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Editorial

Therapeutic aerosols 2—Drugs available by the inhaled route

Inhalation treatment can be said to have stood the test of time, since records can be traced back several thousand years. In ancient Greece, Hippocrates employed the inhalation of vapours distilled in a pot, the lid of which was pierced by a reed;[1] sulphur and arsenic were said to have been used. The patient breathing these hot vapours needed protection with moistened sponges to avoid scalding. The popularity of these inhalation procedures has waxed and waned, as Miller[1] writes—at times they have been over praised and unwisely used, and at other times unreasonably condemned and virtually abandoned. The latter phrase still applies to some extent today.

Until the middle of the present century, inhalation treatment with volatile aromatic substances with a mild irritant action such as menthol, thymol, and eucalyptus and smokes derived from burning various types of plant leaf, notably *Atropa belladonna* and *Datura strammonium,* was quite commonly recommended for disorders of the upper and lower airways. Several present day pharmaceuticals used for respiratory treatment have been derived from ancient remedies[2]—for example, khellin was the predecessor of cromoglycate, while burning *Datura strammonium* leaves form the basis of the asthma cigarette, which is still available from herbalists.

These substances have been largely replaced by the range of modern pharmaceuticals available for inhalation either from a metered dose inhaler (MDI), dry powder inhaler, or nebuliser or for the nose by nasal spray. Although the MDI is the most popular method of administering bronchodilator and corticosteroid aerosols, the nebuliser has the great merit of flexibility—virtually any drug solution or suspension can be nebulised. Most drugs are inhaled for topical treatment of the upper and lower respiratory tract, but some may also be given as aerosols for their systemic effect.

Beta agonists

Beta agonists are undoubtedly the most common type of drug given by inhalation from an MDI. Volumes have been written about them and their administration.[3] Reiterating most of this would be like taking "coals to Newcastle" for the readers of *Thorax* and therefore only selected aspects will be mentioned.

The naturally occurring catecholamine adrenaline was the earliest of these drugs to be given by inhalation,[4] followed by isoprenaline (isopropylnoradrenaline) in about 1960. Since adrenaline, however, stimulates both α and β receptors in the heart and periphery and isoprenaline stimulates β_1 and β_2 receptors, both drugs may give rise to undesirable cardiovascular side effects such as tachycardia or arrhythmias. Adrenaline, whether given by injection or by inhalation, is now little used in Britain. It is, however, still given by injection for acute asthma in young patients and it is still available on prescription for use in an MDI or in a hand held "squeeze bulb" inhaler in a mixture that also contains atropine methonitrate and papaverine hydrochloride (Brovon). Furthermore, MDIs containing adrenaline are freely available over the counter in the United States.

Chemical manipulation of the side chains of the adrenaline and isoprenaline molecules has led to the development of sympathomimetic drugs possessing a more selective action on respiratory β_2 receptors. Salbutamol, terbutaline, and fenoterol are the best known of these compounds, but at least 14 related drugs have been described.[5] While cardiovascular side effects are much reduced, skeletal muscle tremor and cramps are occasionally noted, even with the small doses taken by inhalation. One potential drawback of treatment with β agonists is a fall in arterial oxygen tension owing to a transient worsening of ventilation:perfusion ratios.[6] This is seen particularly in severe acute asthma, where hypoxaemia may already be substantial. The potential effect on the heart of increasing hypoxaemia must be considered. Supplemental oxygen treatment should, however, readily relieve this hypoxaemia.[7] Although early experience with isoprenaline suggested that β agonists might be inherently short acting, the selective β_2 agonists have been shown to be active for up to seven hours.[8]

In Britain β agonists given by inhalation are the

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standard first line of treatment in asthma and chronic obstructive airways disease, in which they may be used on demand for relief of symptoms as they arise or as regular maintenance treatment to avert symptoms. Their preventive effect is particularly well seen in the suppression of exercise induced asthma.[9] Inhaled treatment with β agonists alone may control mild asthma. Combined with cromoglycate they will control symptoms in most patients with extrinsic asthma and combined with inhaled corticosteroids in most patients with intrinsic asthma. Given in sufficient dosage an inhaled β agonist may control attacks of severe acute asthma. Sometimes this is given in conjunction with parenteral β agonists or methyl xanthines and usually treatment is supplemented by systemic corticosteroids. Nebulised salbutamol has been particularly successful in the treatment of children in hospital with severe acute asthmatic attacks,[10] but its domiciliary use in such cases needs to be carefully supervised and help must be sought early if there is a poor response.[11]

