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Respiratory Research Review™

Making Education Easy

Issue 91 – 2013

In this issue:

Abbreviations used in this issue

FeNO = fraction of exhaled nitric oxide
FEV_1 = forced expiratory volume in 1 second
ICS = inhaled corticosteroid
IL = interleukin
LABA = long-acting β2-agonists
MDI = metered dose inhaler
OR = odds ratio

Welcome to issue 91 of Respiratory Research Review.

Selecting articles authored by New Zealanders has been one of the guiding principles when selecting articles for this issue. NZ authors contribute widely to the international asthma literature.

Mitesh Patel and colleagues from the Medical Research Institute of NZ in Wellington investigate SMART (Single inhaler Maintenance and Rescue Therapy) in a 'real-life' setting of 300 patients with a recent asthma exacerbation. Because they had *a priori* concerns of medication overuse, delayed seeking of medical review and ultimately a higher burden of corticosteroids, they used electronic monitors to measure date and time of MDI use. As outlined below, SMART therapy delivered in every aspect. The NZ study is followed by a European study using a SMART-type regimen using beclometasone and formoterol, finding very similar positive outcomes. The SMART regimen was used inside a management plan, and an American group reminds us of the importance of such plans for therapy adherence and patient satisfaction.

Phillippa Ellwood from Auckland is using ISAAC data to describe a relationship between fast-food consumption and asthma, rhinitis and eczema, with milk, eggs, cereals, fruits and vegetables having protective effects. An American group reports an attenuating effect on bronchoconstriction after taking a lipid fraction extract of NZ green-lipped mussels. We finish off reviewing three articles: effect of an IL-4/IL-13 antagonist on asthma control, a trial of propranolol controlling asthma and the possible novel disease of asthmatic granulomatosis.

We hope you enjoy the selection, and we are happy to respond to feedback.

Kind regards

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Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations

Authors: Patel M et al, for the SMART Study Group

Summary: Patients aged 16–65 years with a recent asthma exacerbation were randomised to SMART (two actuations of budesonide/formoterol 200µg/6µg twice daily via a combination MDI, with one additional actuation for symptom relief as needed; n=151) or a standard fixed-dose regimen (two actuations of budesonide/formoterol 200µg/6µg twice daily via a combination MDI with 1–2 actuations of salbutamol 100µg by MDI for symptom relief as needed; n=152). Compared with the standard regimen, SMART was associated with: i) no significant difference in the proportion of participants with ≥1 high-use episode of β-agonist (primary outcome; 84% vs. 68%; p=0.058); ii) significantly fewer days of high use (5.1 vs. 8.9; p=0.01); iii) significantly fewer days of high use without medical review among participants with ≥1 high-use episode (8.5 vs. 18.3; p=0.001); iv) significantly greater inhaled budesonide use (943.5 vs. 684.3 µg/day; p=0.006); v) significantly lower oral corticosteroid exposure (77.5 vs. 126.6mg prednisone; p=0.011); vi) no significant difference in composite systemic corticosteroid exposure (793.7 vs. 772.1mg prednisone equivalents per year; p=0.76); and vii) a significantly lower weighted mean severe asthma exacerbation rate (0.53 vs. 0.97; p=0.004).

Comment: The SMART regimen has been around for at least a decade – what is special about this article in the first edition of Lancet Respir Med? It is an investigator initiated trial funded by the Health Research Council of New Zealand. Patients were all-comers between the ages of 16 and 65 years with a physician diagnosis of asthma, and electronic monitors were used to monitor actual use. The results support the SMART regimen; SMART let to higher ICSs, but less oral steroid courses because of significantly fewer asthma exacerbations. **Bottom line: SMART has a favourable risk-benefit profile and can be recommended for adults with severe asthma.**

Reference: Lancet Respir Med 2013;1(1):32–42
http://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2813%2970007-9/fulltext

Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma

Authors: Papi A et al

Summary: Following a 2-week run-in period of beclometasone/formoterol 100µg/6µg per inhalation twice daily plus salbutamol 100µg as required via MDI, patients with asthma (not fully controlled, FEV_1 ≥60% of predicted) were randomly allocated to receive maintenance with beclometasone/formoterol 100µg/6µg twice daily with as-needed reliever therapy with either beclometasone/formoterol 100µg/6µg (evaluable n=852) or salbutamol 100µg (849). Compared with the salbutamol reliever group, the beclometasone/formoterol reliever group had a significantly longer time to first exacerbation (primary outcome: 209 vs. 134 days; hazard ratio 0.64 [95% CI 0.49, 0.82]; p=0.0005) and a significantly lower severe exacerbation rate (12% vs. 18%; p=0.0003). The beclomethasone/formoterol reliever arm also had significantly better improvements for symptoms, days with mild exacerbations, asthma control days, reliever use and lung function parameters, and a similarly low rate of serious adverse events, compared with the salbutamol reliever arm.

