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Classic therapies revisited

Challenges in changing to non-chlorofluorocarbon inhalers in the treatment of asthma

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Summary

The chlorofluorocarbon (CFC)-based metered dose inhaler, which has been the mainstay of the management of obstructive lung diseases, will soon be phased out world wide and replaced by CFC-free devices. Patients will have to be changed to the devices in a co-ordinated manner to avoid any risk to their health and safety. The different shapes and aerosol delivery characteristics of the new inhalers, as well as their distinctive taste, could add to the levels of poor drug use already experienced in asthma. From previous change scenarios in disease management, the potential for unstable asthma control is a real possibility with all the attendant costs. By using the time available before CFC-based inhalers are withdrawn, there is an opportunity to enhance asthma management during this period of change.

Keywords: metered dose inhalers; asthma; chlorofluorocarbons

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Chlorofluorocarbons (CFCs) have been used in industry, in domestic appliances and in medicine, particularly as the propellant in pressurised metered dose inhalers (MDIs) for asthmatics, for many years. However, concerns that CFCs were causing depletion of atmospheric ozone has prompted a change to alternatives. Medicine has been one of the last areas to change because of the lack of reasonable alternatives, but over the next 2 to 4 years, the 2.5 million patients in the UK currently using CFC-based MDIs for asthma or chronic obstructive airways diseases will need to be changed to a non-CFC device.[1] This is in accordance with the terms of the Montreal Protocol and subsequent European legislation.[2 3] This paper discusses the key management issues affecting primary and secondary care, and policy makers in the UK, but similar issues arise internationally: in most European countries, the timeframes for withdrawal will be similar but in developing countries they may be substantially longer.

Scale of current prescribing

In 1995, MDIs accounted for 83% of all prescriptions for short-acting β2-agonists and 78% of all prescriptions for inhaled steroids in the UK,[1] a total of approximately 39 million devices. The scale of the change-over is therefore enormous and has been described recently as the largest enforced change in medication ever to take place in the UK.[4]

Timescale for change

The European Union has suggested that CFCs will no longer be made available for the production of CFC-based MDIs for key drugs, salbutamol and beclomethasone, "when two alternative CFC-free inhaler products are available from two different producers",[3] and the alternative product is shown to be an effective replacement. After this, there will be a period when manufacturers use up existing stocks of CFCs and of already manufactured CFC inhalers. The transition will therefore not be sudden, but will take place over a period of several months. Other less widely used drugs do not have this protection and could be replaced at very short notice. It is intended that the transition should be complete by 2003.

The alternative propellant is a hydrofluoroalkane, which has been extensively investigated by the pharmaceutical industry and which meets the requirements of both European and American drug licencing agencies. Hydrofluroalkanes have detectable clinical effects only at very high doses and for the purposes of MDIs are effectively inert.[1] They will be associated with a change in taste and a loss of the 'cold freon' effect experienced with the use of CFC-based MDIs.

There are already two salbutamol MDIs using hydrofluoroalkane as a propellant with more coming on-stream before the end of 1999 (table 1). The clock therefore has started to tick for salbutamol CFC-based MDIs, which will disappear from the market probably by mid-2000 (and in the case of one major manufacturer, by August 1999). The CFC-free MDIs seem bioequivalent to the CFC-based products, and transition should be relatively easy. The situation with beclomethasone is more complex. Corticosteroids for inhalation have always been difficult to formulate, and so far only one producer has a CFC-free beclomethasone MDI available. This is, however, not identical to existing formulations in that the dose range is different, because of differences in the particle size and deposition, and subsequent bioavailability. However, other CFC-free beclomethasones with dosing similar to existing products are expected before the end of the year (table 1). In the beclomethasone-containing CFC-free MDIs, ethanol is used to improve drug solubility in some, and this may be of concern to some patient groups.

