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CHARACTERIZATION OF DOSE DELIVERY AND SPRAY PATTERN OF A METERED-DOSE FLUNISOLIDE NASAL SPRAY

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ABSTRACT

Flunisolide is a synthetic fluorinated corticosteroid with significant anti-inflammatory and anti-allergic activities. Flunisolide nasal solution (Nasalide®) is delivered by a unique pump-activated, non-propellant, metered-dose device. A previous paper (1) reported droplet size characterization of the nasal spray by a cascade impactor. This report describes the remaining physical characterizations, namely dose delivery and spray pattern, of this metered-dose delivery system as well as the suitability of the system for a therapeutic corticosteroid nasal solution.

Actuation of flunisolide nasal spray units by 10 subjects over time demonstrated good constancy of dose delivery for up to

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24 days of use. The average dose delivery was 0.737 ± 0.040 gm/day (grand mean ± s.d.).

Actuation of similar units by 17 subjects over time showed good constancy of spray pattern, which was defined as the long and short diameters of the impaction pattern of the spray on a TLC plate, for the entire lifetime of the unit.

INTRODUCTION

Flunisolide (6α-fluoro-11β,16α,17,21 tetra-hydroxy-pregna-1,4-diene-3,20-dione-16,17-acetonide) is a synthetic fluorinated corcitosteroid with significant anti-inflammatory and anti-allergic activities. Flunisolide nasal spray (Nasalide®) produces the desired therapeutic action of corticosteroid in the nasal mucosa via topical application in the treatment of allergic rhinitis. The delivery system of Nasalide® is a unique pump-activated, non-propellant, metered dose device that delivers a gentle spray of solution mist to the nostril. The device consists of four basic elements: a plastic bottle, a cap, a pump, and a shroud (plus its dust cap). Flunisolide nasal solution is packaged in a plastic bottle and capped, with the pump and shroud presented unassembled. At the time of dispensation by the pharmacist to the patient, the original cap is removed from the bottle and discarded, and the pump/shroud system is assembled onto the bottle.

The system is operated by rapid, firm finger and thumb pressure on the shroud and the base of the bottle, which forces a

metered amount of drug solution up through the actuator to exit as a fine spray at the orifice. Metering is accomplished by the length of stroke of the pump piston which forces the drug solution through the orifice. The design of the meter chamber and the sealing action of the steel ball upon release of the actuator provide a fixed volume of drug solution for dosing. Each actuation of the pump system administers approximately 100 µl of solution. The solution consists of flunisolide (0.25 mg/ml) in an aqueous vehicle containing propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate and benzalkonium chloride. To the authors' knowledge, Nasalide® is the first non-fluorocarbon metered-dose nasal solution in the U.S. market.

For a metered-dose nasal spray, there are at least three major physical characteristics to be concerned: (a) the droplet size of the spray; (b) the dose delivery of the spray; and (c) the spray pattern. The droplet size affects both efficacy and extent of possible side effects because small droplets can reach lower respiratory system while large droplets are localized in the nose (2-4). The dose delivery certainly has profound effect on the therapy. The spray pattern can influence the deposition of droplets in the nasal cavity. Moreover, the spray pattern was found to be a useful test for detecting defects in size and shape of the actuator orifice of the spray unit (5, 6). A previous paper (1) reported droplet size characterization of the nasal spray by a cascade impactor. This report describes the remaining physical characterizations, namely the dose delivery and the

spray pattern, of this metered-dose delivery system as well as the suitability of the system for delivering a therapeutic corticosteroid nasal solution.

EXPERIMENTAL

Dose Delivery Study

Ten subjects were each supplied with 25 ml of flunisolide nasal solution in a complete pump unit. The subjects were instructed to actuate their nasal spray units into inverted beakers 4 sprays in the morning and 4 sprays in the afternoon (the direction of use for Nasalide® is 4 sprays, 2 sprays each nostril, b. i. d.) on consecutive working days until the units ceased delivery. The weight difference of a spray unit before and after the 4 consecutive sprays was determined every morning and afternoon, using an analytical balance[1].

Spray Pattern Study

Seventeen subjects were each supplied with 25 ml of flunisolide nasal solution in a complete pump unit. The subjects were instructed to actuate their nasal spray units in the same manner as in the delivery study above. The spray pattern was measured on every other day of use.

Measurement of the Spray Pattern

A three-walled Plexiglas® chamber was made to house the nasal spray unit and a TLC plate[2], as shown in Figure 1. The

[1]Arbor Electronic Balances, Arbor Lab., Inc., Palo Alto, CA 94303.

