

Future options for aerosol delivery to children

Authors' affiliations:

H. Bisgaard, Department of Paediatrics, National University Hospital, Copenhagen, Denmark

Correspondence to:

Dr H. Bisgaard
Department of Paediatrics
National University Hospital
Rigshospitalet
Copenhagen
Denmark
Tel. +45 35 45 48 13
Fax: +45 35 45 48 12
E-mail: Bisgaard@RH.DK

Key words: aerosol treatment; AirPac[®]; asthma; automatic spacer; electrostatic charge; intelligent devices; spacers; young children.

There is an increasing awareness of the importance of reliable aerosol delivery, with emphasis on the dose delivered to the lungs, optimal clinical control, cost-effectiveness, and safety in children. Dose prescription should relate to the expected lung dose rather than the factory-dispensed dose, as at present. The device determines the lung dose. Clearly, therefore, the device should be considered an integral part of the prescription. Drug approval processes should clearly specify the device, and discourage the use of other devices. This would rationalize the choice of devices. Important new insights into factors essential for drug delivery to the airways have been acquired in recent years. Nasal inhalation increases systemic bioavailability, reduces lung dose, and adds to its variability; hence, face masks to prevent nasal breathing have been developed. Similarly, dead space in the inspiratory line causes a proportional reduction in lung dose; hence, attention should be paid to reducing such dead space. Plastics in spacers cause a rapid loss of drug due to electrostatic attraction of the aerosol. The residence time of the aerosol, i.e., the time available for inhalation, is increased in nonelectrostatic spacers, allowing less compliant children enough time to obtain a full dose. Eliminating the electrostatic charge can change the lung dose by several times; hence, nonelectrostatic materials should be used in future spacer devices. Compliance is the biggest problem in drug delivery to children. The inhaler design process should be reversed, adapting technology to the child. Interactive microchip technology should provide intelligent devices that react to correct handling and breathing maneuvers. An intelligent nebulizer has been developed that adapts nebulization to the child's breathing pattern, nebulizing only during inhalation and avoiding loss

To cite this article:

Bisgaard H. Future options for aerosol delivery to children.

Allergy 1999; 54, 97-103.

Copyright © Munksgaard 1999

ISSN 0105-4538

of aerosol during exhalation. An automatic device (AirPac[®]) has been developed that transforms a dry-powder inhaler, Turbuhaler[®], into a spacer. In addition to the general advantages of spacer treatment, this device offers the advantage of a drug aerosol delivered without use of propellants or additives. The mechanical actuation ensures highly repeatable drug delivery. Finally, a nonelectrostatic, tower-shaped spacer provides a stable aerosol, which remains airborne for a prolonged period. The spacer is equipped with a face mask that prevents nasal breathing. Such features should improve our ability to treat young children with inhaled drug aerosols.

The prescribed dose should predict the lung dose

Hitherto, aerosol therapy has been based on nominal dose (or labeled) doses, which define the factory-dispensed dose. This concept is maintained in international treatment guidelines, and dose recommendations are given as nominal doses without adjustment for the device used (1, 2). An alternative approach has been to use the dose leaving the device; i.e., the dose delivered to the patient.

However, both the metered dose and the delivered dose bear little relation to the lung bioavailability of the drug (lung dose). Clinical practice would be improved if the prescribed dose was related to the lung dose, since this is the dose that determines clinical control and risk of side-effects and is a decisive factor in the cost-effectiveness of treatment (3).

Clinical control is determined by the lung dose. The clinical effect of the inhaled β_2 -agonist is related to the lung dose measured concomitantly (4), and reducing the fine-particle dose has been shown to reduce the clinical effect of β_2 -agonists (5, 6). Monodisperse particles of β_2 -agonists can reach the relevant regions of the airways more effectively than polydisperse aerosol (7). In the future, such monodisperse aerosols may become available in clinical practice, allowing defined regions of the airways to be treated, and the dose of such monodisperse aerosol may show even better correlations with the clinical effect.

