March 2007

Family Physician Airways Group of Canada

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Chair Report 2006 ~ A year in review

The year 2006 was quite eventful for the FPAGC. We have been involved in multiple guidelines, seen other new respiratory guidelines arise, been involved in lots of CME's, and have been involved in National decision-making groups to change the face of Respiratory Medicine in Canada. We have made lots of new friends and have many new members, and to all of you I say, welcome.

FPAGC representation occurred at the Asthma Guideline update meeting in June 2006 at Niagara-on-the-Lake. Dr. Andrew McIvor chaired this meeting and a publication is pending. Personally, I have been tasked with creating some cases and reviewing the continuum.

We were also represented at the COPD guidelines update meeting in October 2006 in Ottawa. Dr. Dennis O'Donnell chaired this meeting and again a publication is pending. Members of the FPAGC executive are working on a COPD Action Plan. You will likely be contacted by our Research chair, Dr. Andrew Cave, regarding participation in a study to validate our COPD Action Plan.

This year also showed the release of Sleep Apnea guidelines, with this group chaired by Dr. John Fleetham. I will do a review on this topic for the newsletter also.

Our annual general meeting occurred in conjunction with the Canadian COPD Alliance meeting in Calgary in November 06. Excellent presentations were given by Dr. Rob Hauptman on COPD vs CHF, by Dr. Tony Ciaravella re: Asthma Sucks and by myself on the new GINA guidelines (released November 13, 2006).

Executive members presented also at ASED 7, at the AAFP annual assembly in Washington in Sept.2006, at the Canadian College of Family Physicians FMF in November 2006, at the Ontario College of Family Physicians Annual meeting in November 2006, at the Newfoundland College of Family Physicians meeting in October 2006 and at the Alberta Respiratory Disease Symposium in April 2006. Special thanks to Drs. Clare Hawkins, Alain Couet, Robert Hauptman, and Robert Woodland for their contributions.

We have also been represented at policy decision meetings such as: Health Canada re: acceptable medication applications for new respiratory products; the Canadian Metropolitan TB committee; and the National Respiratory Framework of Health in 2006. We will also be at the table for the meeting in March 2007 on Improving Drug Benefits for Children with Asthma. Special thanks to Dr. Gord Dyck and Dr. John Rea for these initiatives.

New respiratory therapies are popping up including in Canada a new inhaled corticosteroid called **Ciclesonide** (trade name **Alvesco**) and **Omalizumab** (trade name **Xolair**). In the USA, a smoking cessation medication called **Varenicline** (trade name **Chantrix**) has been released and is expected in Canada. We expect a new quinolone from Abbott Pharma this coming year also.

Finally, we have to remember, and do not worry, I will remind you, about the upcoming IPCRG meetings. May 2008 will bring us to Seville, Spain and we are looking at the end of May in Toronto for the 2010 meeting. Preliminary discussions with the University of Toronto for certification have started.

2007 is here! Happy New Year to you all, and may your year be peaceful, happy and successful.

ALAN KAPLAN, MD CCFP(EM), CHAIR, FPAGC

Canadian Lung Association Respiratory Health Pre-Summit Workshop

April 26-27, 2006

Dr. Alan Kaplan, MD CCFP(EM)

Executive Summary

Background

I was invited to be a member of the National Framework on Respiratory Health as a representative of the FPAGC. This group was created when, in March 2006, the Canadian Lung Association (CLA) initiated the planning of a stakeholder workshop to bring together parties interested in collaborating on the development of a National Framework on Respiratory Health.

With funding assistance from Health Canada, the Public Health Agency of Canada, and the pharmaceutical industry, the CLA hosted the "Breathing Matters" Pre-Summit Workshop on April 26-27th in Ottawa.

The workshop objectives were to:

- consider the opportunities available to develop a strategy to improve the respiratory health of Canadians;
- review the current environment, including the political landscape, the range of respiratory health issues, activities and interests, stakeholders' key interests and issues, and activities in provincial/territorial jurisdictions;
- determine preliminary goals in three broad areas (chronic disease, infectious disease, environmental health and tobacco), ie. success indicators in 3,5,10 years;
- consider how we might integrate this into the risk management model developed as a foundation for other health strategies (e.g. Cancer Strategy for Canada); and,
- provide sufficient input to allow for the creation of a plan to develop a framework that would be presented at a future Summit.

The group's vision… *To advance respiratory health for Canadians through policy leadership, innovation, research, and education.*

Four working groups were set up:

- Chronic Disease and Respiratory Health
- Infectious Disease and Respiratory Health
- Environment and Respiratory Health
- Tobacco Control and Respiratory Health

At that meeting, there was significant interest and momentum in moving forward quickly, yet realizing that this endeavour is a significant undertaking that will likely take 2-3 years or more to achieve real progress. As a beginning step, participants agreed that establishment of an Advisory Committee (10-12 members) and Terms of Reference for this group would be important. Participants were asked at the workshop to self-identify and/or recommend appropriate expertise from across the continuum of care and respiratory health field, to form the membership of the Advisory Committee and any sub-committees as deemed appropriate. The CLA will act quickly to finalize the membership and convene the Committee before the end of June. The Committee will be tasked with identifying and scoping the key elements of a framework, initiating working groups for asset mapping and gap analysis; as well as the planning of a larger Respiratory Health Summit to be held in the Spring of 2007.

Participants also expressed interest in a mechanism for sharing information and being kept apprised of progress, challenges, etc., on an ongoing basis. The CLA committed to creating a listserve on their website for this purpose, and it is available at summit@lung.ca.

The Pre-Summit was organized to begin to better understand the current assets and gaps and to come to initial agreement on what needs to be done to move forward. Provincial governments have done some significant work on approaches to particular lung disease issues, but there are not a lot of integrated lung health strategies at the provincial level. The integration piece is missing. The combined direct and indirect cost of lung disease is $8.5 billion, and growing. Unfortunately, there are many competing interests for medical conditions such as cancer and cardiovascular disease, all looking for government money. This group will hopefully be able to compete with these other well organized agencies.

A perception audit survey showed that there is a demonstrated high interest from the community in developing a comprehensive respiratory health framework. Survey respondents identified the top six priorities for discussion as being: public education and awareness; provincial and federal integration and coordination of effort; chronic diseases; access to diagnosis, drugs, disease management; prevention; and, environmental contributors. Also, the top six lung diseases requiring discussion were identified as being: asthma; COPD; occupational lung disease; cancer; sleep apnea; and, influenza.

A number of experts discussed strategies in dealing with government, community needs, private sector needs and even presented what was happening in other countries - the Australian National Asthma Action Plan, the World Health Organization (WHO) Strategy for the Prevention and Control of Chronic Respiratory Disease, and the European Lung White Book, to assess successes in other countries to plan out our strategy here. Representatives of the Canadian Labour Congress stressed the need of prevention at home and in the workplace. Insurance industry representatives also were interested in prevention of claims, rather than just having to pay for them!

