Optimizing inhaled drug delivery in patients with asthma

CATHERINE JACKSON

BRIAN LIPWORTH

SUMMARY. Successful management of asthmatic patients depends on achieving adequate delivery of inhaled drugs to the lung. This assumes particular importance for inhaled corticosteroids where the therapeutic goal should be to achieve a high ratio of airway anti-inflammatory efficacy to local and systemic side effects. The availability of user-friendly inhaler devices requires a critical appraisal of their effectiveness and an evaluation of whether improved lung deposition of anti-asthma drugs translates into improved clinical efficacy. There is evidence to suggest that the routine use of large-volume spacers for inhaled corticosteroids may not be the best first-line option, in that reduced drug delivery is associated with multiple actuations, inhalation delay and the presence of static electricity. Breath-actuated pressurized aerosol devices or dry powder inhaler devices may be a better option for many asthmatic patients, although the efficiency of drug delivery varies considerably between these devices. There is good evidence with a reservoir dry powder inhaler device to show that improved lung deposition translates into better therapeutic response, both in terms of beta$_2$-agonist and corticosteroid delivery. For inhaled corticosteroids, such as fluticasone propionate and budesonide, there is evidence to show that systemic bioactivity is mainly determined by lung bioavailability rather than gastrointestinal bioavailability, because of the absence of first-pass metabolism of these drugs in the lung. There is also evidence to show that the greater glucocorticoid potency of fluticasone propionate translates directly into greater systemic bioactivity, but not into enhanced efficacy, at doses above 1 mg daily. The use of efficient delivery systems, such as the reservoir dry powder inhaler device, may not only improve control of asthma and compliance with therapy, but may also allow dose reduction ('step-down' therapy) and hence may possibly reduce overall prescribing costs in the long term.

Keywords: asthma; drug administration equipment; inhalers; drug dosage; drug therapy.

Introduction

SUCCESSFUL management of asthmatic patients depends on achieving adequate delivery of inhaled drugs to the lung. Over the past three decades the pressurized aerosol metered-dose inhaler has remained the mainstay of drug delivery for asthma. However, there is increasing evidence to show that a large proportion of asthmatic patients do not benefit fully from their anti-asthma drugs simply because of poor inhaler technique with metered-dose inhaler devices.[1-4] This has resulted in the development of user-friendly inhaler devices — large-volume spacers, breath-actuated pressurized aerosol devices and dry powder inhalers — to deliver bronchodilator and anti-inflammatory drugs more efficiently.

The purpose of this discussion paper is to provide a critical appraisal of the effectiveness of these inhaler devices and to evaluate whether improved lung deposition of anti-asthma drugs translates into better disease control. The therapeutic goal of inhaled corticosteroids should be to achieve a high ratio of airway anti-inflammatory efficacy to local and systemic side effects (benefit: risk ratio). Thus, the issues of side effects, in particular systemic side effects, of inhaled corticosteroids will also be addressed, as there is increasing evidence to show that lung bioavailability rather than gastrointestinal bioavailability is the main determinant of systemic bioactivity, especially with newer, more potent drugs such as fluticasone propionate.

Measuring drug deposition in the lung

There are at present two main methods of measuring lung deposition *in vivo*. The first method labels the test drug with radioactive technetium. The lung is then photographed using a gamma camera, and from the data obtained a calculation can be made of total and regional lung deposition. In the second, pharmacokinetic method, subjects inhale a known amount of drug, and the concentration in plasma or urine is measured at various times afterwards. Subjects may rinse their mouths out with activated charcoal to block out absorption of the drug from the mouth or the gastrointestinal tract. Deposition can also be evaluated *in vitro*, by using models that closely mimic particle impaction in the respiratory tree; an example of this is the multi-stage liquid impinger system.

Targeting the lung

There is growing evidence to suggest that some of the new, easier-to-use inhaler devices may improve lung deposition of drugs.