[2]Precoated 250 μm thick Silica Gel GF, Uniplate, Newark, DE 19711

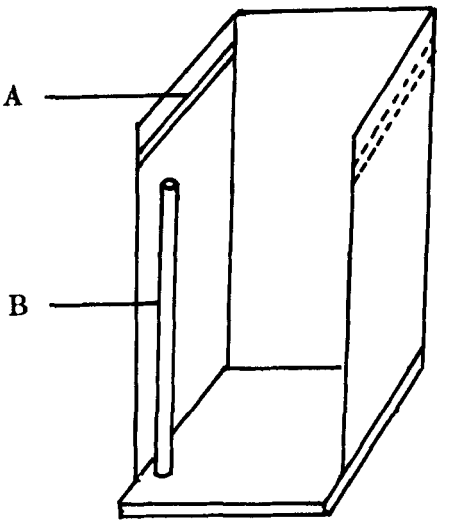

FIGURE 1. Plexiglass spray chamber. Dimensions are 20.5 X 20.5 X 50 cm. Key: A, shelf to hold TLC plate; B, side rod to clamp the nasal spray unit.

plate rested face down at the top of the chamber. The spray unit was clamped to a side rod such that the unit pointed vertically at the center of the TLC plate at a distance of 20 cm. Four sprays were sprayed onto the plate, and the resultant spot on the TLC plate was visualized under UV light, with a Polaroid picture being taken immediately.

The outline of the spot was copied from the Polaroid photograph (Figure 2) to a transparent sheet. The diameter was then measured and converted to true dimension using suitable calibration (a photograph of a ruler taken under identical conditions was employed in this study). Because of the somewhat irregular shape of the spot, both the longest and the shortest diameter (which will be referred to as the long and the short

FIGURE 2. A photograph of the spray pattern on the TLC plate with the long (11.0 cm) and short (7.0 cm) diameters indicated. The central region of the spray showed less optical density because of the artifact of light relection on a wet surface. When visualized under UV light by naked eyes, the region showed the strongest absorption.

diameter in the following text) passing through the same geometric center were measured.

RESULTS AND DISCUSSION

Dose Delivery

Results of the delivery study are shown in Figures 3 and 4. Figure 3 shows the day-to-day delivery variability as a function of time of the delivery data. Each data point represents a mean delivery per day (by summing up the morning 4 sprays and the afternoon 4 sprays, although they were separately determined) of 10 spray units operated by 10 subjects. Figure 4 shows subject-to-subject variation over time of the same data. Each

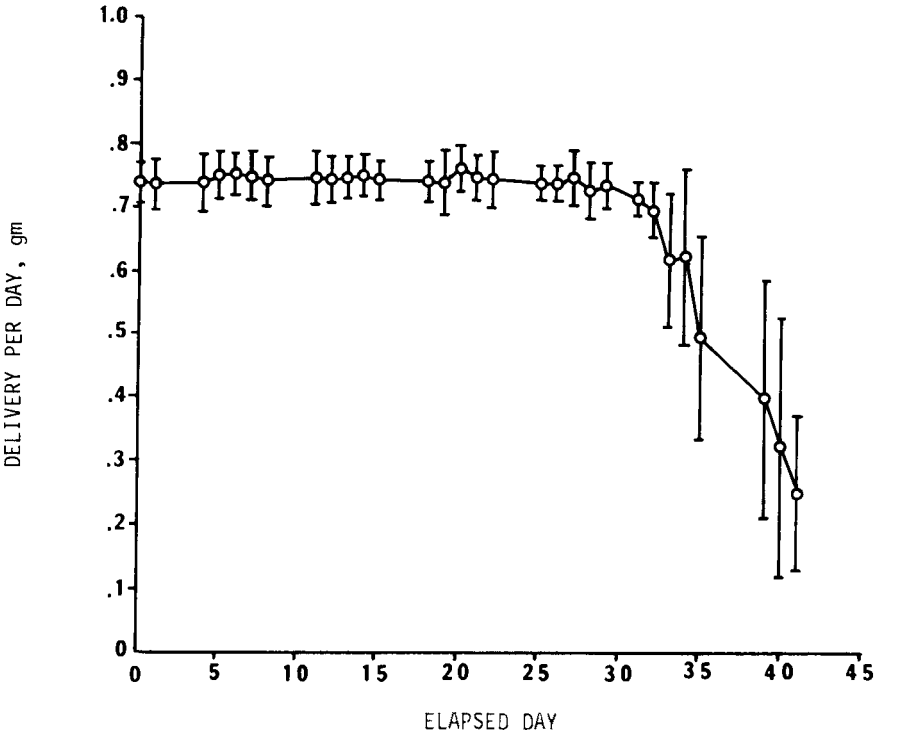

FIGURE 3. Effect of emptying on the dose delivery per day.