Paul Smetanin, Risk Management, President and CEO, Risk Analytica, gave an informative presentation on risk management models He gave several health care examples where risk management models have been successfully used, including the Canadian Strategy for Cancer Control, the National Cancer Institute of Canada, and the Canadian Working Group in HIV and Rehabilitation, among others. In a risk management setting, problems are relative; the process requires measurement of the problem. Paul explained that governments relate well to this concept as it can quantify how bad a situation can be if action is not taken, and how good it can be if certain actions are taken. Such an approach tells governments how their decisions and policies can affect others. His company's approach is to work with physicists, mathematicians, demographers, economists and epidemiologists, who examine each problem from their multi-disciplinary perspectives. There are four 'modules' to the work - an economic module, a disease module, a risk factor module, and a population module. He suggested seven steps:

- Identify, define and agree on the scope of health action you seek to change, influence and/or control.
- Prepare a proposal for government policy to fund a risk management analysis and framework.
- With funding, conduct an analysis of the risks and rewards for specific disease types.
- Assess the results for an initial business case in terms of quantity and quality of life at risk and the economic impacts.
- Assess specific interventions being proposed to augment the business case.
- Determine the areas of action and funding for completion of the "business case".
- Report to key stakeholders the "business case" and "plan of action".

Finally the group devised goals for 3,5, and 10 years in each thematic area and identifying other stakeholders (like me) was felt to be important.

This leaves us with the four working groups. I suggested that they contact CAPE (Canadian Association of Physicians for the Environment) to get medical representation on the environmental front. More to come…

ALAN KAPLAN, MD CCFP(EM), CHAIR, FPAGC

COPD Dissemination and Implementation

Calgary, November 19, 2006

Dr. Gordon Dyck and I attended a meeting of this group to try to decide how to improve the uptake and utilization of the COPD guidelines.

The guidelines have been updated and a publication of this will come out in the next few months (and also in the 2007 issue of the Canadian Practice Guidelines and on their website). Often the difficulty in guidelines is not their creation, but their dissemination. The meeting was also attended by respirologists, members of the CHRP (Canadian Health Respiratory Professionals), pharmacy, and industry.

The guidelines have been advertised in many journals across medical specialties, pharmacy, nursing journals, and RT journals. The key message has been **Treatable and Preventable.**

Tools currently developed:

- Branding, logo, tagline
- Conference booth (a portable booth taken to FP conferences to increase understanding, which I participated at the FMF in Quebec City),
- Slim Jim pamphlet
- Mouse pad
- Clinic area posters
- CD Rom slide kit

Website www.copdguidelines.com has been updated recently PDA version of guidelines (English form is available, the French one will be available in January 2007).

Website activity has been very steady at about 12,000 hits per month on rough average; double last year's activities. It is the number two rank on Google and MSN search engines when searching for "COPD guidelines".

Canadian Pharmacist Association is preparing a total respiratory health update planned for next year. CRHP is developing a slide set for physiotherapists. This is vitally important as many physiotherapists, for instance, do mostly musculoskeletal work and need the update. As many physiotherapists have direct access, there may not be a family doc involved! Exercise training and physiotherapy techniques are important components of a slide kit that is over 100 slides!

A special CME program for respiratory specialists called Controversies in COPD. These controversies including:

- Systemic disease controversy
- FEV_1 controversy
- ICS controversy
- End of life discussion controversy
- The Rehabilitation controversy
- Disease Modification controversy
- AECOPD controversies (prevention and treatment)

I think that there may be a place for those of you who are interested in COPD and are comfortable with the basics to participate in this program. I am working on it…for the IPCRG in 2010 at least!!

MD Analytics did a survey of FPs and Specialists in 2004 and repeated last year (about 200 FPs and 100 FPs) re: awareness, etc. The awareness was higher for specialists as was their utilization. Amazingly, almost half of participants said they never received the guidelines altogether! New tool ideas included screening questionnaires, action plan, and standing orders were valued. Interestingly, statistically, docs were less sure on how to diagnose COPD and how to differentiate it from Asthma. Spirometry access varied from 51% in FPs to 75% in specialists, although those that had them, tended to use them ~80% of the time. We have not changed docs'minds on how we can effect a patient's life who has COPD. Attitudes to drug therapy showed a continued use of short-acting drugs and likely not enough long-acting. A third of docs still feel that there is a role of oral steroids for daily management in non-exacerbation stable COPD (there is NOT!!!)

Dr. Rick Hodder presented on the "Canadian Lung Health Test", which he adapted from his 30 second COPD test. This test is a screening test for obstructive lung disease which is easily utilized in primary care.

Which of your smoking patients should have spirometry?

COPD case finding using a symptom-based questionnaire

R Hodder et al. Eur Respir J 2005

If you are over 40 and currently smoke cigarettes, or have smoked in the past, you may be at risk for developing Chronic Obstructive Pulmonary Disease (also known as 'C.O.P.D.', 'chronic bronchitis', or 'emphysema'). If you are concerned about your lung health, take the "Canadian Lung Health Test".

The Canadian Lung Health Test

Answer 'yes' or 'no' to each of the following five questions:

1. Do you cough regularly?	Yes ❍	No ❍
2. Do you cough up phlegm regularly?	Yes ❍	No ❍
3. Do even simple chores make you short of breath?	Yes ❍	No ❍
4. Do you wheeze when you exert yourself, or at night?	Yes ❍	No ❍
5. Do you get frequent colds that persist longer than those of other people you know?	Yes ❍	No ❍

If you answered "YES" to two or more of these questions, you may have COPD. Ask your doctor to test you for lung disease.

Stats Canada will include this in Canadian health questionnaire with 5000 people screened with spirometry. This "test" will be used as a screening questionnaire by the COPD guidelines committee; although we recognize that it will pick up Asthma as well. It picked up about 20%. In addition, studies have shown that only 10% of people know what spirometry even means!!

COPD Dissemination and Implementation

Continued

Canadian Lung Association (www.lung.ca) has created Breath Works, an approach for patients with COPD which include a multi-moduled program for patients with COPD, a website, a telephone answering line, and advocacy. There are six call centers across Canada.

The phone number for accessing materials or for patients to call, is 1 866 717 COPD (2673) or website www.breathworks.ca or in French www.poumon.ca/actionair at 1 866 717 MPOC (6762).

We then reviewed COPD Action plans (see other note on this issue) and standing orders for AECOPD in the hospitalized patient for future tools to be used in the guidelines.

This was a positive meeting showing that this group representing the CTS is interested in reaching target audiences with the COPD guidelines. The target audience is physician, RT, nurse, physio, and other health care workers/educators. The goal is improved COPD care across the country.

CNAC Toronto, Ontario

December 8, 2006

Alan Kaplan, MD
CCFP(EM)

Canadian Network for Asthma Care meeting occurred in Toronto.

CNAC is a group of organizations who work together to further asthma care in Canada. I will report on the issues in Asthma that affect Family Physicians in Canada.

One of the key functions of CNAC is the process of certifying asthma educators. We are the only country in the world that has a national certification system for our educators. This ensures that the same messages are being delivered from BC to Newfoundland. CNAC has certified more people every year: 1999-267, 2000-101, 2001-78, 2002-63, 2003-67, 2004-75, 2005-121. The issue of recertification has come up, and not everyone has recertified, issues of cost, workplace issues, time, and perceived need were barriers. Recertification is needed after five years (extended to seven years as the process was just clearly laid out) to continue claiming to be a CAE. Cheryl Connors at CNAC can be contacted to see if an educators certification is up to date. Approximately 273 certificants have been recertified.

