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Respiratory tract deposition of ^{99m}Tc-labelled drug particles administered via a dry powder inhaler

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Summary

Drug particle deposition in respiratory tract after inhalation from dry powder inhaler was evaluated. Disodium cromoglycate particles were labelled with a pure γ-radiator, ^{99m}Tc, using a co-precipitation technique based on spray drying. Labelled drug particles were mixed with lactose, packed in gelatin capsules and inhaled using the dry powder inhaler. Fractional deposition in the whole lung area, upper airways and stomach as well as in the inhaler was monitored using a gamma camera. Inhalations of 7 patients showed that on average 16.4% of the dry powder dose was deposited in bronchial and alveolar stages of the lungs. This fraction is almost twice as large as the previously reported lung depositions after administration from the metered dose asthma aerosols. The majority of the drug not deposited in the lungs remained in the inhaler. Thus there was clearly less of the untherapeutically used drug in the mouth, oesophagus and stomach than after administration from metered dose aerosols. The results pointed out a better bioavailability of the drug dose administered with the dry powder drug from than with the conventional metered dose aerosol drug form. The behaviour of the drug particles during the inhalation is, however, strongly dependent on the formulation of the powder mixture as well as on the construction of the powder inhaler.

Introduction

The inhaled route has several well-recognized advantages over other routes of administration of drugs to the respiratory tract (Newman and Clarke 1983). By inhaling the drug doses directly to their receptor sites within the bronchial tree, drug doses can be held as small as possible. Therefore undesirable side-effects can be minimized and drug response can be detected rapidly (Gonda and Byron, 1978; Webb et al., 1982). Due to the anatomy and physiology of the human lungs, particle size is the most critical parameter of the drug deposition in the respiratory tract (Clarke and Pavia, 1984). The accepted optimum size for inhaled drug particles is between 0.5 and 7 μm (Davies et al., 1976).

Metered dose aerosols are used conventionally to deliver antiasthmatic agents to the respiratory tract. According to the previously published results, only a relatively small portion of the aerosol dose is deposited in the therapeutically effective bronchial and alveolar stages of the lungs (Newman et al., 1981). An important problem for

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asthmatic patients using metered dose aerosols is the difficulty to co-ordinate the delivery of the metered dose with inspiration (Crompton, 1982). Some 14% of asthmatic patients do not learn to use pressurized aerosols satisfactorily (Paterson and Crompton, 1976).

Recently dry powder inhalation has become an alternative to aerosol therapy. In dry powder inhaler systems the micronized drug is mixed with large carrier particles. This powder mixture is then put into hard gelatin capsules. The carrier material makes the powder less cohesive and better flowing and thus easier to handle during manufacturing processes. Lactose is the most commonly used carrier. During inhalation the small drug particles should separate from their agglomerations or from the surfaces of carrier particles and deposit in the bronchial and alveolar stages of the respiratory tract. Cohesion forces between drug particles and adhesion forces between drug and carrier particles are the most critical factors with respect to the redispersion of the micronized drug particles in the inspired air (Byron, 1986). With the dry powder drug form, patients can deliver the drug dose more easily from the device in the inspired air flow than with the metered dose aerosol (Bell et al., 1971).

Direct labelling of antiasthmatic drugs with radiotracer is difficult because these molecules rarely contain an element which has a suitable radionuclide (Hallworth, 1983). Only one bronchodilator agent, namely ipratropium bromide, has been successfully labelled with bromine-77 (Spiro et al., 1984). Therefore the deposition of the inhaled particles has usually been studied using non-medical aerosols. ^{99m}Tc-labelled Teflon particles have been widely used as model particles in these deposition studies (Newman et al., 1981, 1982, 1984a, 1986). Radioactive Teflon particles were administered with metered dose aerosols and the deposition of these particles were monitored with the gamma camera.

As far as the authors know, deposition of drug particles after administration from the dry powder inhalation drug form has not been monitored directly using a radiotracer technique. Fuller and Collier (1983) have pointed out with pharmacokinetic assessment that after the inhalation of disodium cromoglycate in dry powder form, 6–20% of the dose reached the plasma. Besides the fraction deposited in the lungs, this amount includes also the drug that had been absorbed from the upper airways and stomach. The common assumption is that the drug particle deposition in the lungs is slightly smaller from the dry powder inhalers than from the pressurized aerosols (Byron, 1986). Thus the recommended dry powder drug doses are larger than the corresponding aerosol drug doses.