Comment: This article, published in the same edition of the new Lancet Respir Med, examined a similar principle. This time the European investigators compared a low-dose extra-fine beclometasone/formoterol combination inhaler in two regimens: fixed-dose combination product and salbutamol as needed with the SMART instructions for the combination product. The main outcomes are: a) asthma can be controlled with a lower dose of extra-fine inhaler medications; b) overuse of β-agonist can be reduced; and c) **our bottom line: single inhaler maintenance and reliever treatment reduced the time to a severe asthma exacerbation.**

Reference: Lancet Respir Med 2013;1(1):23–31
http://tinyurl.com/LancetResp-1-23

Asthma action plans and patient satisfaction among women with asthma

Authors: Patel MR et al

Summary: These authors performed a cross-sectional analysis of baseline data for 808 women with asthma who were participants in a randomised trial evaluating a self-management programme; 84% of the women were satisfied with their asthma care and 48% had a physician-written asthma action plan. Compared with women with an action plan, those without one were significantly less likely to: i) take their asthma medication as prescribed ($p<0.001$); ii) initiate a discussion about asthma with their physician ($p<0.001$); iii) own a peak flow meter ($p<0.001$); and iv) report being dissatisfied with their asthma care (adjusted OR 2.07 [95% CI 1.35, 3.17; $p<0.001$]).

Comment: Summarising large randomised trials for publication may create unintentional gaps in the message. Both of the above trials used their regimen in the framework of a written asthma management plan. These American authors went back to analyse data from two American trials, with the particular focus on the effect of an asthma management plan on women. They found that almost half of the participants did not have a management plan. **Bottom line: participants without a management plan were less likely to own a peak flow meter, take asthma medications and initiate discussion about asthma, and were less satisfied with their asthma management.**

Reference: Chest 2012;142(5):1143–9

http://tinyurl.com/Chest-142-1143

Impact of maternal use of asthma-controller therapy on perinatal outcomes

Authors: Cossette B et al

Summary: These researchers analysed data for 7376 pregnancies in a cohort of Canadian women who had asthma while giving birth, 8.8% and 59.6% of which were associated with LABA and ICS exposure, respectively; all LABA recipients also received ICSs. The overall respective prevalences of low birthweight, preterm birth and small for gestational age were 7.7%, 9.5% and 13.5%. No association was seen between use of LABAs and these pregnancy outcomes, but nonsignificant trends were seen for increased prevalences with mean daily ICS fluticasone-equivalent doses of >125µg.

Comment: Uncontrolled asthma has been associated with low birthweight, preterm birth and small for gestational age. These Canadian authors reported, over a decade, on a cohort of woman with asthma giving birth. Of the 7376 pregnancies, 56.9% were exposed to an ICS and 8.8% to a LABA. Reassuringly, neither the use of a LABA nor the use of low/moderate dose of an ICS was associated with low birthweight, preterm birth or small for gestational age. It is less clear if the association with high-dose ICSs reflects a drug effect or more severe asthma. **Bottom line: standard asthma therapy including the use of LABAs appears to be safe in pregnancy.**

Reference: Thorax 2013;68(8):724–30

http://thorax.bmj.com/content/68/8/724.abstract

Respiratory Research Review

Independent commentary by Associate Professor Lutz Beckert, Respiratory Physician at Christchurch Hospital.

For full bio CLICK HERE

Research Review publications are intended for New Zealand health professionals.

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

Short-term impact of the smokefree legislation in England on emergency hospital admissions for asthma among adults

Authors: Sims M et al

Summary: This population-based research, using a generalised additive model adjusted for seasonality, variation in population size and region-specific, nonlinear, long-term trends, found that England's smoke-free legislation resulted in an immediate 4.9% reduction in adult emergency admissions for asthma, or an estimated reduction of 1900 admissions annually during the first 3 years since the legislation was introduced.