Beta agonists have the useful merit of increasing the rate of mucociliary clearance, which is known to be abnormally slow in many patients with obstructive airways disease.[12] Studies of the effect on clearance of aerosolised β agonists, however, have not reached unanimous conclusions. Improvement of clearance has been demonstrated after the administration of adrenaline and isoprenaline,[13] salbutamol,[14] and orciprenaline,[15] although the doses used were larger than those usually required for bronchodilatation. In clinical practice patients often remark on improved expectoration after inhaling these drugs, though bronchodilatation alone may improve coughing efficiency.

One feature of treatment with β agonists which is insufficiently appreciated is the wide variation in the dose administered by the various routes. It should be noted that the small dose of drug reaching the lungs and activating β receptors is responsible for most of the bronchodilator effect[16] and the cardiovascular side effects.[17] Absorption of drug into the systemic circulation via the lung may also play a part.[18] Most of the dose from an MDI is deposited in the oropharynx.[19] Some of this may be absorbed through the buccal mucosa,[20] though most is swallowed and converted to an inactive metabolite during its passage through the wall of the intestine or the liver.[18] About 75% (and in the case of isoprenaline 90%) of the oral dose is converted, so that the required oral dose is typically greater than the inhaled dose by a factor of 10. With the nebuliser most of the non-inhaled drug is retained within the device itself.[21]

To give an example, the inhaled dose of salbutamol from an MDI is usually 200 μg, of which about 10% or 20 μg will be deposited within the bronchial tree[18,19] and stimulate β receptors. By contrast, the nebulised dose is usually 5 mg in 1 ml (diluted with, say, 3 ml of saline). Of this 5 mg, 10% or 500 μg will reach the lungs,[21] 25 times more than the lung dose achieved with the MDI. Nevertheless, if the effect of dose is taken into account by the construction of dose response curves it is found that the curves achieved with MDI and nebuliser are almost identical.[22] A lung dose of only 30 μg fenoterol delivered by nebuliser has been shown to cause maximal bronchodilatation in a group of asthmatics with FEV_1s ranging from 27% to 78% of the normal predicted value.[23] Arguably an increase in the dose from a nebuliser might be beneficial if the degree of bronchoconstriction is severe and the number of β receptors to be stimulated is increased. Fears that the large doses of β agonist conventionally given by nebuliser may be harmful are probably unfounded, although whether these doses are usually required is another matter and needs further investigation.

Other bronchodilators

ANTICHOLINERGIC DRUGS

Anticholinergic drugs act by blocking the muscarinic action of acetylcholine. Atropine is an effective bronchodilator and has been used for many years but it has the undesirable side effect of drying airway secretions. It may also precipitate glaucoma and in men it may induce urinary retention. The synthetic anticholinergic agent ipratropium bromide appears to be free from these side effects in the doses normally delivered.[24] It is an effective bronchodilator at a dose one tenth of that required to inhibit saliva production and one fiftieth of that causing tachycardia.[3] It has a slightly slower onset of action than the β agonists but its duration of action is similar. Ipratropium bromide delivered by nebuliser has been used successfully to control acute asthma,[25] though here it is unlikely to supplant the β agonists. In some bronchitic patients with airways obstruction ipratropium may give dramatic relief, but occasionally paradoxical bronchoconstriction is noted.[26] When ipratropium is given in conjunction with a β agonist additional bronchodilatation may be achieved,[27] although the extent of this varies from patient to patient.[28] It has been suggested that ipratropium and the β agonists may act preferentially on different parts of the bronchial tree, but the evidence has been conflicting. Some studies have shown that anticholinergic agents act on large conducting airways and β agonists on small airways;[29,30] others suggest that ipratropium is equally effective in both large

and small airways,[31 32] and yet others that β agonists act chiefly on large airways.[33] The final answer is awaited.