The value of CAEs is quite clear. Education is one of the key steps in management of Asthma and with the paucity of Family Physicians in our country, having these people to assist us with our patients is very important!

CNAC has been approached for endorsement. In that, we have decided to create a framework for the proper review of requests for consistent responses to this issue. Key components of this include lack of bias, importance in Asthma care, and role of CAEs.

CAEP, the Canadian Association of Emergency Physicians, have decided that they do not need to be involved with CNAC as they do not feel that the ER is related to these issues. Certainly, most hospitals have asthma educators (and if not, SHOULD!!) and asthma education clinics are a common referral from the ER. Thus, I will be happy to offer to report to CAEP, and will so offer to Dr. Brian Rowe.

ASED 8

Eighty-eight percent of respondants were very satisfied with the ASED 7, and this will be built on for ASED 8. We are hoping to include a family physician theme, to improve the potential relationships out there.

Asthma Guidelines

Adult asthma guidelines were reviewed at a meeting in June 2006. Recent GINA guidelines will be used as the basis of these, and they will be given a Canadian flavour. Pediatric asthma guidelines, led by Dr. Allan Becker, have been published and disseminated with moderate success.

ASED 8 will be in Halifax, with the theme: "Turning the Tides, Promoting Respiratory Health through change" on November 15-17, 2007. Dr. Andrew McIvor is the chair of this scientific committee and I am on the committee.

Louis McCrae from the Public Health Agency of Canada presented stats on asthma updated to 2005 which will be placed on the government of Canada website early in 2007.

Next meeting in May 2007.

New Drug Review in Asthma:

The efficacy and safety of ciclesonide: a pharmacological perspective

Alvesco, or Ciclesonide has received NOC this fall and is the newest inhaled steroid on the market. This article will review this new respiratory medicine. It is currently only received NOC for adults over 18, but is indicated outside Canada for pediatric use.

Introduction

- Asthma is one of the most common chronic inflammatory disorders of the airways and can significantly impact quality of life[1]; numerous reports have shown increases in asthma prevalence, mortality and morbidity over the past 30 years in various countries.[2-4]
- Current estimates suggest that 255,000 people died of asthma in 2005 and that this figure may increase by up to 20% in the next 10 years.[2]
- The associated social and economic burden of asthma is also increasing[5]; for example, the total costs of asthma in the United States are estimated to have increased between the mid-1980s and the mid-1990s from approximately $4.5 billion to over $10 billion.[6, 7]
- Current worldwide treatment guidelines recommend the use of inhaled corticosteroids (ICS) as the evidence-based treatment of choice for most asthma patients.[8-11]
- Corticosteroids act by binding to glucocorticoid receptors in the cytoplasm of target cells[12]. An activated glucocorticoid receptor–corticosteroid complex subsequently forms that moves across the nuclear membrane and targets specific genes for activation.[13]
- ICS effectively treat asthma as they alter the production of mediators within the pathways involved in airway inflammation.[14-16]
- ICS can significantly reduce airway inflammation and hyperresponsiveness, improve lung function, reduce asthma symptoms, decrease acute episodes requiring urgent care, and reduce the need for rescue medication.[1, 16-20]
- Early intervention with ICS in the treatment of persistent asthma has improved clinical outcomes due to the effects of ICS on airway remodeling.[18, 21]
- However, unwanted systemic and oropharyngeal adverse events (AEs) remain a concern due to ICS activity at non-pulmonary sites:
  - Systemic AEs may result from ICS suppression of hypothalamic–pituitary–adrenal (HPA)-axis function, which is usually associated with long-term use of high-dose ICS. Systemic AEs can potentially include cataracts, osteoporosis and decreased growth velocity in children.[1, 18, 22-25]
  - Oropharyngeal AEs include candidiasis, dysphonia, reflex coughing, bronchospasm and pharyngitis.[23, 24]
- In addition, the global asthma patient and physician survey[26] has reported that 9% of patients switched or discontinued their asthma treatment due to the inconvenience of the treatment. Treatment non-compliance can result in an increase in mortality, symptoms, nocturnal awakenings, exacerbations, rescue medication use and visits to physicians.[26]
- There is, therefore, a dichotomy between the need to maintain the efficacy but reduce the associated AEs of ICS.
- The efficacy and safety profiles of ICS are influenced by the pharmacology of the drug.[27, 28]
- The currently available ICS (beclomethasone dipropionate, budesonide, fluticasone propionate and mometasone furoate) possess some of the desired pharmacological parameters, such as low oral bioavailability, high pulmonary deposition and residence times, and high protein binding.[18, 29]
- The development of new ICS focuses on four characteristics:[29, 30]
  - Selectivity for the target site
  - Activation specifically at the target site
  - Prolonged activity at the target site
  - Decreased potential for AEs
- Ciclesonide is a novel ICS agent that is currently available in a number of countries worldwide for the treatment of persistent asthma.
- Several clinical studies have shown the efficacy and safety of once-daily ciclesonide in placebo-controlled and comparative studies.[31-45]
- The objective of this review is to summarize the pharmacological characteristics of ciclesonide relative to other currently available ICS and an 'ideal' ICS.

Selectivity for the target site – pulmonary deposition

- An ICS with a high pulmonary deposition is likely to have enhanced efficacy
- Typically, hydrofluoroalkane (HFA)-metered-dose inhalers (MDI) deliver a higher proportion of the dose to the lung than alternative delivery devices.[30, 46]
- 53%[47], 52%[48] and 32%[49] of the dose is deposited in the lungs for beclomethasone dipropionate, ciclesonide (both delivered via HFA–MDI) and budesonide (delivered via DPI), respectively.
- Particle size is also important in determining the proportion of the ICS that is deposited in the lungs; larger particles (>6 µm) are more likely to be deposited in the oropharynx.[24]
- Across the class of ICS agents, beclomethasone dipropionate and ciclesonide delivered by HFA–MDI have the smallest particles[47, 48], whereas fluticasone propionate delivered by dry powder inhaler (DPI) has the largest particles.[50]

- In two separate studies comparing the oropharyngeal deposition of ciclesonide with fluticasone propionate[51] and with budesonide[52], oropharyngeal ciclesonide concentrations were 50% and 30% that of oropharyngeal fluticasone propionate and budesonide concentrations, respectively.
- Of even more relevance, oropharyngeal exposure to the pharmacologically active form of ciclesonide has been found to be 12.5-fold lower than exposure to fluticasone propionate[51] and 25-fold lower than exposure to budesonide.[52]

Activation at the target site – pulmonary activation

- Prodrugs are designed to become active in target organs only. Prodrug ICS, such as beclomethasone dipropionate[53], are activated in the airway epithelium thereby decreasing the potential for oropharyngeal AEs.[18]
- Ciclesonide is converted to the active metabolite desisobutyryl ciclesonide (des-CIC) by esterases in the airway epithelium (Figure 1).[54-58]
- Oropharyngeal conversion of ciclesonide to des-CIC is as low as 4%.[51, 52]
- Ciclesonide has a low relative receptor affinity compared with des-CIC and is, therefore, predominantly inactive at non-pulmonary sites.[54]
- A recent *in vitro* study showed both rapid and prolonged effects of ciclesonide/des-CIC on the inhibition of inflammatory mediators produced by human bronchial cells.[58]

