Therapeutic aerosols in children

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The use and variety of drugs administered to children as inhaled aerosols is increasing, but little is known about how much drug reaches the lung and how it is distributed there in different age groups. In this article the reasons for measuring aerosol deposition in children are discussed and the potential methods for doing this described. Of the methods available, only the use of radiolabelled aerosols gives accurate information on total lung deposition and distribution. The potential risk of the radiation exposure required for these measurements varies with the age of the child but seems to be small. Properly designed studies are expected to clarify the factors affecting lung deposition in children and identify methods of inhalation associated with efficient and predictable delivery of the drug. Measurements of radioaerosol deposition may therefore be justified in children when this information is expected to lead to improvements in the effectiveness or safety of their treatment.

The use of inhaled drug aerosols is increasing in adults and children because it allows the direct delivery of respiratory drugs to their site of action and minimises systemic adverse effects. Inhaled drugs used in children now include bronchodilators, corticosteroids, tribavirin, and an assortment of antibiotics, and the potential value of inhaled DNase, amiloride, surfactants, and mucolytic agents is being assessed. The lung also offers a large surface area for rapid systemic absorption of a drug, which avoids pre-systemic metabolism in the gut and liver and is a potential, new non-invasive route for established systemic treatments such as opiates for pain control¹ and perhaps insulin for diabetes.^{2,3}

A major shortfall of the method, however, is the uncertainty about how much drug is delivered to the lung and how this is affected by the nebuliser, the method of inhalation (face mask or mouthpiece), the age and size of the child, and the particle size of the aerosol. There are no statutory regulations requiring manufacturers to test the efficiency of inhalation apparatus, and the amount of drug reaching the lungs by using different apparatus has seldom been evaluated. This is in stark contrast to the regulations concerning new formulations of established oral treatments, in which bioequivalence must be established by the manufacturers before a product licence is granted. In adults lung deposition varies distinctly with the type of inhalation apparatus, including its particle size characteristics and total aerosol output, and is affected by the mode of inhalation and the presence of lung disease. There is very little information available on lung deposition in children.

Aerosol deposition in children

Aerosol deposition is probably different in children compared with adults. A smaller proportion of aerosol produced by a jet nebuliser may be inhaled by children

because of their reduced minute ventilation. Conversely, reduction in tidal volume may result in less air entrainment, reduced dilution of aerosol, and increased deposition.⁴ This may have implications for using agents such as methacholine to test the responsiveness of the airways in children as the concentration of drug that is being delivered may vary depending on the child's size and degree of entrainment of aerosol.⁵ The larger relative deadspace in children may be associated with the exhalation of an increased fraction of the inhaled aerosol. Because the size of their airways is smaller an increase in the central deposition of larger particles is expected.⁶ This effect may be magnified by the high rates of flow found in the major airways of children. The increased use of nasal breathing is also expected to reduce the amount of aerosol reaching the lower respiratory tract,^{7,8} and the optimum size range of particles for use in children may be smaller than that recommended for adults as smaller particles are more likely to penetrate the nose and smaller diameter major airways to reach the peripheral lung. Although a reduced total amount of aerosol may reach the lungs of children, concentrations of the inhaled drug at the site of action may be larger because the lungs of children are small.⁶

Aerosol deposition may be reduced in children because some may be less skilful in using certain inhalation apparatus—for example, metered dose inhalers. Some nebulised treatments, notably pentamidine, are irritant to the upper respiratory tract and unpleasant to inhale, and some nebulised treatments—for example, antibiotics—may necessitate multiple treatments each day and therefore considerable time being spent on inhalation. Persuading children to inhale these aerosols may be difficult, and reduced compliance will clearly affect the deposition achieved.

The need to measure deposition

For some drugs, notably bronchodilators, adequate delivery to their site of action can be inferred by measuring their effect on lung function.^{9,10} For others, such as antimicrobials and surfactants, there are no easily measured pharmacodynamic effects. Though the efficacy of these treatments may have been proved by using one particular method of inhalation, use of an alternative could be associated with failure of treatment because of a reduced efficiency of aerosol delivery. Conversely, increased efficiency of delivery could improve the clinical effects of treatment or allow reduced nebuliser doses of the drugs to be used. The resulting financial savings might be considerable for some of the newer agents. For many drug aerosols there may also be hazards associated with the inadvertent delivery of excessive amounts. Evidence of this is scanty because of a basic lack of knowledge of drug delivery by different apparatus in different groups of patients; the systemic consequences of excessive β adrenoreceptor agonist treatment and high doses of steroids are, however, well known. For drugs with a narrow

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Six of these children may have asthma, and their skill in using inhalation apparatus may vary

therapeutic ratio such as inhaled fentanyl or insulin the consequences of both overdelivery and underdelivery could be large.

