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Effect of extension devices on the drug deposition from inhalation aerosols

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Summary

Disodium cromoglycate particles were labelled with pure γ-radiator ^{99m}Tc using a novel co-precipitation technique based on spray drying. Drug particles were inhaled by 7 healthy volunteers from metered dose aerosols connected either with conventional actuators or with 3 types of extension devices. The fractional deposition of radioactive drug particles in the respiratory tract as well as in the gastrointestinal region was monitored using a gamma camera. All the extension devices studied increased clearly the fraction of the drug dose deposited in the respiratory tract and especially in the alveolar region. The spacer device with the controlled flow rate of inspiration was noticed to be the most effective system for the administration of drug from metered dose aerosols.

Introduction

The inhalation of antiasthmatic agents is a logical means of treating an asthma since it is possible to deliver drug particles directly onto the mucosa of the tracheobronchial and alveolar regions of the respiratory tract. Drug particles or droplets small enough to penetrate into the therapeutically significant area are administered using either pressurized aerosols, dry powder devices or nebulizers.

Metered dose aerosols are used primarily to deliver drug doses into the respiratory tract. Antiasthmatic agents are widely available in an aerosol drug form. The active ingredient is commonly suspended in liquid chlorofluorocarbon propellents and packed into small aerosol containers. Through the metering valve patients deliver a certain dose of the drug during their inspiration. Metered dose aerosols contain several hundred doses in a compact container.

Although asthma aerosols are apparently easy to use, many patients found it difficult to release the aerosol dose with the co-ordination of their respiratory cycle (Crompton, 1982). Even about 14% of asthmatic patients have been shown to use this drug form totally ineffectively (Paterson and Crompton, 1976). On the other hand, medication can also fail because the delivered droplets containing suspended drug particles in liquid propel-

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lent are too large and have too high a speed (Byron, 1986). Mainly for this reason the majority of the aerosol dose is usually deposited in the mucose layers of the upper airways and so is swallowed (Newman et al., 1981a). It is possible to increase the fraction of drug dose deposited in the therapeutical region by means of controlled inhalation techniques (Pavia et al., 1977). It is often laborious to train these effective inhalation techniques to the asthmatic patients. Especially the elderly and young children found it difficult to learn a correct inhalation technique (Power and Dash, 1985).

Several inhalation aids have been developed to improve the inhalation of drug doses from metered dose aerosols. Most often these devices are differently constructed extension tubes connected to the aerosol container. The two initially introduced apparatuses are an open extension tube (Inhalet) and a pearly shaped spacer (Nebuhaler) (Moren, 1978). Recently a collapsible holding chamber (InspirEase) has also become available (Newman et al., 1986). In these extension devices the speed of the delivered droplets should decrease and the propellent should evaporate. Therefore the drug particles ought to be less likely to contact the upper airways. Holding chambers (Nebuhaler, InspirEase) have a one-way inhalation valve in the mouthpiece and therefore the co-ordination of the dose delivery with inspiration is not necessary.

Newman et al. (1981b, 1984, 1986) have detected the effect of different extension devices on the particle deposition using a radiotracer technique. In these studies ^{99m}Tc-labelled non-medical Teflon particles were inhaled with and without the extension devices. Increasing deposition in the whole lung area and decreasing deposition in the upper airways was monitored.

In this study the new radiolabelling method of the drug particles recently described by Vidgren et al. (1987a) was used. Thus it was possible to study the deposition of real drug particles in the respiratory tract. Labelled disodium cromoglycate particles were, firstly, inhaled using a conventional actuator device. Secondly, deposition patterns of drug particles administered by 3 different extension tubes (Inhalet, Nebuhaler and InspirEase) were monitored using a gamma camera.

Materials and Methods

Labelling of the drug particles

Disodium cromoglycate (BP 1980, Chemisell, Italy) particles were labelled using the spray-drying technique previously described by Vidgren et al. (1987a). Drug was dissolved in 50 ml of water to give a 6% w/w solution. 1 ml of 0.9% w/w sodium chloride solution containing ^{99m}Tc was added to the drug solution. This mixture was spray-dried (Buchi Minispray dryer, type 190, F.R.G.) at the feed rate of 60 ml/min. The air input temperature during drying was about 180 °C and the outlet temperature was about 80 °C. The throughput of air was 2.4 m^3/min and the nozzle air pressure was 800 N · l. The mean aerodynamic diameter of ^{99m}Tc-labelled disodium cromoglycate particles measured microscopically ($n = 400$) was 3.8 ± 0.05 μm.

