International Journal of Pharmaceutics, 1 (1978) 205–212

DRUG DEPOSITION OF PRESSURIZED INHALATION AEROSOLS I. INFLUENCE OF ACTUATOR TUBE DESIGN

FOLKE MORÉN

*AB Draco *, Research and Development Laboratories Fack, S-221 01 Lund (Sweden)*

(Received January 13th, 1978)
(Accepted February 1st, 1978)

SUMMARY

The droplet size from a pressurized aerosol is dependent on time for evaporation of the propellants or distance from the actuator orifice. In order to investigate the influence of the evaporation of the propellants five tubes of various lengths and diameters were attached to a conventional inhalation aerosol actuator using Bricanyl, terbutaline sulphate, as a model.

Nine healthy volunteers inhaled eight doses in each test from the conventional actuator alone or combined with the various tubes. The firing of dose was coordinated with the inhalation and for three selected designs the inhalation was voluntarily delayed for 5 sec after the firing. The drug deposited in the actuator, tube and mouth was analyzed spectrophotometrically. It was found that the deposition of drug in the mouth could be reduced significantly by attaching an additional tube to the actuator. The total loss of drug substance in the actuator, tube and mouth could also be reduced significantly indicating the possibility of increasing the availability of drug to the airways. When the inhalation was voluntarily delayed for 5 sec the total loss of terbutaline sulphate in actuator, tube and mouth increased compared to the corresponding tests with coordinated inhalation.

INTRODUCTION

Only a minor part of the dose administered from a pressurized aerosol for inhalation is available for therapeutic effect in the airways, and a major part is swallowed into the gastrointestinal tract both after deposition in the oral cavity and as a result of the mucociliary clearance (Nilsson et al., 1976; Blackwell et al., 1970; Walker et al., 1972).

It is desirable to reduce the high local concentration in the mouth in order to avoid local side-effects (Clark et al., 1975; Connolly, 1975). This could be achieved either by

* Subsidiary to AB Astra, Sweden.

depositing a part of the drug substance before entering the oral cavity, or by increasing the proportion of drug substance inhaled into the airways. An increase in the proportion of drug substance into the airways could also result in a better and more consistent therapeutic effect of the drug administered.

It is well-known that some patients have difficulty in inhaling drugs from pressurized aerosols (Paterson and Crompton, 1976; Arvastston et al., 1976; Orehek et al., 1976). Automatic devices have been designed to overcome the difficulty in coordinating the release of drug and inhalation by releasing the bolus of drug in the early phase of an inspiration. However, the therapeutic effect was not improved by using automatic devices compared to conventional aerosols on trained patients (Thiringer, 1972; Coady et al., 1976). Probably the optimal effect is not obtained with an automatic device as it has been shown that the therapeutic effect was improved when the drug from a conventional pressurized aerosol was inhaled near the end of a deep inhalation compared to the beginning of a deep inhalation (Riley et al., 1976).

In order to investigate the possibility of decreasing the proportion of drug deposited in the mouth and increasing the proportion reaching the airways, tubes of various designs were attached to the conventional actuator and were tested on healthy volunteers. The firing of dose was coordinated with the inhalation. Comparison were also made with delayed inhalation after the firing of the dose to obtain an indication of the importance of the coordination.

MATERIALS AND METHODS

A pressurized aerosol was used giving theoretically 0.25 mg terbutaline sulphate per actuation with the chlorofluorocarbons 11, 12 and 114 as propellants (Bricanyl, AB Draco, Sweden). In the tests the conventional oral actuator was used alone and in combination with straight glass tubes (50 or 100 mm length; 24 or 32 mm inner diameter), as well as a long pear-shaped glass tube (250 mm length; 130 mm maximum inner diameter) (Figs. 1 and 2). The tubes were all provided with 6 openings of 5 mm diameter close to the connection of the actuator. In the tests of delayed inhalation these openings were covered with a Teflon tape to avoid leakage of the aerosol cloud through the openings. The tubes were chosen in order to indicate the importance of different lengths and diameters. The pear-shaded tube was designed to follow the shape of the aerosol cloud when it was leaving the actuator orifice (Morén and Wetterlin, 1976). The volume of the pear-shaped tube was one litre and in all tests it was emptied by two deep inhalations, contrary to the tests with the other tubes and the conventional actuator the small volumes of which were emptied in one deep inhalation.