In view of these arguments it is clear that further research is needed to characterise the patterns of aerosol deposition in children. This needs to encompass the various types of metered dose inhaler and nebuliser available. Children of different ages and with different illnesses should be studied. Clinical trials of new inhaled treatments should include data on delivery of the agents concerned to the lung and systemically, just as blood concentrations of agents are measured when new systemic preparations are tested. Questions that need to be answered are: Can adequate quantities of drug be delivered to the lungs of children of all ages? Can specific areas of the lungs be targeted with certain drugs? Which nebulisers should be used for the various age groups of children? and What is the effect of age, size, and breathing pattern on the total and regional deposition of inhaled drugs?¹¹

Indirect assessment of aerosol delivery

The answers to some of these questions may be predicted by using experimental models. Delivery of aerosol during simulated normal breathing or mechanical ventilation can be measured by fluoroscopy, by using radionuclides, or by directly measuring drug delivery¹²⁻¹⁵ and may give invaluable information on the best way of administering aerosols under these conditions. The experiments entail the use of a model of the respiratory tract connected to the nebuliser apparatus under study and to a ventilator that mimics the conditions of spontaneous breathing or mechanical ventilation. A filter placed at the end of the model trachea or bronchi traps particles that would penetrate the lower respiratory tract and a second filter placed at the expiration port of the model traps the particles that would be wasted. Deposition of fluorescent marker, radionuclide, or drug in these filters and on other components of the model can be measured and the amounts depositing on the apparatus, being wasted to the atmosphere, and reaching the respiratory tract calculated. Though these models help in predicting delivery of particles as far as the lower respiratory tract, they give no information on the distribution of

deposition within the lungs or on the proportion of aerosol that is exhaled. Studies on animals may also be useful,¹⁶⁻¹⁹ but the amount of aerosol penetrating through an endotracheal tube or reaching the lungs of an animal may not accurately predict lung delivery in children.

Once in vitro and animal studies have shown that suitable aerosol delivery to the lower respiratory tract may be obtained it is necessary to proceed to measurements in patients. The amount of aerosol inhaled can be measured without hazard by using a fluorescent label. The label is incorporated into the nebuliser solution and while the aerosol is being inhaled by the subject the proportion lost to the atmosphere or exhaled is trapped in a filter. At the end of the experiment labelled material deposited on the apparatus and filter is eluted and measured. Label not found at these sites is assumed to have been inhaled. Of course it is not possible to determine the proportions of the inhaled aerosol that have penetrated the lungs, been deposited in the upper respiratory tract, or been swallowed, and the method gives no information on the distribution of aerosol within the lung. For drugs designed to have a systemic effect the efficiency of delivery may be assessed by measuring blood concentrations. Some information on the pulmonary delivery of locally active aerosols can be inferred from blood or urinary concentrations of drugs that are not absorbed much from the gut or buccal mucosa—for example, excretion of sodium cromoglycate into the urine gives a crude impression of the pulmonary delivery of the drug.⁸ For drugs that are absorbed in the gut, such as salbutamol, delivery to the lung can be inferred from the urinary recovery over 30 minutes after inhalation, a period which encompasses the peak effect of the drug but is before most gastrointestinal absorption occurs.²⁰ This method is crude because over this period considerable gastrointestinal absorption may occur, and the absorption, distribution, and urinary excretion of inhaled drug may not be complete. The method does not allow comparison of delivery between different types of patient because the extent of the inaccuracies introduced by these factors will vary. Although ingestion of activated charcoal immediately before inhalation will almost completely abolish the problem of gastrointestinal absorption,^{21,22} the problems of variable lung absorption and elimination remain. None of these methods give any information on the distribution of aerosol in the lung after inhalation.

