References
1. British Thoracic Society, British Paediatric Association, Research Unit of the Royal College of Physicians of London *et al*. Guidelines on the management of asthma. *Thorax* 1993; **48:** S1-24.
2. Siafakas N M, Vermeire P, Pride N B *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Euro Resp J* 1995; **8:** 1398-440.
3. British Thoracic Society, National Asthma Campaign, Royal College of Physicians *et al*. The British Guidelines on Asthma Management. *Thorax* 1997; **51:** S1-21.
4. Silverman E K, Speizer F E. Risk factors for the development of chronic obstructive pulmonary disease. *Med Clin North Am* 1996; **80:** 501-22.
5. Mak V. Chronic obstructive pulmonary disease (COPD). The UK perspective. Version 1.2. *Chest Medicine On-Line* 1996; http://www.priory.com/chest.htm.
6. Ogushi F, Hubbard R C, Vogelmeier C *et al*. Risk factors for emphysema. Cigarette smoking is associated with a reduction in the association rate constant of lung α_1-antitrypsin for neutrophil elastase. *J Clin Invest* 1991; **87:** 1060-5.
7. Whitehead M. Inequalities in health. In: Townsend P, Davidsen N, eds. *The Black Report*. London, Penguin 1988.
8. National Asthma and Respiratory Training Centre. *Training manual for COPD*, 1997.

Review

Inhalation devices used in the treatment of asthma

E N Evans and P Ebden

British Thoracic Society guidelines on asthma management[1] encourage inhaled drug delivery. This review summarises the different delivery systems, including their equivalence in terms of drug delivery and bio-availability.

Aerosol inhalers

Pressurised metered-dose inhalers (pMDIs)

These are the most widely used inhalational devices. The canister is sealed with a metering valve, delivering respirable (<5 µm in diameter) and larger particles. The drug is suspended in a propellant, which until recently consisted only of chlorofluorocarbons (CFCs), with added lubricants and surfactants. The dose of the inhaled drug delivered depends upon shaking the device to mix the contents. Various devices deliver up to four hundred doses, the canister's lifetime depends on the volume of drug delivered per actuation.

Advantages of pMDIs include resistance to moisture and low cost. One disadvantage is the difficulty in co-ordinating the actuation of the device with inhalation. Lung deposition from a pMDI, or modified pressurised aerosol (see below) is affected by the position of the inhaler in relation to the lips, lung volume at inhalation, inhaled flow rate (enhanced with rates of 30 l/min) and breath-holding after inhalation for 10 sec.[2] Other problems include the lack of a dose counter and the 'cold Freon' effect, with the patient stopping inhalation as the aerosol reaches the throat. Despite these problems, many patients can still use pMDIs satisfactorily.

Generic formulations of salbutamol and beclomethasone dipropionate (BDP) are available for use with pMDIs, but evidence regarding bioequivalence is limited. Although some studies of salbutamol pMDIs have shown significant differences in total delivered dose[3] and significant differences in broncho-dilation;[4] they have not been supported by other comparisons of salbutamol delivered by pMDIs.[5] In these studies the statistical power is small and the methodology not stand-ardised. Three generic BDP preparations were reported to have different aerodynamic particle size distributions[6] and hence the clinical effects may be different.

Breath-actuated metered-dose inhalers (BA MDIs)

These use pressurised canisters and therefore have many characteristics of pMDIs, including CFC propellants, no dose counter and the 'cold Freon' effect. The devices use springs for activation, which require priming and are triggered by the patient inhaling at flow rates of 30 l/min or more. BA MDIs eliminate the co-ordination necessary with pMDIs, but some patients are startled by the release of the spring causing glottic closure. This can be overcome by using a quieter mechanism, such as with Easi-Breathe®. The clinical efficacy of the BDP Autohaler® has been shown to be equivalent to a correctly used pMDI in asthmatics.[7]

Chlorofluorocarbon-free metered-dose inhalers

Chlorofluorocarbons (CFCs) cause destruction of the ozone layer. Although the Montreal Protocol[8] demands the phasing out of CFC use, time has been allowed to develop alternative propellants for pharmaceuticals. Interest lies with two hydrofluoroalkanes, HFA 134a and HFA 227 which have different properties from CFCs. Each combination of drug and propellant needs to be assessed and developed for clinical safety, reliability and efficacy.

