

Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug

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Abstract

Background—Aerosols generated from metered dose inhalers may be highly charged. The aim of this study was to determine whether lining the walls of a polycarbonate spacer device with an antistatic agent would result in an increase in drug output. The effects of multiple actuations of drug into the spacer device and increasing residence time of drug within the spacer were also determined.

Methods—The amount of sodium cromoglycate contained in particles of various size available for inhalation (per 5 mg actuation) from a 750 ml polycarbonate spacer was determined by impinger measurement and spectrophotometric assay.

Results—Lining the spacer with an antistatic agent increased the mean (SD) amount of sodium cromoglycate in particles $<5 \mu\text{m}$ available for inhalation (per 5 mg actuation) by 244% from 0.59 (0.03) to 1.44 (0.2) mg). When there was a 20 second interval between actuation into the spacer device and inhalation, sodium cromoglycate available for inhalation in particles $<5 \mu\text{m}$ decreased by 67% (from 0.59 (0.03) mg to 0.2 (0.01) mg). Use of the spacer device increased sodium cromoglycate available for inhalation in respirable particles ($<5 \mu\text{m}$) by 18% compared with direct delivery by metered dose inhaler. Multiple actuations into the spacer decreased the amount of sodium cromoglycate available for inhalation in particles $<5 \mu\text{m}$ by 31% after two actuations and 56% after three actuations.

Conclusions—Multiple actuations of sodium cromoglycate into a spacer device before inhalation should be avoided, and inhalation from spacer devices should take place immediately after actuation to ensure maximum dose. Lining of a standard spacer device with an antistatic agent significantly increased output of sodium cromoglycate. This may have implications for improved therapeutic response and drug cost.

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To combat the problems of high oral deposition and coordination difficulties associated with pressurised inhalers,¹ many companies have designed and developed spacer devices.

The key features of a spacer device are a chamber or reservoir where the discharged aerosol cloud can be held, and a one way demand valve which allows air to be drawn through the chamber on inspiration but prevents air passing through the chamber on expiration. These devices may be modified by adding a face mask to allow use by preschool children as an alternative to nebulisation.²

Comparative studies between sodium cromoglycate 1 mg and 5 mg metered dose inhalers have confirmed that the 5 mg inhaler is clinically more effective and has a longer duration of action. Knowledge of the dose of sodium cromoglycate available for patients to inhale therefore appears to be important. A polycarbonate large volume spacer device has been developed (Fisonair; Fisons Ltd) for the delivery of sodium cromoglycate. Little is known about the output of sodium cromoglycate (5 mg) from this device, however, or how best to use it. For example, aerosol particles generated from a metered dose inhaler are highly charged and may be attracted electrostatically to the polycarbonate walls of the spacer device, decreasing the amount of drug available for inhalation.

In addition, many patients prescribed two actuations of sodium cromoglycate via a spacer device will actuate twice into the device and then inhale as this is more convenient. Mothers of young children often actuate drug into a spacer device and allow several seconds to elapse before they can coax their child to breathe adequately from the device. The effect of these techniques on drug output is not known.

The purpose of this study was to determine: (1) whether lining internal walls of a spacer device with an antistatic agent would reduce electrostatic deposition of particles and thus increase the dose available to patients for inhalation; (2) the effect on the therapeutic dose of delivering multiple actuations of sodium cromoglycate (5 mg per actuation) into the spacer device before inhaling the aerosol cloud; (3) the effect on the available therapeutic dose of the time the drug resides in the spacer device before inhalation.

Methods

A multistage liquid impinger³ was used to assess the aerodynamic particle size distribution of the aerosolised clouds. The device consists of a throat that contains a right

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angled bend (to simulate the oropharynx) and four impaction stages. Stages 1, 2, and 3 consist of impaction jets together with sintered glass collecting discs. The fourth stage consists of a narrow jet aimed at the base of the collection chamber.

The impinger had been calibrated by sampling an aerosol of dibutyl phthalate droplets that had been sized by a Malvern laser device (Malvern 3600; Malvern Ltd). A 50% cutoff diameter was derived for each stage of the device and was expressed in terms of aerodynamic diameter. The aerodynamic diameter of a droplet is the diameter of a unit density spherical particle with the same settling velocity as the droplet in question.

TEST METHOD

Initially a standard metered dose inhaler of sodium cromoglycate (5 mg) was assessed. The mouthpiece of the metered dose inhaler was connected to the impinger with a small rubber sock and air was drawn through the apparatus at a flow rate of 60 l/min. The aerosol was then discharged through the impinger. This was repeated on four occasions to facilitate the chemical assay procedures. The metered dose inhaler was shaken between each actuation. Each experiment was repeated on four occasions.