Table 1 Launch timetable for CFC-free MDIs

Drug	*Company*	*Product*	*Date of availability*	*Comment*
Salbutamol	Glaxo-Wellcome	Ventolin Evohaler	currently available	CFC Ventolin likely to be withdrawn gradually from Aug 1999
		Ventolin Easibreathe	Aug 1999	
	3M	Airomir	currently available	
	Baker Norton		probably Sept–Oct 1999	
Beclomethasone	Glaxo Wellcome	Becotide Evohaler	probably 2001	
		Becotide Easibreathe	probably late 2001	
	3M	Qvar	currently available	Important dosing issue; requires half the dose of CFC-based MDI for similar effect
	Baker Norton		late 1999	Already available in some European countries
Fluticasone	Glaxo Wellcome	Flixotide Evohaler	October 1999	

There is little information on the likely availability of CFC-free terbutaline, budesonide, ipratropium, eformoterol or oxitropium. Given the relatively large proportion of some of these used as dry powder devices, there may be little incentive for some manufacturers to produce a CFC-free product. In general, the major manufacturers have adopted a reasonable policy of producing new devices similar in presentation to existing devices and with dose-for-dose compatibility.

Cost implications of transition

There are substantial cost implications of the transition for the National Health Service (NHS). These arise in part from the increased costs of the new MDIs (although these are the same price as the *branded* equivalents they replace) over the widely used existing *generic* MDIs which they will replace (generic prescribing is currently about 60% for bronchodilators and 40% for steroids; generic salbutamol inhalers cost £1.80 compared to £2.30 for branded CFC-based or CFC-free inhalers, and about £8 for an equivalent dry powder device). A second factor increasing the costs is the likelihood that many patients will transfer not to an MDI, but to the substantially more expensive dry powder inhalers, which are of course also CFC-free. Many experts argue that this would be clinically appropriate given the difficulties of using MDIs,[5] but it is not our purpose to pursue this here.

The potential increase in NHS costs has been modelled,[6] using several possible scenarios. Switching to the existing CFC-free salbutamol MDI alternatives does not present a large financial risk – an increase of £1.5 to £6 million on current costs of £40 million. If CFC-free generic MDIs become available, this risk will be further reduced. However, if dry powder inhalers are utilised then the risk could be substantial. A total switch to dry powder inhalers could quadruple the current salbutamol prescribing costs, an increase of over £120 million.

Similarly, the financial risk of switching beclomethasone to a CFC-free MDI is not enormous (an increase of about £6 million on a current spend of about £100 million), but a switch to fluticasone would produce significant increases of up to £100 million. If the alternative used is a dry powder inhaler then the risk could be more substantial still – an increase of up to £150 million.

These scenarios assume an extreme situation, of a total switch from current prescribing of MDIs to alternative devices. A complete switch to any therapy is unrealistic, but provides insight into likely implications and financial risks. These increased costs and their implications for the single budget held by primary care groups need to be considered, since there will be no additional funding for this transition and any increase in costs here will be met from a decrease in some other parts of the health services. This emphasises the need to manage the transition carefully.

Clinical effects of the transition

In theory, the transition should have no deleterious effects on patient care; patients will receive a product of similar effectiveness. However, there is considerable potential for patient harm from the confusion likely to occur and anxiety engendered around the time of change. Patients will be unfamiliar with the new

devices, and will be aware of a change in taste and sensation when using the new inhalers. This may lead to a lack of confidence in the efficacy of the new device and possibly poor compliance. This confusion will be increased if patients are dispensed CFC-free and CFC-based MDIs indiscriminately during the overlap period when both are available, or when a patient is concurrently given both CFC-free MDIs (salbutamol) and CFC-based MDIs (beclomethasone), as is almost inevitable given the timing of the withdrawal and availability. A particularly hazardous time for such changes is when patients move between primary and secondary care. The result could be an increase in acute asthmatic attacks requiring hospitalisation, although this measure has been shown in the past to be poorly correlated to the quality of prescribing of anti-asthma therapy.[7] The more important loss may be more subtle, in the general quality of care received by patients with asthma and in their ability to manage their own condition; both of these areas have been substantially improved in recent years and the progress made may be lost during the transition.

