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Aerosol distribution in the nose

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SUMMARY

Using a cast of the human nose the intranasal distribution of drugs, delivered from pressurized aerosols and nebulizers was studied. The results indicate that a pressurized aerosol should be used twice in each nostril to give an acceptable drug distribution, and also that an automized pump is preferable for a plastic-bottle nebulizer with regard to drug distribution.

INTRODUCTION

In the last decades there has been a steadily increasing use of topically applied aerosol drugs in the treatment of airways diseases. Advanced aerosol technology, correct choise of preservatives, proper knowledge of drug distribution and absorption, as well as investigation of drug-induced changes of histological parameters and mucociliary activity are all prerequisites for a correct topical therapy, offering optimal effect on the disease, with a minimal risk of side-effects. While a series of such studies have been carried out for inhaled aerosols (Iravani and Melville, 1975; Muir, 1972; Stuart, 1973), there is almost a total lack of published reports with regard to intranasal medication. Only few publications have appeared dealing with the effect of preservatives on the nasal mucosa (Mygind et al., 1974), drug effect on the mucociliary transport (Simon et al., in press), absorption of intranasally applied substances (Naumann, 1961), and histological examination of the treated mucosa (Mygind et al., in press). Therefore, a study of intranasal drug distribution was initiated with particular stress on the investigation of freon-propelled, pressurized aerosols, now often used for the medication of the corticosteroid, beclomethasone dipropionat.

MATERIAL AND METHODS

Using a suitable Silastic material, a negative imprint of an adult cadaver nose was taken, and from this a positive plastic cast was made. A plane plastic plate constituted the "septal wall". The cavity of the nasal cast could be closed medially by an additional plastic plate, airtight attached to the cast by an ointment. Posteriorly the cast was connected with a suction pump through a tube, fit for an adaptor, placed in "rhinopharynx". By adjusting the suction pressure, a given air-flow through the artificial nose could be achieved, and

measured using a rhinomanometer (Nasal Resistance Meter, Mercury Electronics, Glasgow). In this way a slow inhalation (25 l/min.), as well as a quick, sniff-like inhalation (50–70 l/min.) could be imitated.

Two types of freon-propelled, pressurized aerosols were tested, one with a valve size of 63 µl (Becotide) and one with 25 µl (Beconase) (Allen and Hanburys). Ordinarily these aerosols deliver 50 µg of the corticosteroid, beclomethasone dipropionate per puff, but in these canisters the drug had been replaced by toluidine blue, which was delivered with similar particle size and with similar air-velocity as the drug (D. Rhodes, Allen and Hanburys, personal communication). To make sure that the active drug and the toluidine blue were distributed in the same way, 100 puffs from a Beconase inhaler were given into the nasal cast. One piece of filter paper (1 × 2 cm), soaked in 30 µl alcohol was placed on that part of the "septal wall", which was hit by a maximum amount of toluidine blue (see Figure 1). Another piece of paper was placed on the lower, posterior part of the "septum", which is an area, not hit by any demonstrable amount of dye. The paper strips were than placed in tubes, containing 150 µl alcohol each. Ten-fold dilution of the eluent fluid were used for McKensie vasoconstrictor skin test for the demonstration of glucocorticoid activity (McKensie and Stoughton, 1962) in two normal persons.