For the Fisonair spacer device the aerosol was discharged into the device and, after a delay of about one second, the mouthpiece of the Fisonair spacer was connected to the impinger and the aerosol drawn from the spacer. Again the test flow rate was 60 l/min and the procedure was repeated on four occasions to facilitate the chemical assay procedure. This allowed comparison of the dose delivered from the Fisonair with that delivered from a standard adaptor.

The first actuation from the metered dose inhaler was discarded for each experiment and no more than 20 actuations were used from the same inhaler. The time interval between actuations was 10–15 seconds.

Effect of antistatic agent on drug delivery

The inner walls of the Fisonair spacer device were lined with a thin film of a commercially available antistatic spray (Antistat) and left for 24 hours. As before the aerosol was discharged into the spacer device and, after a delay of one second, it was drawn from the device into the impinger. Again the test flow rate was 60 l/min and the procedure was repeated on five occasions. The effect of the antistatic lining on residence time was also studied. The aerosol was discharged into the spacer device lined with antistatic and left for 20 seconds before the spacer was emptied via the impinger. This experiment was repeated on four occasions.

Multiple dosing

To investigate the effect of multiple actuations into the Fisonair without an antistatic lining before inhalation by the patient the following study was conducted. Sodium cromoglycate was discharged into the spacer after

which the standard adaptor was shaken and sodium cromoglycate was fired into the spacer. One second later the device was connected to the impinger and the aerosol drawn from the device. The dose available to the patient after two actuations into the device could therefore be assessed. This was repeated with three actuations of sodium cromoglycate (5 mg). Each experiment was repeated on four occasions.

Effect of residence time delay

The residence time is the period between actuation of the metered dose inhaler into the spacer device and connection to the multi-stage liquid impinger. To investigate the effective residence time on output from the Fisonair, residence times of 1, 5, 10, and 20 seconds were examined. For example, one actuation was placed in the Fisonair and five seconds later the drug was sucked from the Fisonair through the impinger. This was repeated on five occasions to facilitate chemical assay procedures. Each experiment was repeated on four occasions for the residence times chosen.

Drug assay

After the drug had been drawn into the impinger the various stages were washed out with dihydrochlorofluoromethane and distilled water. The washings were filtered and the sodium cromoglycate crystals collected. Filters were washed quantitatively into 100 ml volumetric flasks. Dihydrochlorofluoromethane washes surfactant from the drug particles. Anhydrous sodium cromoglycate was assayed spectrophotometrically with a wavelength of 356 nm. The spectrophotometer had previously been calibrated with solutions of known concentrations of sodium cromoglycate. The absorbance for a 1% solution using a 1 cm silica cuvette was measured as 166 units.

With the data acquired from the multistage impinger, together with the 50% cutoff diameter for each stage of the device, a plot of aerodynamic size against cumulative percentage undersize was constructed. From this graph the following measurements were calculated: (1) mass median aerodynamic diameter (MMAD) which is the diameter of a droplet such that half of the aerosol mass was contained in smaller droplets and half in larger droplets; (2) geometric standard deviation (GSD) (ratio of the 84.1% diameter to 50% of the MMAD) which is a measure of the width of the droplet distribution; (3) the amount of drug contained in particles < 3 μm and < 5 μm in diameter.

After each study the spacer device and actuator were also washed out to collect any sodium cromoglycate left inside. The total dose from the metered dose inhaler could therefore be determined. When an antistatic agent was used on the spacer device, spectrophotometric assay of the spacer contents was not performed.

A known concentration of sodium cromoglycate was measured spectrophotometrically

Effect of delivery methods of sodium cromoglycate on drug output.

Method of delivery of sodium cromoglycate	Mean (SD) amount of sodium cromoglycate per 5 mg actuation (mg)			
	In particles <5 μ m	In particles <3 μ m	Mean (SD) MMAD (μ m)	Mean (SD) GSD
Directly from metered dose inhalers	0.5(0.06)	0.19(0.02)	10.5(0.05)	1.9(0.004)
Via Fisonair spacer device				
Effect of multiple actuations				
One actuation before inhalation	0.59(0.03)	0.24(0.03)	5.3(0.04)	1.9(0.04)
Two actuations before inhalation	0.41(0.03)	0.21(0.02)	5.48(0.09)	1.93(0.01)
Three actuations before inhalation	0.26(0.02)	0.1(0.01)	5.65(0.15)	1.84(0.03)
Effect of residence time				
No time delay before inhalation	0.59(0.03)	0.24(0.01)	5.3(0.04)	1.9(0.04)
5 second delay before inhalation	0.48(0.06)	0.22(0.03)	4.93(0.04)	1.92(0.06)
10 second delay before inhalation	0.23(0.02)	0.18(0.01)	3.75(0.1)	2.9(0.08)
20 second delay before inhalation	0.2(0.01)	0.11(0.01)	4.7(0.18)	2.17(0.01)
Effect of antistatic lining				
No time delay before inhalation	1.44(0.2)	0.6(0.15)	5.23(0.09)	1.88(0.06)
20 second delay before inhalation	0.52(0.04)	0.24(0.03)	5.25(0.23)	1.88(0.12)

MMAD—mass median aerodynamic diameter; GSD—geometric standard deviation.

on several occasions to determine the coefficient of variation of the assay. Humidity and temperature were measured during the study period.