Pressurized aerosols

In a study using directly radiolabelled salbutamol, use of a breath-actuated pressurized aerosol device (Autohaler®, 3M) raised lung deposition to 21% from the 7% achieved using a metered-dose inhaler, in patients with poor inhaler technique.[5] Surprisingly, teaching good coordinators the correct technique for using a metered-dose inhaler decreased lung deposition from 19% to 13% of the dose.[5]

One of the main problems with all pressurized aerosol devices is the 'cold freon effect' resulting from impaction of a high-velocity aerosol jet on the back of the throat. This results in a gag reflex, with only minimal drug reaching the airway. One possible way of avoiding this effect is to use a low-velocity pressurized aerosol, such as the Gentlehaler® (not available in the United Kingdom), which is a modified metered-dose actuator device, thus obviating the cold freon effect. In a plasma pharmacokinetic study, lung bioavailability of inhaled salbutamol was shown to be 33% greater using the Gentlehaler compared with a metered-dose inhaler.[6]

C Jackson, BSc, MRCGP, general practitioner, Dundee and research fellow, Department of Clinical Pharmacology, Ninewells Hospital and Medical School, University of Dundee. B Lipworth, BSc, MD, FRCPE, senior lecturer in clinical pharmacology and honorary consultant respiratory physician, Ninewells Hospital and Medical School, University of Dundee.
Submitted: 10 October 1994; accepted: 27 February 1995.

In a similar type of pharmacokinetic study, it was shown that innovator formulation (Ventolin®, A&H) and generic formulations of metered-dose inhaled salbutamol had equivalent lung bioavailability.[7] This suggests that, for salbutamol at least, generic formulations may substitute for the innovator formulation, with concomitant cost benefits.

Spacer devices

Use of spacer devices is another method of increasing lung deposition of drugs. Newman and colleagues showed that a large-volume spacer device (Nebuhaler®, Astra) dramatically improved the pattern of deposition of Teflon®-coated microspheres.[8] It was found that a metered-dose inhaler alone deposited 9% of the inhaled dose in the lung, with 81% being deposited in the oropharynx. However, after a single puff using the spacer, lung deposition increased to 21% of the dose and oropharyngeal deposition decreased to 17%, with 56% remaining in the Nebuhaler. It should be noted that in this study a cruder method to assess deposition was used than those available today: patients inhaled radiolabelled Teflon microspheres rather than a radiolabelled drug.

Studies such as this clearly show that spacer devices increase drug deposition in the lung and reduce oropharyngeal deposition. This results in improved efficacy and lowers the risk of developing local side effects such as oral candidiasis and dysphonia. In this respect, Toogood and colleagues performed a dose-ranging study of budesonide delivered by a metered-dose inhaler using a 120 ml collapsible tube spacer (Astra), a 750 ml large-volume spacer (Nebuhaler) and the metered-dose inhaler alone. Anti-asthmatic efficacy was improved 1.8-fold and 2.1-fold with the tube spacer and large-volume spacer, respectively, along with a 0.06-fold and 0.1-fold lower incidence of oral candidiasis, respectively.[9]

There are also, however, data to suggest that drug delivery from large-volume spacers may be highly dependent on the technique of the patient. O'Callaghan and colleagues, in an *in-vitro* study using a multistage liquid impinger system to mimic the human respiratory tract, showed that the delivery of respirable particles (<5 μm) of sodium cromoglycate from a 750 ml spacer (Fisonair®, Fisons) was 18% (per 5 mg metered dose) greater than using the metered-dose inhaler alone.[10] Furthermore, multiple actuations into the spacer device decreased delivery of respirable particles by 31% after two actuations and by 56% after three actuations (percentage figures refer to overall availability rather than per metered dose). Having a 20-second delay between actuation into the spacer and inhalation resulted in a 67% fall in drug delivery from the spacer.[10] Interestingly, lining the spacer with an antistatic coating improved drug delivery by 244%. Similar findings have been described using the Volumatic® (A&H) spacer with beclomethasone dipropionate and using the Nebuhaler spacer with budesonide.[11,12]

These studies show that precise instructions for using large-volume spacers and strategies for reducing the amount of static electricity in such spacers are required. This has implications for compliance in that patients may be taking an excessive number of inhalations resulting from impaired lung delivery. It should be recognized that following precise instructions is time consuming and such instructions are unlikely to be adhered to if the patient has to take several drugs using a large-volume spacer and a large number of inhalations each day.