Prolonged activity at the target site – lipophilicity

- Increased lipophilicity is associated with a longer pulmonary residence time.[30]
- Across the class of ICS agents, ciclesonide and des-CIC have the highest lipophilicities, followed by fluticasone propionate and then the pharmacologically active form of beclomethasone dipropionate. Budesonide has the lowest lipophilicity.[30, 59]
- Ciclesonide's high lipophilicity allows slow dissolution in the lung and slow diffusion through the cell membranes; once-daily dosing is, therefore, possible.[60]
- Once-daily dosing may improve patient compliance due to an easier daily routine.[61]
- In addition, budesonide and des-CIC undergo reversible fatty acid conjugation in the lung, which may prolong their action by creating a slow-release storage depot.[56, 59]
- ICS are released from this depot by the action of lipase.[18]

Decreased adverse events – binding, bioavailability and clearance

- High receptor binding affinities, along with longer half-lives, are positively correlated with both increased efficacy and an increased potential for systemic AEs.[62]
  - Ciclesonide has a low receptor affinity, whereas, like other ICS, des-CIC has a high receptor affinity[54] (Table 1).
  - The short half-lives of ciclesonide (0.7 hours) and des-CIC (approximately 3.5 hours)[63] are similar to those of the other ICS, and may reduce the potential for systemic AEs (Table 1).
- High plasma protein binding may result in decreased systemic bioavailability and a decreased likelihood of systemic AEs since only the unbound drug is pharmacologically active.[18]
  - The protein binding of ciclesonide and its active compound has been shown to be similar to other ICS (99%[63]; Table 1).
- Drug that escapes first-pass metabolism in the liver enters the systemic circulation unchanged, potentially causing extrapulmonary AEs.[28]
  - Ciclesonide is metabolized to at least five metabolites in the liver.[57]
  - In addition, all ICS have high clearance rates[18]; des-CIC has a very high apparent clearance rate and a low systemic bioavailability (<1%).[64]
- Summary:
  - Likely due to the above metabolic differences, it has been shown that Ciclesonide has less adrenal suppression than fluticasone at both low and high doses. Interestingly, there is no suppression of adrenal function at either low or high range doses of Ciclesonide in contrast to fluticasone. (ref A).

Summary

- The 'ideal' ICS needs to be highly efficacious yet at the same time must have minimal associated AEs (Figure 2).
- The efficacy and safety profiles of ICS are influenced by the pharmacology of the drug.[27, 28]
- Currently available ICS show some of the desired pharmacological parameters required of an 'ideal' ICS.[18]
- Ciclesonide has many of the characteristics of an 'ideal' ICS.[65]
- The efficacy of ciclesonide is a result of a high pulmonary deposition[48], a prolonged pulmonary residence time[56, 66, 67] and a high receptor affinity.[54]
- The safety of ciclesonide is a result of a low oropharyngeal deposition[51], targeted activation[18], high protein binding (99%)[63], a rapid apparent systemic clearance rate[64] and a low systemic bioavailability (<1%)[64]
- The ability for once-daily dosing of ciclesonide may result from the prolonged lung residence time of des-CIC[56, 66, 67]. Once-daily dosing may improve patient compliance due to an easier daily routine[61]
- Low dose cic is considered ≤ 200, medium dose 201-400 and high dose > 400 (chart below)
- It is available as an MDI inhaler in doses of 50, 100 and 200 ug strengths

Acknowledgements

The authors would like to thank Nathan Price-Lloyd, PhD, Medicus International, for his editorial assistance with this manuscript. Editorial assistance was funded by ALTANA Pharma.

In view of the large number of references they are not produced here but can be supplied by the FPAGC office.

Editors Note:

A novel pharmacologic agent leads to clinical trials and real life experience. The clinical experience of beclomenthasone and more so with Budesonide, and Fluticasone is extensive. Outcome trials with larger numbers, and comparison trials between Ciclesonide and existing agents have not been done. Enthusiasm for the pharmacologic properties that have been identified may not be borne out completely in clinical medicine. The future will declare how well Ciclesonide matches up to the excellent performance of the agents we currently use. I view every agent as a tool that may be best suited for an individual patient. The more tools, the better. GD

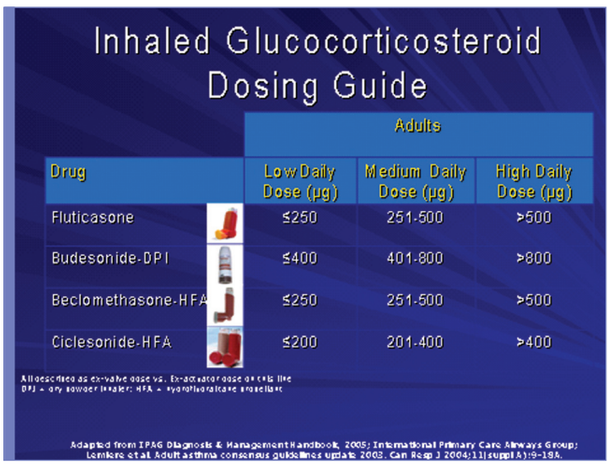


Table 1. Selected properties of inhaled corticosteroids.

	Receptor affinity*	Half-life (hrs)	Protein binding (%)
Beclomethasone dipropionate[53, 68-70]	1022	0.5	—
Budesonide[68-71]	935	2.8	88
Ciclesonide (des-CIC)[63, 68-70]	12 1200	0.7 3.5	99
Fluticasone dipropionate[68-70, 72]	1800	7.8	90-99
Mometasone furoate[68-70, 73]	2700	—	98-99

*Relative to a reference value of 100 for dexamethasone.

Figure 1. Metabolism of ciclesonide to desisobutyryl ciclesonide in the airways.

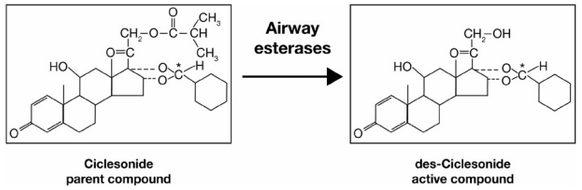
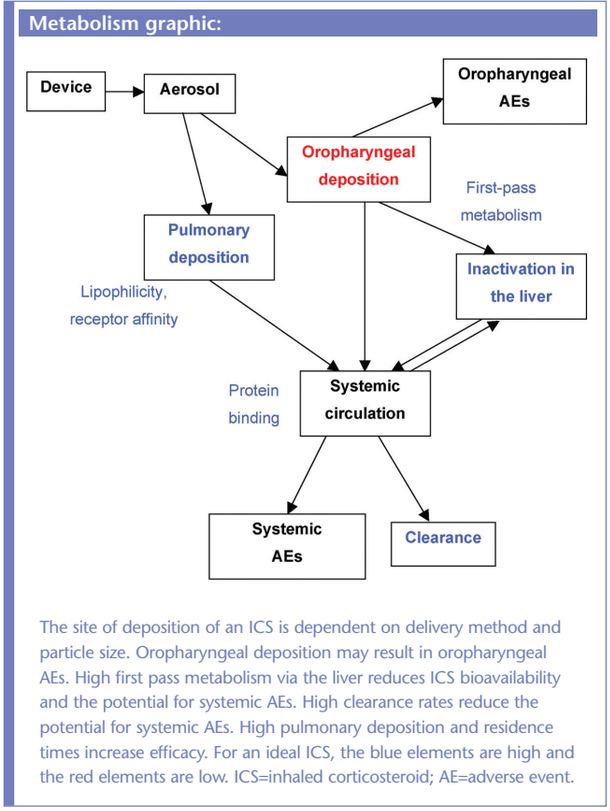


Figure 2. Simplified flow chart illustrating the pathways of inhaled corticosteroids in the human body.