The risk of local and systemic side-effects is increased by oral drug deposition. Increasing the fraction delivered to the lung allows reduction of the prescribed dose, and hence reduces the risk of side-effects.

Price is normally based on the factory-dispensed dose, whereas the clinical effect is determined by the lung dose. Therefore, the effectiveness of the device, i.e., the lung dose

obtained from the factory-dispensed dose, determines the cost-effectiveness of treatment (8). Inefficient devices, which provide a low lung dose, cause a large loss of drug. This is likely to outweigh almost any price of the device if the cost-effectiveness is estimated over time.

Drugs with a broad therapeutic index and a low price, such as β_2 -agonists, are less sensitive to the device used, since high doses may be used to ensure optimal effect at the expense of negligible side-effects at a reasonable price. Therefore, different devices may be used for β_2 -agonists and inhaled steroids; in the future, it may be preferable to have simple devices for the former and high-precision devices for the latter.

In the future, the steroid dose prescribed should reflect the lung dose. Such a requirement is self-evident when drugs with a narrow therapeutic index, such as insulin, are considered. Current attempts to develop devices for the delivery of inhaled insulin may drive the development of new inhalers in which the prescribed dose reflects the drug's bioavailability. This would improve the accuracy of steroid dosing in clinical practice.

Rationalized choice of drug and device

Careful clinical practice often implies doubling or halving the dose during dose titration. Lung doses from different devices often vary greatly. Therefore, changing the device may easily negate or exaggerate the effect of dose titration, thereby compromising clinical control or increasing the risk of side-effects. Thus, dose prescription or recommendations are meaningless unless the device is defined and its effect on lung dose is known. Hence, the drug and delivery device should be considered together and should be approved together. Currently, drugs are approved after careful scrutiny of aerosol performance. However, devices such as spacers and nebulizers may be marketed with little or no documentation of their performance. Since such devices markedly affect drug delivery, rational inhalation therapy could be improved if the approval process covered both the drug and any device used for its delivery. The drug and device should be considered together as a medical specialty, and similar requirements should apply to the drug and device, in recognition of the unity of the two. Such a procedure would reduce the number of add-on devices, thereby reducing the ever-increasing number of drug and device combinations, and improving information on the expected drug bioavailability. A choice from fewer, but better documented, drug-

device combinations would improve the accuracy of drug dosing in clinical practice.

Factors contributing to device efficiency in children

Nasal inhalation

The nose efficiently filters particles from the inhaled air and thus could reduce the amount of drug inhaled. One study reported that the lung dose was reduced by half in schoolchildren inhaling through the nose, compared with mouth inhalation (9). This filter effect appears to be inversely related to age, and the lower airways seem less well protected in younger children (10). The efficiency of nasal filtration is unknown in very young children. It is, however, likely that lung dose is reduced with nasal inhalation, even in infants. Such a filter effect in the nose is unfortunate for at least three reasons. First, the nasal mucosa readily absorbs most drugs, which thereby bypass the first-pass metabolism of the liver, and thus nasal inhalation adds significantly to the systemic bioavailability of inhaled drugs. Secondly, nasal breathing reduces lung dose, which hampers clinical control, cost-effectiveness, and safety of treatment, as described above. Finally, changing between nasal and mouth breathing will vary the lung dose and increase the variability of dosing. Inhalation of aerosolized drug for the lower airways should therefore be via the mouth only.

Dead space

Any volume common to the inspiratory and expiratory lines in a device is dead space, a fact which means that a drug in this volume will not contribute to the lung dose but will be lost in each breath. Dead space between inlet and outlet valves should therefore be avoided. A certain dead space cannot be avoided in a face mask, but should be minimized by reducing the volume of the face mask.

