stances when the MDI cannot be used.

Children can use MDIs effectively, although spacers or holding chambers may be necessary under age 10 years, with the addition of a mask under about age 3 years. The number of puffs should not necessarily be reduced for pediatric administration, and increased dosage may be appropriate in this patient group as well as in adults. As in adults, dosages and schedules should be adjusted individually, using objective assessment of pulmonary function whenever possible.

Considerable controversy has arisen about potential health hazards to care-givers from repeated administration of aerosols such as pentamidine and ribavirin to patients. As discussed by Kaemerek (see page 1104), the final word on this controversy is not yet in. Because these drugs do appear to enter the bodies of the nurses and respiratory care practitioners who administer them, and because such exposure may occur repeatedly over months or years, it would seem prudent to adhere to the protective precautions described in the consensus document while awaiting more definitive information on any possible health risk.

Finally, the consensus conference addressed the environmentally sensitive issue of the use of chlorofluorocarbon (CFC) propellants in medical aerosols. Although this use is minuscule (0.4 to 0.5 percent of world CFC production), clinical aerosol use will be affected by the planned global ban on CFCs by the year 2000. Not all medications currently packaged in MDIs can be delivered via dry-powder aerosol, and the process of developing and approving new propellants is sufficiently lengthy that clinicians may soon need to find alternative means of delivery for several commonly prescribed agents available today primarily by MDI.

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The Environmental Impact of Chlorofluorocarbon Use in Metered Dose Inhalers

It is difficult to conceive of the treatment of asthma and chronic obstructive pulmonary disease (COPD) without the ability to deliver bronchodilators, steroids, and sodium cromoglycate by metered dose inhaler (MDI). The introduction of MDIs met with rapid acceptance by both physicians and patients because of their efficacy, safety, and convenience. Unfortunately, the propellant gas used to generate the medication aerosol in all MDIs is a mixture of chlorofluorocarbons (CFCs), and the continued availability of CFCs for use in medical aerosol therapy is in jeopardy.

Chlorofluorocarbons (Freons) have wide application as cooling fluids in refrigeration equipment, as foam-blowing agents for polystyrene and polyurethane, as industrial solvents and cleaning agents, and as propellants for a variety of commercial products sold in spray canisters. The chemical stability of CFCs that renders them relatively safe and nontoxic is also what causes them to be so threatening to the global environment. There are no known mechanisms for CFC decomposition in the lower atmosphere (troposphere). Once these compounds are released into the environment, they slowly rise to the upper atmosphere (stratosphere), where they are gradually decomposed by solar ultraviolet (UV) radiation. The CFCs in use today have long residence times in the atmosphere, from 60 to almost 200 years. Although CFC accumulation in the atmosphere contributes to global warming through the greenhouse effect, it is depletion of stratospheric ozone that has driven the international effort to reduce CFC emissions.

Molina and Rowland\(^2\) first hypothesized in 1974 that photolytic decomposition of CFCs in the stratosphere would generate chlorine radicals, which would in turn cause the catalytic destruction of ozone. Worldwide public attention became focused on the problem of ozone depletion, however, only after Farman and co-workers\(^3\) reported on an Antarctic "ozone hole" in 1985. It now appears that the problem affects the entire globe. Recently released data from the U.S. Environmental Protection Agency (EPA)\(^4\) indicate that there has been a 4 to 5 percent loss of stratospheric ozone in the northern midlatitudes over the past decade.

What are the biologic consequences of global ozone depletion? Ultraviolet light in the B and C wavelengths spans the full photoabsorption spectrum of DNA. Because the stratospheric ozone layer shields the earth’s surface from virtually all UV-C and most of the less damaging UV-B, its integrity is vital to the protection of the genome of the vast majority of living organisms. In terms of human health, UV exposure is most strongly linked to the etiology of cataracts and skin cancer. The EPA has estimated that a 1 percent decrease in stratospheric ozone concentration will result in a 1 to 3 percent increase in nonmelanoma skin cancer and a 0.8 to 1.5 percent increase in deaths due to malignant melanoma.\(^5\) Given the current rate of ozone depletion, a major epidemic of skin cancer could result.