The study was also extended to; (1) A plastic-bottle nebulizer, which delivered

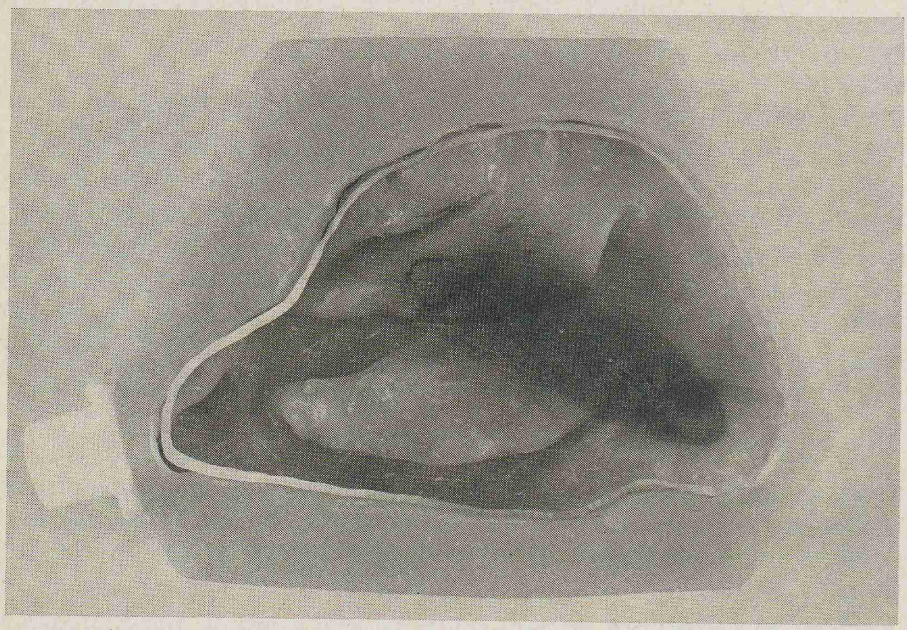

Figure 1. Using a cast of a human nose it is illustrated that toluidine blue and with that the active drug, delivered from a pressurized aerosol (Becotide) almost "hit the mucosa like a bullet from a gun".

about 0.07 ml of a solution per squeeze (Otrivin, CIBA). (2) An automized pump without propellants, delivering a constant fluid volume of 0.14 ml (Lomusal, Fisons). (3) An ordinary drop-bottle, used for the application of ephedrine. Finally, the distribution from a deVilbiss nebulizer no. 15 was studied. One puff of 0.1 ml was given in the upper and one in the lower part of the nose, imitating the procedure used for allergen provocation in studies of drugs inhibitory action on immediate type-I allergic nasal reactions (Mygind et al., 1977).

RESULTS

When the pressurized aerosols were used a white vapour, certainly consisting of the freon gas, was seen in all parts of the nose, leaking out through the "posterior nostril". A very faint blue-colouring of the entire nasal cast, following several hundred puffs indicates that small amounts of toluidine blue might be distributed diffusely in the nose, similar to the freon gas. But it was a consistent finding that the large part of toluidine blue was distributed totally different from the pattern described for the freon. As seen in Figures 1–3 only a narrow zone of the cast, positioned around the lengthened axis of the aerosol adaptor, was hit by any large amount of dye. 100 puffs, each of 50 μg toluidine blue, was necessary to get the staining, illustrated in Figures 1–2.

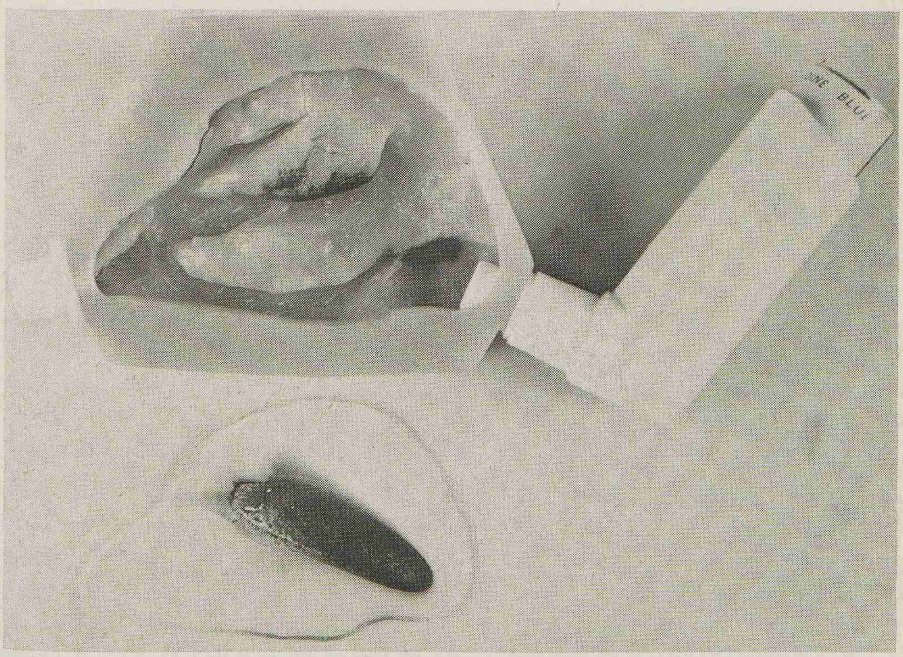

Figure 2. In accordance with ordinary use the nasal adaptor and with that the direction of the drug is turned against the nasal septum, which gives an unwanted, maximal distribution on the nasal wall. The large valve aerosol (Becotide) is used.