Results

Lining the spacer with an antistatic agent increased output of sodium cromoglycate to give a 288% and 315% increase in the amount of drug available to the patient in particles < 5 μ m and < 3 μ m diameter respectively compared with drug delivered directly from the metered dose inhaler. Compared with the same spacer without an antistatic lining this represents a 244% and 250% increase in drug output of particles < 5 μ m and < 3 μ m, respectively (table, fig 1).

Sodium cromoglycate recovered from the spacer device decreased with increasing residence time (table, fig 2). A 20 second residence time resulted in a fall in sodium cromoglycate of 67% and 55% in particles < 5 μ m and < 3 μ m, respectively. When an antistatic agent was used to line the spacer the amount of sodium cromoglycate available

for inhalation after a 20 second residence time was increased (table). Compared with a drug residence time of 20 seconds in a spacer device without an antistatic lining there was a 260% and 218% increase in sodium cromoglycate released in particles < 5 μ m and < 3 μ m, respectively (fig 2).

The mean (SD) MMAD and GSD of the aerosol cloud discharged directly from the metered dose inhaler or via the spacer device are shown in the table. Use of the spacer increased the amount of sodium cromoglycate available for inhalation by a mean of 18% (in particles < 5 μ m) and 26% (in particles < 3 μ m) compared with delivery directly from the metered dose inhaler (fig 1).

Multiple actuations into the spacer decreased the amount of drug available per actuation (table). There was a fall of sodium cromoglycate in particles < 5 μ m of 31% per actuation after two actuations, and 56% per actuation after three actuations (fig 3).

The mean (SD) recovery of sodium cromoglycate per 5 mg shot was 4.7 (0.27) mg. The coefficient of variation for the assay of sodium cromoglycate was 2.5%. The mean

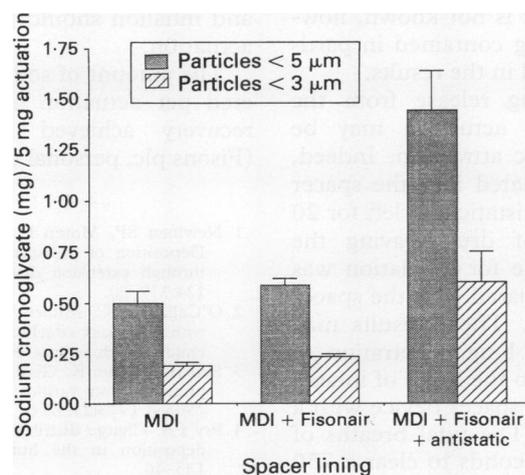


Figure 1 Mean (SD) amount of sodium cromoglycate contained in particles < 5 μ m and < 3 μ m available to the patient when delivered by metered dose inhaler (MDI) alone, via the Fisonair spacer device, or via the Fisonair with an antistatic lining.

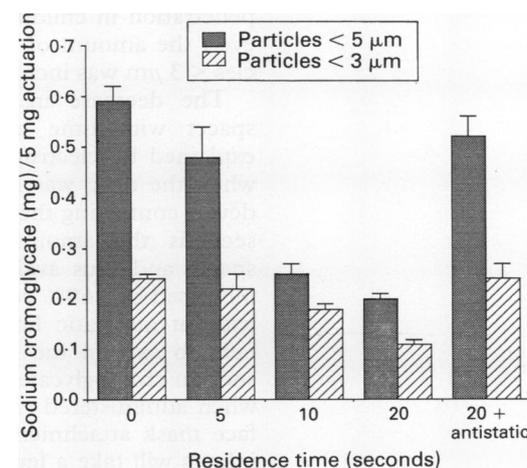
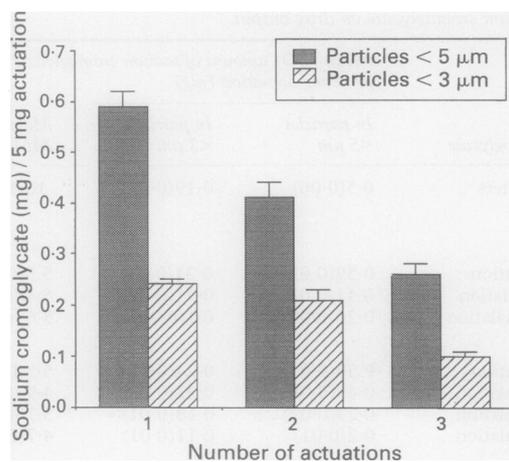


Figure 2 Mean (SD) amount of sodium cromoglycate available to the patient in particles < 5 μ m and < 3 μ m per 5 mg actuation following various lengths of residence time within the spacer. The amount of sodium cromoglycate available at 20 seconds when the spacer was lined with an antistatic agent is also shown.