Nine healthy volunteers were trained to fire the dose at the beginning of a deep inhalation and to exhale outside of the actuator. The volunteers were instructed to close their lips tightly around the tube before the firing of each dose and during the inspiration. When using the pear-shaped tube the exhalation was followed by a second deep inhalation. On each occasion eight doses were administered with an interval of 1 min between each dose. Eight doses were chosen to get sufficient amounts of drug deposited for the analytical assay. The volunteers were instructed not to swallow any saliva during the test, but were allowed to spit out saliva into a beaker. After the eight inhalations the mouth

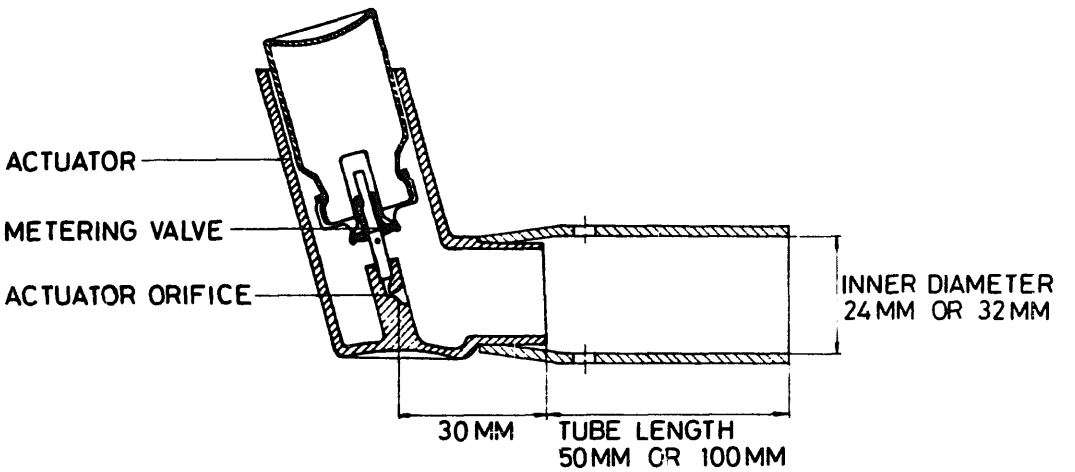

Fig. 1. Pressurized aerosol and conventional oral actuator combined with tubes of 50 or 100 mm length; 24 or 32 mm inner diameter.

was rinsed three times with 10 ml of distilled water and the washings were added to the beaker. In separate studies it was found that 74–88% was kept in the first washing and 93–96% in the sum of the first three washings.

In a second type of test the conventional actuator alone and in combination with the tube of 100 mm length, 32 mm inner diameter and the long pear-shaped tube were also used in a modified way as the firing of the dose was not followed by a deep inhalation until 5 sec after the firing. Otherwise the procedure was the same as described above for the inhalation coordinated with the dose firing. The nine volunteers were tested with each of the nine various ways of inhalation in a random order. After each test the actuator and the tube were washed with ethanol–water 50 : 50 and the mouth washings

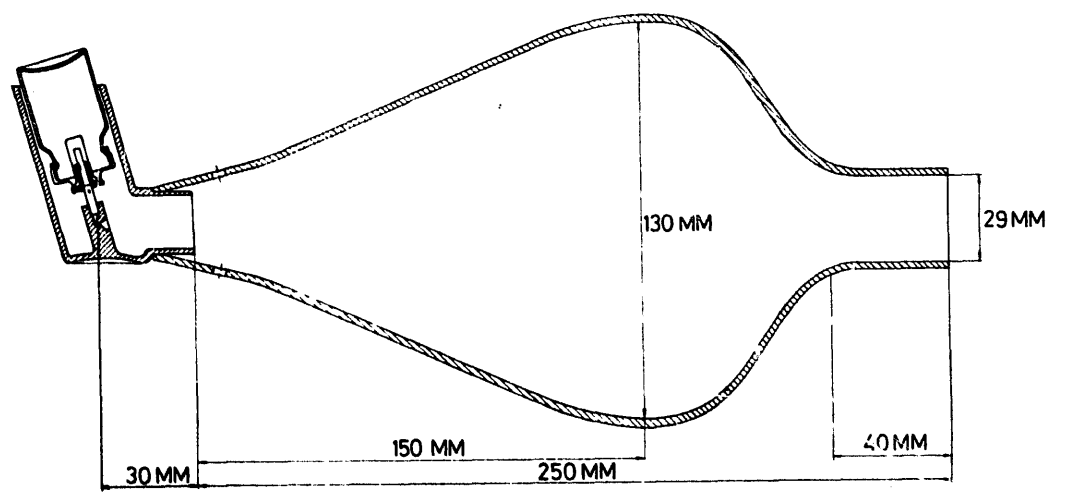

Fig. 2. Pressurized aerosol and conventional oral actuator combined with tube of 250 mm length and 130 mm maximum inner diameter.

were diluted with ethanol to 50 ml. These solutions were spectrophotometrically assayed for terbutaline sulphate after reaction with 4-aminoantipyrine and potassium ferricyanide at pH 9.5 (in principle according to Koshy and Mitchner (1963)). To 2.00 ml of sample solution were added 0.50 ml of 0.16% 4-aminoantipyrine in 1 mol $\cdot l^{-1}$ tris–buffer pH 9.5 and 0.50 ml of 0.64% potassium ferricyanide in 1 mol $\cdot l^{-1}$ tris–buffer pH 9.5. The absorbance was measured at 550 nm after 30 sec.