The site of deposition of an ICS is dependent on delivery method and particle size. Oropharyngeal deposition may result in oropharyngeal AEs. High first pass metabolism via the liver reduces ICS bioavailability and the potential for systemic AEs. High clearance rates reduce the potential for systemic AEs. High pulmonary deposition and residence times increase efficacy. For an ideal ICS, the blue elements are high and the red elements are low. ICS=inhaled corticosteroid; AE=adverse event.

What is new for Smoking Cessation?

Dr. Alan Kaplan, MD CCFP(EM)

Nides M, et al. Smoking cessation with varenicline, a selective $\alpha 4\beta_2$ nicotine Acetylcholine receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med August 14/28, 2006;166:1561-8.

Who among us is not frustrated at our lack of success in getting our patients to quit smoking? The repiratory complications are clear, as are the cardiovascular risks and the increased risk of malignancy. In fact, cigarette smoking is the leading cause of premature death worldwide. The real frustration is that, although there are some smokers who really do enjoy smoking, most smokers really want to quit. While adding medications to the smoking cessation plan increases the success rate; however, at one year, the abstinence rate is only 7 to 30 percent.

In May 2006 the US FDA approved Varenicline (Chantix) which is a new pharmacologic agent that specifically targets the nicotine receptor site that rewards smokers. It is a partial agonist/antagonist of the nicotine receptor. It has been released in a dosage pack for the first month that gradually escalates the dosage to avoid the common side effect of nausea (30%, although only about 3% will have to stop the medicine). Another common side effect is dreams, although discussion of this with Dr. Gordon Ford, a Calgary Respirologist and chair of the Canadian COPD Alliance who has done some research with this in Canada, most patients liked their dreams! This medication is not yet in Canada, but will hopefully be approved this coming year.

Nides and colleagues evaluated the effectiveness, tolerability, and safety of three varenicline dosages. The randomized, double-blind, placebo-controlled study compared varenicline with bupropion (Wellbutrin) and placebo for smoking cessation. Participants were randomly selected to receive varenicline (0.3 mg once daily, 1.0 mg once daily, or 1.0 mg twice daily) for six weeks plus one week of placebo or extended-release bupropion (150 mg twice daily) or placebo for seven weeks.

Inclusion criteria were smoking an average of at least 10 cigarettes per day during the previous year, no abstinence period of more than three months in the previous year, and good general health. During the study, participants were evaluated and given standardized smoking cessation counseling weekly. Effectiveness was determined using a smoking diary and breath carbon dioxide measurements. The measurements were repeated at weeks 12, 24, and 52.

Six hundred and thirty eight participants were distributed to the three groups, the average smoking consumption was about a pack per day for almost a quarter of a century. At week 4, those receiving 1.0 mg of varenicline twice daily had a 48.0 percent quit rate, and those receiving 1.0 mg once daily had a 37.3 percent quit rate, compared with a 17.1 percent quit rate for placebo. The bupropion quit rate was 33.3 percent. The quit rate for 1.0 mg of varenicline twice daily during the four- to 52-week follow-up period was 14.4 percent, which was significantly higher than the placebo rate. The bupropion group quit rate during that period was similar to placebo. The discontinuation rates for all treatments were similar.

In Europe, there has recently been released a medication that works on the endocannabinoid system called Accomplia which is touted to decrease both smoking and weight by decreasing the reward centres that are acted on by endogenous cannabinoids. This will be even slower to reach the Canadian market, but is certainly of great interest. Varenicline plus counseling is effective for short- and long-term smoking cessation. It will add to our treatment choices to assist patients in their efforts to abstain from cigarette smoking and also hopefully, reduce the risk of relapse.

Review of Canadian Thoracic Society Guidelines Diagnosis and Treatment of Sleep Disordered Breathing in Adults

Dr. Alan Kaplan, MD CCFP(EM)

Canadian Thoracic Society guidelines: diagnosis and treatment of sleep disordered breathing in adults. Fleetham J, et al Canadian Respiratory Journal; October 2006, Volume 13, Number 7:387-392

Sleep disordered breathing is very common in your practice. Recently guidelines have been created by the Sleep Disordered Breathing group led by Dr. John Fleetham. I have reviewed these guidelines and created a summary of these for our newsletter. This is an example of one of those conditions that we do not know a lot about! I hope that after you read this, you will realize who should be tested and also gain an understanding of the patients you should expect to have the testing assessed for. In addition, in many locales, you as the Family Doc will be responsible for follow-up —– this guideline will assist with that as well. We are all worried about the rules of reporting to the Ministry of Transport — the risks to driving were also detailed in the guidelines.

Classically people present with sleep disordered breathing in a subtle way. A targeted history looking for daytime sleepiness, snoring, apnea (often history needed from a spouse), and lack of refreshing sleep is needed. Improper sleep can lead to impaired concentration and decision making, and potentially even creating unsafe conditions for certain high risk activities including driving.

If there is associated hypoxemia, then secondary complications such as coronary artery disease, erythrocytosis and right heart failure can occur.

Testing requires a proper sleep study done by trained personnel. A nocturnal oximeter monitoring showing hypoxemia can be a useful screen, but will miss obstruction that does not cause actual hypoxemia.

Treatment is reviewed and includes weight loss, oral appliances, upper airway surgery and CPAP. Titration of CPAP must occur with further sleep studies to decide the optimum pressure needed to bypass the upper airway obstruction.

There are three syndromes, each quite distinct that will be reviewed. They include obstructive sleep apnea-hypopnea syndrome, central sleep apnea-hypopnea syndrome including Cheyne-Stokes breathing syndrome, and sleep hypoventilation syndrome. Each syndrome has diagnostic criteria.

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS)

Diagnostic criteria

The individual must fulfill criterion A or B, plus criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors;
B. Two or more of the following that are not better explained by other factors:
   1. Choking or gasping during sleep,
   2. Recurrent awakenings from sleep,
   3. Unrefreshing sleep,
   4. Daytime fatigue,
   5. Impaired concentration;
C. Sleep monitoring demonstrates five or more obstructive apneas/hypopneas per hour during sleep.

What defines an Obstructive apnea/hypopnea event?

An event characterized by a transient reduction in, or complete cessation of, breathing with maintained or increasing respiratory effort. These events must last 10 seconds or longer and fulfill criterion — A or B below. Some people feel that there should also be a ≥ 4% oxygen desaturation.

A. A clear decrease (>50%) from baseline in the amplitude of nasal pressure or respiratory inductance plethysmography sum tracing. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals with an unstable breathing pattern).
B. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with an oxygen desaturation of ≥ 4% or an arousal.