Preparation of the metering dose aerosols

Firstly, 100 mg of sorbitan trioleas (Span 85, Atlas, Belgium) was dissolved in 20.7 g of liquided propellent dichlorodifluoromethane (Freon P12). Secondly, 6.21 g of liquid dichlorotetrafluoroethane (Freon P114) was added to the mixture of P12 and Span 85 at a temperature of −70 °C. Thirdly, 2.53 g of ^{99m}Tc-labelled disodium cromoglycate was dispersed in the above-mentioned solution using a homogenizer (Ultra-Turrax, type TP 18/10, IKA Werk, F.R.G.). The samples of 8.28 g of the suspension were filled into metal aerosol containers (Presspart, U.K.). The containers were closed with 50 μl metering valves (Riker, U.K.). 7.24 g of P12 was filled through the metering valve. Each dose contained 1 mg of ^{99m}Tc-labelled disodium cromoglycate and an activity of 400 kBq (10 μCi).

Inhalation of the drug doses

Seven healthy informed volunteers took part in the in vivo inhalation test which was carried out under supervision. Before inhalation the lung function was measured, and the 80% lung volume of the maximum vital capacity was carefully trained. It was noticed that all the volunteers were able to repeat this depth of the breath with a deviation lower than 5%.

Freshly prepared aerosol containers were carefully shaken and connected with the conventional aerosol actuator. Just before the gamma camera measurement, 10 doses from the metering dose aerosols were taken using the conventional actuator, Inhalet (Astra Pharmaceuticals, Sweden), Nebuhaler (Astra Pharmaceuticals, Sweden) and InspirEase (Key Pharmaceuticals, U.S.A.). With a conventional aerosol actuator or Inhalet, 10 doses were taken separately as carefully as possible. Respectively with Nebuhaler and InspirEase two doses of the drug were delivered to the holding chamber and inhaled. This was repeated 5 times. The total activity of the disodium cromoglycate taken by every volunteer was about 4 MBq (100 μCi). The 80% depth of the breath was accomplished using the plain actuator, Inhalet and Nebuhaler. The flow rate of inspiration was approximately 55–70 litres/min. In InspirEase there exists a special reed which makes a sound for restricting the flow rate of inspiration. This rate was about 20 litres/min being thus clearly smaller than that used with other inhalation systems tested. Inhalations were in every case followed by 5 s of breath-holding. The activity retained in the actuator as well as the fractions deposited into the lung area or into the upper airways and stomach were determined immediately after the inhalation of ^{99m}Tc-labelled drug doses.

Measurement and calculation of the deposition

The measurements of deposition were done with the large field gamma camera (Type 400T, General Electric, WI, U.S.A.) equipped with a low energy all purpose collimator. The energy window was 10% for the ^{99m}Tc-energy peak (140 keV).

All measurements were done for each person in the anteroposterior and posteroanterior view in the same measurement geometry for 5 min per view in the sitting position. The data were collected to the Gamma-11-system with PDP 11/34 computer (Digital Equipment Corp., MA, U.S.A.) with 64×64 position collection matrix. All the results were calculated after correction of the background radiation and time decay of ^{99m}Tc. The geometric mean counts were calculated for the lung region and the results were listed for the device, upper airways and lungs. For the individual correction of attenuation in different body thicknesses the point source measurement in the opposite site of the subject was done. The correction factor for the dose measured in air were solved with the calibration curve, which was measured at various depths of water as an attenuation and scattering material (Newman, 1983). Ten puffs of aerosol deposit an initial lung burden of 400 kBq (10 μCi) ^{99m}Tc, and the radiation dose to the lung resulting from this amount of activity does not exceed 4 mrad.

Results and Discussion

After evaporation of the propellents from the aerosol droplets, the individual particle properties of the airborne drug particles are the most dominating feature of the drug particle behaviour during the inhalation. In this study disodium cromoglycate was co-precipitated with ^{99m}Tc using the spray drying technique. Spray-dried particles are more homogeneous and have some physical properties different from conventionally used mechanically micronized disodium cromoglycate particles (Vidgren et al., 1987b). According to in vitro results recently presented by Vidgren et al. (1987b), the spherical spray-dried particles with the optimum particle size are aerodynamically some more advantageous than the generally used mechanically micronized particles of disodium cromoglycate in inhalation therapy. Although the deposition characteristics of the spray-dried material are slightly different from those of mechanically micronized disodium cromoglycate particles, the labelling method used in this study is suitable for performing this kind of comparison of different inhalation devices. On the other hand, this method is clearly more physiological than the use of insoluble Teflon particles labelled with ^{99m}Tc.