Electrostatics in plastic devices

Electrostatic charge is inherent in all plastic devices, including plastic spacers. Aerosol particles, including particles from pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), and nebulizers, are also electrostatically charged. The charge is not predictable but may vary at random. The net effect of these charges is adsorption of aerosol particles onto plastic surfaces. This will sig-

nificantly reduce the drug aerosol available for inhalation from plastic spacers. In a recent study in schoolchildren, lung dose increased by approximately 2.5-fold when an ordinary plastic spacer (Babyhaler) was used, compared with the same spacer after antistatic priming (11). Such a change in lung dose is obviously clinically important. Electrostatic attraction causes a continuous and rapid disappearance of the aerosol; in plastic spacers, the aerosol half-life is typically 10 s, compared with 30 s if the electrostatic charge is abolished in spacers of similar size and shape (12). Because of this short residence time, the inhalation must be coordinated immediately after actuation of the pMDI into a plastic spacer if a significant and variable reduction in dose is to be avoided. This requirement negates one of the major advantages of a spacer: that it does not need good coordination between actuation and inhalation, a factor which is clearly of special importance in young children. Young children breathe irregularly when presented with a face mask, often showing shallow and irregular breathing with spells of breath-holds. Therefore, the aerosol should be stable over a prolonged period to allow the child to obtain the full dose despite such irregular breathing. A long residence time is very important to ensure adequate delivery of aerosol to young children.

Preventing electrostatic charge

The electrostatic charge of plastic spacers may be reduced in many ways (Table 1). Antistatic paints have been used successfully (13), and immersion in household detergents is also effective, although the effect apparently wears off within days or weeks (14). If detergent is used, it is very important not to wash the spacer in water or to dry the plastic with a cloth, since this immediately recharges the spacer. Benzalkonium chloride is effective in neutralizing the electrostatic charge of plastic spacers (12). The repeated

Table 1.

Possible antistatic treatments of plastic spacers

- Antistatic paint (13)
- Detergent (14)
- Repeated use of pMDI (12)
- Benzalkonium chloride (12)

Issues to be addressed before use of any priming procedure

- Stability of coating
- Interaction between drug and coating
- Toxicity from inhalation of residues of the chemical used for coating
- Compliance with coating procedure

use of the pMDI itself primes the plastic to some extent (12), but, as with other priming procedures, this effect is reversible with ordinary washing. In view of the number of plastic spacers in use, it is important to provide standardized recommendations on priming to control the effect of electrostatic charge. However, before such recommendations can be defined, a number of issues should be studied (Table 1). The numerous priming options should be compared with respect to stability of effect during use. Any toxicity from inhaled residues of the chemical used for priming also has to be studied. Possible interactions between priming chemicals and the aerosolized drug should be tested, and patient compliance with priming procedures should be considered. However, it seems obvious that manufacturers of spacer devices should use only non-electrostatic materials in the future. Certainly, it is not satisfactory to require the patient to remember a certain priming procedure, a practice which is likely to jeopardize compliance.

Metal spacers are an obvious, robust, and safe choice for a nonelectrostatic spacer (15, 16). Metal carries no charge, no matter how it is handled, and requires no chemical treatment. Alternatively, it is possible to mix a conductive material into the plastic during the molding procedure to produce a nonelectrostatic material (carbon black), and other nonelectrostatic materials may be developed in the future. It is an obvious requirement that nonelectrostatic devices be used in the future, and health authorities should require such devices in future registrations.

Sedimentation of the aerosol

Sedimentation of drug particles in the aerosol is another factor that reduces the available aerosol, and shortens the time available for inhalation after actuation. In a narrow spacer, the sedimentation distance is short, and hence the passive fallout of aerosol is faster in small-volume tube-spacers than in large-volume spacers; this is the main reason for the increased dose delivered from large-volume spacers. In a tower-shaped spacer, the distance from the aerosol particles to the spacer wall is increased, and thus the effect of sedimentation is minimized and the aerosol particles remain airborne, ready for inhalation, over a long period.

"User-friendly" devices

Consumer demand is likely to play an increasing role in inhaler design in the future. First and foremost, a device that is appealing to the child will be preferred. In addition,

refillable devices will probably be preferred to current disposable devices. A dose counter should be required to warn the patient when the device is nearly empty.

