Inhalational therapy produces more rapid onset of action, greater degree of bronchodilation, increased potency, low cost and side effects, when compared with systemic or oral therapy of the same agent. Inhalable drugs have been available in the form of metered dose inhaler (MDI) and wet nebulizer (NEB) for the past forty years. Effectiveness of inhalational therapy depends upon the particle size and mass of stable and suspendable particles (aerosol) delivered to the lungs. Since particles smaller than 5um only get deposited within the lungs, a device with narrow distribution of particle size is likely to generate high respimble fraction. Final deposition within the airways also depends upon the velocity, inertia, sedimentation, changes in particle size due to evaporation, and distance or direction travelled by the particles before being deposited. For effective deposition of aerosol within the lung, convenience and understanding of inhalational technique is also as important as consistency in production and delivery of particles of relatively uniform size.

**Metered Dose Inhaler (MDI)**

Inhalational therapy has been in use since ancient times when breathing flumes containing anticholinergic compounds were used for airways diseases. MDIs were introduced in 1956 as a result of a suggestion from a child; today it is the most effective and convenient way of delivering aerosol. In Europe 70% of all the beta-agonists are prescribed as MDI, although at least 50% of all adults and large proportion of children are unable to learn the proper use of the device. When properly used, MDI can deliver within the lungs, only 10-15% of the total aerosol released, 80% gets immediately deposited within the oropharynx on account of large particle size and high velocity. In most of the patients failure to proper use results from poor coordination during inhalation and halting breathing due to so called “cold Freon” effect resulting from cold propellent hitting the pharynx. Low pressure aerosol device has been devised to reduce oropharyngeal impact. Improper inhalational technique is an important limitation to the use of MDI. Medical personnel responsible for educating patients, themselves may not understand the factors responsible for optimum delivery of aerosol. In one study, 50% of the non pulmonary faculty could correctly perform, 4 out of 7 steps recommended for proper MDI use. In the same study respiratory therapist and nurses showed better performance.

**Nebulizer (NEB)**

Alternative source of aerosol is available in the form of Jet or Ultrasonic Nebulizer. A nebulizer does not require inhalational coordination and breath-holding. Since it is not effort-dependent, patients find it more convenient. The MDI/NEB equivalent dosages vary between 1:1 to 10:1. Airways response and lung deposition depends upon difference in dosage, administration technique, nebulizer system efficiency and severity of airway obstruction. Generally 10 puffs of MDI will deliver same amount of a bronchodilator (Albuterol) as 2.5 mg through nebulizer. In another study, 10 puffs of MDI were found equivalent to 5 mg of nebulized Terbutaline. An MDI producing particles with smaller mass median diameter is likely to deliver more aerosol than a NED generating large particles, and hence improved expected bronchodilatory response. If properly used, MDI and a NED are equally effective, but it is a common impression by both patients and physicians that NED provides greater relief of dyspnoea and eases sputum expectoration. While comparing MDI and NED, degree of bronchodilation achieved is probably a reflection of the dose of a bronchodilator and not mode of administration. Inadequate dose is a for greater problem than toxic dosage. No cardiac arrhythmias were observed with MDI while using 50-80 times of the normal daily dosage. NEB remains the standard mode of therapy for
emergency and indoor patients. The Expert Panel on the management of Asthma (NIH-1991) has recommended delivery of aerosolized bronchodilators through wet nebulizer for acute asthma and management in emergency department. NED unit of the same batch and manufacturer may differ in the production of aerosol. With the passage of time concentration of dmg within the remaining solution in nebulizing chamber increases due to disproportionate increase in fluid output. There is need to check periodic efficacy and standardization of nebulizers, which might result in discarding of the machines and hence further increase in the cost of NED therapy. Frequency of malfunction, variability in rate of nebulization and inconsistency in particle size are not uncommon. While evaluating different models of Jet-NED variation in nebulization ratio ranged from 57-129%. Changes in solute concentration, droplet size and output, plus wide variation in performance of NED-delivery system may be responsible for failure of therapy than dose response. Only 34-59% of the dose leaves Jet-NED as compared with 90% from MDI. Ultrasonic-NEB (U/S-NED) uses pizoelectric crystals to produce vibrations which are transferred to a liquid resulting in aerosolization. Newer models of U/S-NED are more efficacious since they produce more respirable particles. On critical review of comparative studies, MDI and NEB when used in equivalent dosages, are equally effective, while NED is more convenient to use on indoor basis. NED is still considered first line therapy in emergency department, though whenever NED is found superior to MDI, it is always because of relatively higher dosages. Since drugs in solution form can only be used, this mode of therapy has its limitation.