Diagnosis:

Level I (complete laboratory polysomnography) remains the accepted standard for evaluation of SDB and is the test of choice. Other tests like level two and three studies can be useful in triaging patients and assisting the decisions for patients with comorbidities. Oxygen saturation monitoring can also be helpful, but does not differentiate the different types of problems. The testing centres should have the appropriate experience and training and have an appropriate quality assurance program. The reading physician should be trained in the diagnosis of sleep disordered breathing.

Severity criteria

Severity of the OSAHS has two components: severity of daytime sleepiness and of overnight monitoring. The rating of severity for the syndrome should be based on the most severe component.

A. Sleepiness
   1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or traveling as a passenger.
   2. Moderate: Unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. Examples include uncontrollable sleepiness that is likely to occur while attending activities such as concerts, meetings, or presentations.
   3. Severe: Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking, or driving.

B. Apnea/Hypopnea Index (AHI)
   1. Mild: 5 to 15 events per hour
   2. Moderate: greater than 15 to 30 events per hour
   3. Severe: greater than 30 events per hour

Central Sleep Apnea-Hypopnea Syndrome (CSAHS)/ Cheyne-Stokes Breathing Syndrome (CSBS)

This syndrome includes idiopathic (primary) central sleep apnea, central sleep apnea-hypopnea due to Cheyne Stokes breathing syndrome, high altitude periodic breathing, and central sleep apnea-hypopnea due to drug or substance abuse. The latter two disorders are diagnosed in the appropriate setting and were not described further in the guidelines.

CSBS is associated with an increased mortality in patients with heart failure. Optimal medical management is the first line therapy for CSBS in patients with heart failure. CPAP and/or oxygen are not recommended as routine therapy for patients with CSBS and heart failure. Unfortunately, there are no proven therapies for idiopathic CSAHS.

a) Idiopathic (Primary) Sleep Apnea-Hypopnea Syndromes (CSAHS)

Diagnostic criteria

The individual must not be explained by the presence of another cause like a medical problem or drugs and must fulfill criteria A, B, and C.

A. At least one of the following symptoms that is not explained by other factors:
   1. Excessive daytime sleepiness or fatigue
   2. Frequent nocturnal awakenings

B. Sleep monitoring demonstrates 5 or more central apnea/hypopneas per hour of sleep.

C. Normocapnia while awake (PaCO2 35-45 mmHg)

Central apnea/hypopnea event

An event, which must last 10 seconds or longer is characterized by absent or reduced tidal volume with absent or reduced thoracoabdominal movement, respectively. On testing there should be a clear decrease (>50%) from baseline in the amplitude of nasal pressure or respiratory inductance plethysmography (see definition of baseline in OSAHS) with proportional reductions in ribcage and abdominal movements.

b) Cheyne-Stokes breathing syndrome (CSBS)

Diagnostic criteria

The individual must have a serious medical illness, such as cardiac or neurologic disease.

Sleep monitoring demonstrates:

1. 10 or more central sleep apneas or hypopneas per hour of sleep.
2. The presence of a cyclical crescendo and decrescendo change in breathing amplitude that may or may not be associated with arousals from sleep.

Sleep Hypoventilation Syndrome (SHVS)

All patients with suspected SHVS require urgent referral for specialist assessment and long term follow up. CPAP is the first line treatment for patients with SHVS when there is associated upper airway obstruction. Assisted ventilation (bi-level positive airway pressure with or without a timed back-up rate, and pressure-cycled and volume-cycled ventilators) should be considered if CPAP fails to improve daytime and nocturnal gas exchange. Oxygen should be considered in patients who have persistent hypoxemia despite treatment with CPAP or assisted ventilation. Treatment should be initiated in an intensive care unit, sleep laboratory, or other closely monitored setting with appropriate support to ensure safe and effective implementation of CPAP/assisted ventilation/oxygen. The effectiveness of treatment should be verified with attended polysomnography and an arterial blood gas to objectively assess the impact on daytime and nocturnal gas exchange.

Diagnostic criteria

The individual must fulfill criteria A and B:

A. One or more of the following:
   1. Right heart failure
   2. Pulmonary hypertension
   3. Excessive daytime sleepiness that is not explained by other factors
   4. Erythrocytosis
   5. Hypercapnia during wakefulness (PaCO2 > 45 mmHg)

B. Sleep monitoring demonstrates one or both of the following:
   1. An increase in PaCO2 during sleep > 10 mmHg from awake supine values
   2. Sustained hypoxemia (SaO2 <90%) during sleep not related to apnea or hypopnea.

Severity criteria

SHVS is described as severe if at least one of the following are present:

A. Awake hypoxemia PO2 <60 mmHg or SaO2 <90%
B. Arterial oxygen saturation <85% for more than 50% of the sleep time
C. Right heart failure, biventricular failure or pulmonary hypertension secondary to SHVS

REFERRAL decisions, what should we suggest/request?

All patients who have suspected SDB should complete an assessment of daytime sleepiness such as the Epworth sleepiness scale (ESS) questionnaire to subjectively assess the degree of pre-treatment sleepiness. This is a questionnaire that you can request from your local sleep laboratory and I suggest filling it in and sending it in along with your referral to improve the clinic ability to triage. We have to fill in the requisition in a way that allows proper triage decisions.

Patients with suspected sleep disordered breathing should be referred for medical specialist assessment and/or polysomnography and triaged by the following categories and criteria:

Priority 1 (Urgent)

Patients with:

- major daytime sleepiness (ESS 15 or greater); and
- safety critical occupation

Or patients with:

- one or more of the following
- co-morbid disease; or
- overnight home oximetry which reveals >30/hour 4% desaturations.

Priority 2

Patients with:

- major daytime sleepiness (ESS 15 or greater); but
- without safety critical occupation.

Priority 3

Patients without:

- major daytime sleepiness (i.e., ESS <15); or
- co-morbid diseases; or
- safety critical occupation.

Co-morbid disease include: ischemic heart disease, cerebrovascular disease, congestive heart failure, refractory systemic hypertension, obstructive/restrictive lung disease, pulmonary hypertension, hypercapnic respiratory failure, pregnancy.

What defines Safety critical occupations or at high risk of a motor vehicle collision?

Individuals working with machinery, or employed in hazardous occupations. Truck, taxi, bus drivers; railway engineers, airline pilots, air traffic controllers, aircraft mechanics, ship captains and pilots. Car drivers who admit to having fallen asleep while driving within the last two years. (All patients who are considered to be in a safety critical occupation should be told to cease their occupation and/or personal driving until after their medical assessment has been completed and/or appropriate treatment has been established).

Waiting Times

While we all understand in primary care that there are real issues with wait times for consultants, this group took the very large/brave step of actually defining what they feel are the appropriate wait times for consultations and sleep studies. Medical specialist assessment and/or polysomnography should be **arranged and completed** by the following times after referral:

- Priority 1 (Urgent) cases, within 2 to 4 weeks;
- Priority 2 cases, within 2 months; and
- Priority 3 cases, within 6 months

What about Driving?

There is an increased risk of motor vehicle collisions in untreated patients with OSAHS.