Dry powder devices

Dry powder inhaler devices may also improve the lung deposition of corticosteroids and beta$_2$-agonists. For example, a study compared deposition of radiolabelled terbutaline and budesonide inhaled from a reservoir dry powder inhaler device (Turbohaler®, Astra) by healthy volunteers.[13] Subjects inhaled budesonide at two different inspiratory flow rates, similar to those achieved by asthmatic patients in everyday general practice. At the faster rate of 60 l min^{-1}, the Turbohaler deposited a mean of 28% of the budesonide dose in the lung. At the slower rate of 35 l min^{-1} this fell to 15%. Volunteers who inhaled terbutaline at the faster rate achieved a mean deposition of 27% of the terbutaline dose. This clearly shows that it is the device rather than the drug being inhaled that determines lung deposition characteristics.

As with inhalation of anti-asthma drugs via pressurized aerosols, local side effects, such as candidiasis and dysphonia, can occur; rinsing the mouth with water after using a dry powder inhaler markedly reduces the incidence of local side effects. For example, in a prospective two-year follow-up study, the incidence of local side effects was found to be 17%–24% for budesonide or beclomethasone dipropionate inhaled using a spacer device, compared with 6% for budesonide inhaled using the Turbohaler, with mouth rinsing after use of the latter.[14] This clearly shows that even when using large-volume spacers, patients should be advised to rinse their mouths after use in order to reduce local side effects.

Lung deposition and clinical efficacy

Lung deposition using a spacer device or a dry powder inhaler is clearly higher than the 7% most patients manage using metered-dose inhalers. However, does improved lung deposition translate into better clinical efficacy? Melchor and colleagues, using directly radiolabelled salbutamol, reported on the lung deposition from a metered-dose inhaler, with or without a spacer device (Volumatic), and from a dry powder device (Diskhaler®, A&H).[15] In asthmatic patients, the mean drug deposition was 18% from the metered-dose inhaler used properly, 19% using the spacer device and 11% using the dry powder device. Furthermore, use of the spacer device deposited significantly more salbutamol in the peripheral portion of the lung than did the metered-dose inhaler alone, 39% versus 30% (as a percentage of total lung deposition); use of the dry powder inhaler achieved 28% peripheral deposition. Despite these differences, all three methods produced a similar degree of bronchodilation with a standard 200 μg dose of salbutamol.

The same group of investigators also compared a metered-dose inhaler, a dry powder inhaler (Rotahaler®, A&H) and a jet nebulizer (Acorn®, Medic-Aid) in asthmatic patients, using the method involving radiolabelled Teflon microspheres to assess deposition of salbutamol.[16] Total lung deposition was found to be 11%, 9% and 10% using the metered-dose inhaler, Rotahaler and Acorn nebulizer, respectively, with peripheral deposition (as a percentage of total lung deposition) being 16%, 13% and 24%, respectively. However, despite better peripheral penetration using the nebulizer, the bronchodilator response to 400 μg salbutamol was less using the nebulizer when compared with the metered-dose inhaler at the same dose of salbutamol.

Taken together, these two studies[15,16] suggest that the degree of peripheral deposition, as assessed by direct or indirect radiolabelling methods, is a poor correlate of bronchodilator efficacy.

However, a direct comparison study, using the urinary pharmacokinetic method, showed that lung deposition of terbutaline was 8% using a metered-dose inhaler and 22% using the Turbohaler dry powder inhaler.[17] Furthermore, the bronchodilation produced by 0.25 mg terbutaline from the Turbohaler was equivalent to that produced by 0.5 mg terbutaline from a metered-dose inhaler, in keeping with the approximate 2: 1 deposition ratio described above. This is also supported by another study

which compared bronchodilation produced by terbutaline from the Turbohaler with that produced using the Nebuhaler spacer device in patients admitted to an emergency ward with acute severe airway obstruction: the Turbohaler approximately doubled the improvement in forced expiratory volume in one second (FEV_1) seen when the Nebuhaler was used.[18] Interestingly, with salbutamol, the same 2: 1 dose ratio for bronchodilator efficacy was seen when comparing the Turbohaler with a metered-dose inhaler.[19] In a dose–response study comparing the bronchodilator efficacy of salbutamol inhaled from the Turbohaler with that from the Diskhaler, a relative 2: 1 dose ratio was observed.[20]