The first CFC-free pMDI is Airomir®; a suspension of salbutamol sulphate in HFA 134a. Trials show this combination to be safe and effective with no dosage adjustment required compared with existing CFC inhalers,[9] which are also suspension products. This may not apply to other CFC-free propellants with drugs reformulated in solution. Solution aerosols result in smaller droplets (<2 µm) for some drugs (including corticosteroids), increasing lung deposition, which may require dose reduction.[10] The smaller particles cause less oropharyngeal deposition, making spacer use less important. Change in taste of the new propellant is expected, with a possible reduction in the 'cold Freon' effect. Airomir® does not contain a dose counter; the dose of salbutamol remains constant until the last two to three actuations,[11] an advantage when determining if a device is empty. The development of patented CFC-free propellants has obvious financial implications for generic substitutions in pMDIs.

Spacer devices

Plastic spacers (holding chambers) were introduced for

Emrys Evans
Registrar in Medicine

31 The Paddocks, Tonna, Neath, West Glamorgan, SA11 3FD.

Philip Ebden
Consultant Physician and Senior Lecturer in Respiratory Medicine

Llanelli/Dinefwr NHS Trust, Prince Philip Hospital, Bryngwynmawr Dafen, Llanelli, Carms SA14 8QF.

Correspondence to: Dr Evans

Asthma in Gen Pract 1997; **5(2):** 22-24.

use with pMDIs to overcome poor co-ordination of actuation and the 'cold Freon' effect. They can be large (750 ml, with a low resistance valve), intermediate or small (60-160 ml) volume. Large volume spacers allow the velocity of the aerosol to decrease before inhalation, allowing time for propellant evaporation and reduction in droplet diameter to <5 µm, increasing pulmonary drug deposition. Oropharyngeal problems are reduced with large spacers and high velocity particles are deposited onto the spacer walls.

Multiple actuations of pMDIs and delayed inhalation from the spacer reduces lung bio-availability by more than 50%, compared with a single dose inhaled within a few seconds.[12] These effects are due to static electricity; the half-life of a drug aerosol within the spacer is approximately 10 seconds. Weekly washing, with the spacer left to stand after rinsing, reduces static. Large volume spacers should be replaced every 6-12 months.[1] Metal spacers, which overcome the problem of electrostatic charge, are not yet available in the UK.

Small volume spacers are integral or detachable components of pMDIs. Greater particle deposition onto these spacers reduces oral deposition but some degree of co-ordination is required. Large volume spacers produce a respirable dose equal to, or greater than, from the pMDI, but small volume spacers can be inefficient, the respirable dose reduced to 21-33% for sodium cromoglycate.[13] A study of 12 patients using the Spacehaler®, which consists of a pMDI, a vortex generator and an extended mouthpiece, provided lung deposition comparable to a pMDI for BDP (manufacturers data on file). Further study of 25 asthmatic patients found the bronchodilator effect of salbutamol administered by Spacehaler® was equivalent to that produced by a pMDI plus spacer.[14] The Becloforte Integra® is an intermediate sized (312 ml) collapsible spacer, with an integral pMDI canister. The performance is claimed to be similar to large volume spacers, but the evidence is limited.[15] Paediatric spacers with face masks, are of intermediate size (200-300 ml), making them vulnerable to static. The Babyhaler® has not been compared with other spacers and is not prescribable on the NHS.

Most generic pMDIs will fit a spacing device producing many combinations, but the bioequivalence of such combinations is not known. *In vitro* studies indicate that the performance of a branded steroid pMDI is improved if used with the corresponding branded spacing device,[16] but this does not apply to the generic preparation used through the same spacer. The characteristics of spacers are based on pMDIs using CFC propellants and little is known about how these will perform with CFC-free inhalers. Airomir® can be used via an Aerochamber®, which is now available on prescription.

Dry powder inhalers (DPIs)

These overcome the co-ordination necessary with pMDIs and the use of propellants. To produce an aerosol of particles of respirable size, adequate respiratory effort is needed to create turbulence to disrupt larger particles.