Predicting motor vehicle collisions in patients with OSAHS is inexact due to multiple confounding factors (prior sleep, shift work, medications, and adherence with medical treatments) all of which may influence risk. Physicians should advise all patients with OSAHS about the dangers of driving while sleepy.

Reporting of sleepy drivers by physicians to their motor vehicle departments should be in accordance with local legislation. This does differ by province; in Ontario for instance, the rule is that reporting must occur for any patient that has any medical disorder that MAY cause an increased risk of driving. Patients with OSAHS may safely resume driving once successful treatment has been established and in compliance with local regulations.

Healthcare Utilisation And Economic Impact

Wait times are high and the treatment seems extreme. However, it is clear that the treatment of OSAHS is a cost-effective use of healthcare resources It is clear that patients with

OSAHS have increased health care expenditures for many years prior to diagnosis. In particular, SHVS is the SDB associated with the highest health care expenditures because these patients often require hospitalisation. CPAP decreases health care expenditures during the first two years after diagnosis of OSAHS.

Behavioural And Pharmacologic Treatment

This will be recommended by the sleep physician, but there are things that the Family Doc can do in anticipation.

Weight loss should be encouraged in all obese patients with OSAHS, however attempts to lose weight should not delay the initiation of additional treatment if indicated. Patients should be informed of the potential for alcohol and sedatives to exacerbate OSAHS. Relief of nasal obstruction should not be viewed as a primary treatment for OSAHS, but as an adjunct to facilitate effective treatment with CPAP or oral appliances. Patients with positional OSAHS may derive significant clinical benefit from positional therapy. I have suggested for those patients with sleep disorder on their backs to sew a tennis ball into a pyjama pocket and wear the shirt backwards to assist in keeping them off their backs!

Pharmacological agents (eg. serotonin reuptake inhibitors, progesterone) are not effective therapies for OSAHS. However, awake-promoting agents may be a useful adjunct in the treatment of patients who remain sleepy despite adequate sleep hygiene, and who comply with effective treatment for OSAHS.

What Patients Should Be Treated And How Should They Be Followed

1. All patients with OSAHS should be offered a trial of treatment to improve their symptoms.
2. The indications for treatment of asymptomatic patients with abnormal sleep monitoring are unclear. Treatment may be considered in asymptomatic patients with significant comorbid illness, who work in a safety critical occupation, or who have an AHI>30 events/hour.
3. Treatment adherence should be assessed within 2-4 weeks of initiation of treatment.
4. Patients initiated on treatment should be seen in follow-up within 3 months by a physician or alternate care provider supervised by a physician to assess their symptomatic response to and adherence with treatment.
5. Long-term follow-up by either a primary care provider or sleep-disorders specialist should be arranged in a similar fashion to other chronic diseases.
6. Patient education about the nature, complications, and treatment of OSAHS by a trained healthcare professional (respiratory therapist/nurse/polysomnographic technologist) is an important component of all treatment strategies.

CPAP Therapy

CPAP therapy at fixed pressure works. Titration with a CPAP titration polysomnogram remains the accepted standard to determine optimal CPAP pressure. Other forms like "Automatic CPAP" can also be used. CPAP should be used for at least four hours per night and if not, treatment should be reviewed. Many patients find that they fight the machine, are unable to sleep, or are not comfortable. Do not give up too quickly. Send them back to the therapist for another titration study, a new mask, or humidification first. Treating the nose can often make a difference!

Bi-level ventilation should not be used routinely in OSAHS, and should be reserved for patients with SHVS or patients intolerant of conventional/automatic CPAP.

Oral Appliances

1. Oral appliances are an appropriate first line therapy for patients with mild-moderate OSAHS with minimal daytime symptoms.
2. Oral appliances are an appropriate alternative therapy for patients who are unable to tolerate CPAP.
3. Oral appliances should be fitted by qualified dental practitioners who have undertaken special training in SDB.
4. The use of oral appliances should be monitored clinically following initiation of therapy to allow appliance adjustment and assessment of symptoms and side effects.
5. Patients should undergo follow-up sleep monitoring with the oral appliance to ensure effective treatment.
6. Patients initiated on treatment with an oral appliance should be seen in follow-up by a qualified dental practitioner regularly during the first year and then every year thereafter to monitor treatment adherence, appliance deterioration, and oral health.

G. Upper Airway Surgery

1. The presence of large tonsils in a patient with OSAHS should prompt referral to an otolarygologist for consideration of tonsillectomy.
2. OSAHS should be excluded in patients before they are considered for upper airway surgery for snoring.
3. Patients being offered palatal surgery for snoring should be informed about the failure and success rate of the procedure they are having done, and of the risk of difficulty with CPAP use if they later develop OSAHS.
4. Laser-assisted uvulopalatoplasty (LAUP) is not recommended for the treatment of OSAHS.
5. Uvulopalatopharyngoplasty (UPPP) may be considered in selected patients with OSAHS who have failed CPAP and/or oral appliance treatment.
6. Maxillomandibular surgery may be effective in carefully

selected patients with OSAHS who have failed CPAP and/or oral appliance treatment.

7. Tracheostomy should only be considered in carefully selected patients with OSAHS when all other treatments fail.
8. Most forms of upper airway surgery have not been proven to have benefit for the treatment of OSAHS in controlled clinical trials. New or unproven procedures should be considered experimental and be rigorously tested in research studies prior to widespread implementation in clinical practice.

H. Anaesthesia

This is a particularly relevant issue for us to warn our patients about. These patients are at increased risk of difficult endotracheal intubations and sedatives used post- operatively can increase the severity of the OSAHS post-operatively. The CPAP should be continued immediately after surgery. Ensure adequate monitoring post-operatively with oximetry and potentially even cardiac monitoring if indicated. It is not enough to just put the patient back on their CPAP post-op, they do need to be monitored!

Summary

If you look, you shall find. I am amazed at how common obstructive sleep apnea actually is. Treatment first requires identification. While many people have great difficulty tolerating the CPAP, those that do, frequently are thrilled with the clinical improvements.

I would like to thank Dr. Fleetham for providing me with the information on the guidelines to assist in writing this article. We hope to improve all guideline dissemination with these kind of co-operatives in the future.

Why Use A Valved Holding Chamber (Spacer)

Introduction:

The pressurized metered dose inhaler (pMDI) is the most commonly prescribed method of aerosol delivery, having the advantage of being non-invasive compared with other treatment modalities, such as injection, and allows for topical delivery of medication for the treatment of lung diseases. This type of inhaler can be used to administer bronchodilators, anticholinergics, and anti-inflammatory agents, such as corticosteroids, with low dose-to-dose variability to a broad spectrum of patients with respiratory disease. In addition to the broad range of drugs available in this format, pMDIs are durable, low cost, compact and relatively easy to use (when combined with a VHC).

There are, however, limitations to pMDI aerosol drug therapy that include the need to teach proper technique, since correct inhalation technique is one of the keystones for successful asthma and COPD management. Improper patient technique is commonplace, and requires vigilance even for users who claim to be familiar with their inhaler(s).

Valved Holding Chambers (VHCs), also commonly referred to as "spacers," are designed to optimize medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pMDI and inhalation. For these types of patients, VHCs may offer the potential for better clinical outcomes over using their pMDI alone.