In this study the particles of the antiasthmatic agent, disodium cromoglycate, were labelled with ^{99m}Tc using the co-precipitation technique based on spray drying (Vidgren et al., 1987a). Deposition of drug particles in the human respiratory tract was evaluated after administration from dry powder inhaler.

Materials and Methods

Labelling and evaluation 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 (Büchi 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 Nl.

The effective particle density of the spray dried material was measured with the air comparison pycnometer (Beckman, type 930, U.S.A.) using helium as the inert gas. The effective particle density averaged over 10 measurements with the S.E.M. was 1.82 ± 0.01. The arithmetic mean diameter was evaluated microscopically measuring the Feret diameter of 400 nearly spherical particles. The value of the arithmetic mean diameter with the standard error of the mean was 2.8 ± 0.04 μm. The behaviour of the particles in the human respiratory tract is, however, dependent on besides the arithmetic diameter also the density of the

particles. Thus the value of the arithmetic mean diameter was multiplied by the square-root of the effective particle density. The value of this parameter, called mean aerodynamic diameter, was 3.8 $\pm$ 0.05 μm.

Preparation of the dry powder capsules

An equivalent amount of ^{99m}Tc-labelled disodium cromoglycate particles and 325 mesh α-lactose monohydrate particles (DMV, Veghel, The Netherlands) was mixed for 15 min in a 250 ml glass vessel (Turbula, type 2P mixer, Switzerland). Forty mg of the mixed powder were put into each hard gelatin capsule (number 03). Each delivered dose thus contained 20 mg of antiasthmatic drug with an activity of 8 MBq (200 μCi).

Delivery of the inhalation doses

Seven healthy volunteers took part in the in vivo inhalation test. They were fully informed of the nature of the study, 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 volume deviating at most by 5%.

The dry powder packed in the gelatin capsule was delivered with the commercial inhaler (I.S.F. Inhalatore, Italy). The drug doses delivered from the dry powder capsules contained the same amounts of active ingredient and lactose carrier as was mentioned in the British Pharmacopoeia. The amount of active substance was the same as stated for the commercially available dry powder preparation. Every patient had their own powder inhaler ensuring that the system of delivery was dry and clean.

One capsule from the powder inhaler was taken as carefully as possible by the 80% volume of the breath from the maximum forced vital capacity. The inhalation was done using approximately the flow rate of 55–70 litres/min. Inhalation was followed by 5 s of breath-holding. The activity retained in a dry powder inhaler was measured immediately after the inhalation.

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 of the same measured 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 $\times$ 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 inhaler, lungs and upper airways. For the individual correction of attenuation in different body thicknesses the point source measurement in 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 in various depths of water as an attenuation and scattering material (Newman and Clarke, 1983). The radiation dose to the lung resulting from one dry powder capsule does not exceed 8 mrad.

Results and Discussion

In this study the dry powder drug form was formulated using spray dried disodium cromoglycate particles instead of conventionally used mechanically micronized particles. The particle and powder properties of the spray dried particles are different than those of micronized particles (Vidgren et al., 1987b). Spray dried particles are spherical in shape and they are also slightly less cohesive in nature. Thus the redispersion of the mechanically micronized particles from the lactose carrier particles as well as the whole deposition pattern may be different compared with those of the spray dried particles. Due to the labelling technique based on spray drying the method used in this study is suitable especially in the comparison studies of different drug forms, inhalation techniques and inhalation aids but not in the clinical comparisons of commercial products containing mechanically micronized drug particles.

The results presented in this study were obtained using the same measuring method as the previously presented results which described the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate administered from the metered dose aerosols (Vidgren et al., 1987a). Thus the deposition results of the both papers are possible to be directly compared.

Typical gamma camera photograph obtained after the administration of the labelled drug particles with the dry powder inhaler is shown in Fig. 1. Fractional depositions of the drug particles are presented separately for every volunteer in Fig. 2 and as mean values in Fig. 3. The mean fraction of the dose retained in an inhaler system was nearly 40%. The corresponding amount retained in a conventional aerosol actuator has been generally noticed to be less than 10% (Newman et al., 1984b; Vidgren et al., 1987a). The difference between these two figures is due to the more complicated technical structure of the dry powder inhaler compared with the aerosol actuator. Dry powder inhaler contains several solid walls in which the cohesive drug particles may easily stick. Some of the agglomerates containing lactose carrier particles and small drug particles may also be strong enough to oppose the breaking in the inspired air flow. During the administration of the drug dose from the metered dose aerosol the evaporating propellent forces, due to the high pressure, cause the drug particles to effectively move out of the actuator into the mouth.