Spinhaler® was the first of the DPIs, using a rotor mechanism to expel the drug and together with Rotahaler®, which has a coarse net to de-aggregate the particles, require reloading with a capsule containing a single dose. Aerohaler® uses capsules delivering up to six doses before reloading. These devices are inexpensive (apart from Intal®), but the capsules may be susceptible to moisture and Rotahaler® requires a large inspiratory effort (90 l/min) to inhale the drug through the mouthpiece. Diskhaler® contains a coarse net to create turbulence. The drug is contained within four or eight foil blistered discs. Reloading can be difficult and the devices, like most DPIs, are more expensive than the corresponding pMDIs. Pulmonary deposition from these devices is about 6-11%,[17] up to 50% less than a pMDI used with a spacer.[17]

Turbohaler® and Accuhaler® (Discus®) are multidose devices. Turbohaler® releases a unit volume of drug into two, high resistance, spiral channels, creating a vortex, optimising particle size if the inspiratory flow rate is >30 l/min. The device indicates when 20 doses are left and does not utilise a carrier, reducing the taste of the drug (possibly a disadvantage) and cough. Thorsson[18] found the Turbohaler® to be more effective than a pMDI, with twice the lung deposition of terbutaline and budesonide. However, work by Ruffin[19] does not reach the same conclusions.

Accuhaler® contains a foil strip of 60 blisters, each containing a unit dose of drug with lactose carrier. Dose consistency at different airflows is reported[20] but data on lung deposition is limited. Clinical effectiveness is equal to delivery through Diskhaler® (for salmeterol and fluticasone propionate) and fluticasone propionate 200 µg per day, delivered via Accuhaler®, has been shown to be more effective than budesonide 400 µg daily through Turbohaler®.[21]

Conclusion

Information regarding lung deposition and therapeutic equivalence of the drug/device combinations is limited, especially for the new inhalation devices and generic preparations. Recommendations for determining bioequivalence of inhaled medications have been published[22] and these will have to include CFC-free propellants.

There are many combinations of medication and inhalers, allowing the selection of the most appropriate device for each patient. The breath-actuated devices, with their newer technologies, are more expensive than the pMDIs, but these devices may be cost-effective if they can improve the patient's asthmatic control.■

References

1. British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London *et al.* The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997; **52:** S1-10.
2. Newman S P, Pavia D, Garland N *et al.* Effects of various inhalation modes on the deposition of radioactive pressurised aerosols. *Eur J Respir Dis* 1982; **119:** S57-65.
3. Saarelainen P and Sovijarvic R. Comparison of acute bronchodilation effects of two preparations of salbutamol aerosol in asthma. *Curr Ther Res* 1991; **50:** 224-30.
4. Chhabra S. Differing bioavailability of salbutamol metered-dose inhalers. *J Asthma* 1987; **24:** 215-8.
5. Vidgren P, Silvasti M, Vidgren M *et al.* *In vitro* behaviour and therapeutic response of salbutamol particles administered from two metered-dose aerosols. *Pharmazie* 1991; **46:** 41-3.
6. Kenyon C J, Dewsbury N J and Newman S P. Differences in