The percentage retention of terbutalin sulphate in actuator, tube and mouth were calculated based upon the dose delivery by the valve for each aerosol. The dose delivery by the valve was in principle performed as described in the British Pharmaceutical Codex (1973) for Isoprenaline Aerosol Inhalation. Five doses were fired from the valve without actuator into a small beaker containing 20 ml of chloroform. This was transferred to a tube and shaken with 15.00 ml of 0.005 mol $\cdot l^{-1}$ sulphuric acid. The absorbance of the water phase was measured at the maximum for terbutaline, 275 nm, and at 300 nm. The volunteers kept the same aerosol and actuator throughout the tests. The mean dose delivery by the valve was 0.225 (S.D. ± 0.009) mg of terbutaline sulphate determined before the start and at the end of the tests for the aerosols used. The total loss was calculated as the sum of retention in actuator, tube and mouth.

The tests were planned according to the Latin square design with nine tests, nine persons and nine occasions. However, it was found to be unsuitable to use the usual analysis of a Latin square design as the variance was markedly inhomogeneous. The tests were instead divided into two groups with group 1 covering all tests with tubes and with group 2 covering all tests with the conventional actuator. The tests in group 1 were analyzed according to the model for a randomized block design with persons as the block factor. The tests in group 2 were compared by *t*-test, paired comparisons. Paired comparisons were also used to compare a test in group 1 with a test in group 2. The variables terbutaline sulphate in mouth and total loss (sum of terbutaline sulphate in actuator, tube and mouth) were regarded to be of special interest, and therefore these variables were analyzed statistically.

RESULTS

The terbutaline sulphate found in actuator, tube and mouth as well as total loss (sum of amounts in actuator, tube and mouth) after firing of dose in the beginning of a deep inhalation are presented in Table 1 and the results after delayed inhalation in Table 2. The analyses of variance for deposition of terbutaline sulphate in the mouth and total loss are given in Tables 3 and 4.

Deposition in the mouth

For the statistical analysis the tests in group 1 were divided into short tubes (B and D) and long tubes (C, E, F, H and I). Designations are according to Tables 1 and 2. The difference between B and D was significant ($P < 0.05$). Within the group of long tubes there were no significant differences ($P > 0.05$), but the average difference between short tubes and long tubes was significant ($P < 0.001$). There was no significant difference between A and G. The residual standard deviation in group 1 was estimated as 4.25 (df = 48). The difference between one test within group 1 and one within group 2 was always significant ($P < 0.001$).

TABLE 1

PER CENT OF THE DELIVERED TERBUTALINE SULPHATE DOSE FOUND IN ACTUATOR, TUBE AND MOUTH. DOSE FIRED AT THE BEGINNING OF A DEEP INHALATION

Mean values from nine volunteers.

Addition to the standard device	Per cent deposited			
	Actuator	Tube	Mouth	Sum
A. None	6.0	–	47.9	53.9
B. Tube, 24 × 50 mm	6.0	24.9	17.6	48.5
C. Tube, 24 × 100 mm	7.1	38.3	8.9	54.3
D. Tube, 32 × 50 mm	6.8	13.4	22.3	42.5
E. Tube, 32 × 100 mm	6.1	23.1	10.4	39.6
F. Tube, pear-shaped	5.4	17.7	8.1	31.2

TABLE 2

PER CENT OF THE DELIVERED TERBUTALINE SULPHATE DOSE FOUND IN ACTUATOR, TUBE AND MOUTH. DEEP INHALATION FIVE SECONDS AFTER FIRING OF A DOSE

Mean values from nine volunteers.

Addition to the standard device	Per cent deposited			
	Actuator	Tube	Mouth	Sum
G. None	13.2	–	51.4	64.6
H, Tube, 32 × 100 mm	14.3	35.1	6.1	55.5
I. Tube, pear-shaped	8.1	22.1	6.8	37.0

TABLE 3

DEPOSITION OF TERBUTALINE SULPHATE IN THE MOUTH. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; F = variance ratio.