MDI+Spacing Device (MDI-SD)

Patients with acute asthma and acute exacerbation of COPD are unable to make adequate use of MDI. Efficiency and delivery through MDI can be improved by using a Spacing Chamber, which not only eliminates the need for patient coordination or breath-holding but eliminates adverse side effects, like pharyngeal deposition. They are portable cheap and do not require electricity. Every medical practitioner should keep a Spacer with him for patient teaching. Compared with NED, MDI-SD delivers full dose of a beta-agonist more frequently and at no extra cost. Moreover, the effectiveness of beta-agonists delivered through NED or MDI-SD is found equal, even in acute asthma. Substitution of MDI for NED can be successfully accomplished through proper guidance and patient education at significantly reduced cost of health care. In one such study $83000= were saved annually by the hospital and $300,000= per year on charges to the patients. SD are available in various shapes and sizes. As steroids are more often used particularly in asthma, with SD there is little risk of pharyngeal deposition. Physically handicapped patients with deformity or weakness of hands and patients on artificial airways can benefit from modification of SD.

Limitations of MDI

Inspite of all the merits, MDI has its own limitations. A patient may develop acute attack inspite of maintenance dose. With the passage of time, some MDI become less effective since dose emitted through each actuation declines as metered chamber does not fill uniformly after about 85% of the original suspension has been consumed. The liquid propellent with decreasing dose of the drug continues to be emitted for sometimes. This problem may arise when inhaler is used beyond specified number of actuations, which may vary from 100-240 puffs per canister. It is difficult for any patient to keep a correct record of used actuations and there is no reliable criteria to find out that the medication is about to run out. No package insert contains any information on guidelines for this problem. MDI is powered by two or Three chioro fluorocarbon (CFC) propellants (Freongas) to give the desired vapour pressure and spray characteristics. CFCs, especially F11/F12, are generally used, in MDI, as referigerant, as foam blowing agent and in cleansing of electronic industry. They are non-toxic and non-inflammable. In 1974 it was realised that CFC could be harmful to the environment. On diffusion into stratosphere CFC degenerates by ultraviolet light resulting in built-up of chlorine and
hence depletion of ozone. One atom of chlorine can destroy 100,000 atoms of ozone. Ozone hole over the Antarctic was discovered by a survey team in late 1980s. Depletion of ozone can cause skin cancer, cataract, reduced crop yield and aquatic food, as well as greenhouse effect on eaa. During Helsinki meeting of 1989 representatives of 80 nations decided to eliminate CFCs. So far the date agreed to ban CFCs is 1995, unless brought forward under political pressure. Since medical aerosol accounts for 0.5% of total CFC consumption worldwide, even if it is excluded from the ban, commercially it would not be feasible to continue to produce on such a small scale, practically it is impossible to store enough CFC for the future use.

**MDI Substitutes**

International Society for Aerosol in Medicine discussed CFC replacement in 1991 and it seems unlikely that a perfect or even a satisfactory replacement will become available till 1995. Surfactants such as oleic acid, sothitan trioleate and soya lecithine though are nontoxic like CFCs, however, many asthmatic patients have experienced cough and airflow obstruction as a direct result of inhalation of the propellant gases. Since MDI is not used properly by 50% of the patients and irritant cough is experienced in 30% who use it, this itself is enough reason to search for an alternative drug delivery system. Multidose Dry Powder Inhalers (DPI) are now available. Spinhaler or Rotahaler requires gelatin capsule loading before each use. Diskhaler contains 4-8 doses and so requires frequent replacement, while Turbohaler contains 200 dosages. DPIs contain no CFC, are breath actuated, can be learnt easily even by children and carry minimal risk of overdosage. A large volume spacer deposits 21% of the dose within the lung, (10% in oropharynx and 56% remains within the chamber), as compared to MDI which deposits 10-15%, while DPI delivers 10-15% of the dose in lungs and 70-80% on the oropharynx. While trying to find comparable doses, 12-24 ug of Fenoterol in capsule was found equivalent to 12 ug through MDI. DPIs require an inspiratory flow of 30-50 L/min, and the amount of drug delivered may vary depending upon the force of inhalation applied. They are also affected by ambient humidity, as relative humidity of 85% may decrease the delivery of predetermined dose. Large-volume spacer cannot be attached to a DPI. So far DPIs seem to be the only but poor substitute for MDIs. However, it is hoped that advanced technology will result in the development of new devices, battery operated pocket size nebulizers have already been introduced, till then DPI seems to be the only answer.

**References**