Reversing the design process

Compliance is by far the biggest problem in drug delivery to children. Children can adapt themselves and perform amazing skills if the task appeals to them. Certainly, the currently available devices are not adapted to the child; all available devices for children are smaller versions of adult devices, with no attempt made to make their appearance and handling appealing to the child. Obviously, the conventional device technology determines the final design of the device. In the future, the design process should be reversed, taking the child's world as the starting point and adapting technology to that, as opposed to the present strategy of attempting to adapt the child to the technology.

Interactive devices – the "Tamagotchi Inhaler"

Reinforcing a desirable performance by positive feedback is an obvious way to promote positive compliance. Even young children can be taught to perform the most difficult maneuvers, provided they find the task interesting and are encouraged. Microchip technology has invaded toys of all kinds, bringing life and interaction into games and toys. Such a use of electronics to create a reinforcing feedback between the child and the aerosol device has not yet been explored. In the future, devices should signal a correct and completed inhalation by light and sound, and may indicate when a new inhalation is due and when a new dispenser is needed. The "Tamagotchi Inhaler" may turn the inhaler into the child's toy rather than the doctor's device, and this is certain to improve compliance.

New developments in devices for aerosol delivery

Face mask

A face mask has recently been developed which allows only mouth breathing. A septum separates the nose from the mouth within the face mask, preventing nasal breathing. Since young children are habitual nose breathers, this may be less acceptable to them at first, but initial experience has shown that acceptance is soon obtained. As described above, mouth breathing increases the lung dose and is likely to

reduce the systemic bioavailability, as well as the variability, of the lung dose. In preliminary tests, this face mask successfully prevented air leakage from the nose in a group of 0.5–4-year-old children. The face mask is designed to have minimal dead space, and the inlet and outlet valves are integrated into the mask, a design which avoids dead space in the inhalation and exhalation lines. These features can be expected to improve delivery of aerosol to the lungs.

Intelligent nebulizers

Most nebulizers deliver a constant flow of aerosol during both inspiration and expiration. The flow of aerosol during expiration may result in excessive exposure of the patient's skin and eyes to the drug. Loss of aerosol to the environment may also result in unwanted exposure of parents or other caregivers to drug aerosol. Together with the residue of drug trapped in the nebulizer, loss of drug during expiration causes an unpredictable loss of the drug, a loss which prevents accurate dosing and limits the repeatability and cost-effectiveness of treatment. Nevertheless, prolonged delivery of aerosol may be the one advantage of nebulizer aerosol delivery, a fact which explains the common clinical impression that nebulizer treatment is very effective during exacerbations. The nebulizer does deliver aerosol over a prolonged period, allowing for even very irregular and shallow breathing.

The recent development of an intelligent nebulizer may promote the nebulizer to a state-of-the-art drug-delivery device. This device takes advantage of microchip technology to adapt aerosol delivery to the breathing pattern of the patient. The nebulizer continuously monitors the breathing pattern, attempting to predict and adapt to changes. A pressure transducer monitors the shape of the breathing pattern and uses three breathing cycles to predict the

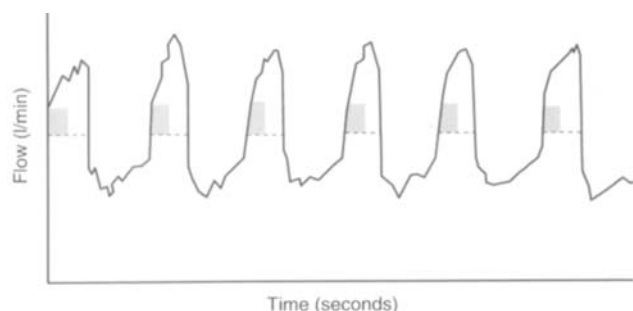


Figure 1. Intelligent nebulizer principle. Pressure transducer senses breathing pattern, using three previous inhalation profiles to predict coming inhalation, and uses this prediction to deliver aerosol during first half of inhalation.