Learning from earlier examples of change

It is worth considering some of the issues highlighted in earlier cases of enforced changes in patient medication:

- patients were resistant to change because of misinformation about new drugs, in particular patients who had been long-standing users of the previous medication[8]
- crisis cases occurred when existing supplies of a drug were withdrawn from pharmacists and replaced with the newer variety[9]
- patients objected to a change being imposed upon them without their views being taken into consideration[10]
- specific problems involved errors in prescribing and in dispensing, often for hospital in-patients, with patients being given the wrong preparation or switched between preparations inadvertently (Novartis Pharmaceuticals, personal communication).

Planning and communication (or the lack of it) between patients and prescribers appeared to be the basis of most of the problems experienced. Some of these lessons have been taken on board: for instance, Glaxo Wellcome will have sufficient supplies of CFC-based Ventolin in reserve to allow for the complete withdrawal of the CFC-free product should serious product defects be found. Learning from past lessons, the transition could be used positively as an opportunity to review the management of all patients using MDIs, and encourage patient education. It is essential that patients be active partners in the transition.

Policies for change

There has been limited national guidance on the transition.[11] Most health authorities are attempting to introduce a policy to manage the transition which must be done in a co-ordinated fashion between hospitals, primary care, and community pharmacies. Inevitably, the bulk of the work in the transition will fall in primary care, on general practitioners, their practice nurses, who are often heavily involved in the management and education of asthmatics, and on community pharmacists. Hospitals will also have a role to play. Clearly, where there is a local policy, it is important that all adhere to it so as to minimise the likelihood of treatment failure.

At a recent conference involving these key constituencies,[12] it was generally agreed that the transition to salbutamol CFC-free MDIs was relatively straightforward and could start immediately. In contrast, the switch to beclomethasone was more complex because of the lack of choice of suitable devices, and most delegates felt it appropriate to delay this change until more devices were available.

A number of different models could be adopted to manage the transition (table 2). We are currently evaluating these models, which are described in detail elsewhere.[13] Most authorities and practices have adopted a policy midway between options 2 and 3, with much repetition of work between health authorities.

Education and information

How patients are to be informed of the changes is an issue in itself. There is evidence that in asthma, written information alone is insufficient for patient compliance and enforced change[14 15] and has no significant effect on morbidity.[16] Limited (information only) asthma education does not reduce hospitalisation

Table 2 Options for managing change

Options	*Advantages*	*Disadvantages*
Option 1 Do nothing	No expenditure for commissioning authorities in the short term	Forgoes the opportunity to improve the quality of prescribing and management of asthma patients. Risk of the pharmaceutical industry managing the change throughout the transition period to meet its own agenda
Option 2 Independent local guidance on reviewing and switching patients between products using an evidence-based approach	Quality issues addressed in both prescribing and management	Duplication of activity in different commissioning authorities with attendant costs. Risk of conflicting guidance between different authorities. The ability of purchasers to influence the behaviour of prescribers is impaired
Option 3 A co-ordinated national/regional transition guidelines products using an evidence-based approach	The scale of additional expenditure is contained. Effective prescribing and management is achieved. Conflicting recommendations and duplication of effort are minimised. There is improvement in the care of patients with asthma	

rates or visits to the doctor for asthma attacks nor reduce time lost from work. Neither does it change asthma medication usage or improve lung function. The only advantage identified is the improvement in patients' perception of their symptoms.[17] Although education has been shown to improve patients' knowledge of asthma, clinical outcomes do not necessarily change and this should be borne in mind when evaluating transition outcomes.