Comment: This article uses rather complex statistics to ensure robust data modelling. The researchers explored the impact of the 'natural' experiment of the July 1st, 2007 introduction of smoke-free legislation on the number of adult emergency admissions. Similar studies have been published for Ireland, Kentucky, Delaware and NZ, reporting reductions of 5–40% (NZ 16%); however, many of these studies had methodological limitations. The year following the introduction of the smoke-free legislation, about 1900 admissions with asthma were prevented in the UK. **Bottom line: smoke-free legislation reduced asthma admissions by about 5% a year.**

Reference: Thorax 2013;68(7):619–24

http://thorax.bmj.com/content/68/7/619.abstract

Do fast foods cause asthma, rhinoconjunctivitis and eczema?

Authors: Ellwood P et al, the ISAAC Phase III Study Group

Summary: This paper reported global findings from phase III of the ISAAC (International Study of Asthma and Allergies in Childhood), in which patients aged 13–14 years and parents/guardians of children aged 6–7 years completed questionnaires on asthma, rhinoconjunctivitis, eczema and food intake behaviours over a 12-month period. Consumption of fruit ≥3 times per week was associated with an apparent protective effect against severe asthma in adolescents and children (respective ORs 0.89 [95% CI 0.82, 0.97] and 0.86 [0.76, 0.97]), while consumption of fast food ≥3 times per week increased the severe asthma risk (1.39 [1.30, 1.49] and 1.27 [1.13, 1.42]) and risks of severe rhinoconjunctivitis and severe eczema.

Comment: In this study, the Auckland-led research group interrogated the ISAAC database to correlate self-reported asthma symptoms with different dietary behaviours from 319,196 adolescents and 181,631 children. The main results were that milk, eggs, meat, fruit, cereal and vegetables were either protective or associated with less severe wheeze or rhinitis if consumed ≥3 times per week. Particularly in adolescents, the consumption of fast food, butter, margarine and pasta were all positively associated with asthma. **Bottom line: fast food may contribute to increased asthma, rhinoconjunctivitis and eczema in adolescents and children.**

Reference: Thorax 2013;68(4):351–60

http://thorax.bmj.com/content/68/4/351

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Marine lipid fraction PCSO-524™ (lyprinol®/omega XL®) of the New Zealand green lipped mussel attenuates hyperpnea-induced bronchoconstriction in asthma

Authors: Mickleborough TD et al

Summary: Patients with asthma and documented hyperventilation-induced bronchoconstriction received 3 weeks of dietary supplementation with NZ Green-lipped mussel extract (PCSO-524™) and placebo in a randomised, crossover design with a 2-week washout. Compared with placebo and pretreatment usual diet, the inclusion of PCSO-524™ was associated with a significant reduction in maximum fall in post-eucapnic voluntary hyperpnoea FEV_1 (–8.4% vs. –22.5% and –19.3%, respectively; $p<0.05$). PCSO-524™ also significantly reduced rescue medication use and pre- and post-eucapnic voluntary hyperpnoea levels of exhaled breath condensate cysteinyl leukotrienes and 8-isoprostane and urinary 9α, 11β-prostaglandin-F2 and Clara (CC16) protein, while exhaled breath condensate pH and asthma symptom scores were significantly improved ($p<0.05$ for all).

Comment: These American authors investigated the effect of a NZ green-lipped mussel extract. They recruited 20 participants with asthma and randomised them in a crossover design to receive either the mussel extract or placebo. Their endpoints were a loss of asthma control using eucapnic hyperventilation, FeNO and breath condensate markers. Participant using the mussel extract had a lesser fall in FEV_1 after challenge testing, lower levels of FeNO and a reduction of inflammatory markers in exhaled breath condensate. **Bottom line: the mussel extract seems to reduce airway inflammation and provide protection against hyperventilation-induced bronchoconstriction.**

Reference: Respir Med 2013;107(8):1152–63

http://www.resmedjournal.com/article/S0954-6111%2813%2900139-X/abstract

Dupilumab in persistent asthma with elevated eosinophil levels

Authors: Wenzel S et al

Summary: Patients with persistent, moderate-to-severe asthma (blood eosinophil count ≥300 cells/μL or a sputum eosinophil level ≥3%) who used medium- to high-dose ICSs (tapered and discontinued over weeks 6–9) and LABAs (continued until week 4) received subcutaneous dupilumab 300mg (n=52) or placebo (n=52) once weekly. Compared with placebo, dupilumab was associated with a significantly lower asthma exacerbation rate (6% vs. 44%; OR 0.08 [95% CI 0.02, 0.28; p<0.001]), significant improvements in most lung function and asthma control measures, and reductions in biomarkers associated with Th2-driven inflammation, but more injection-site reactions, nasopharyngitis, nausea and headache.