METHYL XANTHINES

Given orally, the methyl xanthines, of which theophylline and aminophylline (and caffeine) are the best known, have been the first line treatment for asthma in the United States for many years, although they may soon be superseded by inhaled β agonists. Oral administration of methyl xanthines requires careful adjustment of the dose to exploit a "therapeutic window" represented by plasma concentrations of from 10 to 20 μg/ml if the optimum effect is to be obtained without producing unacceptable side effects ranging from headache, nausea, and abdominal discomfort to fatal fits.[34] The inhaled route offers the prospect of symptomatic control with low blood concentrations and minimal risk of side effects. It is possible to produce useful bronchodilatation but the methyl xanthines are much less effective than β agonists administered by aerosol.[35] Furthermore, they have an unpleasant bitter taste,[36] although conceivably this could be disguised by the addition of flavouring agents.

Sodium cromoglycate

Sodium cromoglycate is a very powerful prophylactic drug for asthma[37] and an example of one which is effective only by the inhaled route, since gastrointestinal absorption is poor. It prevents the degranulation of mast cells and hence the release of chemical mediators in the airway walls. In normal subjects, moreover, cromoglycate has the ability to modify the airway response to respiratory heat loss,[38] which is relevant to its particular effect in exercise induced asthma. Further, this drug may have minor bronchodilator effects.[38a] Undoubtedly it has revolutionised the management of extrinsic asthma and particularly exercise induced asthma, and may also be effective in late onset asthma.

The well known Spinhaler, developed in the late 1960s, for delivery of cromoglycate in powder form, represented a novel approach to the administration of drugs by inhalation, although it had been preceded by another dry powder device, the Aerohaler, in 1949.[39] Recently cromoglycate has been formulated for administration by an MDI. Curiously, the standard 2 mg dose of sodium cromoglycate from an MDI (two puffs) has roughly the same effect as 20 mg of powder in each spincap, which emphasises the relative inefficiency of dry powder inhalation, even though a broadly similar percentage of the dose is likely to reach the lungs from the two devices.[18] Cromoglycate is also available for use in nebulisers as a solution, which may be particularly useful for treating asthmatic children as they may have difficulty using the spinhaler or MDI.

Corticosteroids

Inhaled corticosteroids are highly effective in controlling asthma and can achieve this without inducing systemic side effects. The drugs used (beclomethasone dipropionate, betamethasone valerate, triamcinolone acetonide, and budesonide) exert a topical effect in the lungs but are inactivated when absorbed from the gut. The doses required are tiny (400–800 μg daily), plasma levels are low, and therefore systemic side effects (including adrenal suppression) are minimal.[40] Many patients taking oral corticosteroids below the dose level of 10 mg prednisolone daily to control their asthma are able to switch entirely to the much smaller dose of inhaled corticosteroids.

Recently an MDI containing a high dose of beclomethasone dipropionate has been introduced (Becloforte). It contains 250 μg a dose, five times more than the standard preparation (Becotide). This formulation improves control in patients with more severe asthma and may permit treatment with oral steroids to be reduced or stopped in up to two thirds of patients who are inadequately controlled on conventional doses of beclomethasone.[41] There is little evidence of abnormal adrenal function in patients taking up to 1500 μg of high dose beclomethasone daily, but above this level adrenal suppression is observed in some patients.[42] It has been suggested that high dose treatment with inhaled steroids may achieve satisfactory control when given only twice daily, and this appears to be so in those with stable asthma. In unstable asthma, however, there is a case for taking doses four times daily for otherwise a prohibitive number of puffs may be required.[43]

Oropharyngeal candidiasis is a recognised side effect of treatment with inhaled steroids; the incidence varies widely (0–91%) in different study populations,[44] probably depending on the criteria used to define the condition. In a recent study clinically confirmed candidiasis was present in 9% of patients on low dose beclomethasone and 12% on the high dose—an insignificant difference.[41] These figures increased to 13·5% and 17% respectively when patients with local symptoms who did not have clinically confirmed candidiasis were included. The incidence of this complication may be related to the number of puffs taken rather than the total dose of steroid inhaled. The candidiasis usually resolves either spontaneously or with appropriate treatment, and only occasionally does it prove necessary to stop the steroid. In patients who are immunocomprom-

ised for any reason further action may be necessary. The frequency of candidiasis is reduced by the use of a spacer device with the MDI,[45] reflecting the reduction in oropharyngeal deposition achieved by such means.[46]