following inhalation. At the start of the inhalation, a dose of aerosol is delivered during 50% of the expected inspiration time, thereby preventing loss of aerosol during exhalation (Fig. 1). Regrettably, the loss of drug is unchanged, as the nebulizer is charged with respules similar to those used in other nebulizers. Therefore, the potential improvement in cost-effectiveness is not obtained, as the aerosol saved during exhalation is later discharged in the almost full respule. The nebulizer is hand-held, although still dependent on airflow from a bulky pump. Naturally, prediction of future breathing patterns from past breathing maneuvers cannot be completely reliable, but this device provides a nebulizer with the inherent advantage of a prolonged time for aerosol delivery, but without the disadvantage of erratic aerosol delivery during expiration.

Automatic spacer for Turbuhaler® (AirPac®)

The combination of a spacer and face mask with a pMDI was the breakthrough that allowed the benefits of inhaled therapy to be offered to the large number of young patients with wheezing. However, pMDIs have significant disadvantages. Lubricants, surfactants, and propellants are released with each drug dose from a pMDI. The lubricants and surfactants in pMDIs may irritate the airways and cause cough or, in some patients, more prolonged bronchoconstriction (17–25). CFC propellants are being phased out by international agreement because of their effect on the atmospheric ozone layer (26–30), but, although the replacement HFA propellants have no ozone-depleting effect, they still have adverse environmental potential, as they are important greenhouse gases (with an effect some 2000 times greater than that of carbon dioxide) (30–32). Repeatability of dosing from most pMDIs is probably low in clinical practice since CFC pMDIs contain a suspension of drug particles, and the drug and propellant separate within the canister. There is a risk of dosing from an inappropriately dilute or concentrated drug suspension unless the canister is shaken and primed immediately before use, and even this maneuver may not ensure consistent dosing (33, 34).

Because of these drawbacks of the pMDI, it has been suggested that a DPI can be adapted as the drug dispenser with a spacer device for young children (35). DPIs lack propellants and other potentially harmful additives; hence, this new concept maintains the advantage of a pMDI plus spacer without the disadvantages of the pMDI.

The working principle is a mechanical “inhalation” from the DPI into a spacer (Fig. 2). This “inhalation” is caused by the release of a spring-loaded piston underneath the spacer