Certainly due to a higher linear velocity in the small valve aerosol (Beconase) a slightly larger part of the dye reached the upper and posterior parts of the nose, compared with the large valve aerosol (Becotide), which gave more staining in the anterior part, but in principle, toluidine blue distribution was similar with these two aerosols.

In accordance with general use, the adaptor pointed slightly towards the septal wall, with a 15° deviation from the saggital plane. It is obvious from Figure 2 that this pratice gave an unwanted distribution of the toluidine blue, with the chief part being deposited on the septal wall. Furthermore, the relative small amount of dye on the lateral wall was distributed unevenly due to the characteristic relief, caused by the nasal turbinates.

The small as well as the large valve aerosols were released during slow (25 l/min.) and during quick (50–75 l/min.) "inhalation". This caused no significant changes in the dye distribution. Possibly, the total amount, deposited in the nose was slightly reduced following quick inhalation, but the difference was so slight that it was invisible on the photographs. Figure 3 shows that one puff in the upper and one in the lower part of the nose may distribute the toluidine blue from a pressurized aerosol over a larger "mucosal" surface.

The McKensie tests for the demonstration of glucocorticoid activity were negative for the paper strips, placed on the lower, posterior part of the "septal wall", but positive in dilution 1:100 for the paper strips, placed in the area of maximum dye deposition, which strongly suggests that the active drug is distributed similarly to the toluidine blue.

One squeeze of the plastic-bottle nebulizer, containing 1% toluidine blue, gave a stained area, which compared with the pressurized aerosols, was broader and shorter. As seen in Figures 4 and 5 the delivered amount of dye, as well as its distribution was highly dependent on whether strong or weak hand-power had been used.

Toluidine blue delivered from the automized pump was distributed on large areas of the nasal lining. The stained zone was broad as well as deep, and considerable amounts of dye were deposited on the lateral wall. Some large droplets were seen in the anterior part of the nose (Figure 6).

The direction of the point of a deVilbiss nebulizer was of importance for the distribution of dye, which by and large was identical to that obtained from a vigorously squeezed, plastic-bottle nebulizer, apart from some large droplets in the posterior part of the nose, following use of the deVilbiss nebulizer (Figure 7). When a nebulizer was used the dye reached deeper parts of the nose during simultaneous "inhalation", and a quick sniff-like inhalation was capable of moving already deposited droplets in the posterior direction. When 2–3 drops were delivered from a drop-bottle on "hanging head" only a small part of the nasal lining was reached by the solution (Figure 8.)

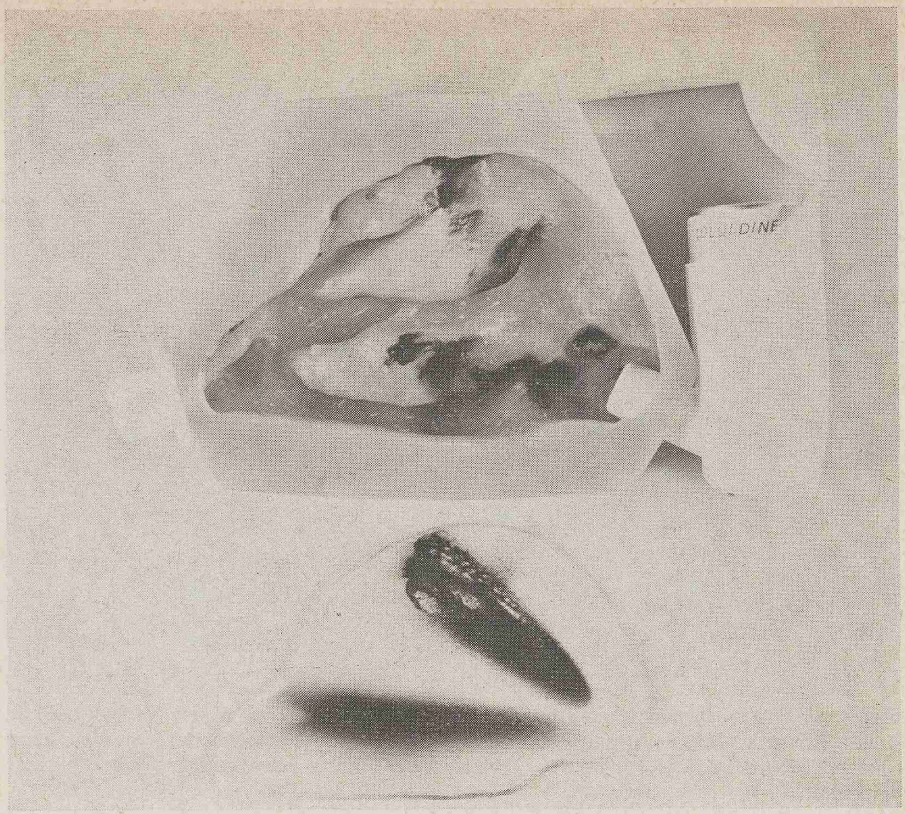

Figure 3. One puff in the upper part and one puff in the lower part of the nose gives a reasonable good drug distribution. The small valve aerosol (Beconase) is used.