There are similar urinary pharmacokinetic data for budesonide; 32% lung deposition was achieved using the Turbohaler and 15% using a metered-dose inhaler, with the Turbohaler exhibiting less variability between individuals than did the metered-dose inhaler.[21] Lung deposition of budesonide was approximately twofold greater with the Turbohaler dry powder inhaler compared with the Nebuhaler spacer device.[22] How does this twofold greater deposition translate into clinical efficacy for delivery of inhaled corticosteroid? In a double-blind double-dummy crossover study of 241 stable asthmatic children controlled on 400 μg per day or 800 μg per day of budesonide via the Nebuhaler, their usual maintenance dosage was halved, resulting in a relapse of 126 children.[23] Of these 126 patients, 64 were randomized to continue with their usual budesonide dose via the Nebuhaler, with the other 62 being randomized to use half their usual dose of budesonide via the Turbohaler. After nine weeks of evaluation, there were no differences between the two groups in terms of symptom control, peak expiratory flow rate control, FEV_1 or exercise response. Similar findings have also been described in adults when changing from using beclomethasone dipropionate via a spacer device to budesonide from the Turbohaler, with a 40% reduction in corticosteroid dose being achieved.[24]

These studies clearly show that improved deposition, as assessed by the pharmacokinetic method, translates into clinical efficacy for delivery of both inhaled corticosteroids and $beta_2$-agonists, at least when using the Turbohaler dry powder inhaler device.

Lung deposition and systemic side effects

It is important to consider the risk of systemic side effects of anti-asthma drugs inhaled via inhaler devices. Systemic side effects are of increasing concern, especially with respect to high-dose inhaled corticosteroids. Nonetheless, it can be difficult to dissociate the effects of high-dose inhaled steroids on adrenal suppression and on bone loss from the legacy of previous courses of oral prednisolone.

Against this background, the availability of the potent inhaled corticosteroid fluticasone propionate has aroused considerable interest and debate. What is the relevance of lung deposition to systemic bioavailability of inhaled corticosteroids? Fluticasone propionate, and the more established inhaled corticosteroid, budesonide, are less bioavailable than beclomethasone dipropionate after gastrointestinal absorption. Clearly the risk of developing systemic side effects relates to the amount of drug that reaches the systemic circulation. Following inhalation of a drug, three absorption sites contribute to the concentration reached in the systemic circulation: the oropharynx, the gastrointestinal tract and the lung. Oropharyngeal deposition makes only a small contribution to the absorption of a corticosteroid, with most of the drug reaching the gastrointestinal tract after being swallowed.[22] However, first-pass metabolism in the liver inactivates 89% of a dose of budesonide and 99% of fluticasone propionate.[25,26] There is no published pharmacokinetic data on the hepatic first-pass metabolism of beclomethasone dipropionate. Even at very high doses of inhaled corticosteroid, hepatic inactivation therefore results in gastrointestinal absorption only accounting for a relatively small proportion of systemic availability of the drug. For example, in a study evaluating adrenal suppression with budesonide inhaled from the Turbohaler, rinsing the mouth with water[27] or with activated charcoal[22] reduced systemic absorption by approximately 15%–20%. The major determinant of systemic absorption is therefore the amount of budesonide or fluticasone propionate deposited in the lung that is not inactivated by first-pass metabolism. For beclomethasone dipropionate inhaled from the Diskhaler it has been shown that swallowing activated charcoal reduced adrenal suppression by approximately 48%;[28] this suggests that beclomethasone dipropionate has a lower degree of first-pass metabolism than either budesonide or fluticasone propionate.

