International Journal of Pharmaceutics, 64 (1990) 1–6
Elsevier

IJP 02129

Research Papers

Radiotracer evaluation of the deposition of drug particles inhaled from a new powder inhaler

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(Received 19 January 1990)
(Modified version received 1 March 1990)
(Accepted 14 March 1990)

Key words: Disodium cromoglycate; Inhalation dosage form; Deposition pattern; Asthma therapy

Summary

Deposition of ^{99m}Tc-labelled particles of disodium cromoglycate in the human respiratory tract after inhalation either from the conventional metered dose aerosol or from the new Ingelheim powder inhaler (FO II) was compared. Fractional deposition in the whole lung area, in the upper airways and in the device was measured using a gamma camera. Eight healthy informed volunteers participated in the inhalation test. The lung deposition of the inhaled drug was about 9% using the conventional aerosol actuator with the short plastic mouthpiece whereas, using the Ingelheim powder inhaler, on average 20% deposition in the whole lung area was achieved. In addition, with the Ingelheim inhaler drug particles seemed to be deposited in the more peripheral parts of the respiratory tract. The upper airway deposition was also reduced with the Ingelheim powder inhaler. On the other hand, a larger fraction of the drug dose was retained in the Ingelheim inhaler than in the aerosol actuator.

Introduction

Metered dose aerosols are primarily used for delivering antiasthmatic agents directly to their site of action in the human respiratory tract. Although these metered dose aerosols are apparently easy to use, many patients, especially elderly people and children, find it difficult to use these devices correctly (Paterson and Crompton, 1976; Epstein et al., 1979; Crompton 1982). This is mainly due to the fact that delivery of the aerosol dose should be co-ordinated with the inspiration of the patient. In addition, aerosol therapy can fail because the delivered aerosol droplets have too high a speed or the unevaporated propellant droplets have too large a size for penetrating down the trachea (Byron, 1986). Furthermore, many patients felt that the propellants irritated their upper airways (Moren et al., 1985). For avoiding these problems dry powder dosage forms have recently been developed.

Dry powder dosage forms are generally formulated by mixing the cohesive micronized drug particles with carrier particles. Thus, it is possible to enhance the flowability of powder mixtures and therefore allow the accurate filling of gelatin capsules primarily used as unit dose system in the dry powder dosage form. Inert sugars, such as lactose and glucose, are commonly used as carriers. During inhalation drug particles are dispersed from their agglomerates or from the surface of carrier

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particles by the energy of the inspired air flow (Sackner et al., 1981). Redispersed small drug particles should then be deposited in the therapeutically significant regions of the lungs. This separation stage is the critical phase from the point of view of drug response (Bell et al., 1971). It is evident that the construction of the powder device has a great effect on the stage of the redispersion (Vidgren et al., 1988). Thus, the therapeutically significant lung deposition can be enhanced by optimizing the powder device.

According to clinical studies, a similar therapeutic response can be achieved both with metered dose aerosols and with dry powder inhalers (Hetzel and Clark, 1977, Harris and Rothwel, 1981). In this study the deposition of inhaled drug particles in the human lungs was compared after administration of a drug dose either from the metered dose aerosol or from the powder inhaler of Boehringer Ingelheim (Ingelheim inhaler) with the new construction.

Air channels in this recently introduced device have been designed to cause vibration of the capsule by the inhaled air stream. This phenomenon is supposed to enhance the emptying of a capsule and the redispersion of drug particles from the surface of carrier particles. According to the manufacturer only a moderately low flow rate of inspired air is needed for the liberation of the inhalable drug particles. The efficacy of the powder device in delivering the drug dose into the therapeutically important lung region can be estimated by clinical trials, e.g. bronchodilator tests. These studies are, however, quite laborious and expensive to perform and in addition they do not give accurate information on the localization of the inhaled drug particles in the human respiratory tract. Such data can be conveniently obtained using gamma labelled particles. As far as the authors know, no in vivo deposition studies with the radiotracer technique have been performed with this new device.