The other local complication is dysphonia, the incidence of which also varies widely (0–55%).[44] A typical bilateral adductor vocal cord deformity with bowing of the cords on phonation has been described, which probably represents a local steroid myopathy; it is reversible within a few weeks of stopping treatment with inhaled steroids.[44]

Combination inhalers

Inhalers containing two or more drugs have been used for some time with varying degrees of acceptability. Brovon and Intal Co (cromoglycate and isoprenaline) are examples. These have been criticised because the required dose of one of the compounds might lead to an excessive intake of the other. Thus the flexibility of using, say, a β agonist for relief of wheeze and cromoglycate for prevention is lost. Recently further combinations have appeared—for example, fenoterol plus ipratropium (Duovent) and salbutamol plus beclomethasone (Ventide). They may improve compliance when patients are in a stable state but at the expense of therapeutic flexibility and with the risk of misconceptions—though this is not to deny their usefulness.

Water, saline, and mucolytic aerosols

Tenacious bronchial secretions may accumulate in chronic bronchitis, bronchiectasis, cystic fibrosis, and asthma. Traditionally, aerosols have been used in an attempt to liquefy these secretions and help sputum clearance, either by mucociliary action or coughing.

Water has been inhaled for many years, exemplified by the steam aerosol and vapour produced from a boiling kettle for treating childhood croup. Early studies showed that the inhalation of water aerosol does liquefy and clear secretions.[47] It may also be an irritant, however, and cause bronchoconstriction in asthmatics.[48] The vogue for inhaling medicinal waters with an increased mineral content at some European spas is not supported by any objective evidence of its efficacy. Fortunately, only a tiny amount (about 10%) of the nebulised water will enter the lungs and it is probably harmless. This is not to deny that a water aerosol may be a useful means of humidifying the inspired air. Here a word of caution is needed. With some ultrasonic nebulisers the volume of inhaled water might be such as to cause pulmonary oedema. Isotonic fluid such as saline should be used if the inhaled liquid volume is more than a few millilitres.

Saline aerosol is bland and may well improve mucociliary clearance, particularly in a hypertonic concentration (7·1%), when it facilitates expectoration.[49] It may liquefy sputum by enhancing chloride (and water) flux across the bronchial mucosa.[50]

Mucolytic aerosols are also widely used. *N*-acetylcysteine (Airbron) is the best known in Britain and 2 mercaptoethane sulphonate (Mistabron) in Europe.[51] Mistabron appeared to enhance mucociliary clearance in patients with chronic bronchitis,[52] although the results did not quite reach statistical significance—a feature of so many studies of mucolytics. In patients with cystic fibrosis, however, inhaled Mistabron significantly improved respiratory function, although there was no change in cough frequency, sputum volume, or the frequency of antibiotic prescriptions compared with the pretreatment period.[53]

Antihistamines

Antihistamines have rarely been given as aerosols since they are said to have no effect in asthma. Recently, however, two inhaled H_1 receptor antagonists (clemastine and chlorpheniramine) have been shown to have a bronchodilator effect in asthmatic children[54] and clemastine aerosol can prevent exercise induced asthma.[55] Inhalation may permit a greater quantity of drug to reach the lungs than is possible after oral administration without giving rise to undesirable side effects, notably sedation,[56] and antihistamine aerosols should perhaps be reconsidered.

Antibiotics

The value of antibiotic aerosols in respiratory tract infections has been questioned in the past and they have been thought to have little advantage over systemic treatment.[57] Higher drug concentrations in the sputum, however, may be attained with inhalation than with oral treatment. A combination of two nebulised antibiotic solutions (carbenicillin and gentamicin) was found recently to be effective in treating respiratory infections in patients with cystic fibrosis.[58] Other types of aerosolised antibiotics may prove clinically useful, particularly where an antibiotic may be harmful if present systemically. Unfavourable past reports of antibiotic aerosols are likely to have been due in part to incorrect nebulisation resulting in inadequate drug concentrations in the lung periphery. Antibiotic solutions are more viscous than water or saline and are more difficult to nebulise. Further work on antibiotic aerosols is

required to characterise the particle size and the aerosol output required to achieve effective concentrations in the lung.