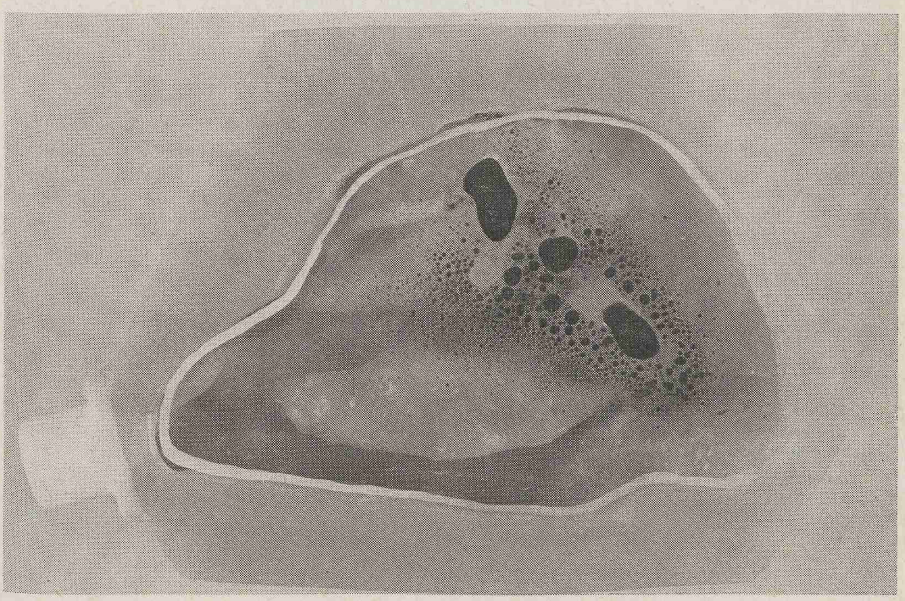

Figure 4. The distribution of a drug, delivered from a plastic-bottle nebulizer is somewhat better than that obtained with a single puff from a pressurized aerosol.

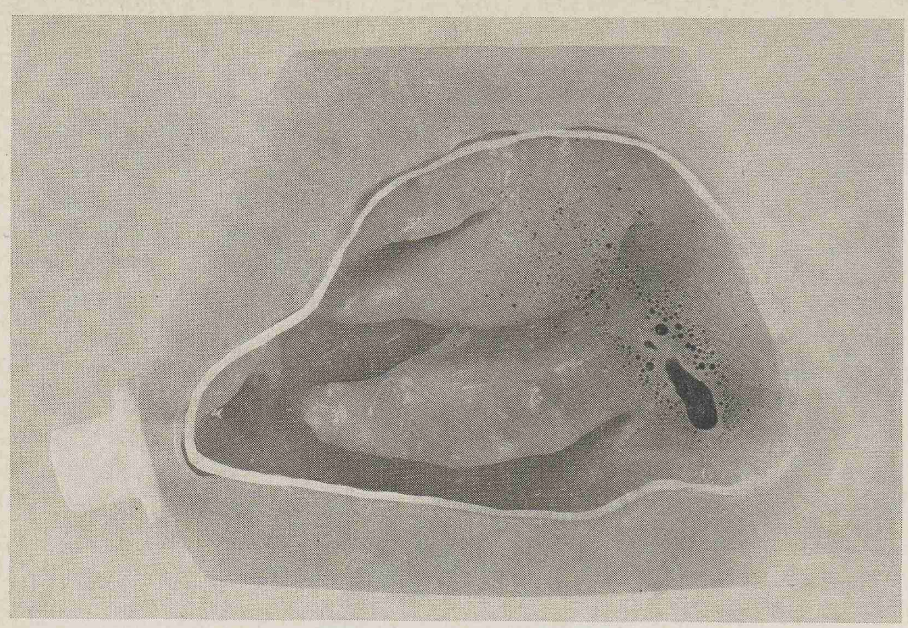

Figure 5. The dosage delivered from a plastic-bottle nebulizer is highly variable. While Figure 4 illustrates the dosage given by "a strong hand", this figure illustrates "a weak hand squeeze". Therefore, a plastic-bottle nebulizer is not suitable when a fairly accurate dosage is required.