There is little doubt that inhaled corticosteroids produce systemic effects at high doses (greater than 1 mg daily), although it is unclear whether these are clinically relevant. Furthermore, differences in systemic bioactivity have emerged between beclomethasone dipropionate and fluticasone propionate. In a study of 154 moderate to severe asthmatic patients, 1 mg fluticasone propionate daily was as effective as 2 mg beclomethasone dipropionate daily from a metered-dose inhaler at controlling symptoms of asthma.[29] Interestingly, despite a twofold difference in dosage, beclomethasone dipropionate produced only a 1.3-fold greater adrenal suppression. This suggests that, if anything, fluticasone propionate exhibits greater systemic activity than beclomethasone dipropionate on a microgram equivalent basis when given via the same device. In another study, however, no significant difference between fluticasone propionate and beclomethasone dipropionate in adrenal suppression was demonstrated, both given at a dose of 1.5 mg daily by metered-dose inhalers to 274 patients with moderate to severe asthma, with fluticasone propionate producing only a 4% difference in peak expiratory flow rate measurements.[30] Further, in a trial involving 134 moderate to severe asthmatic patients, the use of 1.6 mg of beclomethasone dipropionate daily from the Diskhaler had a similar effect on control of asthma as 2.0 mg of fluticasone propionate daily from the Diskhaler. Fluticasone propionate produced marked adrenal suppression at four weeks which was maintained at 12 weeks, while this was not observed with beclomethasone dipropionate at 12 weeks.[31]

These studies show that the greater glucocorticoid potency of fluticasone propionate does not translate into enhanced efficacy but does translate directly into greater systemic bioactivity; this is explained by the efficacy dose–response curve being flat at above doses of 1 mg daily while the systemic bioactivity dose–response curve is steep at above doses of 1 mg daily.

Two studies in healthy volunteers have compared the systemic effects of fluticasone propionate with those of budesonide administered via dry powder inhaler devices, used in conjunction with mouth rinsing. Grahnen and colleagues compared single doses of 250 μg, 500 μg and 1000 μg of fluticasone propionate, taken using the Diskhaler, with a single 800 μg dose of budesonide, taken using the Turbohaler.[32] Fluticasone propionate produced dose-dependent adrenal suppression as assessed by serial plasma cortisol concentrations measured over 20 hours after inhalation: 8% with the 250 μg dose, 19% with the 500 μg dose, and 28% with the 1000 μg dose; budesonide (800 μg dose) produced 16% adrenal suppression. After seven repeated doses of fluticasone propionate administered as a 1000 μg dose twice daily, there was 66% adrenal suppression compared with placebo. The authors suggested that fluticasone might therefore exhibit greater systemic potency than budesonide on a microgram equivalent basis.

In the second, chronic dosing, study a crossover comparison was made between budesonide inhaled from the Turbohaler with fluticasone propionate inhaled from the Diskhaler;[33] doses were 800 μg and 750 μg, respectively, daily for one week followed by 1600 μg and 1500 μg, respectively, daily for a further week. It was found that the lower doses of both drugs blunted the cortisol response to stimulation by an ACTH (corticotrophin) analogue, tetracosactrin. However, with correction for differences in lung deposition between the two dry powder devices, it appeared that fluticasone propionate exhibited greater systemic bioactivity than budesonide on a microgram equivalent basis. Reassuringly, neither drug, even at high doses, suppressed bone formation, as assessed by plasma osteocalcin, a biochemical marker of osteoblast activity.[33]

Taken together the above two studies suggest that the greater the degree of potency of a corticosteroid on the airway, the greater its systemic steroidal bioactivity, at least for adrenal suppression with fluticasone propionate. This is now supported by a dose-ranging crossover study of asthmatic patients that compared adrenal suppression resulting from single doses of budesonide (400 μg, 1000 μg, 1600 μg and 2000 μg), fluticasone propionate (500 μg, 1000 μg, 1500 μg and 2000 μg) and placebo; doses were given by metered-dose inhalation at 22.00 hours.[34] At 08.00 hours the following morning, serum cortisol and ACTH concentrations were measured and the urinary concentration of cortisol was measured using an overnight (10-hour) urine sample. For urinary cortisol levels, there was significant suppression observed with 500 μg of fluticasone propionate but not with 400 μg of budesonide. For serum measurements, fluticasone propionate exhibited significantly greater suppression than budesonide of serum cortisol and ACTH, at an approximate 3: 1 ratio. At the 2000 μg dose, the percentage suppression (compared with placebo) of serum cortisol was 65% with fluticasone propionate and 26% with budesonide and suppression of serum ACTH was 44% with fluticasone propionate and 13% with budesonide. At the two highest doses of both drugs, 15 of the 24 doses of fluticasone propionate produced serum cortisol levels below the normal limit of 150 nmol l^{-1} while five of the 24 doses of budesonide produced serum cortisol levels below normal; this difference was significant.