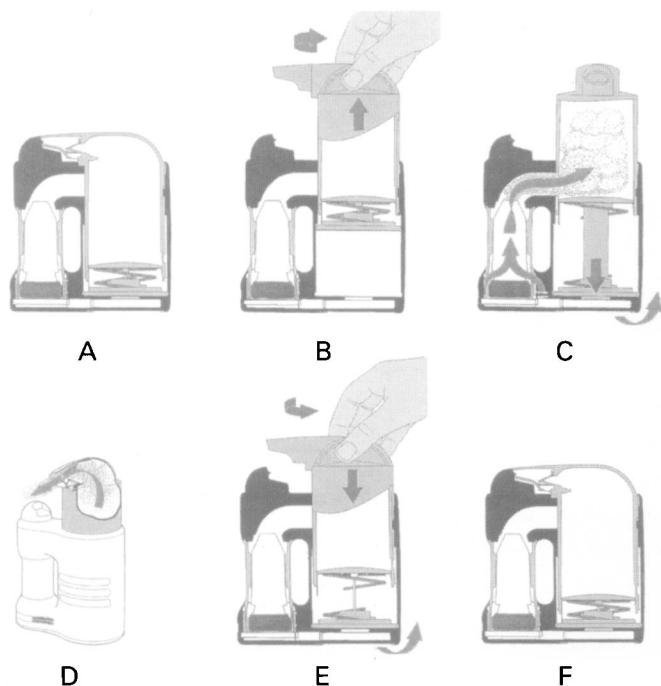


Figure 2. Mechanism of action of AirPac[®]. A) Transverse section of device as it appears when not in use. Drug to be delivered is contained within Turbuhaler, on left. Spacer chamber in its closed state, beneath which is spring under tension, is on right. B) Spacer chamber is lifted and turned just past 90° to prime Turbuhaler. Simultaneously, spring is released. C) Release of spring leads to rapid expansion of spacer chamber volume. One-way valve at mouthpiece prevents air from entering, so that partial vacuum develops, drawing air up through Turbuhaler and into tower-shaped spacer. This action produces drug aerosol which persists as stable cloud in spacer chamber. Half-life of fine-particle fraction is 82 s. D) This external view of device shows aerosol path through mouthpiece. Face mask may be fitted for use by younger children. E) After inhalation is achieved, spacer chamber is rotated back 90° to its original direction and then pushed firmly down. This action compresses spring, evacuating excess air from device, and allowing mouthpiece to rest in protected groove. F) Transverse section of device as it appears when returned to its original position after use.

chamber. Releasing the piston provides a repeatable ideal inhalation flow profile with a maximum of 60 l/min. The "inhalation" draws the metered dose as an aerosol from

Turbuhaler into the spacer. After the subject breathes from the spacer, the piston is compressed upon the spring and locks in place ready for the next use. As a consequence of the standardized nature of the mechanical actuation, there is no requirement for forced inspiration or good coordination, and the repeatability of dosing is high.

In vitro tests with the prototype have shown that AirPac produces a fine-particle aerosol with a mass median aerodynamic diameter of 2.8 μm , and a remarkably stable aerosol. The half-life of the fine-particle aerosol in the spacer is approximately 1.5 min, due to the nonelectrostatic properties of the spacer and its tower shape, features which maximize the settling distance for the particles. Even in the case of a noncompliant toddler, who may breath-hold or perform periods of shallow breathing, passive fallout of aerosol will have little effect on the dose obtained.

In summary, the mechanical actuation of Turbuhaler into a spacer (AirPac) provides a new form of spacer device for aerosol treatment. In addition to the general advantages of spacer treatment, the automatic spacer offers the advantage of a drug aerosol delivered without use of propellants, lubricants, surfactants, or other harmful additives. The mechanical actuation ensures a high repeatability of drug delivery. Finally, the tower-shaped spacer and the nonelectrostatic properties ensure a stable aerosol, which remains airborne for a prolonged period. This makes coordination and forced inspiration unnecessary, and should permit effective inhalation, even by children who have previously been unable to use spacer devices effectively.

In conclusion, AirPac utilizes the new knowledge of the essential aspects of device efficiency in children that has been obtained in recent years. Such developments should improve our ability to treat young children with inhaled drug aerosols.

References

- Warner J. Asthma: a follow up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992;67:240-248.
- National Asthma Education and Prevention Program. *Guidelines for the diagnosis and management of asthma*. Bethesda, MD: National Institutes of Health, April 1997 (NIH Publication no. 97-4051).
- Bisgaard H. Delivery of inhaled medication to children. *J Asthma* 1997;34:443-467.
- Borgström L, Derom E, Ståhl E, Wählin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. *Am J Respir Crit Care Med* 1996;153:1636-1640.
- Löfdahl CG, Andersson L, Bondesson E, et al. Salbutamol doses inhaled via Turbuhaler give a better bronchodilating effect than when given via a pressurized metered dose inhaler. *Eur Respir J* 1996;10:2474-2478.
- Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H. Flow dependent effect of formoterol dry powder inhaled from the nebulizer. *Eur Respir J* 1996;10:2105-2109.
- Zahnen P, Go LT, Lammers JWJ. The optimal particle size for beta-adrenergic aerosols in mild asthmatics. *Int J Pharm* 1994;107:211-217.
- Bisgaard H. Drug delivery from inhaler devices. *BMJ* 1996;313:895-896.