The Role of Valved Holding Chambers (VHCs)

National and international guidelines all recommend the inhaled route as the preferred method of delivery for medications to treat Asthma and COPD [GINA, 2003; NIH, 2002; BTS/SIGN, 2004; GOLD, 2003]. For Asthma, the GINA guidelines draw attention to the requirement for co-ordination of actuation of the pMDI with inhalation and recommend that a spacer device be used where appropriate, particularly in children. In infants and preschool children, in whom active co-operation cannot be expected, a pMDI used with a spacer and facemask is recommended as the device of choice for maintenance treatment. As co-operation improves, often around the age of 4 to 6 years, it further recommends that the child is encouraged to use a mouthpiece rather than facemask attachment to the spacer [GINA, 2003].

The Canadian Pediatric Asthma Consensus Guidelines recommend that the pMDI (pressurized metered dose inhaler) and holding chamber be used in place of the wet nebulizer in children of all ages, in both acute and chronic care settings.

Valved Holding Chambers are widely used for the delivery of inhaled maintenance treatment for asthma and COPD and also as an alternative to nebulizer therapy in the management of acute asthma.

Factors Affecting Medication Delivery and Deposition From pMDIs and VHCs

Numerous factors can affect the deposition of inhaled aerosol particles (Table below). These can be sub-divided into inhaler- and patient-characteristics.

Table: Factors that affect lung deposition of aerosols from inhalers and VHCs.

DEVICE-RELATED	PATIENT-RELATED
1. Aerosol characteristics – particularly particle size distribution	1. Inhalation technique
2. pMDI plume formation and interaction with the VHC when present	2. Age
3. Electrostatic charge – associated with the aerosol and VHC	3. Disease modality and severity
4. Size (volume) of VHC	4. Emotional state
5. Valve function	

Device-related Factors

Inhaler characteristics that affect deposition in the lung include particle size distribution, aerosol plume formation and growth following actuation of the pMDI (especially important with HFA pMDIs), as well as the electrostatic charge properties of the inhaler and VHC. The volume of the VHC and the function of both inhalation and exhalation valves (if an exhalation valve is present) can also affect the amount of drug that reaches the lungs.

There is a relationship between particle size and lung deposition. Smaller particles (less than 5 μm) are able to reach the lower airways improving clinical efficacy resulting in more efficient deposition of the finer particle to receptors in peripheral regions of the lungs. In the context of pMDI-based therapy reformulation from CFC to HFA propellants have reduced the mass median aerodynamic diameter (3.5 μm to 1.1 μm) improving clinical efficacy resulting in more efficient deposition of a finer particle to receptors in peripheral regions of the lungs. These medicines have also introduced solvents such as ethanol that evaporate more slowly upon actuation, resulting in an aerosol plume in which particles travel at lower velocities (so-called 'soft plume' behavior), and softer sensation of the actuation for the patient. Even though these characteristics exist, a VHC is still needed with these formulations, as there is still a significant ballistic fraction emitted from the inhaler actuator that would otherwise impact in the oropharynx, as well as to ensure coordination of inhalation maneuver.

Electrostatic charges arise as the result of friction (triboelectrification), generated by the contact and separation of dissimilar materials, such as the formulation particles and the components of the inhaler that are electrical insulators. Studies have indicated that electrically-charged aerosols may affect both total and regional lung deposition. Recently, non-static valved holding chambers made of static dissipative materials have been introduced allowing for longer hang-time (10-15 seconds) of the medication in the chamber, thereby addressing the electrostatic charge issue by making the medication available to the patient for a longer period of time.

Patient-Related Factors

Patient-related factors include inhalation technique (tidal breathing or a maneuver such as slow, deep inhalation followed by a breath-hold) as well as age and disease severity. The flow rate achieved during inhalation governs how the aerosol will behave past the lips, with more oropharyngeal impaction taking place at a higher flow rate. Some devices, such as DPIs are designed to deliver a uniform mass of medication over a wide range of flow rates (30 to 90 L/min), that are suitable for older children (>5 to 6 years) and adults. However, patients may not be able to use these devices as a result of coordination problems, or they may not achieve sufficient flow rate to disperse the powder into particles that are sufficiently small to penetrate to the lungs. pMDI- or nebulizer-based delivery do not rely on a minimal flow rate which allows for its use in infants and small children.

Chronic Obstructive Pulmonary Disease (COPD), being a condition associated with adults, in particular the elderly, does not have age-related recommendations. Hence, pMDIs, DPIs or nebulizers are used, depending upon the formulation prescribed. However, the use of a facemask rather than mouthpiece has been recently recommended for older patients according to the guidelines from the joint American College of Chest Physicians (ACCP)/American College of Asthma, Allergy and Immunology (ACAAI).

The emotional state of the patient can greatly impact drug delivery by inhalation. It has been demonstrated that the amount of drug that reaches the lungs following use of a VHC with facemask can be significantly decreased in infants who are distressed (i.e. crying), compared to those who are calm.

Conclusion

Valved Holding Chambers (VHCs), also commonly referred to as "spacers," are designed to optimize medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation.

It is important to note that most federal, provincial and private insurance plans fully cover the cost of a VHC on an annual basis.

If you would like to obtain a FREE patient counseling package (it includes both VHC demonstrator product and patient counseling tools), please fill out the attached fax back request to Trudell Medical International at 1-519-455-7858.

Family Physician Airways Group of Canada

Please Fax Request to:

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❑ YES, I WOULD LIKE TO RECEIVE A PATIENT COUNSELING ESSENTIAL KIT FOR MY OFFICE.

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease (TORCH)

Dr. Alan Kaplan, MD CCFP(EM)

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., Jørgen Vestbo, M.D., for the TORCH investigators New England Journal of Medicine March 2007

The results of the TORCH study have been eagerly awaited for many months. This extremely important study looked at mortality in COPD. Up until now, no medication other than oxygen has been able to prove a mortality benefit in COPD.

Methods

They conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily (combination regimen called Advair in Canada), administered with a single inhaler, with placebo, salmeterol alone (Serevent in Canada), or fluticasone propionate alone (Flovent in Canada) for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed.

Results

Of 6,112 patients in the efficacy population, 875 died within 3 years after the start of the study treatment. All-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group.

Thus there was a difference against placebo for Advair of 2.6 percentage points or a reduction in the risk of death of **17.5%** with those treated with Advair. (p=0.052)

The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. As compared with placebo, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values (p<0.001 for all comparisons with placebo)

Editors comment:

There was a 17.5% reduction in the death rate, but it did not quite reach statistical significance. There were significant benefits in **all** other outcomes among these patients. I will review this study in more detail in the next newsletter, but I can tell you that even though according to this statistical analysis it was not considered significant, with some other factors thrown in, it was. We will be using this study as a key recommendation in the upcoming COPD guidelines being spearheaded by Dr.Dennis O'Donnell to be released later this year.

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The Family Physicians Airways Group of Canada is committed to helping those with airway diseases lead a full life. The group is dedicated to helping all family physicians maintain and increase their skill in assisting those with asthma and COPD. The strategy of the Group is to maintain a speaker bank, a data base, and practical tools to help physicians attain in these skills.

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