

PJ PRACTICE CHECKLIST

**CFC-FREE
INHALERS**

As yet, only a few chlorofluorocarbon-free metered dose inhalers are available but others are being developed and are expected to be marketed soon. As the move to these new inhalers gets under way, this card explains why the change is necessary and outlines points to bear in mind to make the changeover as smooth and as safe as possible

WHY ARE PROPELLANTS BEING CHANGED?

The change from the standard chlorofluorocarbon (CFC) propellants is being made for environmental reasons, not for any safety or clinical reasons. As a result of recognition that CFCs destroyed stratospheric ozone, an international agreement was reached to phase out their use (The Montreal Protocol, 19c,7). Pharmaceutical metered dose inhalers were regarded as essential and were exempted from the January, 1995, deadline for cessation of use until a suitable alternative became available. Two consortia of pharmaceutical manufacturers have since undertaken extensive testing of two alternative propellants, hydrofluoroalkane-134a (HFA-134a) and hydrofluoroalkane-227 (HFA-227), for use in CFC-free MDIs. The two HFAs are much less damaging than CFCs to the earth's ozone layer.

WHY HAS IT TAKEN SO LONG TO REFORMULATE MDIs?

The HFAs have different physical properties to the CFCs. Surfactants such as lecithin, oleic acid and sorbitan trioleate, which were previously used to suspend the drug particles in the CFC formulations, were found to be insoluble in the HFAs. Moreover, incompatibility problems between the new propellants and the standard valve elastomers also surfaced. As a result, redesign of the whole MDI delivery

systems became necessary. New production lines also had to be set up as the existing lines were unsuitable.

HOW ARE THE CFC-FREE MDIs TESTED?

Both *in vitro* and *in vivo* methods are used. The *in vitro* assessments include

measurement of particle size distribution, particle deposition in physical impactors which aim to simulate the aerodynamics of the spray in the lung, and reliability and consistency of dose delivery from start to exhaustion. Clinical testing includes equivalence testing for efficacy against currently licensed CFC products in asthma patients, using outcome measures such as

one-second forced expiratory volume (FEV1). Safety assessments are also undertaken in attempts to identify acute toxicity such as bronchospasm and enhanced systemic effects. Both expected and unexpected adverse effects are recorded.

POINTS TO NOTE

- HFA inhalers may feel and taste different to CFC inhalers. Patients should be reassured that this should not affect the efficacy of their products
- Despite extensive testing, unanticipated problems may emerge with wider use of the reformulated products. Asking patients to report any problems in use of the new products is worthwhile. This should be done in a way that does not promote anxiety
- Dose reduction will generally be needed when transferring patients from CFC-beclomethasone inhalers to 3M's Qvar beclomethasone inhaler. Qvar is not currently licensed for use in children. Only spacer devices specifically identified in the summary of product characteristics of a particular CFC-free inhaler should be used
- Entry in the pharmacy-held patient records of the date when the patient first switched over to the reformulated product is recommended
- The changeover provides an ideal opportunity for pharmacists to ensure that patients are using the right inhalation technique
- Airomir and Qvar contain small amounts of alcohol in the formulation. While these levels are of no consequence clinically, the presence of alcohol may make the formulations unacceptable to some users on religious grounds



ARE THE CFC-FREE INHALERS TOTALLY SAFE?

In theory, the HFA-based MDIs should be as safe as the existing products because of the extensive testing prior to marketing. However, given that the products are new, they may well have adverse effects which will not surface until a much larger population of patients has been exposed. In particular, new excipients are being used and the clearance of some of the new aerosol excipients from the lungs is poorly defined. There have also been reports of supra-bioavailability of corticosteroids formulated in the CFC-free systems. Vigilance by patients, prescribers and pharmacists is therefore essential.

WHY ARE BIOEQUIVALENCE STUDIES NOT ADEQUATE?