Materials and Methods

Labelling and evaluation of the drug particles

Disodium cromoglycate (BP 1988, Chemisell, Italy) particles were labelled using the spray drying technique (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 a feed rate of 60 ml/min. The air input temperature during drying was about 180 °C and the outlet temperature approx. 80 °C. The throughput of air was 2.4 m^3/min and the nozzle air pressure was 800 Nl. Disodium cromoglycate particles obtained by the spray drying process had a mean aerodynamic diameter of 2.4 ± 0.1 μm. Drug particles of this size are suitable for inhalation even into the peripheral parts of the human respiratory tract.

Preparation of the metered dose aerosol

Firstly, 100 mg of sorbitan trioleas (Span 85, Atlas, Belgium) was dissolved in 20.7 g of liquefied propellant, 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. The containers were closed with 50 μl metering valves. 7.24 g of P12 was filled through the metering valve.

Preparation of the dry powder mixture

An equivalent amount of ^{99m}Tc-labelled disodium cromoglycate particles and lactose particles was mixed for 15 min in a 250 ml glass vessel (Turbula, type 2P mixer, Switzerland). 40 mg of this powder mixture was filled into each gelatin capsule (size no. 3, supplied by Boehringer Ingelheim) to be used as a unit dose system in this study.

Delivery of the inhalation doses

Eight healthy, non-smoking, volunteers took part in the in vivo inhalation test. They were fully informed of the nature of the study, which was carried out under medical supervision. Before inhalation the volunteers were carefully trained to

be able to use both inhalers correctly. Just before the gamma camera measurement 10 doses from the metered dose aerosol were taken separately through the conventional aerosol actuator (Boehringer Ingelheim). Respectively, one capsule was pierced with the Ingelheim inhaler and the powder mixture was inhaled. Inhalation was followed each time by holding breath for 5 s. The activity retained in a dry powder inhaler or in a aerosol actuator was measured immediately after the inhalation.

Measurement and calculation of the deposition

Measurements of deposition were made 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 taken for each person in the anteroposterior and posteroanterior view of the same measurement geometry for 5 min per view in a sitting position. The data were collected in a Gamma-11-system with PDP 11/34 computer (Digital Equipment Corp., MA, U.S.A.) with a 64×64 position collection matrix and analysed later in a random manner. 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 lungs, upper airways and the inhaler.

This standard trial plan was accepted by the Ethical Committee of Kuopio University Central Hospital, Kuopio, Finland.

Statistical testing

The differences between the devices in deposition results were tested using a non-parametric Mann-Whitney U-test.

Results and Discussion

Due to the labelling method the inhalation dosage forms tested in this study were 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 slightly different from those of micronized particles (Vidgren et al., 1987b). Spray-dried particles are more spherical in shape and are also slightly less cohesive in nature. The method used in this study is suitable especially in comparison studies of different dosage forms, inhalation techniques and inhalation devices but not in clinical comparisons of commercial products containing mechanically micronized drug particles. In this study based on the above labelling method, the lung deposition as well as the drug amount retained in the aerosol and powder devices was determined with a gamma camera. The remainder of the drug dose was deposited in the upper airways and subsequently transported into the stomach.

The fraction of the delivered drug doses retained in the devices was very significantly higher for the Ingelheim inhaler than for the conventional aerosol inhaler ($p < 0.01$). (Fig. 1). The mean fraction of the dose retained in a powder

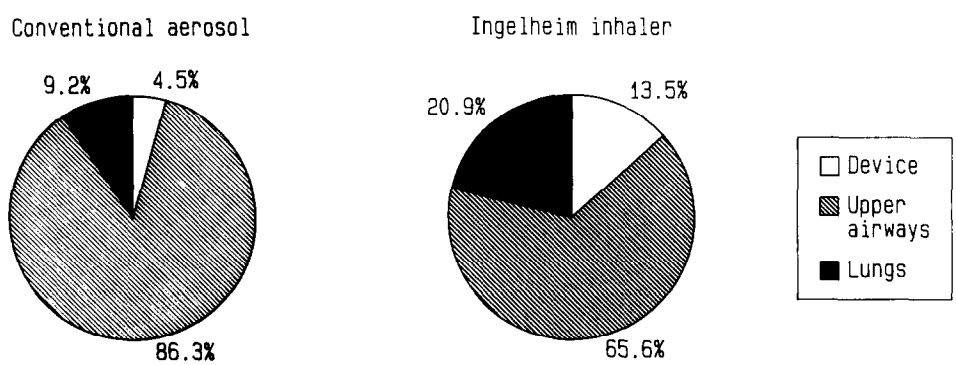

Fig. 1. The mean fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate after inhalation either from a conventional metered dose aerosol or from the Ingelheim inhaler.

device was 13.5%. The corresponding amount retained in the conventional aerosol actuator was found to be 4.5%. The difference between these two figures is due to the more complicated technical structure of the dry powder inhaler compared to that of the aerosol actuator. Dry powder inhaler contains several solid walls to which the cohesive drug particles may easily adhere. In addition, the plastic material of the device may have an effect on the fraction of the drug dose retained in the inhalation device.