General practitioners and hospital specialists need more comprehensive dose-ranging comparisons of fluticasone propionate, budesonide and beclomethasone dipropionate given by the same type of device to patients with asthma. This is particularly relevant with regard to asthmatic children, following recent concerns about the effects of high-dose inhaled corticosteroids on growth. However, it is conceivable that patients with more severe airflow obstruction might be protected against systemic steroidal effects, because reduced airway calibre would tend to reduce absorption from the lung.

The way forward for delivery of inhaled corticosteroids

Until recently, the optimal way for delivering inhaled corticosteroid has been the large-volume spacer. This policy requires reappraisal in the light of studies showing that drug delivery from spacers is considerably diminished when used with multiple actuations or inhalation delay, along with the presence of static electricity. Thus, asthmatic patients with disease relapse should as a first step have their technique for using the spacer carefully scrutinized. Improved lung deposition with certain dry powder inhaler devices appears to translate into better efficacy in terms of delivery of both corticosteroids and $beta_2$-agonists. Routine use of mouth rinsing will reduce the propensity for local side effects when using inhaled corticosteroids from dry powder devices as well as from spacer devices. These factors, along with ease of use, should result in improved compliance with therapy and control of asthma, and possible reduction in corticosteroid dosage and hence in overall prescribing costs in the long term.

High doses of inhaled corticosteroids (greater than 1 mg daily) produce dose-related systemic absorption and side effects; general practitioners can reduce these risks by following the 'step-down phase' recommended in British Thoracic Society guidelines.[35] Once the patient's symptoms, peak expiratory flow rate measurements or $beta_2$-agonist use have shown that the patient's asthma is optimally controlled, the inhaled corticosteroid dose should be tapered down in 200–400 μg dose steps each month. Irrespective of the drug or device, general practitioners should not regard the dose of inhaled corticosteroid as being fixed, but rather as being fluid, varying over a period of months.

The appropriate implementation of British Thoracic Society guidelines along with the use of more effective delivery devices should therefore help general practitioners to optimize inhaled asthma therapy. Studies also suggest that lung bioavailability rather than gastrointestinal bioavailability is the major determinant of systemic bioactivity of inhaled corticosteroids. For new drugs such as fluticasone propionate with enhanced steroidal potency, this appears to translate into greater systemic bioactivity on a microgram equivalent basis in comparison with more established drugs such as beclomethasone dipropionate and budesonide. As discussed, studies with fluticasone propionate suggest that at doses greater than 1 mg daily, marked increases in systemic bioactivity are accompanied by only marginal increases in efficacy. Hence at high doses, fluticasone propionate has a worse benefit: risk ratio than beclomethasone dipropionate or budesonide. Although the enhanced lung deposition achieved with the reservoir dry powder inhaler device produces greater systemic bioavailability, it is likely that this will be offset by being able to use a lower maintenance dose for long-term control of asthma.

Conclusion

Enhanced lung deposition of anti-asthma drugs which can be achieved by the use of efficient inhaler devices, as discussed in this paper, will result in greater efficacy of those drugs. Consequently, a lower maintenance dose of inhaled corticosteroid will be required during the 'step-down phase' of asthma management guidelines. Attention to detail such as the routine use of mouth rinsing after use of an inhaler device will reduce local side effects. Systemic side effects of inhaled corticosteroids, such as fluticasone propionate and budesonide, mainly result from lung bioavailability rather than gastrointestinal bioavailability, because of the absence of first-pass metabolism of these drugs in the lung. At high doses (greater than 1 mg daily), the enhanced potency of fluticasone propionate translates into greater systemic bioactivity but not into enhanced efficacy.