The delivery of aerosol spray by means of high pressure has been noticed to lead to the inertial impaction of drug particles onto the mucose layers of the mouth and upper parts of the respiratory tract. This is followed by the swallowing of the drug into the stomach. In our previous study, more than 80% of the aerosol drug dose was deposited in the mouth, oesophagus and stomach. The corresponding untherapeutically used fraction

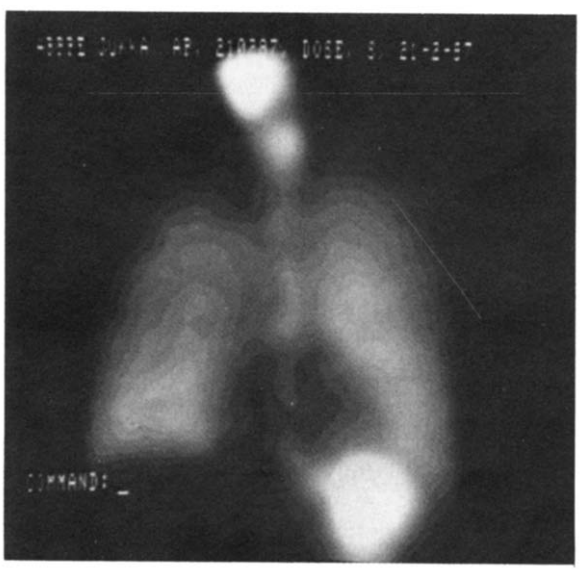

Fig. 1. Typical gamma camera photograph from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate after administration with the dry powder inhaler.

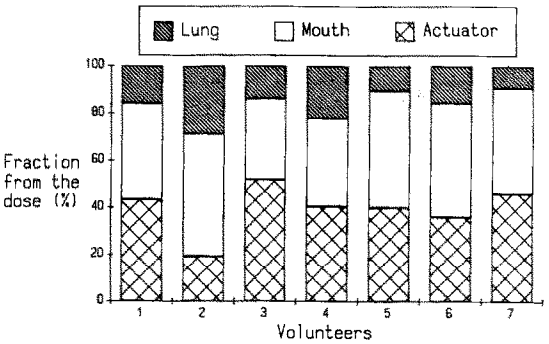

Fig. 2. Fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate separately in 7 volunteers after administration with the dry powder inhaler.

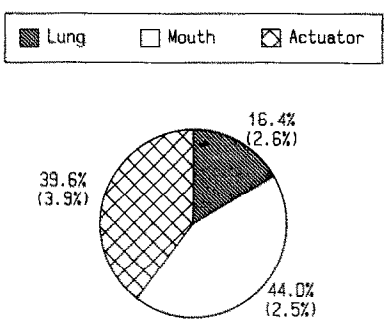

Fig. 3. The mean fractional deposition and the standard error of the mean of ^{99m}Tc labelled particles of disodium cromoglycate after administration with the dry powder inhaler.

of the dry powder dose was clearly less, this being 44% (Fig. 3). This is due to the fact that the particles delivered from the dry powder inhaler do not have as high a velocity as particles in an aerosol cloud. Small drug particles are thus more effectively inhaled into the lungs with only a moderately effective and smooth inspiration. However, drug particles which do not redisperse from the coarser carrier particles or from agglomerates are retained in the upper airways.

The mean lung deposition obtained after the administration from dry powder inhaler was over 16% (Fig. 3). This deposition is nearly twice as high as the previously presented deposition from the conventional metered dose aerosol (Vidgren et al., 1987a). Thus the spray dried drug particles seemed to redisperse effectively from the surface of lactose carrier and reasonable quantities of this material deposited in the therapeutic regions of the respiratory tract.

It has been widely documentated (Newman et al., 1981, 1984b, 1986; Vidgren et al., 1987a) that only on average 6–9% of the aerosol dose reached the whole lung area of the respiratory tract. Even smaller portions can be detected in the patients with a poor inhalation technique (Paterson and Crompton, 1976). The main reason to use dry powder inhalers has been a better patient compliance (Power and Dash, 1985). On the basis of the results presented in this study it is reasonable to suppose that the dry powder drug form gives a greater deposition of the drug dose to the whole lung area and therefore this drug form may even be more advantageous than a conventional aerosol in inhalation therapy. It must, however, be remembered that the drug particle deposition is strongly dependent on the formulation of the powder mixture used in drug form as well as on the construction of the inhalation device.

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