for some acute exacerbations.[10]

One study has shown that LABAs increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.[11] The risk of serious asthma-related events attributable to FDA approved LABAs was greatest among children.[12] These findings prompted the FDA to issue boxed warnings of asthma-related death for all LABAs including vilanterol in Breo Ellipta and Salmeterol in Seretide/Advair. [13]

However, in 2010 the FDA lifted boxed warnings from the drug labels of medicines that contain both an inhaled corticosteroid and LABA.[14] The decision was based on 4 trials carried out by sponsors of the combination drug products. Some have said allowing the companies to conduct their own trials brings into question the validity of the findings.

A 2010 study of registered drug trials found those funded by industry were less likely to be published within 2 years of study completion and were more likely to report positive outcomes than were trials funded by other sources.[15]

Dr Marcia Angell, former editor in chief of the New England Journal of Medicine, wrote: "It is simply no longer possible to believe much of the clinical research that is published, or to rely on the

judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor." [16]

LABA medications: prescribe with care

There is still concern with LABA medications both with and without ICS. They should be used with caution and only prescribed for asthma not otherwise controlled with ICS therapy alone. [17]

Medications containing short acting beta agonists include Ventolin, Respigen, and Salamol. Medications containing long acting beta agonists include Serevent and Oxis and the combination inhalers: Symbicort, Seretide, Vannair and Breo Ellipta.

Beta agonists, hyperventilation and inflammation

One rarely mentioned effect of beta- adrenoceptor stimulation is increased ventilation, i.e. an increase in both rate and volume of breathing, measured as the minute volume. Patients with asthma hyperventilate during an asthma attack. Furthermore, hyperventilation makes asthma worse.[17]

One possible mechanism for the pro-inflammatory action of these medications is that they stimulate respiratory drive and promote over-breathing. So, by helping reduce the need for bronchodilator medication, symptoms are better controlled, and, in many cases, less preventer steroid medication is required.

What you can do

We instruct our clients not to make any changes to prescribed medication without first consulting your prescribing doctor/specialist.

If your asthma is poorly managed and/or you are needing more than 3-4 puffs of your reliever medication a week we advise you to review your asthma management plan with your doctor.

The Buteyko Breathing Clinic offers a natural way to control and prevent asthma and other breathing-related disorders. If you or your doctor would like to know more about our breathing retraining programme, please don't hesitate to contact the clinic on 09-360 6291 or info@buteykobreathing.nz

Prepared by: Glenn White BSc MSc MBIBH
Practitioner trainer/ Director Buteyko Breathing Clinics
1 May 2018

REFERENCES

[1] Marketos SG, Ballas CN. J Asthma. 1982;19(4):263-9
https://www.ncbi.nlm.nih.gov/pubmed/6757243

[2] Parkinson, P. Smash Asthma, The wisdom of wheezing 2015 Resource Books
http://www.resourcebooks.co.nz/smash_asthma.html

[3] Speizer, F, Doll, R. A Century of Asthma Deaths in Young People. Br Med. J. Jul 27, 1968
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1986204/

[4] Fox, WH. Asthma 1995
https://www.amazon.com/Asthma-Your-Suffering-Really-Necessary/dp/0709057059

[5] Spitzer, WO., et al. N Engl J Med February 1992; 326:501-506
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892047/

[6] Holgate, ST. Allergy Asthma Immunol Res. 2010 July;2(3):165-171.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892047/

[7] Pearce, N. et al End of the New Zealand asthma mortality epidemic. The Lancet Vol 345 January 7, 1995
https://www.thelancet.com/journals/lancet/article/PIIS0140673695911596/abstract

[8] Pearce N. The use of beta agonists and the risk of death and near death from asthma. J Clin Epidemiology. 2009;62:582–587. https://www.ncbi.nlm.nih.gov/pubmed/19422997

[9] Salpeter, SR, Buckley NS, Ormiston TM and Salpeter EE., Meta-analysis: Effect of Long-Acting -Agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006https://www.ncbi.nlm.nih.gov/pubmed/16754916

[10] Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: Respiratory tolerance to regular ß$_2$-agonist use in patients with asthma. Ann Intern Med. 2004; 140:802-13 https://www.ncbi.nlm.nih.gov/pubmed/15148067

[11] Salpeter, SR et al Long-acting Beta-Agonists with and Without Inhaled Corticosteroids and Catastrophic Asthma Events. The American Journal of Medicine 2010 123, 322-328 https://www.ncbi.nlm.nih.gov/pubmed/20176343

[12] McMahon AW Pediatrics. 2011 Nov;128(5)
https://www.ncbi.nlm.nih.gov/pubmed/22025595

[13] FDA Breo Ellipta safety information
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204275s002lbl.pdf

[14] FDA Drug Safety Communication Dec 2017
https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm590001.htm

[15] Bourgeois, FT Ann Intern Med. 2010 Aug 3; 153(3): 158–166.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3374868/

[16] Angell M. Drug Companies & Doctors: A Story of Corruption. The New York Review of Books magazine.
http://www.nybooks.com/articles/2009/01/15/drug-companies-doctorsa-story-of-corruption/

[17] Deeney C, The Pharmaceutical Journal 12 August 2006 pp 193-5
https://pdfs.semanticscholar.org/fce5/4f6bf6246bb5ae38b801089d4223230c7ab5.pdf