References

1. Crompton GK. Problems patients having using pressurised aerosol inhalers. *Eur J Respir Dis* 1982; **63** suppl 119: 101-104.
2. Hilton S. An audit of inhaler technique among asthma patients of 34 general practitioners. *Br J Gen Pract* 1990; **40:** 505-506.
3. Pedersen S. Choice of inhalation therapy in paediatrics. *Eur Respir Rev* 1994; **4:** 86-89.
4. Siafakas NM, Bouros D. Choice of inhalation therapy in adults. *Eur Respir Rev* 1994; **4:** 78-81.
5. Newman SP, Weisz AWB, Talaee N, Clark SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991; **46:** 712-716.
6. Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary $beta_2$-adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered dose inhaler and modified actuator device. *Br J Clin Pharmacol* 1993; **36:** 445-450.

7. Clark DJ, Smith JG, Clark G, *et al.* Lung bioavailability of generic and innovator formulations of inhaled salbutamol. *Eur Respir J* 1995; **8** suppl 19: s259.
8. Newman SP, Millar AB, Lennard-Jones TR, *et al.* Improvement of pressurised aerosol deposition with Nebuhaler spacer device. *Thorax* 1984; **39:** 935-941.
9. Toogood JH, Baskerville J, Jennings B, *et al.* Use of spacers to facilitate inhaled corticosteroid treatment of asthma. *Am Rev Respir Dis* 1984; **129:** 723-729.
10. O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. *Thorax* 1993; **48:** 603-606.
11. O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: what dose is available for inhalation? *Thorax* 1994; **49:** 961-964.
12. Barry PW, O'Callaghan CO. The effect of delay, multiple actuations and spacer static charge on the *in vitro* delivery of budesonide from the Nebuhaler. *Br J Clin Pharmacol* 1995; **40:** 76-78.
13. Borgstrom L, Bondesson E, Moren F, *et al.* Lung deposition of budesonide inhaled via Turbohaler: a comparison with terbutaline sulphate in normal subjects. *Eur Respir J* 1994; **7:** 69-73.
14. Selroos O, Backman R, Forsen KO, *et al.* Local side effects during 4-year treatment with inhaled corticosteroids — a comparison between pressurized metered dose inhalers and Turbohaler. *Allergy* 1994; **49:** 888-890.
15. Melchor R, Biddiscombe MF, Mak VHF, *et al.* Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. *Thorax* 1993; **48:** 506-511.
16. Zainudin BNZ, Biddiscombe M, Tolfree SEJ, *et al.* Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised aerosol metered dose inhaler, as a dry powder and as a nebulised solution. *Thorax* 1990; **45:** 469-473.
17. Derom E, Wahlin-Boll E, Borgstrom L, *et al.* Pulmonary deposition and effect of terbutaline administered by metered dose inhaler or Turbohaler. *Thorax* 1994; **49:** 402P.
18. Tonnesen F, Laursen LC, Evald T, *et al.* Bronchodilating effect of terbutaline powder in acute severe bronchial obstruction. *Chest* 1994; **105:** 697-700.
19. Lofdahl CG, Anderson L, Carlsson LG, *et al.* Lower nominal dose required of inhaled salbutamol via Turbohaler compared with pressurised metered-dose inhaler for the same bronchodilatory effect. *Am J Respir Crit Care Med* 1994; **149:** a219.
20. Carlsson LG, Aruestrom E, Friberg K, *et al.* Half the dose of salbutamol required via Turbohaler compared with Diskhaler for the same bronchodilating effect. *Eur Respir J* 1995; **8** suppl 19: s201.
21. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbohaler is twice that from a pressurised metered-dose inhaler (pMDI). *Eur Respir J* 1994; **7:** 1839-1844.
22. Pedersen S, Steffensen G, Ohlsson SV. The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbohaler. *Br J Clin Pharmacol* 1993; **36:** 211-214.
23. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993; **69:** 130-133.
24. Selroos O, Backman R, Forsen KO, *et al.* Clinical efficacy of budesonide Turbohaler compared with that of beclomethasone dipropionate pMDI with Volumatic spacer. A 2-year randomized study in 102 asthma patients. *Allergy* 1994; **49:** 833-836.
25. Ryrfeldt A, Andersson P, Edsbacker S, *et al.* Pharmacokinetics of budesonide, a selective glucocorticoid. *Eur J Respir Dis* 1982; **63** suppl 122: 86-95.
26. Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990; **84** suppl a: 25-29.
27. Selroos O, Halme M. Effect of a Volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax* 1991; **46:** 891-894.
28. Trescoli-Serrano C, Ward MJ, Rajput R, Garcia-Zorco M. Does swallowed charcoal affect gastrointestinal absorption of inhaled beclomethasone? *Eur Respir J* 1995; **8** suppl 19: s304.
29. Barnes NC, Marone G, di Maria GU, *et al.* A comparison of fluticasone propionate, 1 mg daily with beclomethasone dipropionate, 2 mg daily in the treatment of severe asthma. *Eur Respir J* 1993; **6:** 877-884.
30. Fabbri L, Burge PS, Croonenborgh L, *et al.* Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax* 1993; **48:** 817-823.
31. Boe J, Bakke P, Rodolen T, *et al.* High dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. *Eur Respir J* 1994; **7:** 2179-2184.
32. Grahnen A, Eckernas SA, Brundin RM, Ling-Andersson A. An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994; **38:** 521-525.
33. Grove A, Allam C, McFarlane LC, *et al.* A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects. *Br J Clin Pharmacol* 1994; **38:** 527-532.
34. Clark DJ, Grove A, Cargill RJ, *et al.* Increased adrenal suppression with fluticasone propionate versus budesonide given by MDI in asthmatics. *Eur Respir J* 1995; **8** suppl 19: s303.
35. British Thoracic Society. Guidelines for the management of asthma: a summary. *BMJ* 1993; **306:** 776-782.