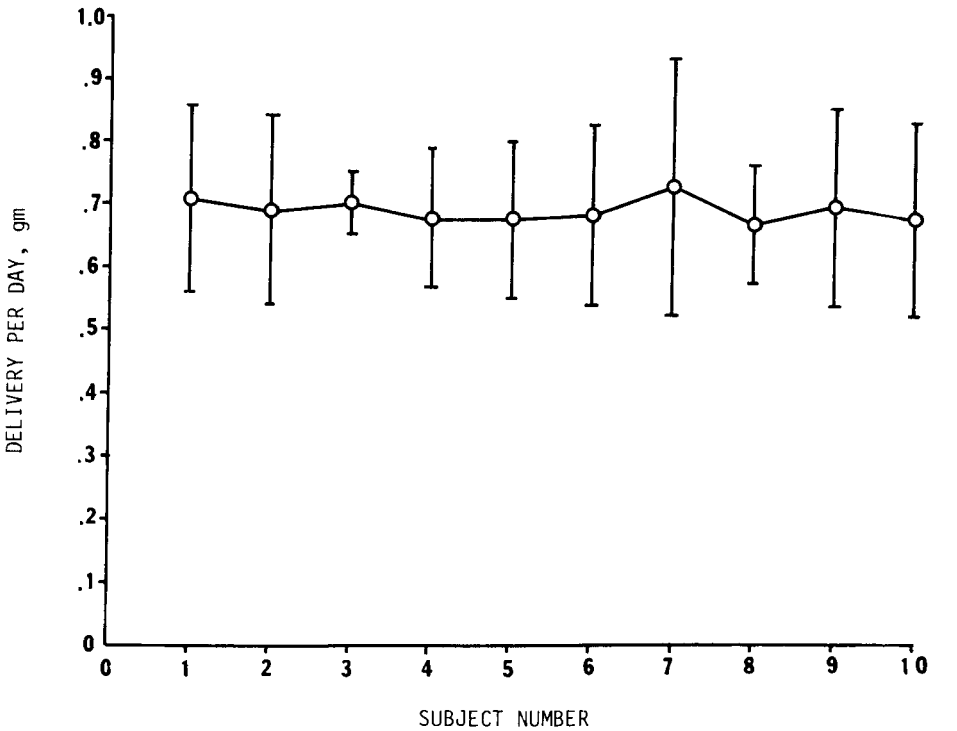

FIGURE 4. Subject-to-subject variation of the dose delivery per day.

data point represents a mean delivery per day of 24 days of use prior to depletion of the unit. The day-to-day variation is seen to be quite small. It is also apparent from Figure 3 that absence of use for several days (i.e. sitting over a weekend) has virtually no effect on the dose delivery. These results are in good agreement with previous data on placebo[3]. The amount of nasal solution delivered was 0.737 ± 0.040 (grand mean ± s.d.) gm/day for up to 24 days of use, after which the effect of depletion is seen in lower mean deliveries and wider standard deviations. The calculated delivery of flunisolide is therefore 177.2 ± 9.6 µg/day based on the concentration (0.025% W/V) and density (1.04 gm/ml) of the formulation.

Duration of Use

Figure 3 reveals that the usage lifetime of the units was approximately 24 days of use. Beyond this period, the delivery per day decreased markedly to below 85% of the average delivery during the first 24 day period. It indicates that the remaining solution (about 3 to 5 ml) is not satisfactorily deliverable from the unit. Consequently, the total number of sprays per unit was approximately 200, representing roughly 20.8 gm (20 ml) of formulation deliverable from the unit.

Spray Pattern

Figure 5 shows the effect of emptying on the long and short diameters of the spray pattern delivered by the 17 subjects over the lifetime of the units. It is apparent that the spray pattern

[3]Unpublished data.