Figure 3 Effect of multiple actuations into the standard unlined polycarbonate spacer device on mean (SD) amount of drug available per actuation contained in particles $< 5 \mu\text{m}$ and $< 3 \mu\text{m}$.



(SD) humidity over the study period was 55(3)% and the mean (SD) temperature of the room over the study period was 23(2) $^{\circ}\text{C}$.

Discussion

Aerosols produced by atomisation are often highly charged to an extent which is not likely to occur naturally.⁴ Increased particle deposition on surfaces as a result of electric charges on aerosol particles is recognised. The placing of a unipolar electric charge on particles has been found to increase the deposition in the respiratory tract.⁵ In a study of penetration of particles through the human nose Pattle⁶ found that 10–30% of the mass of particles of mass median diameter 0.05–0.4 μm was deposited. He suggested this deposition may be due to electrostatic charges carried by these particles.

We hypothesised that the polycarbonate surface of the spacer device may enhance electrostatic attraction and deposition of drug on the spacer walls. This was confirmed. Use of an antistatic spray increased the drug contained in respirable particles ($< 5 \mu\text{m}$) leaving the spacer by 244%. The ideal particle size for inhalation of drugs is often quoted as $< 5 \mu\text{m}$. As the ideal size of particles for lung penetration in childhood is not known, however, the amount of drug contained in particles $< 3 \mu\text{m}$ was included in the results.

The decrease in drug release from the spacer with time after actuation may be explained by electrostatic attraction. Indeed, when the drug was actuated into the spacer device containing the antistatic and left for 20 seconds the amount of drug leaving the spacer and thus available for inhalation was increased by 260% compared with the spacer without antistatic lining. These results may help to explain the low lung penetration of sodium cromoglycate into the lungs of infants when administered via a spacer device with a face mask attachment.⁷ The tidal breaths of infants will take a few seconds to clear a 750 ml spacer of aerosol during which time the amount of drug available is falling rapidly.

We feel that the use of an antistatic lining for spacer devices will considerably increase drug availability to patients. This has immense implications with regard to clinical benefit from enhanced deposition and also to the cost of treatment. For example, the 5 mg

sodium cromoglycate inhaler is advised to be given in a dose of two actuations twice daily. With the spacer device lined with an antistatic agent only one actuation twice daily may be needed. The antistatic spray in the study should not be used for patients as toxicity may be a problem. Non-toxic antistatic agents suitable for patient use are now available and are under evaluation. It is not possible to say if other drugs will be affected in a similar way. Each drug and alteration of spacer lining will require individual testing.

Actuation of sodium cromoglycate 5 mg inhalers directly into a standard polycarbonate 750 ml spacer device resulted in an 18% increase in dose delivered in the respirable range ($< 5 \mu\text{m}$) compared with direct actuation from a metered dose inhaler. In practice this would mean higher lung deposition of sodium cromoglycate. The greater length of the spacer device compared with the throat results in less impaction of the rapidly moving aerosol.

In paediatric practice it is common for parents and patients to place multiple actuations into the spacer device and then inhale for convenience. Experiments with multiple actuations of sodium cromoglycate (5 mg) into a spacer have shown that there is a substantial decrease in drug released in particles of $< 5 \mu\text{m}$ diameter compared with a single dose delivered from the same device. This may be due in part to a rapid increase in pressure within the spacer with actuations forcing drug from previous actuations on to the wall. In addition, collisions between aerosol particles may be important. The possibility of collision with agglomeration of particles may be reflected by the slight increase of particle size (MMAD) with multiple actuations.

To ensure maximum dosage we found that inhalation from the spacer should take place as soon as possible after actuation. The dose in respirable particles ($< 5 \mu\text{m}$) decreased to less than 50% within 10 seconds of actuation. Subsequent studies with other antiasthma aerosols and spacer devices (unpublished results) support our findings that multiple actuations into the spacer should be avoided and inhalation should follow immediately after actuation.

The amount of sodium cromoglycate recovered per actuation agrees closely with drug recovery achieved by the manufacturers (Fisons plc, personal communication).

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