Address for correspondence

Dr C Jackson, Department of Clinical Pharmacology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY.

● digest ● digest ● digest ● digest ● digest ●

Teenage health care

THE government's *Health of the young nation* campaign is underway. It therefore seems timely to read Joan Griffith's editorial in the *American Family Physician*. This gives 13 tips on 'how doctors can improve their approach to young people and increase their trust in their physician'.

In our time-starved National Health Service, Griffith's advice to 'take time to establish good rapport' may at times be difficult to follow. However, as the author says, 'such time is well spent, especially prior to discussing sensitive issues', for 'good rapport opens the door through which adolescents can address their hidden agendas'.

Further tips include: 'establish the limits of confidentiality early'. Griffith points out that this saves future difficulties, especially when the doctor finds that he or she is dealing with possible suicidal tendency, drug use, or sexual or physical abuse.

Is the American system of medical care for this age group so different from that of the United Kingdom? For the overworked general practitioner in the UK there is perhaps less incentive to discover the adolescent's hidden agenda, for once Pandora's box is opened, more work beckons. Yet general practitioner satisfaction, as well as the future health of our young patients and society's health, require that distressed adolescents reveal their secret problems to sources of help. As the author points out, 'the staggering statistics of new morbidities amongst adolescents weigh heavily on our society, and should motivate us to improve our outreach to the adolescent population'.

Why is it that most of the research into primary care for adolescents comes from the United States of America? The Royal College of General Practitioners working party on adolescents believes that it is time that general practitioners in the UK studied in greater depth teenage consultations and general practitioner communication skills for this age group. Perhaps it is too much to hope that more resources for such research will be forthcoming from those responsible for the government's *Health of the young nation* campaign.

CHRIS DONOVAN
General practitioner, London and chairman, RCGP working party on adolescents

Source: Griffith JR. Building bridges, not walls: caring for the adolescent [editorial]. *Am Fam Physician* 1995; **51:** 732,734,737,741.

● digest ● digest ● digest ● digest ● digest ●