

Editorials

CFC transition: the Emperor's new clothes. Each class of drug deserves a delivery system that meets its own requirements

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It is likely that two related but very different events during this coming year will form milestones in the history of aerosol therapy. One is likely to represent a genuine advance, ushering a new era in which aerosol delivery systems will be used to deliver potent systemically acting drugs via the lungs. The other will be the culmination of an enormously expensive exercise aimed at perpetuating inappropriate technology.

It seems probable that, during the later part of 2000, the FDA will grant a licence to deliver insulin as an aerosol. The most exciting aspect of this is that, for the first time in half a century, an aerosol delivery system has been developed specifically to fulfil a specific task.¹ The biggest market in North America for inhaled insulin is likely to be in the treatment of type II diabetes and, although the potential for significant adverse events related to swings in blood sugar is probably less than in those with traditional insulin dependent diabetes, it is still necessary to deliver the insulin in reproducible quantities to the lungs. If successful, this product is likely to be the first of a new generation of products designed to deliver systemically acting drugs via the respiratory tract. This concept is not new; early pioneers working with jet nebulisers in the 1930s and pressurised metered dose inhalers (pMDIs) in the 1950s considered delivering insulin as an aerosol but soon abandoned the idea because they realised that delivery of drug to the lung was so unpredictable that it was not possible to utilise aerosolised insulin safely with those devices.

In contrast, this year is also likely to see the widespread introduction of chlorofluorocarbon (CFC) free pMDIs delivering inhaled steroids.² This “seamless” transition in which hydrofluorocarbon (HFC) replacement devices have been detuned to perform as badly as their predecessors has been greeted with some enthusiasm by a number of influential clinicians yet, on reflection, this must represent one of the most costly mistakes in the history of pharmaceutical development. The process has been hugely expensive in financial terms, costing more than a billion dollars—the equivalent of bringing five or six new therapeutic compounds to market. The real cost, however, will be borne by the patients who are now likely to have these devices inflicted upon them during the coming years.

To understand why the advent of CFC replacement pMDIs delivering inhaled corticosteroids as inefficiently and as unreliably as their CFC forebears should not be a cause for celebration we should briefly review the development of inhaled therapy for the treatment of asthma. The concept of a portable delivery system for bronchodilating agents surfaced almost 200 years ago with the advent of asthma cigarettes.³ These took an existing technology and used it to deliver anticholinergic agents. Unpredictable

drug delivery and frequent side effects led to their replacement with other delivery systems and agents. Jet nebulisers appeared in the 1930s when a baffle was added to an atomiser to produce droplets small enough to be inhaled, and some two decades later the pMDI was developed as a portable multidose alternative to the rubber bulb hand held nebulisers. The pMDI was developed specifically to provide a portable multidose delivery system for β agonists that would enable patients to obtain rapid relief wherever they were. The great advantage of the inhaled route for these agents was speed of onset, with maximal bronchodilation being achieved in minutes rather than in hours as is the case with β agonists delivered orally.⁴ It was also noted that systemic side effects were substantially less than those observed when the same bronchodilation was achieved using the oral route. Thus, delivering β agonists directly to their site of action in the lung also conferred benefits in terms of their therapeutic index. However, the improved safety profile is only relative and, as with any form of drug therapy, adverse events do occur with inhaled medication if excessive doses are used, as illustrated by the epidemic of asthma deaths in the 1960s associated with high dose, non-selective β agonists.⁵

It was clear from the earliest days of the pMDI that this delivery system was not capable of delivering drugs in reproducible quantities to the lungs. However, the wide therapeutic index, even with non-selective β agonists, permitted supramaximal doses to be used that could compensate for poor technique. The rapid onset of action provided immediate feedback so that failure to deliver adequate quantities of drug to the lungs due to poor technique could be compensated for by the administration of additional doses.