With orally administered products, comparison of blood level profiles is usually adequate for bioequivalence testing because systemic effects are generally intended. With inhalation aerosols, the aim is usually to target the lungs and high blood levels are not wanted. Therefore, bioequivalence testing based on blood levels is unsatisfactory. Bioequivalence testing based on the pharmacodynamics of the drugs tends to be insensitive and inequivalent products may appear to be bioequivalent. One-second forced expiratory volume (FEV1), for example, is insensitive in the context of bioequivalence testing of bronchodilators.

For corticosteroids aerosols, comparison of pharmacodynamic effects is even more complex as they are used on a prophylactic basis and longitudinal testing would be required for valid comparisons. Any such testing which has been undertaken is relatively short-term compared with the possible life-time use of inhalers from childhood. An increase in complications,

DELIVERY OF DRUGS TO THE LUNG

WHAT IS THE RATIONALE FOR THE DIRECT DELIVERY OF DRUGS TO THE LUNG?

Direct delivery of drugs to the lung aims to maximise the benefit:risk ratio of potentially toxic drugs when a local action on the lung is required. Smaller doses of drug are required than with alternative methods and dose-dependent adverse effects can be minimised. Moreover, by direct targeting to the lung, response to drugs such as bronchodilators is more rapid than with other routes of administration. The inhalation route is also being investigated for the systemic delivery of drugs such as proteins and peptides in order to bypass metabolism in the digestive tract. For lung delivery of drugs for local action, the aim is to deliver the drug to its target site as efficiently as possible. For most lung diseases, this means delivering drugs to the alveoli.

WHAT IS THE THERAPEUTIC RATIO OF AN INHALATION?

The term therapeutic ratio is essentially the benefit:risk ratio. This is a construct which is very difficult to measure and for inhalation therapy it is common to express it indirectly as the ratio of the amount of drug becoming systemically bioavailable through the lungs to the total amount reaching the systemic circulation (ie, the sum of the amounts absorbed from the lung, oropharynx and gastrointestinal tract). In practice, these amounts are also very difficult to measure and there is much controversy in the literature about how this is best done and, indeed, whether any of the available methods are satisfactory.

such as cataracts, stunted growth and loss of bone density leading to bone fractures, may take years to become obvious. Therefore, while the supra-bioavailability of some of the newer CFC-free aerosols may be marketed as an advance, this might turn out to be a health problem. Unfortunately, we shall not know until millions of patients have been exposed to the new products. Downward dose titration of supra-bioavailable corticosteroid formulations will generally be needed to minimise or avoid this risk.

WHY IS THE INTRODUCTION OF THE HFA AEROSOLS BEING PHASED?

Phased introductions allow the manufacturers to introduce their high volume products sooner than would be the

case if comprehensive national distribution were to be adopted from day one. An added benefit is that, should problems surface, these could be identified sooner with localised phased introductions than with nationwide introductions. Such approaches are widely used in market research for new products.

WHAT CAN THE PHARMACIST DO TO HELP?

By being alert, pharmacists should be able to identify any acute problems arising from a switch from conventional to CFC-free inhalers. These problems may include loss of asthma control and development of adverse reactions. However, it is important that false alarms are not raised. The differences in physico-chemical properties of the CFC and the HFA will make products formulated with the latter feel different to the former and the use of different excipients may impart different sensory properties to the new formulations. This may worry some patients who may then erroneously report adverse effects.

This card has been written by Professor Alain Li Wan Po of the centre for evidencebased pharmacotherapy at Aston University

Reassurance about these differences at the outset may help minimise this potential problem. Switching back to CFC inhalers should be discouraged unless there is clear evidence of harm. Patients may need reeducation about proper inhalation techniques and, indeed, the switch may provide an opportunity for checking that patients are using their aerosols optimally. The switch to HFA inhalers is a major public health venture and all parties involved are hoping that it will be successful. This checklist illustrates that pharmacists can make an important contribution to this success.

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