It is generally supposed that in the dry powder dosage form agglomerates containing carrier particles and small drug particles may be stable enough to oppose the breaking in inspired air flow (Smith et al., 1980). Thus, a relatively large fraction of the dose is assumed to be deposited in the upper airways. According to the results of this study, however, a statistically very significantly smaller fraction of the drug dose was delivered from the Ingelheim inhaler than from the aerosol preparation deposited in the upper airways ($p < 0.01$) (Fig. 1). Therefore, the Ingelheim inhaler appears to disperse the drug particles effectively from the carrier particles. Redispersed drug particles are thus more prone to follow the inspired air flow than the delivered aerosol spray. The delivery of the aerosol spray by means of high pressure leads to the inertial impaction of drug particles on the mucous layers of the upper airways.

There were statistical differences between the results for lung deposition of the metered dose aerosol and Ingelheim inhaler ($p < 0.01$). The lung deposition achieved with the metered dose aerosol was 9.2%, being nearly the same as reported in the previous deposition studies of inhalation aerosols (Newman et al., 1981, 1984; Vidgren et al., 1987a). The corresponding fraction for the Ingelheim inhaler was 20.9%, which demonstrates remarkably higher lung deposition than has been achieved with other powder devices using the same research protocol (Vidgren et al., 1988). The lung deposition obtained with this new powder device is at the same level as has been documented for the metered dose aerosols connected to the most advantageous inhalation aids, e.g. spacer devices (Vidgren et al., 1987c).

The individual variation among the volunteers was in the same range as that obtained previously and which has also been generally reported in similar kinds of deposition studies (Newman et al., 1981, 1984; Vidgren et al., 1988) (Fig. 2). These variations between individuals are partially due to differences in respiratory anatomy and in lung function of the volunteers. It is, however, possible to compare the individual deposition patterns monitored for both devices tested (Fig. 3). With the Ingelheim inhaler a better lung deposition was achieved for all the volunteers than with the conventionally used metered dose aerosol.

A clear difference can be demonstrated between the deposition patterns of the inhaled drug doses. This can readily be seen from the deposition patterns of the gamma scintigraphs (Fig. 4). With the metered dose aerosol, less activity was

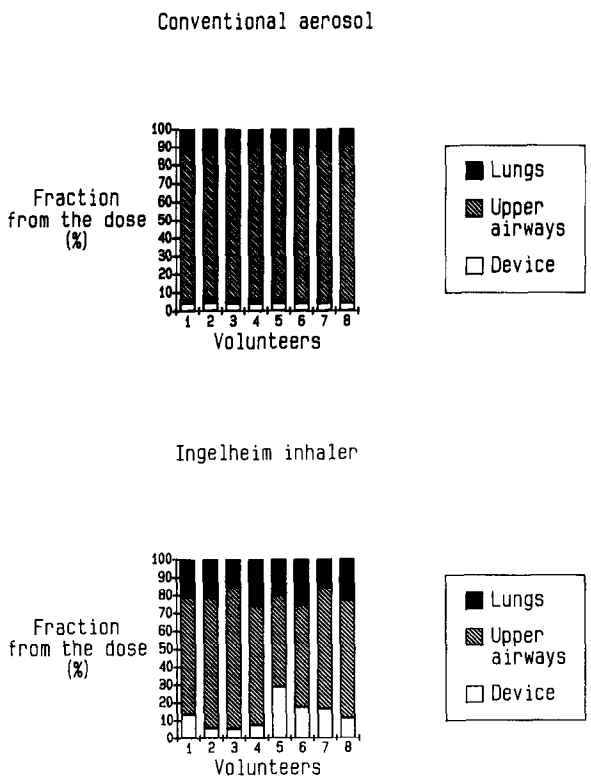

Fig. 2. Fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate separately in 8 volunteers after inhalation either from a conventional metered dose aerosol or from the Ingelheim inhaler.