Measuring lung deposition

For most inhaled drugs there seems to be no alternative to the use of radioaerosols for measuring drug deposition and distribution in the lungs. A directly labelled drug or a suitable indirect marker are added to the nebuliser or inhaler, and deposition in the lungs is detected by using a gammacamera. Researchers have been reluctant to use these methods in the past because of the perceived hazard of using radionuclides in children, but can the real danger of these methods be calculated? For our method of measuring pulmonary deposition 7.4 MBq of human serum albumin labelled with technetium-99m is delivered to the patient as an aerosol (assuming that 20% of the 37 MBq placed in the nebuliser is inhaled or swallowed).²³ According to the International Commission on Radiological Protection this delivers an effective dose equivalent of 0.34 and 0.16 mSv for children aged 5 and 15 years, respectively.²⁴ In addition, tissue attenuation is measured by recording a transmission scan from a ^{99m}technetium flood source (or a flood source labelled with cobalt-57); for this the effective dose equivalent is estimated as 0.003 mSv. Finally, a lung ventilation

outline image is obtained by administering 74 MBq of xenon-133 gas to obtain a 10 second breathhold image. The effective dose equivalent for this procedure has been estimated from the 30 second breathhold dosimetry estimate given by the International Commission on Radiological Protection.²⁴ Owing to the nature of the dynamic retention of xenon gas inside the lungs and other tissues, a 10 second breathhold cannot be assumed to give one third of the radiation dose of a 30 second breathhold procedure. The dose will clearly be less for a 30 second breathhold procedure, however, and so an intermediate factor of 0.75 is taken as the ratio of the effective dose equivalent for a 10 second procedure to that of a 30 second procedure. This factor is likely to err on the side of caution and result in a slightly higher effective dose equivalent than actually received. An effective dose equivalent of 0.036 and 0.014 mSv for children aged 5 and 15 years, respectively, is obtained for this part of the procedure.

The total dose estimated for the aerosol and administrations of ¹³³xenon and the transmission scan is therefore 0.38 and 0.18 mSv for 5 and 15 year old children respectively. To put these doses into perspective they can be compared with the exposure to x rays to produce a radiograph of the skull (0.15 mSv) or thoracic spine (0.9 mSv). Both are well within the range of variation in natural background radiation received by the general public (the mean background dose in the United Kingdom is about 2 mSv).

The International Commission on Radiological Protection gives risk factors for fatal cancers for radiation exposure of the entire population (that is, all ages, both sexes) as 5×10^{-5} per mSv.²⁵ For non-fatal cancers and severe hereditary effects the factors are 10^{-5} and 1.3×10^{-5} per mSv respectively. These combine to give a total risk factor of 7.3×10^{-5} per mSv. For children these risks may be two or three times higher.²⁵

The 0.18 mSv dose to a 15 year old results in a risk of about one in 10^5 of fatal malignancy (assuming that the risk is no greater than for an adult). The 0.38 mSv dose of a 5 year old would result in a life time risk of about one in 20000 (taking a factor of 2.5 for increased sensitivity of children to radiation). This can be compared with the one in 1300 natural risk of fatal childhood cancer before the age of 15.²⁶ The total life time risk (that is, fatal, non-fatal, and severe hereditary) would be about one in 15000 for a 5 year old (assuming that this overall risk is increased by a factor of 2.5) and one in 75000 for a 15 year old.^{26 27} The highest radiation dose of 0.38 mSv, however, is equivalent to the radiation received by living for three days in parts of Cornwall or about two months elsewhere in the United Kingdom.

The potential benefits of measuring inhaled drug deposition in children, we believe, would justify this small risk in these children who have a disease that may benefit from new aerosol treatments, and such experiments can be ethically justified provided that informed parental consent is obtained.

The results of the limited radioaerosol studies of drug deposition in children indicate the potential value of these methods. Alderson *et al* studied children with cystic fibrosis aged between 1^{1/2} and 16 years and found that total nebulised aerosol deposition increased with age and that there was a U shaped relation between minute ventilation and deposition, with maximum deposition occurring at a ventilation of 15 l/min.²⁸ More recently we have shown that in children between 8 and 17 with HIV infection the pulmonary deposition of pentamidine given by nebuliser is not related to height, and lung concentrations of pentamidine were higher in younger and smaller children. Large central airways deposition was particularly high in this group.⁶ In keeping with this Chua *et al* have reported that age

had no effect on total nebulised aerosol deposition in patients with cystic fibrosis aged 5 to 15 years, but the use of a facemask was less than half as efficient as use of a mouthpiece.²⁹ The apparent discrepancies between these studies may be explained by differences in the age groups studied, the nebuliser equipment and drugs used, and the patients' underlying lung disease. Further studies are necessary to clarify these differences.

Conclusions

There can be no doubt that the use of radiolabelled tracers offers an accurate and convenient method of studying drug delivery. If the measurement of delivery is coupled with measurements of clinical outcome then appropriate treatment can be adopted and inappropriate treatment discarded. The risks associated with the radiation are small compared with the potential risks of using inappropriate doses of therapeutic aerosols or inadequate apparatus in children.

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