Factor	df	SS	MS	F
Tubes	6	2015	336	18.6 [b]
short (B,D)	1	98	98	5.4 [a]
long (C,E,F,H,I)	4	107	26.7	1.5 NS
short against long	1	1810	1810	100 [b]
Individuals	8	930	116	
Tubes × individuals	48	868	18.1	

[a] $P < 0.05$.
[b] $P < 0.001$; NS, not significant ($P > 0.05$).

TABLE 4

TOTAL LOSS OF TERBULINE SULPHATE. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; F = variance ratio

Factor	df	SS	MS	F
Tubes (B,C,D,E,F,H,I)	6	4457	743	29.2 [a]
Individuals	8	5630	704	
Tubes X individuals	48	1219	25.4	

[a] $P < 0.001$.

The use of an additional tube to the actuator reduced the drug deposition in the oral cavity significantly. The 100 mm long tube was more effective than the 50 mm tube. A further increase as in the 250 mm long pear-shaped tube did not give any significant improvement. The tubes of 32 mm diameter gave higher drug deposition than those of 24 mm but the difference was statistically significant only for the shorter tubes. A voluntary delay of the inhalation by 5 sec did not affect the deposition significantly for any of the three actuator-tube combinations.

Total loss

Statistical analysis showed that there were significant differences ($P < 0.001$) within group 1 (B, C, D, E, F, H and I). Using paired t-tests within group 1 the difference between two average values must exceed 4.8 to be significant at $P < 0.05$, 6.4 to be significant at $P < 0.01$ and 8.3 to be significant at $P < 0.001$. The difference between A and G was almost significant (P close to 0.05). The residual standard deviation in group 1 was estimated as 5.04 (df = 48).

The use of additional tubes of 24 mm diameter reduced the amount of drug deposited in the mouth. However, the total loss was almost at the same level as a corresponding amount deposited on the tube walls. In the wider tubes less drug was deposited, resulting in a lower total loss of drug in actuator, tube and mouth. This fact indicates that more drug reaches the airways when wider tubes were used and the pear-shaped tube appears to be most effective in this respect. The increase in tube length from 50 mm to 100 mm had little influence on the total loss. When the inhalation was delayed for 5 sec after firing of the dose the total loss increased due to higher deposition in the actuator and the tubes.

DISCUSSION

When a dose is fired from the pressurized aerosol a metered volume of propellants containing a suspension of micronized terbutaline sulphate is released through the actuator orifice. However, only a minor proportion of the propellants flashes immediately into vapour as the propellants leave the orifice (Wiener, 1958). The flashing is so rapid that the heat required for the change of phase from liquid to gas is taken from the propellants. Thus the remaining liquid propellant droplets are cooled down. Further evaporation of the liquid droplets occurs during passage through the air as energy is acquired from the

surrounding atmosphere; the rate of evaporation is low compared to the initial flashing. The size of the droplets containing the micronized drug substance thus depends on the time for evaporation of the propellants or distance from the actuator orifice. The impaction of drug substance is dependent on the size and velocity of these droplets as long as the propellants have not evaporated, but after the evaporation of the propellants the impaction is dependent on the particle size and velocity of the micronized drug substance.

In all tests performed the deposited drug substance in actuator, tube and mouth has been analyzed. By constructing the volunteers to close their lips tightly around the oral openings during the tests, precautions were made to avoid leakage of the aerosol cloud before the droplets were inhaled. It cannot be determined if the leakage was completely eliminated but, on the other hand, droplets that possibly leaked out of the mouth after firing of the dose were not easily deposited as they were stable enough to change direction from the original direction of firing without impaction. Therefore, it is not likely that a possible leakage of aerosol droplets out of the mouth would have influenced the amount of deposited drug substance to any major extent.

When firing a dose from a pressurized aerosol into the air it can be seen that the aerosol cloud leaving the actuator orifice is conical in shape. As the distance increases from the orifice the velocity of the droplets decreases. The results in the present study show that the amount of terbutaline sulphate deposited in the mouth after inhalation from a conventional pressurized aerosol can be reduced considerably by the addition of a tube to the actuator. A tube of 100 mm length is more efficient in this respect than a tube of 50 mm, but the diameter also seems to be of some importance. This effect is probably dependent on where the conical aerosol cloud touches the tube wall. When the tube is short a larger proportion of the droplets is impacted in the oral cavity of the tube. The pear-shaped tube was designed to allow a minimum of contact between the conical aerosol cloud and the tube wall in the initial distance. The use of this tube also resulted in a low deposition in the tube considering its length.