Potential problems of the inhaled route

The advantages of aerosols have been propounded but what of their disadvantages? It has been suggested that therapeutic aerosols might not be able to reach the appropriate receptor sites in the lung in the face of severe airways obstruction or mucus hypersecretion. In practice bronchodilator aerosols seem able to improve lung function as reflected by tests of both large and small airways in most cases,[59] suggesting adequate aerosol distribution. In the treatment of a severe acute asthmatic attack, however, treatment with subcutaneous adrenaline or β_2 agonist may be required since nebulised bronchodilators may be effective only after the patient has actually begun to expectorate sputum.[60]

There seem to be few long term side effects associated with the regular intake of aerosolised bronchodilators, cromoglycate, or corticosteroids. Contrary to popular opinion, there is no addictive effect of regular bronchodilator treatment and, oddly enough, although tolerance or tachyphylaxis to β agonists can occur in normal subjects this is not generally seen in asthmatic patients with conventional doses.[61]

The safety of inhaled bronchodilators has been the subject of much debate. The use of metered dose isoprenaline aerosols was linked statistically to the epidemic of deaths from asthma in the late 1960s,[62] in which 3500 patients were said to have died. This epidemic is now thought to have been caused primarily by an overreliance on the use of isoprenaline MDIs and a failure of patients to seek medical advice when their asthma worsened, rather than by a direct toxic effect of the inhalers themselves.[63] This topic is discussed in a recent editorial.[64]

A similar increase in deaths from asthma has occurred in New Zealand since 1976,[65] though an increased incidence of asthma has been noted at the same time. The suggestion that the increase may have resulted from the combination of high dose β agonists and theophylline[66] seems unlikely. Overreliance on nebulised bronchodilators, leading to delay in seeking expert advice when the patient's asthma may be deteriorating disastrously,[67] is more plausible. The problem is not the nebulised bronchodilator aerosol itself but rather poor education of patients about the limitations of aerosol treatment and the threshold for seeking medical help if the bronchodilator fails to bring relief. As mentioned earlier, the optimum dose for nebulised bronchodilators (and other drugs) needs to be better defined.

Chlorofluorocarbon propellants used in MDIs can cause palpitations if they are inhaled in sufficient quantity,[68] but this should occur only if they are used excessively over a very short period.[69] Extremely large doses of oral salbutamol can be given with apparent safety, at least in normal subjects.[70] Pressurised inhalers are thus thought to be safe if used in the recommended manner,[71] and given the tiny drug dose administered this would appear to be reasonable. Fears were expressed in the mid 1970s that the use of chlorofluorocarbon propellants might damage the ozone layer in the earth's atmosphere that protects against ultraviolet radiation.[72] Subsequently these propellants have been banned in many countries except for medical use. MDIs are unlikely to contribute significantly to environmental problems compared with the unrestricted use of consumer products such as hair sprays and fly killers.

Inhaled drugs for systemic treatment

Some drugs are rapidly absorbed virtually unchanged through the mucosa of the upper airways into the systemic circulation. Others if soluble may be absorbed from the lower airways and alveoli. Glyceryl trinitrate and ergotamine, for example, are both prepared as MDIs and sprayed into the buccal cavity for rapid absorption and control of angina and migraine respectively. As an example of absorption from the lower airways and alveoli, the use of heparin by inhalation has been proposed for systemic anticoagulation.[73]

Absorption through the nasal mucosa is also possible. Nebulised insulin is rapidly absorbed via the nose in dogs, particularly when dissolved in a relatively acid medium; and it has been suggested that this would be a simple and painless method of long term treatment in diabetes.[74] Nicotine given either as a liquid spray or as snuff has been used as a substitute for smoking. The use of a nicotine MDI has also been suggested as a means of enabling smokers to obtain nicotine[75] without having to inhale more harmful components of tobacco smoke, though whether this would replace cigarettes is dubious. These examples stimulate us to consider how other drugs could be inhaled for their systemic effect, offering the potential advantages of a simple route of administration and rapid onset of action.

Aerosol treatment has undoubtedly come a long way in the past two decades. The waxing and waning of popularity referred to by Miller[1] almost certainly reflected the lack of understanding of the principles of aerosol treatment. The recent surge of interest has been generated by the application of scientific

method to the physical, pharmacological, and clinical problems associated with their use. Some of the problems have now been solved and aerosol treatment is on a much firmer scientific basis.

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