When a topically active steroid with significant first pass metabolism was developed in the late 1960s, it was unclear whether the concept of delivering inhaled steroids to treat asthmatic subjects would prove to be useful. It certainly was not evident that it would become the cornerstone of good management used by millions of asthmatics every day. Indeed, a number of previous attempts to use inhaled steroids such as hydrocortisone and dexamethasone had failed, largely because of the associated side effects.⁶ At the time the pMDI was available and an understandable pragmatic decision was made to use this delivery system because it was available. The first trials proved disappointing and it was only the enthusiastic and committed efforts of an allergist from Derby, Dr Harry Morrow-Brown, that permitted the potential of this form of treatment to be identified.⁶ Unfortunately, once the potential benefits of this approach had been identified a decision was taken, probably by default, to continue to use pMDI for inhaled steroids.

It was well known by this time that most patients could not use pMDIs effectively⁷ and by the end of the 1970s most of the numerous failings of the pMDI as a delivery system for inhaled steroids had been identified.⁸ Prominent amongst these were difficulties in coordinating actuation with inhalation, and the side effects resulting from high oropharyngeal doses of drugs with relatively low first pass metabolism such as beclomethasone. Consequently, the holding chambers and spacing devices were developed to compensate for these failings. The first such device used was developed by a paediatrician⁹ and the idea was subsequently taken up by the pharmaceutical companies.

In the late 1980s an opportunity presented itself to reassess the situation following the Montreal protocol which decreed that all CFC use would be phased out.² Unfortunately, instead of stepping back and looking at inhaled corticosteroids afresh, the industry took the collective decision to develop CFC replacements for pMDIs. In contrast, most other industries that use CFCs reacted in horror but then found that technology had moved on, providing opportunities to deliver more effective and cheaper alternatives. At the end of the 20th century the use of pMDIs, with or without holding chambers, remains the most prescribed delivery system for inhaled steroids in the UK and North America, although other European countries have moved away from using pMDIs for steroids. This extremely high use of pMDIs for delivery of inhaled steroids has been partly driven by cost but it has also, to a large extent, been the failure by those involved in aerosol research to focus on the important question—do these devices meet the needs of patients when used to deliver inhaled corticosteroids?

The answer to this question must be a resounding no. There is no question that inhaled steroids have transformed the lives of many asthmatics and if no other devices were made available clinicians and patients could, and would, cope with the limitations of pMDIs. However, it must also be acknowledged that these devices fail many patients and it is likely that the “seamless” transition will be a cause of some embarrassment in coming years. Why should this be so? The greatest failing of these devices for the delivery of inhaled steroids is that they do not deliver the drug reliably and reproducibly to the lungs because of their failure to address the three Cs—compliance, competence, and contrivance. These three quite distinct impediments to effective drug delivery are often loosely thrown together under the heading of compliance, if they are considered at all. This lack of clarity has been a conspicuous feature of pronouncements on aerosol therapy for the last two decades.

The use of pMDIs to administer inhaled steroids fails to address any of these issues, any one of which can prevent effective drug delivery to the lungs. It is important to understand the profound effect of each of these factors if we are to deliver by aerosol drugs such as corticosteroids and long acting β agonists reliably and reproducibly to the lung.

Compliance

It is well known that compliance (or adherence) with inhaled treatment for asthma is poor, although there is little evidence that it is any worse than for oral treatment.¹⁰ Failure to take drugs such as corticosteroids at all, or administering them infrequently, will obviate any potential benefits. The factors influencing compliance are complex and are independent of a number of factors such as age, education, understanding of the disease process, and disease severity.¹⁰ The most accurate tool for assessing compliance would appear to be tossing a coin, which

appears to be as accurate as clinician assessment.¹¹ Clearly, the factors that influence a patient's compliance with a given treatment regime are complex, but the lack of any work addressing the issue of whether delivery system design features can influence compliance is unfortunate. The only clue that features can be included in the design of a device that can influence compliance is derived from a study suggesting that, when patients are aware that compliance is being monitored, compliance/adherence tends to improve.¹² It is possible that other design features may also influence compliance, although it is clear that “liking” a device or finding a device “easy to use” do not affect compliance.¹⁰

In North America the drive to monitor compliance is moving ahead apace and more data may come to light as health care organisations start to monitor compliance as part of their drive to cut costs. It is likely, for example, that the cost associated with exacerbations and hospital admissions will not be met if a patient can be shown to have been non-compliant with their inhaled corticosteroid prior to an exacerbation. The issues of individual liberty to choose to take a form of medication or not, weighed against the benefit to the community and health care provider associated with improving compliance and reducing health care costs through monitoring, have not been discussed in any detail in this country. It is likely to become a major issue in coming years.