It seems to be possible to increase the amount of drug substance into the airways, since the total loss of terbutaline sulphate in actuator, tube and mouth can be influenced by the design of the tube. This effect is probably due to a decreased deposition of the aerosol droplets by allowing further evaporation of the propellants and by reducing initial droplet velocity.

An increased proportion of drug into the airways from each dose could result in a more consistent therapeutic effect. However, it is not only the amount of the drug substance into the airways that could influence the effect but also the particle size. It is assumed that the increasing distance to the oral activity and the more complete evaporation of the propellants could result in a better penetration into the airways. When the pear-shaped tube was used the bolus of drug was released into a volume of one litre. Thus the drug was inhaled with a greater part of the inspiratory volume. According to the investigations performed by Riley et al. (1976) this could be positive for the effect of the drug substance as the airways are better dilated near total lung capacity, which might result in better penetration of particles into the lungs.

When the inhalation of the aerosol was voluntarily delayed for 5 sec the total loss of terbutaline sulphate in actuator, tube and mouth increased significantly, or almost signifi-

cantly, compared to the corresponding tests with coordinated inhalation, but the increase was not as great as expected. It is likely that the lack of inspiratory flow when the dose is fired increases the probability of contact between the droplets in the conical aerosol cloud and the walls of the actuator and tube resulting in higher impaction. However, the amount of drug substance deposited in the mouth was not statistically different from the corresponding tests with coordinated inhalation. For a good therapeutic effect of a substance administered to the airways as a pressurized aerosol it is obviously necessary that the firing of the dose is not followed by an exhalation. However, the coordination of the firing of the dose to the beginning of the inspiratory phase does not seem to be as important as free distance for the aerosol droplets to allow an evaporation of the propellants. The therapeutic importance of decreasing the high local concentration of drug substance in the mouth and increasing the availability of drug substance into the airways will be investigated in clinical tests.

ACKNOWLEDGEMENT

I am grateful to Dr. C.J. Lamm who performed the statistical analysis.

REFERENCES

Arvastson, B., Björkander, J., Eklundh, G., Korsgaard, R., Pelkin, S., Riebe, I., Simonsson, B.G., Stiksa, G. and Werner, S., Hur tar patienten sin bronkdilaterande dos-aerosol? Lärkartidningen, 73 (1976) 1407–1409.

Blackwell, E.W., Conolly, M.E., Davies, D.S. and Dollery, C.T., The fate of isoprenaline administered by pressurized aerosols. Br. J. Pharmacol., 39 (1970) 194P–195P.

British Pharmaceutical Codex 645–646 (1973).

Clark, T.J.H., Costello, J.F. and Soutar, C.A., The effects of beclomethasone dipropionate aerosol given in high doses to patients with asthma. Postgrad. Med. J., 51, Suppl. 4, (1975) 72–75.

Coady, T.J., Davies, H.J. and Barnes, P., Evaluation of a breath actuated pressurized aerosol. Clin. Allerg., 6 (1976) 1–6.

Connolly, C.K., Methods of using pressurized aerosols. Br. Med. J., 3 (1975) 21.

Koshy, K.T. and Mitchner, H., Colorimetric determination of phenylephrine using 4-aminoantipyrine. J. Pharm. Sci., 52 (1963) 802–803.

Morén, F. and Wetterlin, K., Swedish Patent Application No. 76 12 448–6 (1976).

Nilsson, H.T., Simonsson, B.G. and Ström, B., The fate of ^{3}H-terbutaline sulphate administered to man as an aerosol. Eur. J. Clin. Pharmacol., 10 (1976) 1–7.

Paterson, I.C. and Crompton, G.K., Use of pressurized aerosols by asthmatic patients. Br. Med. J., 1 (1976) 76–77.

Orehek, J., Gayrard, P., Grimaud, Ch. and Charpin, J., Patient error in use of bronchodilator metered aerosols. Br. Med. J. 1 (1976) 76.

Riley, D.J., Weitz, B.W. and Edelman, N.H., The responses of asthmatic subjects to isoproterenol inhaled at differing lung volumes. Am. Rev. Respir. Dis., 114 (1976) 509–515.

Thiringer, G., Klinisk prövning av isoprenalin autohaler. Läkartidningen, 69, Suppl. 1 (1972) 6–8.

Walker, S.R., Evans, M.E., Richards, A.J. and Paterson, J.W., The clinical pharmacology of oral and inhaled salbutamol. Clin. Pharmacol. Ther., 13 (1972) 861–867.

Wiener, M.V., How to formulate aerosols to obtain the desired spray pattern. J. Soc. Cosmet. Chem., 9 (1958) 289–297.