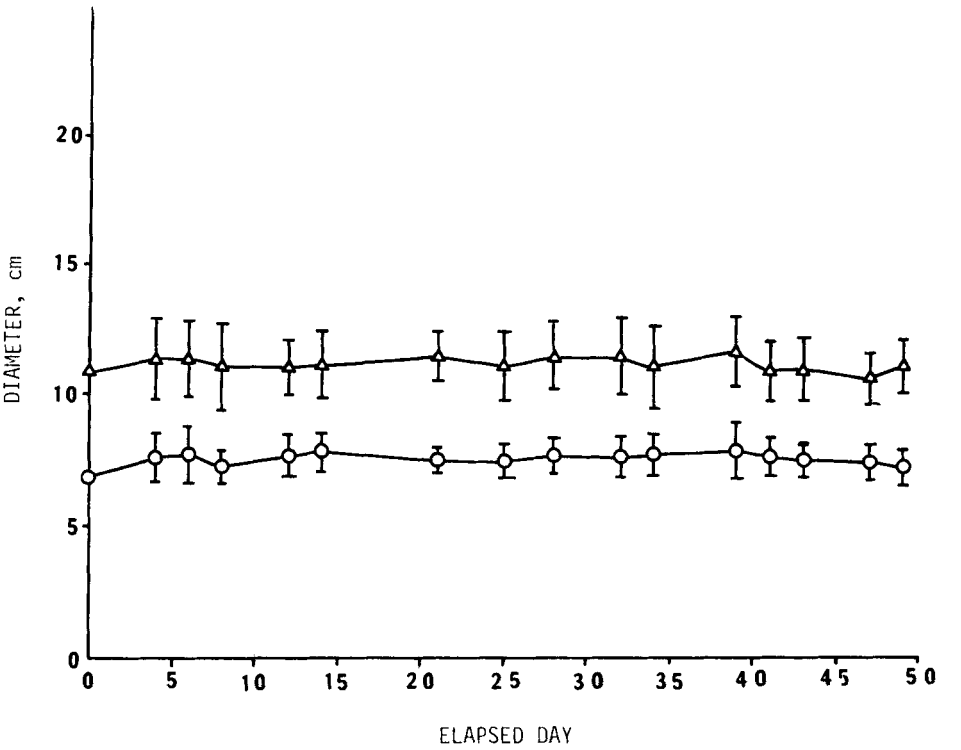

FIGURE 5. Effect of emptying on the spray pattern. Key: Δ, long diameters; O, short diameters; bar represents one standard deviation.

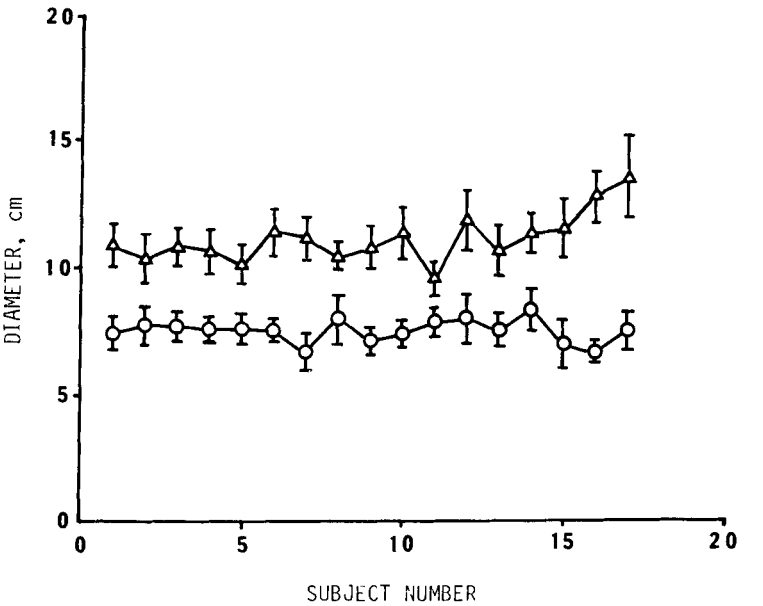

FIGURE 6. Subject-to-subject variation of the spray pattern. Key: Δ, long diameters; O, short diameters; bar represents one standard deviation.

as defined by the long and the short diameters remains essentially constant over time. Subject-to-subject variation is shown in Figure 6, which is a plot of the diameter averaged over day-of-use versus the subject code number. Comparison of Figures 5 and 6 reveals that, in general, the subject-to-subject variability is greater than the day-to-day variability. The mean diameters (grand mean $\pm$ s.d.), 11.1 $\pm$ 1.3 cm and 7.5 $\pm$ 0.8 cm for the long and short diameter respectively, are in good agreement with those observed in a stability study[4] of spray pattern.

CONCLUSION

In conclusion, the metered dose delivery system of Nasalide® solution was shown to be satisfactory from the standpoint of its good constancy of dose delivery and spray pattern.

ACKNOWLEDGEMENT

Paper presented at the APHA meeting, Las Vegas, Nevada, April 1982.

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