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"Metered dose pressurized aerosols and the ozone layer"

Dr. Newman makes the very important point that, all other things being equal with respect to aerosol therapy, aerosol generation and delivery systems should ideally contain the pure drug substance only and should be environmentally friendly. Thus, not only should aerosolization systems minimize the use of CFC's but they should also be prepared in recyclable or rapidly biodegradable containers.

While I agree with Dr. Newman that multidose powder inhalers are characterized by ease of use particularly with regard to breath actuation, convenience and environmental advantages because they do not require pressurization, the presently available devices have disadvantages which clearly limit their utility as an all purpose aerosol generation and delivery system. Thus it is probably premature to suggest phasing out pressurized MDI's.

Since with powder inhalers, unlike pressurized MDI's, the dose actually generated is critically dependent on the inspiratory flow rate and since this may vary widely from patient to patient and from one inhalation to another even in stable patients, they will still require careful instruction to assure full compliance and successful therapy.

In children under the age of 3 or 4, administration is likely to be even less predictable particularly since, when the pure drug substance is used, exhalation through the device prior to inhalation may disperse the dose without either the child or a care giver being aware of the fact. This could also happen in adults, particularly the aged or those with neuromuscular problems such as Parkinsonism, who would also require careful instruction, supervision and/or the addition of a signalling system to make sure that the drug has actually been inhaled.

Unlike the pressurized MDI shown repeatedly to be as effective as nebulizers for treating severe asthma, [1–7], there is, as yet, no data demonstrating that powder inhalers work during severe and life threatening episodes. This is, I believe a major deficiency since it has been demonstrated that, with the Rotahaler and Turbuhaler, inspiratory flow rates below approximately 30 $l \cdot min$, deliver only approximately 25% of the dose obtained at 60 $l \cdot min$ and above [8]. In asphyxic asthma where inspiratory flow rates may be extremely low, the patient may not get effective therapy and if unable to get to a medical facility where nebulized therapy is available may actually die.

A similar, although less acute and serious problem may arise under conditions of high humidity. At a relative humidity of approximately 85% the available dose of medication may decrease to 25% of the usual dose even when inspiratory flow rates are in the appropriate range [9].

Powder inhalers are not suitable for use in infants or patients unable to fully understand or co-operate with the care givers, nor can they be used in ventilator circuits, unlike pressurized canister metered dose inhalers which together with appropriate and widely available valved accessory devices (such as the AeroChamber, AeroChamber with mask for infants, adults and children and the AeroVent for use in ventilator circuits) can be used in virtually any setting and without the need for external power supplies.

It is for the latter reason that nebulizers are not the whole answer since even the most portable of these systems, making use of ultrasonic technology, require a source of electricity. This would make administration of bronchodilator difficult, if not impossible, while hiking, sailing or on a long airplane flight etc.

Thus, no one system is the whole answer to the needs of patients with asthma and COPD requiring aerosol therapy. I believe that it is premature to suggest substituting powder inhalers and nebulizers (definitely a retrograde step) for these highly efficient and readily portable pressurized canister MDI systems whose safety and efficacy have proven themselves for nearly 40 years.

Since HFC 134A has physical characteristics similar to CFC 12, appears in animal studies to date to be equally non toxic and is about to be used widely for refrigeration, this would appear to be a promising substitute for CFC 12 until better powder (or other) aerosol generators can be developed.

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REPLY TO THE LETTER

Reply to Dr Newhouse

As Dr Newhouse suggests, a range of devices, including pressurized MDIs, MDIs with spacers, powder inhalers and nebulisers should ideally be available for inhalation therapy. Certainly, I did not wish to imply that multi-dose powder inhalers might be "all-purpose aerosol generators and delivery systems", and Dr Newhouse has misinterpreted my Editorial [1] if he concludes this. Perhaps we are to some extent at cross-purposes; Dr Newhouse's comments relate especially to the treatment of severe and life-threatening episodes of asthma and to the use of aerosols in ventilator circuits. My Editorial related more to the future use of inhalers by millions of asthmatic patients for day-to-day maintenance therapy in the face of a ban upon the use of CFC propellants within the next 10 years.

These complex issues are the subject of whole conferences, and a balanced discussion is not really possible in the correspondence columns. However, as Dr Newhouse says, widespread proliferation of nebulisers for the day-to-day management of asthma would be a retrograde step, and the choice seems to lie between MDIs containing "environmentally friendly" propellants and devices that do not use propellants at all.