A recent post-marketing surveillance study of a CFC-free salbutamol MDI[18] underlines the importance of this, and is on the one hand reassuring about the safety of CFC-free products, but on the other disquieting about the problems likely to be encountered in the transition. Compared to patients maintained on their existing CFC-based MDI, more patients on a CFC-free salbutamol MDI withdrew from the study (17.6 *vs* 4.8%), largely because of issues other than adverse effects: taste, intercurrent illness, lost to follow-up, and inadvertent prescription errors. The two preparations were similar in safety. A relatively higher drop-out rate on the CFC-free MDI was anticipated. Since the patients on CFC-based MDIs were in effect a survivor population, they were continued on their existing medication, which was acceptable to them, whereas patients starting a new drug are likely to develop adverse reactions early, and some adverse reactions may be only a 'nocebo' response. Also, there may be a tendency to attribute any adverse events to the new inhaler. In other studies, switching from branded to generic inhalers has also shown a 17% drift-back to the original brand.[10] Education might be expected to minimise some of the effects. Its importance was shown in the post-marketing study mentioned above, where a key problem was the high drop-out rate (3.1%) from taste, which represented a failure of education and information – patients had not been warned to expect this.

In our own current research (unpublished), we have found that, where patients have been informed of the change-over by means of a practice information leaflet, approximately 80% of patients changed to the CFC-free MDI salbutamol inhaler satisfactorily, while 20% drifted back to the original brand.

The opportunity for education can also be used to try to improve concordance between doctors and patients in drug use in asthma. In asthma, 40 to 50% of patients typically fail to comply with prescribed treatment,[19] and this is a major potential cause for failure to respond to therapy.[20] Patients and professionals alike are at fault: one study showed that 34% of clinicians can leave out one or more steps when instructing patients on inhaler use.[21] Several factors improving concordance are a good physician/patient relationship, the patient's understanding of the treatment rationale, and ease of use of the preparation.[22] Clearly a poorly managed transition will result in even poorer use of medication with consequent clinical effects and wasted resources.

The transition to CFC-free MDIs will differ from the experimental situations described above in one important respect: patients will not be able to return to their old inhaler should they wish to. It is therefore advisable to use a combination of approaches to prepare patients for the change-over and to let them know how it will affect them as individuals. Patients should be offered a full consultation with their doctor or asthma nurse in addition to any other written information that may be supplied. This provides an opportunity to review all their current medication and enhance general education, perhaps leading to improvement in asthma care. Any deterioration in symptoms can be minimised

Learning points

- CFC-based MDIs are currently the mainstay of the treatment of obstructive lung disease in the UK
- traditional CFC-based inhalers will be withdrawn in response to concerns about the effects of CFCs on the environment; salbutamol CFC-based inhalers will be phased out probably by mid-2000; there is no clear timetable for the phase-out of beclomethasone CFC-based inhalers
- new clinically effective and equivalent CFC-free salbutamol inhalers are now available; beclomethasone inhalers will be delayed
- there will be a substantial cost to switching to CFC-free inhalers
- in the past, patients have suffered harm and needless anxiety during similar 'forced' medication changes
- there is a need for patient education about the transition
- there is an opportunity for improving patient management by increased review of patients over this period and by personalised education
- a coordinated approach must be adopted in primary and secondary care, involving all key stakeholders, especially the patient, to undertaking the change

with timely preparation and good communication between patients and professionals. Therapy can be reviewed in depth and stepped up or down as needed.

In reality, this may or may not happen, purely because the changes that are implemented in primary care will be constrained by available manpower and other indirect prescribing costs. The transition is an interesting early test for clinical governance, which should aim to ensure the quality of the service patients receive (NHS Primary Care Act 1997, Section 5: Primary Care Groups) by promulgating best practice, supporting its implementation and auditing the results both in terms of the process (ie, how many patients were transferred by what date) and the outcome (particularly in terms of any severe clinical deterioration).

Patient information must be in place before any changes occur,[9] and pharmaceutical companies have taken a lead in this, although other groups, including the Department of Health and the National Asthma Campaign are also involved in producing clear patient information leaflets. Many local health authorities will also produce materials explaining how local polices will affect patients.

Conclusions

The transition to CFC-free devices is not an optional exercise. If the risks are to be minimised, a co-ordinated approach involving all the key players, especially the patient, needs to be adopted. In most parts of the country, this will be led by the health authorities. There is an opportunity not merely to minimise risk but to improve the management of asthma by actively reviewing patients and by education.