Deposition patterns of ^{99m}Tc-labelled disodium cromoglycate particles presented separately for all the volunteers are shown in Fig. 1 and the corresponding mean values for the different devices are shown in Fig. 2. The fraction of the dose retained in the device was clearly the smallest for the plain actuator and largest for the extension devices con-

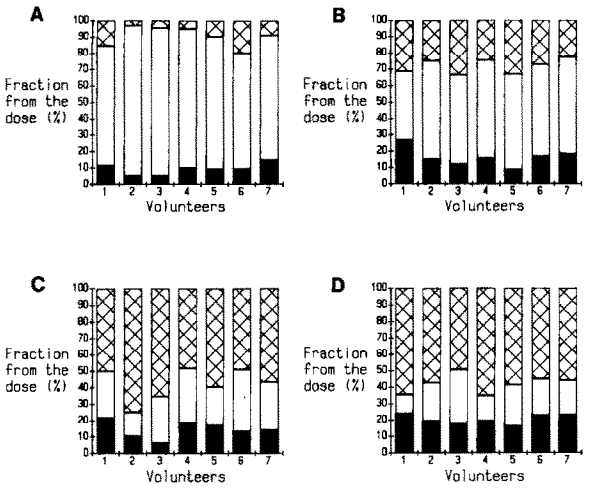

Fig. 1. Fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate separately in 7 volunteers after administration using conventional aerosol actuator (A), Inhalet (B), Nebuhaler (C) and InspirEase (D). Key: ■, lungs; □, upper airways; ▩, device.

taining holding chamber. The more complicated the structure is of the device, the larger the surface area, and the greater the proportion of the drug particles that stick to the walls of the extension tubes. The delivery of the aerosol dose by means of relatively high pressure seems to lead to the collision of drug particles to the plastic walls of the devices. According to the visual examination, the aerosol droplets hit to the walls even before the total evaporation of the propellents. Besides the cohesive nature of the drug particles also the wet nature of the droplets increases the tendency of the airborne particles to stick firmly to the plastic surfaces. This sticking phenomenon is very difficult to avoid with the aerosol drug forms containing liquid or pressurized propellents.

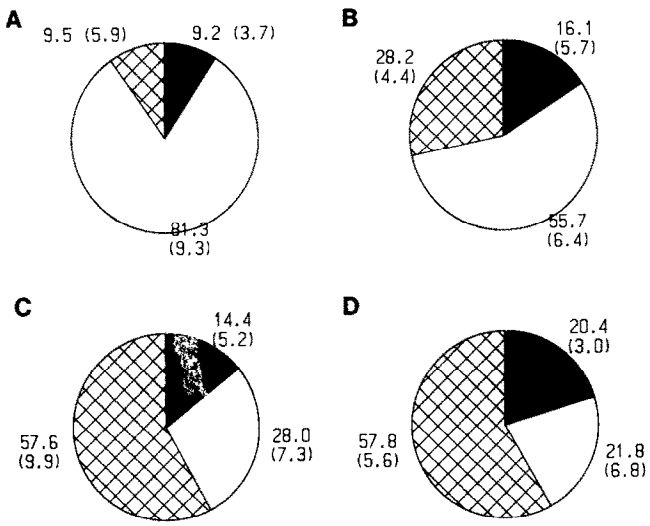

Fig. 2. The mean fractional deposition with the standard deviation of ^{99m}Tc-labelled particles of disodium cromoglycate after administration using conventional aerosol actuator (A), Inhalet (B), Nebuhaler (C) and InspirEase (D). Key: ■, lungs; □; upper airways; ▩, device.

One of the main reasons for using the extension tubes is the possibility of reducing deposition of the drug particles in the upper airways. The adsorption of the particles on the mucosa of the oropharyngeal area may induce serious local side-effects, e.g. candidiasis. On the other hand, after the swallowing of the adsorbed drug, systemic side-effects may also exist. In this study over 80% of the drug dose was deposited in the oropharynx after delivery from the conventional aerosol actuator. This non-therapeutic fraction was possible to be reduced with all the extension tubes, especially with Nebuhaler and InspirEase. These results confirmed the advantageous effect of the extension devices on the deposition of drug particles between respiratory tract and oropharyngeal area. The main reason for the greater respiratory tract deposition is the decreasing particle velocity in the extension devices. This is most evident with InspirEase device with the lowest flow rate of inspiration. Thus the inhaled particles are less prone to the inertial impaction to the mucosae of the upper airways. In the extension tubes and especially in the holding chambers, propellents also have enough time to evaporate before inspiration. Thus the share of small solid particles is larger after administration from aerosols connected with extension devices than from conventional aerosols connected with a short actuator. In addition the decreased oropharyngeal deposition especially with the device containing a holding chamber is partially due to the decreased significance of the co-ordination between drug delivery and inspiration.