aerodynamic particle size distribution of innovator and generic beclomethasone dipropionate aerosols used with and without a large volume spacer. *Thorax* 1995; **50:** 846-50.
7. Woodman K, Bremner P, Burgess C *et al*. A comparative study of the efficacy of beclomethasone dipropionate delivered from a breath activated and conventional metered-dose inhaler in asthmatic patients. *Curr Med Res Opin* 1993; **13:** 61-6.
8. HMSO Miscellaneous No. 1. *Montreal Protocol on Substances that Deplete the Ozone Layer*. London, HMSO, 1988; Cmnd 283.
9. Bleecker E R. Twelve-week efficacy and safety comparison of Airomir (salbutamol sulphate in CFC-free system) and CFC salbutamol. *Br J Clin Pract* 1995; **(Suppl 79):** 35-6.
10. June D. A new generation of inhaler technology. *Br J Clin Pract* 1995; **(Suppl 79):** 18-21.
11. Tansey I. Technological development of Airomir (salbutamol sulphate in CFC-free system) MDI. *Br J Clin Pract* 1995; **(Suppl 79):** 13-5.
12. Clark D J and Lipworth B J. Effect of multiple actuations, delayed inhalation and anti-static treatment on the lung bioavailability of salbutamol via a spacer device. *Thorax* 1996; **51:** 981-4.
13. Woodcock A. Use of spacers with metered-dose inhalers. *Lancet* 1997; **8:** 446.
14. Gunawardena K A, Sohal T, Jones J I *et al*. The Spacehaler® for delivery of salbutamol: a comparison with the metered-dose inhaler plus Volumatic® spacer device. *Respir Med* 1997; **91:** 311-6.
15. Mairs M L. Clinical evaluation of a new compact spacer device for the administration of beclomethasone dipropionate to adult asthmatics. *Br J Clin Res* 1995; **6:** 31-44.
16. Lee M. *Mersey Quality Control Service. Generic Assessment Report No. 3: Beclomethasone inhalers*, June 1994.
17. Melchior E A. Lung deposition of salbutamol. *Thorax* 1993; **48:** 506-11.
18. Thorsson L, Edsbacker S and Conradson T B. Lung deposition of budesonide from Turbohaler is twice that from a pressurised metered-dose inhaler pMDI. *Eur Respir J* 1994; **7:**1839-44.
19. Ruffin R E, Thompson P J, Mitchell C A *et al*. Terbutaline via Turbohaler and pMDI: a study of the relative dose response in patients with asthma. *Am J Resp Crit Care Med* 1997; Abstracts.
20. Brindley A, Sumby B S, Smith I J *et al*. Design, manufacture and dose consistency of the Serevent Diskus inhaler. *Pharm Tech Eur* 1995; **7:** 14-22.
21. Fuller R. The Diskus™: a new multi-dose powder device – efficacy and comparison with Turbohaler™. *J Aerosol Med* 1995; **8:** S11-17.
22. Rodgers D F, Ganderton D. Determining equivalence of inhaled medications – a working report. *Respir Med* 1995; **89:** 253-61.

Tenth Annual Scientific Meeting (ASM): A selection of abstracts presented

M L Levy

Abstract submission forms for the 11th ASM can be obtained from Strategic Medical Publishing, the address can be found alongside. Closing date Saturday 31st January 1998.

At our 10th ASM which was held on 6-7 June this year, we had a record turnout including a delegation of Swedish doctors. The ASM provides an annual opportunity for the presentation of primary care respiratory research and a forum for sharing practical management and research issues, as well as knowledge on the subject. The quality of papers and abstracts presented this year were of a very high standard, some of which are published in this issue of *Asthma in General Practice*. Due to limited space we are unable to publish all those papers that were accepted for the ASM. However, next year we will be producing a special conference supplement, to coincide with the 11th ASM, which will include all those abstracts submitted and selected for presentation at the meeting, providing they are not (or due to be) published elsewhere.

The ASM provided an opportunity for the unveiling of our new logo which reflects the GPIAG's focus upon all respiratory diseases in primary care. The selection of workshops held on the Friday afternoon included a practical, informative session on spirometry which encompassed our new ethos. In addition, this workshop provided a timely introduction to lung function assessment in anticipation of the forthcoming release of the British Thoracic Society guidelines on chronic obstructive pulmonary disease (COPD). An 'Internet Cafe' hosted by the GPIAG Research Unit provided hands on 'net surfing' experience for participants. Workshops during the conference addressed subjects including the management of wheezing pre-school children, COPD, nurse prescribing and the internet.■

Mark Levy
General Practitioner, Asthma in General Practice *Editor*

Correspondence to: Strategic Medical Publishing Ltd, Action International House, Crabtree Office Village, Eversley Way, Thorpe, Egham, Surrey TW20 8RY.

Asthma following childhood pneumonia: a six year follow-up study

C E Clark, School Surgery, Devon

Introduction

A pilot study[1] has suggested that childhood pneumonia may be a marker for undiagnosed asthma. The original cohort studied have been followed-up after six years to explore the association further.

Method

A written questionnaire seeking details of further respiratory illness and any diagnosis or treatment of asthma was sent to the patients' general practitioners (GPs), where they could be traced. A further respiratory symptom questionnaire[2] was sent to the children (or their parents).

Results

One hundred and ten GP letters were sent and 109 replies received (99% response). In combination with the data from the first study there was follow-up information for 122 children (93% of original cohort). The mean follow-up period of this study was 73 months.

Before their pneumonia there were 19 (16%) known asthmatics. The cumulative total at first follow-up

Asthma in Gen Pract 1997; **5(2):** 24.