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1 Anon. Chlorofluorocarbon free inhalers. *Med Resource Cent Bull* 1998;**9**:17–20.
2 United Nations Environment Programme Technology and Economic Assessment Panel of the Montreal Protocol on substances that deplete the ozone layer. Part III: *Update of the 1994 TOC Aerosols Report and the MDI Transition Strategy*. Geneva: TEAP, June 1996.
3 European Community Strategy for the Phaseout of CFCs in Metered Dose Inhalers. Final report. Brussels: European Union, January 1998.
4 Odd R. New inhalers: 'biggest change ever'. *Pharm J* 1998;**260**:296.
5 Dolovich M. Changing delivery methods for obstructive lung diseases. *Curr Opin Pulm Med* 1997;**3**:177–89.
6 Slack R., Ward S, McCabe C, Peters J, Akehurst R. *The transition to CFC-free inhalers.* Occasional Paper No 98/1. Sheffield: School of Health and Related Research, University of Sheffield, 1998.
7 Shelley M, Croft P, Chapman S, Pantin C. Is the ratio of inhaled corticosteroid to bronchodilator a good indicator of the quality of asthma prescribing? Cross sectional study linking prescribing data to data on admissions. *BMJ* 1996; **313**:1124–6.
8 Craven A. All changed. *Commun Outlook* 1985;27 Feb:31–3.
9 Dowell J, Snadden D, Dunbar J. Rapid prescribing change, how do patients respond. *Soc Sci Med* 1996;**43**:1543–9.
10 Dowell JS, Snadden D, Dunbar JA. Changing to generic formulary: how one fundholding practice reduced prescribing costs. *BMJ* 1995;**310**: 505–8.
11 Department of Health (DoH). *CMO's Update 17*. Propellant changes in metered-dose inhalers. London: DoH, 1988.
12 Short D, Chapman S. Managing the transition to CFC-free metered dose inhalers (conference report). *Pharm J* 1999;**262**:198–9.
13 Rannard A, Bundred P, Walley T, Bogg J. *Managing the transition from CFC to CFC-free inhalers*. Monograph Publication, ISBN 0 9534249 0 1. Liverpool: Department of Primary Care, University of Liverpool, 1988.
14 Jenkinson D, Davison J, Jones S, Hawtin P. Comparison of effects of self- management booklet and audiocassette for patients with asthma. *BMJ* 1988;**297**:267–70.
15 Gibson N, Ferguson A, Aitchison T, Paton J. Compliance with inhaled asthma medication in preschool children. *Thorax* 1995;**50**:1274–9.
16 Hilton S. Controlled evaluation of the effects of patient education on asthma morbidity in general practice. *Lancet* 1986;**i**:26–9.
17 Gibson PG, Coughlan J, Wilson AJ, *et al.* The effects of limited (information only) patient education programs on the health outcomes of adults with asthma. In: Cates C, Ducharme F, Gibson P, Jones P, Rowe B, Wolf F, eds, *Airways module of the Cochrane Database of Systematic Reviews,* issue 1. Oxford: The Cochrane Collaboration; 1988.
18 Ayres JG, Frost CD, Holmes WF, Williams DRR, Ward SM. Postmarketing surveillance study of a non-chlorofluorocarbon inhaler according to the safety assessment of marketed medicines guidelines. *BMJ* 1998;**317**:926–30.
19 Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? *Eur J Respir Med* 1994;**7**: 540–9.
20 Horn CR, Clark TJ, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. *Respir Med* 1990;**84**:67–70.
21 Mas JC, Resnick DJ, Feldman BR, Davis WJ. Misuse of metered dose inhalers by house staff members. *Am J Dis Child* 1992;**146**:783–5.
22 Kelloway JS, Wyatt RA, Adlis SA. Comparison of patient's compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med* 1994;**154**:1349–52.