Because of the magnitude of the potential impact of stratospheric ozone depletion on human health, 27 nations signed the Montreal Protocol in September 1987 to cut CFC production by 50 percent by 1999.\(^6\) The protocol called for a continued review of the
applicable science, and it has become clear from data collected after the Montreal meeting that more drastic action is required. It is predicted that only an immediate 85 percent reduction in CFC emissions will stabilize atmospheric concentrations at their current levels. At the most recent meeting of the signatories to the Montreal Protocol in London in June 1990, it was agreed to entirely eliminate CFC production by the year 2000.

The unique properties of the liquefied CFC gases provide the basis of function for all current pressurized MDIs. Typically, MDIs are propelled by a blend of two or three CFCs. Chlorofluorocarbon-12 is the primary propellant, explosively flash-boiling when it is released at room temperature and creating a fine, respirable aerosol of whatever was suspended or dissolved in it; CFC-114 is often used to moderate pressure, alter density, and provide desired solvent characteristics; CFC-11 serves as the primary solvent.

The quantity of CFC gases currently used worldwide in MDIs is approximately 4,500 tons or 0.4 to 0.5 percent of annual production. While any CFC emissions will have negative effects on the environment, the contribution from this level of production to the overall problem is small. Why not simply allow the pharmaceutical industry to continue to use CFCs in MDIs? The rapid phaseout of CFC production will apply considerable economic pressure to pharmaceutical manufacturers of MDIs. It will be increasingly costly and difficult for these manufacturers to obtain sufficient supplies of the CFCs, upon which the proper functioning of the current devices depends.

The reformulation of MDI products with replacement propellants for the current CFC mixture will take considerable time and resources. First, chemical manufacturers must produce sufficient quantities of potential CFC replacements to allow pharmaceutical industry testing. Next, compatibility with current MDI manufacturing processes, container vials, and metering values must be assessed. Chronic inhalational toxicity testing of the replacement propellants would then likely take several years. Once new formulations including the replacement propellants have been developed, these also will need chronic inhalational toxicity testing. If a new formulation appears to be safe and nontoxic at this point, application can then be made to the Food and Drug Administration for permission to conduct clinical efficacy testing. In other words, it will take many years under the current protocol to develop and adequately test reformulated MDI products.

Approximately 25 million Americans suffer from asthma and COPD, and a large proportion of these persons rely on MDI products for relief of respiratory symptoms and prophylaxis against acute exacerbations. While alternatives to the use of MDIs do exist, it is unlikely that all patients currently using them will be able to effectively and conveniently use the available substitutes. Nebulized aqueous solutions of medications are effective but require equipment that is not easily portable and more time to deliver the desired dose. Dry powder inhalers (DPIs), which use the energy of the patient’s inspiratory effort to dispense the drug powder, have been available for some medications for years. While the fact that these inhalers are breath activated allows some patients to achieve better dosing, it is equally true that patients in respiratory distress may not have adequate inspiratory flow rates to properly activate DPIs. Although older DPIs require the loading of a gelatin capsule containing the drug powder prior to each use, more convenient multidose DPIs have been developed. Many patients probably can be successfully switched from MDIs to DPIs, but continued MDI use will be desirable for some (eg, small children, the elderly, and persons with persistent airway hyperresponsiveness).

Pressurized MDIs are an important component of the modern therapeutic approach to the treatment of asthma and COPD, for which a need is likely to exist for the foreseeable future. Currently, CFCs are required for the proper functioning of all MDIs. Since it will take a number of years to develop and test replacement propellants as well as the reformulated MDI products, national and international governmental agencies will need to design specific policy responses for the problem of CFC use in MDIs.

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