Taking these alternatives in turn, there are problems in the search for alternative propellants, which Dr Newhouse dismisses too briefly. HFC 134a is a probable replacement for CFC 12, but this solves only half the problem. Current manufacturing processes require the use of other, less volatile, propellants (CFCs 11 and/or 114) to prepare suspensions in the laboratory and to attain the required vapour pressure and spray pattern. Alternatives to these substances have proved harder to find so far: HCFC 22 and HCFC 123 could be used, but they contain chlorine and thus retain an ozone depletion potential; some other possible propellants are flammable. All the alternative propellants, including HFC 134a, contribute in varying degrees to greenhouse warming, and consequently environmental groups are campaigning to have this entire family of compounds banned. Further, patients will experience the same co-ordination and "cold-Freon" difficulties in using MDIs formulated with new propellants as they experience with existing MDIs; multi-dose powder inhalers entirely overcome these problems.

Multi-dose powder inhalers are new devices, and we are still learning about the types of patients for whom they are suitable and the circumstances in which they may be used. The performance of powder inhalers is flow-rate dependent, but then so is the performance of MDIs as Dr Newhouse and his colleagues have shown [2]. With Turbuhaler used by stable asthmatics, Dr Newhouse and colleagues found an undiminished FEV_1 response to terbutaline sulphate at an inhaled flow rate of 30 $l \cdot min$ compared to 60 $l \cdot min$ [3]. It has been shown that 97 out of 101 randomly selected adult asthmatics could attain this "critical" flow of 30 $l \cdot min$, and also that a patient with a peak expiratory flow of 33 $l \cdot min$ could attain a peak inspiratory flow of 25 $l \cdot min$ through Turbuhaler [4]. Most children > 6 years can attain a flow rate of > 30 $l \cdot min$ through Turbuhaler, although younger children with acute wheeze are predictably less successful in doing so [5].

It seems inevitable to me that multi-dose powder inhalers will be used more widely in the future for the maintenance therapy of asthma. Existing models potentially go a long way towards retaining the practical advantages that have made MDIs popular over many decades, whilst being easier to use and being free of environmental objections.

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LETTER TO THE EDITOR

Effects of frusemide on human airway epithelium

In the June 1990 issue of the Journal, POLOSA *et al.* [1] show that inhalation of 28±2.5 mg of frusemide reduces the bronchial effects of inhaled methacholine and, to a greater degree, of adenosine 5'-monophosphate (AMP) in asthma. Although increase in the group-average geometric mean of the provocation concentration causing a 20% fall in FEV_1 from baseline (PC_{20}) for methacholine is small, and probably due to a large decrease in 4 of 12 subjects (No. 1, 2, 6 and 7), this is an interesting observation that confirms previous findings with 40 mg of inhaled frusemide by FUJIMARA *et al.* [2].

The authors speculate that the small protective effect against methacholine, and some of the inhibitory effects against AMP are best explained by interference with ion transport by airway epithelium. This is supported by our finding that frusemide deposited on the nasal mucosa causes a dose-dependent decrease in transepithelial nasal potential difference (PD) in man [3], a finding which we have subsequently reproduced (MIALON, REGNARD and LOCKHART, unpublished observation). The reduction in nasal PD strongly suggests either reduced electrical resistance or diminished ionic current across this epithelium; the latter being the most likely because of the known effects of frusemide and other loop diuretics on epithelial cells [4-8]. Therefore, we agree with POLOSA *et al.* that a direct effect of frusemide on airway epithelium is very likely, and may account for some of the protective effects of this drug against several bronchial provocants [9], the more so since osmotic stimuli, which certainly interfere with ion transport, induce epithelial-dependent relaxation of isolated guinea pig trachea [10].

However, we disagree with POLOSA *et al.*''s suggestion that frusemide acts *via* inhibition of the Na^+-K^+-ATPase. There is no doubt that Na-K-Cl co-transport of airway, and other, epithelial cells necessitates both establishment and maintenance of a low intracellular Na^+ activity through operation of the Na^+-K^+-ATPase located at the basolateral cell membrane [4-8], and phosphorylation of the co-transporter protein [8, 11]. However, experimental evidence suggests that there is no direct inhibition by loop diuretics of Na^+-K^+-ATPase in animal cells [11], including airway epithelial cells [6]. Rather, loop diuretics oppose Na-K-Cl co-transport through a direct effect on the Na-K-Cl co-transporter.

In conclusion, we do agree that frusemide has very likely a direct effect on airway epithelium that may account, at least in part, for its protective effect against bronchial obstruction induced by several bronchial provocants in asthma [3, 9], but we question the primary effect of frusemide on Na^+-K^+-ATPase suggested by POLOSA *et al.* [1]. We also agree with POLOSA et *al.* that frusemide certainly modifies ion transport and, henceforth, biological activity of other cell types, *e.g.* mast cells, since Na-K-Cl co-transport is a ubiquitary mechanism [11].

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