Competence and contrivance

Unfortunately for those using aerosol therapy, compliance is only one of the three Cs. Patients would normally expect that they would derive benefit from making the decision to comply or adhere to a treatment regime. Sadly, many will fail to derive significant or maximal benefit when they comply with inhaled corticosteroid therapy because of poor drug delivery to the lungs, due either to inadequate competence or contrivance. It is clear that the level of functional illiteracy in developed countries such as the USA and the UK is extremely high, with evidence from studies indicating that a very large part of the community (20–40%) cannot understand and act on an instruction such as “take a tablet after meals”.¹³ To expect such individuals to be able to use pMDIs is wildly optimistic. The issue of competence is particularly a problem in the elderly^{13,14} and is a major factor in the popularity of jet nebulisers in this age group. Central bodies at a national or local level issue guidelines that pMDIs with a holding chamber are as effective as jet nebulisers, but the evidence for this assertion is obtained from studies undertaken in carefully controlled environments. The conclusions from such studies should be that pMDIs with holding chambers can be as or more effective than jet nebulisers. However, these studies generally do not reflect the difficulties experienced by, for example, elderly patients in their own homes.

As noted above, it has been known from the earliest days that pMDIs are difficult to use. To compensate for some of these difficulties, pharmaceutical companies have developed breath actuated devices, holding chambers, and spacers. Although these devices have some intrinsic problems of their own, the real problem with them is that, even when patients know how to use them adequately, having been instructed for some time by the physician and/or nurse, they frequently contrive to use their device in a different manner. While knowing that a holding chamber will reduce the variability in dose associated with coordination problems and reduce oropharyngeal deposition so improving safety for a number of inhaled steroids, many patients will regularly discard their spacer. In a recent study involving patients attending secondary care clinics we found 67% of those prescribed spacers admitted to regularly using

their corticosteroid pMDI without the prescribed holding chamber because they found the chamber “inconvenient” (Everard, unpublished). Many of these patients were pre-school children in whom the parents described asking the child to open their mouth and then firing the pMDI directly into the mouth, a strategy guaranteed to prevent effective drug delivery to the lung. The parents all knew how to use the pMDI/holding chamber appropriately (were competent) but contrived to use them in a manner that rendered them ineffective. Similar levels of “spacer misuse” were described in a recent North American study.¹⁶ Contrivance is also often a problem with breath actuated pMDIs, with many patients failing to inhale deeply after the device actuates because they believe the dose to have been delivered. These patients may be compliant and competent but still have little or no drug reaching the lungs.

Delivery systems in the real world

To develop an informed approach to choosing delivery systems for patients and to develop future systems we should be able to understand how devices perform in routine clinical practice. Unfortunately, despite an endless stream of publications on aerosols over the past decade, few studies have attempted to assess the performance of current devices in routine clinical practice. Most *in vitro* and, indeed, “deposition” studies should be consigned to a “Journal of Irrelevant Aerosol Science”. There are two principal problems. Firstly, most of these “scientific papers” aim to add the “science” to devices developed empirically.⁶ Devices such as pMDIs and most current dry powder inhalers (DPIs) came to market because a therapeutic (pharmacodynamic) effect could be observed. All the “science” has been added since. The regulatory authorities have, of course, had a major role in retarding development of new approaches by making it more cost effective to show that a new device is “equivalent”—that is, as inefficient as previous generations of devices.

The second major problem is that few, if any, of these “scientific” studies have any relevance to patients. There are endless benchtop studies undertaken because they are easy and quick to perform and will generate a publication. For example, there has been a steady procession of papers for almost a decade produced by a very small number of research groups assessing the potential impact of static in polycarbonate holding chambers on drug delivery. These benchtop *in vitro* studies have altered the chambers and the drugs in a myriad of combinations yet all produce the same answer—static in polycarbonate chambers is another cause of variability in drug delivery from devices. The pharmaceutical companies and those involved in aerosol research knew this many years before papers started to appear in the medical literature, yet no action was taken because, despite this issue, patients derived benefit from using holding chambers as they compensate for the problem of inadequate and highly variable delivery to the lungs observed when using pMDIs. Does static in a chamber really matter? Evidence from one study in young asthmatics suggests that the influence of static on the reproducibility of drug delivery to the patient is non-existent or very small in clinical practice.¹⁶ In an ideal world we would use static free chambers, but patient factors introduce variables that dwarf the impact of a single factor such as static.