9. Chua HL, Collis GG, Newbury AM, et al. The influence of age on aerosol deposition in children with cystic fibrosis. *Eur Respir J* 1994;7:2185-2191.
10. Becquemin MH, Swift DL, Bouchikhi A, Roy M, Teillac A. Particle deposition and resistance in the nose of adults and children. *Eur Respir J* 1991;4:694-702.
11. Anhøj J, Bisgaard H, Lipworth B. Effect of electrostatic charge in plastic spacers on the lung delivery of HFA salbutamol in children. *Br J Clin Pharmacol* 1999 (in press).
12. Berg E, Madsen J, Bisgaard H. *In vitro* performance of three combinations of spacers and pressurized metered dose inhalers for treatment in children. *Eur Respir J* 1998;12:472-476.
13. O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. *Thorax* 1993;48:603-606.
14. Wildhaber JH, Devadason SG, Hayden MJ, et al. Electrostatic charge on a plastic spacer device influences the delivery of salbutamol. *Eur Respir J* 1996;9:1943-1946.
15. Bisgaard H. A metal aerosol holding chamber devised for young children with asthma. *Eur Respir J* 1995;8:856-860.
16. Bisgaard H, Anhøj J, Klug B, Berg E. A non-electrostatic spacer for aerosol delivery. *Arch Dis Child* 1995;73:226-230.
17. Cochetto D, Sykes RS, Spector S. Paradoxical bronchospasm after use of inhaled aerosols: a review of the literature. *J Asthma* 1991;28:49-53.
18. Graff-Lonnevig V. Diurnal expiratory flow after inhalation of Freon and fenoterol in childhood asthma. *J Allergy Clin Immunol* 1979;64:534-538.
19. Yarborough J, Mansfield LE, Ting S. Metered dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy* 1985;55:25-27.
20. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta-agonists. *J Allergy Clin Immunol* 1990;85:959-964.
21. Engel T. Patient-related side effects of CFC propellants. *J Aerosol Med* 1991;3:163-167.
22. Wilkinson JRW, Roberts JA, Bradding P, Holgate ST, Howarth PH. Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *BMJ* 1992;305:931-932.
23. Jackson L, Ståhl E, Holgate ST. Terbutaline via pressurised metered dose inhaler (pMDI) and Turbuhaler in highly reactive asthmatic patients. *Eur Respir J* 1994;7:1598-1601.
24. Selroos O, Lofroos AB, Pictinalho A, Riska H. Comparison of terbutaline and placebo from a pressurised metered dose inhaler and a dry powder inhaler in a subgroup of patients with asthma. *Thorax* 1994;49:1228-1230.
25. Shaheen MZ, Ayres JG, Benincasa C. Incidence of acute decreases in peak expiratory flow following the use of metered-dose inhalers in asthmatic patients. *Eur Respir J* 1994;7:2160-2164.
26. Newman SP. Metered dose pressurized aerosols and the ozone layer. *Eur Respir J* 1990;3:495-497.
27. Balmes JR. The environmental impact of chlorofluorocarbon use in metered dose inhalers. *Chest* 1991;100:1101-1102.
28. Pavia D, McLeod L. The environmental impact of inhaled aerosols. *Eur Respir Rev* 1994;4:75-77.
29. D'Souza S. The Montreal Protocol and essential use exemptions. *J Aerosol Med* 1995;8:S13-17.
30. Isaksen ISA. Dual effects of ozone reduction. *Nature* 1994;372:322-323.
31. Smith R. Doctors and climatic change. *BMJ* 1994;309:1384-1385.
32. Hileman B. Scientists warn that disease threats increase as earth warms up. *C & EN* 1995;2:19-20.
33. Cyr TD, Graham SJ, Li RKY, Lovering EG. Low first-spray drug content in albuterol metered-dose inhalers. *Pharmacol Res* 1991;8:658-660.
34. Evcrard ML, Devadason SG, Summers QA, Le Souëf PN. Factors affecting total and "respirable" dose delivered by a salbutamol metered dose inhaler. *Thorax* 1995;50:746-749.
35. Bisgaard H. Automatic actuation of a dry powder inhaler into a nonelectrostatic spacer. *Am J Respir Crit Care Med* 1998;157:518-521.