Typical deposition patterns monitored after administration of drug dose either from conventional

aerosol or InspirEase device are presented in Fig. 3. The patterns for Inhalet and Nebuhaler devices resembled those for InspirEase. Using extension devices, drug particles can be deposited to significantly larger area of the respiratory tract. Thus it is possible to administer a clearly larger fraction of the drug dose to the alveolar region. It is generally assumed that alveolar deposition is therapeutically important (Moren et al., 1985).

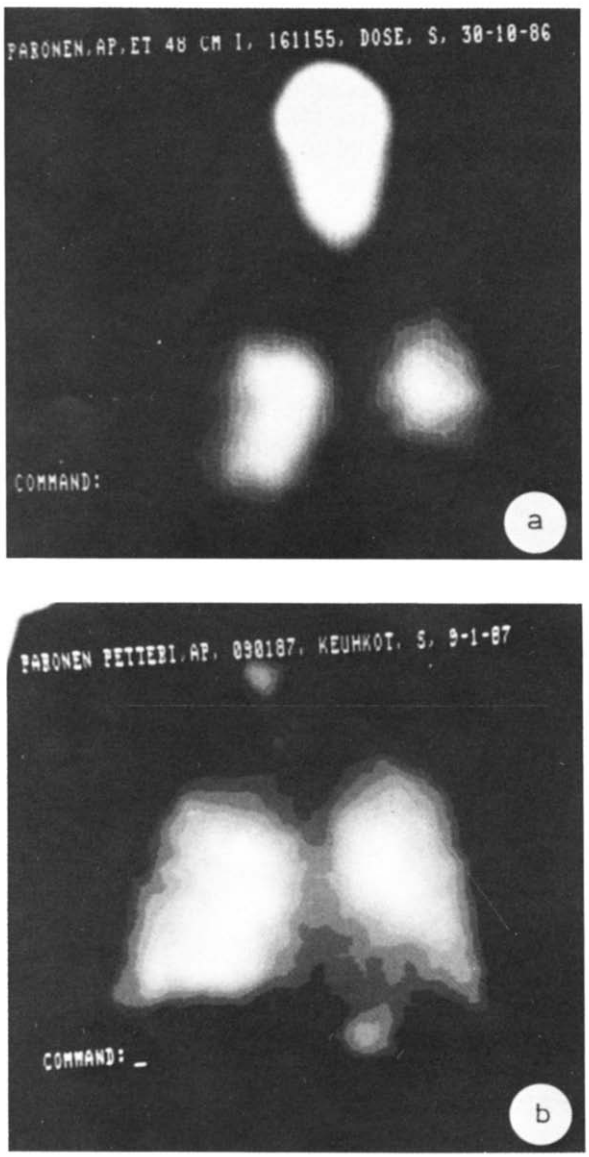

Fig. 3. Typical gamma camera photographs from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate in the respiratory tract after administration using conventional aerosol actuator (A) and InspirEase (B).

The results of this study are slightly different from the previously documented results by Newman et al. (1981b, 1984, 1986). These minor deviations may be partially due to possible differences in the breathing techniques of the volunteers. On the other hand, different deposition behaviour of Teflon particles and real drug particles in the extension devices and upper airways can also be due to the differences in the physical surface properties. Drug particles have different affinities for sticking to the surface of plastic extension devices compared to Teflon particles. It also seems reasonable to assume that Teflon particles prepared by spinning disc method are differently cohesive compared to spray-dried drug particles. The physical properties such as density and particle shape of these two materials are also different and this influences to the aerodynamic behaviour of the particles in the respiratory tract.

According to the results of this study all the evaluated extension devices improved the deposition of drug particles in the respiratory tract and especially in the alveolar region. The InspirEase spacer device was noticed to be more effective than an open extension tube. The reed and sound method for regulating the inspiration from the holding chamber led to the most remarkable increase in the lung deposition of disodium cromoglycate.

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