Comment: It is exciting to see that after decades of fine tuning inhaler therapy, new asthma therapies are emerging targeting cytokinetic regulators of eosinophils, like this antibody against the α subunit of the IL-4 receptor. Michael Wechsler's editorial (N Engl J Med 2013;368[26]:2511–3) makes compelling reading. He gives an overview of emerging asthma therapies, and clarifies that in this phase IIa safety study, only 21% of screened subjects were enrolled and dupilumab only showed an effect after standard therapy with ICSs and LABAs had been withdrawn. **Bottom line: the role of biological agents in the 'real world' is as yet undefined.**

Reference: N Engl J Med 2013;368(26):2455–66

http://www.nejm.org/doi/full/10.1056/NEJMoa1304048

Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma

Authors: Short PM et al

Summary: Patients with mild-to-moderate, ICS-treated asthma received propranolol titrated as tolerated over 6–8 weeks to a maximum dosage of 80 mg/day and placebo in a crossover design; all participants received tiotropium for the first 4–6 weeks of each treatment period. There were no significant between-group differences for post-treatment methacholine and histamine challenges. A partial attenuation of albuterol recovery at 20 minutes after histamine challenge was seen with propranolol versus placebo (FEV_1% mean difference 5.28 [95% CI 2.54, 8.01]; p=0.001). A small deterioration of 2.4% was seen in predicted FEV_1 after chronic β-blockade (p=0.055). There were no significant differences for mini-asthma quality of life questionnaire and asthma control questionnaire scores.

Comment: We have previously commented in Respiratory Research Review (Issue 49) on the potential use of β-blockers in asthma to reduce airway responsiveness to methacholine. This matches nicely with animal data, where 'knockout mice' without a β2-recpetor demonstrate less airway hyper-responsiveness, less mucus hyperplasia and less eosinophilia. It is somewhat disappointing that this trial of propranolol in patients with well-controlled mild to moderately severe asthma tolerated propranolol, but showed a loss in FEV_1 and no effect of protecting from methacholine or histamine challenge. **Bottom line: β-blockers remain contraindicated in asthma.**

Reference: Am J Respir Crit Care Med 2013;187(12):1308–14

http://www.atsjournals.org/doi/abs/10.1164/rccm.201212-2206OC

Asthmatic granulomatosis: a novel disease with asthmatic and granulomatous features

Authors: Wenzel SE et al

Summary: These authors reported pathobiological findings from 10/19 patients with difficult-to-treat severe asthma requiring daily systemic corticosteroid use. As well as small airway changes consistent with asthma, interstitial non-necrotising granulomas were seen on pathology in these ten patients. There was no evidence of hypersensitivity pneumonitis, but 70% had a personal or family history of autoimmune-like disease. The ten case patients received treatment with azathioprine, mycophenolic acid, methotrexate or infliximab, which resulted in a decrease in corticosteroid requirements with improved or maintained FEV_1 in nine of them. Six of the other nine patients manifested asthmatic small airway disease alone or with alveolar septal mononuclear cells, but no granulomas, while three had other pathological findings such as aspiration, pneumonia or thromboemboli.

Comment: It does not happen often nowadays that a new disease is being described. Like many of us, these authors struggle with a small group of about 5–10% of patients with typical asthma who are difficult to manage. They identified a group of 19 out of 170 patients from a severe asthma clinic, and performed video-assisted thoracoscopic lung biopsies, taking a generous wedge resection including deep tissue. The authors reported a group with typical asthma pathology and also ill-defined, non-necrotising granulomas. They reported some success treating this group with azathioprine. **Bottom line: asthma granulomatosis may be a different disease explaining difficult-to-control asthma.**

Reference: Am J Respir Crit Care Med 2012;186(6):501–7

http://tinyurl.com/AJRCCM-186-501