The other type of study commonly published are deposition studies using radiopharmaceuticals, most commonly planar gamma scintigraphy, and pharmacokinetic techniques.¹⁷ These are increasingly being used by pharmaceutical companies to promote their own device, but their relevance to real life is again questionable. Such

studies generally take well trained volunteers, ensure that they are able to use a device optimally, and then study the subject on one or sometimes two occasions. The best these studies can do is provide information regarding the performance of a device under optimal conditions. A recent study indicated the problem with such studies when the supervisor of the study forgot to shake a pMDI canister before use by the first eight patients and this very simple error reduced the lung dose by 54%.¹⁸

The future?

When choosing a device for a class of drugs such as inhaled corticosteroids we would like ideally to choose a device that will reliably and reproducibly deliver drugs to the lungs of patients. It is to our shame that we have not shown that it is indeed beneficial to deliver inhaled corticosteroids to the lungs of patients in reproducible doses. The reason that we do not know that reproducible lung doses of steroids would be beneficial in terms of therapeutic outcomes is that we do not have a device that can do this. There is a little evidence that, even in ideal conditions, dry powder devices may deliver drugs more reproducibly to the lungs of subjects than pMDIs,¹⁹ but whether they are any better than pMDIs with holding chambers is unclear. However, we desperately need evidence from the real world. Future research should be aimed at determining whether design features can positively influence compliance, ensuring that devices are intuitive to use (that is, do not require great competence), and that they provide some mechanism for ensuring that patients use the device appropriately and cannot contrive to use them incorrectly. As noted above, circumstances may provide answers to questions such as whether monitoring compliance or providing direct feedback influence behaviour. The issues of compliance, competence, and contrivance can only be addressed if the needs of the patients are considered first; the technology developed to address these issues is largely irrelevant to both clinician and patients.

By perpetuating the pMDI to deliver inhaled corticosteroids we continue to deliver our most valuable asthma treatment in a device designed almost half a century ago to deliver short acting β agonists. Should inhaled insulin and other novel treatments prove to be successful, the expectation of clinicians and patients will change. Of course, should the pharmaceutical industry choose to develop new devices, they will be faced by many problems such as where the inhaled corticosteroids should be delivered. Current devices deliver polydispersed aerosols, thereby depositing the drug throughout the airways although this distribution is far from uniform. The one company that tried to improve on the old pMDI systems by developing a device that is more “efficient” has been confronted by an issue largely ignored for the past 30 years—namely, whether the pattern of deposition of inhaled corticosteroids in the lung influences their therapeutic index. It is ironic that this should be raised now when for 30 years the whole issue of therapeutic index has been seen largely as a side issue. Ensuring that little or no drug reached the systemic circulation from the gastrointestinal tract by using holding chambers, efficient DPIs, and/or designer inhaled corticosteroids was felt to be sufficient to ensure safety when using these drugs. This culminated in the “more is better” culture of the early 1990s and the pronouncement in the BTS guidelines that doses of up to 2 mg could be used in children with asthma—well outside that stated on any licence.²⁰ Paediatric endocrinologists and respiratory physicians are increasingly concerned about sometimes life threatening adrenal suppression observed in children who inadvertently or deliberately are treated with very high dose inhaled corticosteroids. With current devices and inhaled

steroids our only guide to a “safe” dose is to use the lowest dose that works—a position that has not changed since inhaled corticosteroids were introduced 30 years ago.⁶ It is possible that the dose required to control day to day symptoms is lower than that required for optimal prevention of exacerbations, but further data are required.

By the end of the year we may well come to appreciate that the “seamless” transition to CFC free pMDIs for inhaled corticosteroids represents the Emperor’s new clothes—all promise and no substance—while the endocrinologists will have taken a genuine leap into the 21st century, providing an example of what might be possible.

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