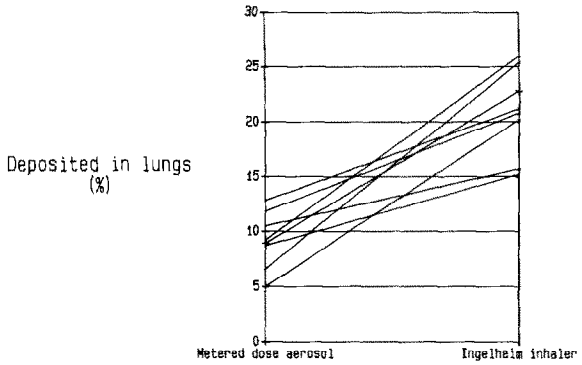

Fig. 3. Lung deposition of ^{99m}Tc-labelled particles of disodium cromoglycate for 8 volunteers after inhalation either from a conventional metered dose aerosol or from the Ingelheim inhaler.

deposited in the lung area and furthermore the inhaled drug particles seemed to be deposited on the branches of the main bronchus. Thus, only a very small portion of the drug particles deposited in the whole lung area reached the therapeutically most important respiratory or alveolar regions of the lungs. On the other hand, the drug particles administered from the Ingelheim inhaler seemed to be distributed more uniformly into the whole lung area. The difference between the deposition patterns of these two devices could be detected for all the volunteers.

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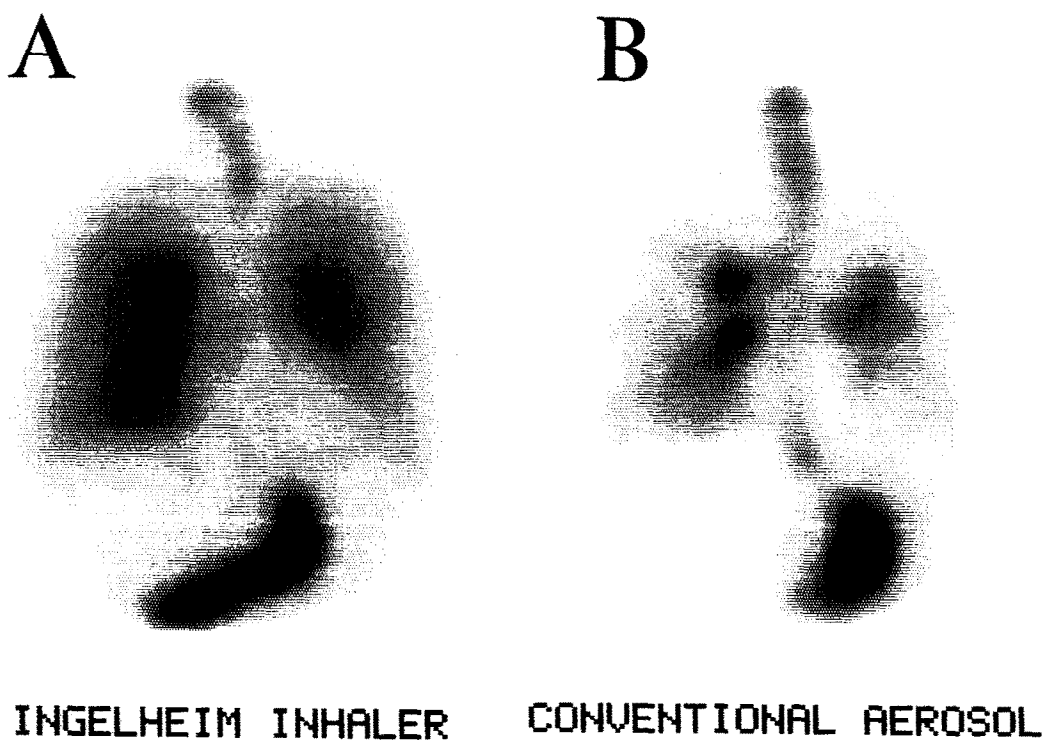

Fig. 4. Typical gamma scintigraphs from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate after inhalation either from the Ingelheim inhaler (A) or from a conventional metered dose aerosol (B).

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