Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

A PROOF OF CONCEPT STUDY TO EVALUATE WHETHER CHRONIC EXPOSURE TO LEVOSALBUTAMOL OR RACEMIC SALBUTAMOL IS ASSOCIATED WITH A REBOUND INCREASE IN AIRWAY HYPER-RESPONSIVENESS IN GENETICALLY SUSCEPTIBLE ASTHMATICS.

Researchers
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Aim
The novel objectives of this study were as follows:
1. To directly compare effects of regularly using two types of asthma reliever inhaler (racemic salbutamol and levosalbutamol) at the point when the drug effect has worn off (i.e. 6 hours post dose) on one of the main hallmarks of asthma (airway hyper-responsiveness or airway twitchiness), in persistent asthmatics who are already receiving asthma preventer treatment (inhaled corticosteroids). In other words, does regular use of either reliever inhaler make the airway twitchiness worse when the drug wears off?
2. To perform the same comparison in patient groups stratified by the genotype of the airway receptor for salbutamol (Beta-2 adrenoceptor 16).

Project Outline/Methodology
We performed a randomised, double-blind, placebo-controlled, triple crossover trial comparing 2 weeks of regular treatment with either inhaled racemic salbutamol (200µg qid); levosalbutamol (100µg qid); or placebo on methacholine PC_{20} (provoctive concentration causing 20% fall in FEV_1 – which is a measure of airway twitchiness) 6 hours post dose in 30 mild to moderate persistent asthmatics receiving inhaled corticosteroids – 15 patients had the homozygous Arginine genotype of the Beta-2 adrenoceptor gene (Arg16), and 15 patients had the homozygous glycine (Gly16) genotype.
Domiciliary peak expiratory flow (PEF) was recorded as a secondary outcome measure.

Key Results
There was no worsening of airway twitchiness to after chronic treatment with either racemic salbutamol or levosalbutamol compared to placebo; nor between airway receptor genotypes. Both active treatments improved morning PEF in Gly16 but not Arg16 patients; while evening PEF improved in both Gly16 and Arg16 patients.

Conclusions
Chronic use of either racemic salbutamol or levosalbutamol asthma relievers, in addition to background preventer treatment, did not cause worsening of airway twitchiness 6 hours post dose compared to placebo; with no difference seen between beta-2 adrenoceptor genotypes.

What does this study add to the field?
Patients may take their reliever inhaler regularly, despite it only being prescribed for on-demand use. Frequent salbutamol can be detrimental in asthma in terms of worsening lung function over time; as can the type of salbutamol formulation and beta-2 adrenoceptor 16 genotype (Arginine homozygotes or heterozygotes). We found no worsening of airway twitchiness comparing two types of regular reliever inhalers in steroid-treated asthmatics, irrespective of their airway Beta-2 adrenoceptor genotype.

Implications for Practice or Policy
It is reassuring to know that regular expsoure to racemic salbutamol or levosalbutamol does not cause rebound worsening of airway twitchiness in asthmatics, irrespective of their airway beta-2 adrenoceptor genotype, provided they are also receiving background inhaled corticosteroid preventer therapy.

Where to next?
Further longer term real-life prospective studies are now required to further examinine this question, particularly looking at asthma control outcomes (e.g. Asthma Control Questionnaire) in gentotype stratified patients, comparing alternative 2nd line long-acting (12-24h) bronchodilator therapies.

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