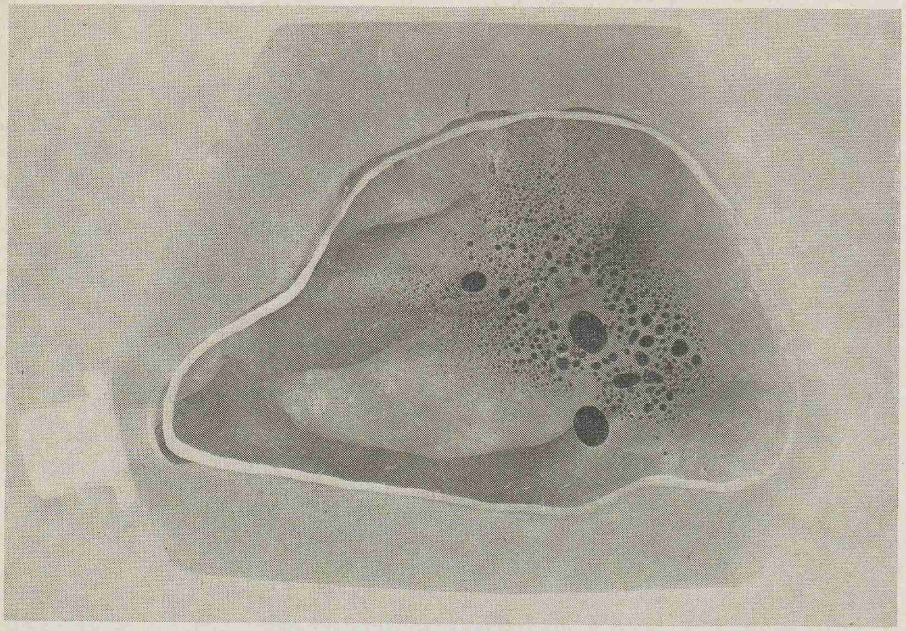

Figure 6. An automized pump gives a constant volume of a solution, which is being distributed efficiently in the nose, also on the lateral wall.

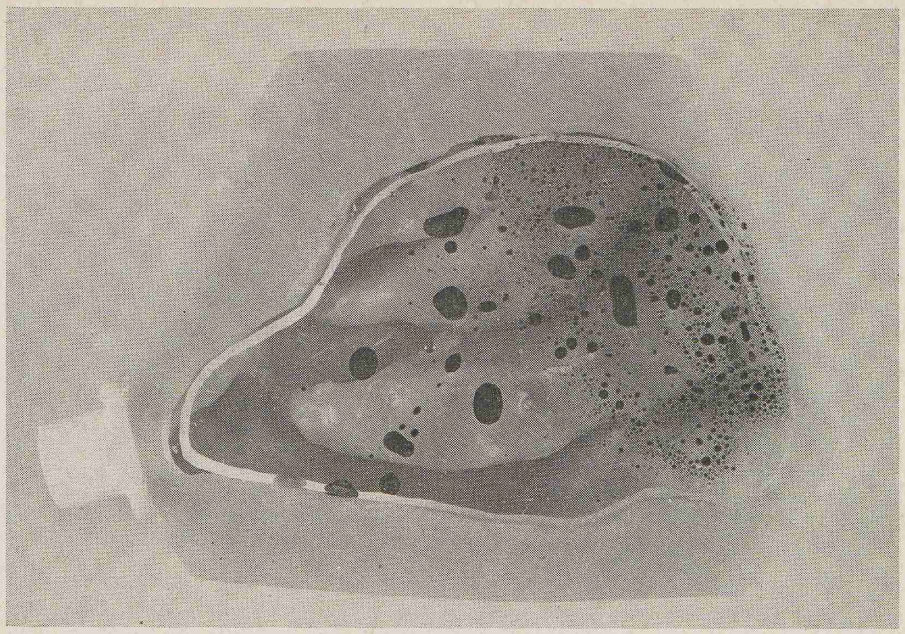

Figure 7. Drug distribution from a deVilbiss nebulizer is quite similar to that obtained with a vigorously squeezed plastic-bottle nebulizer. On the photo the nebulizer has been used in two different directions.

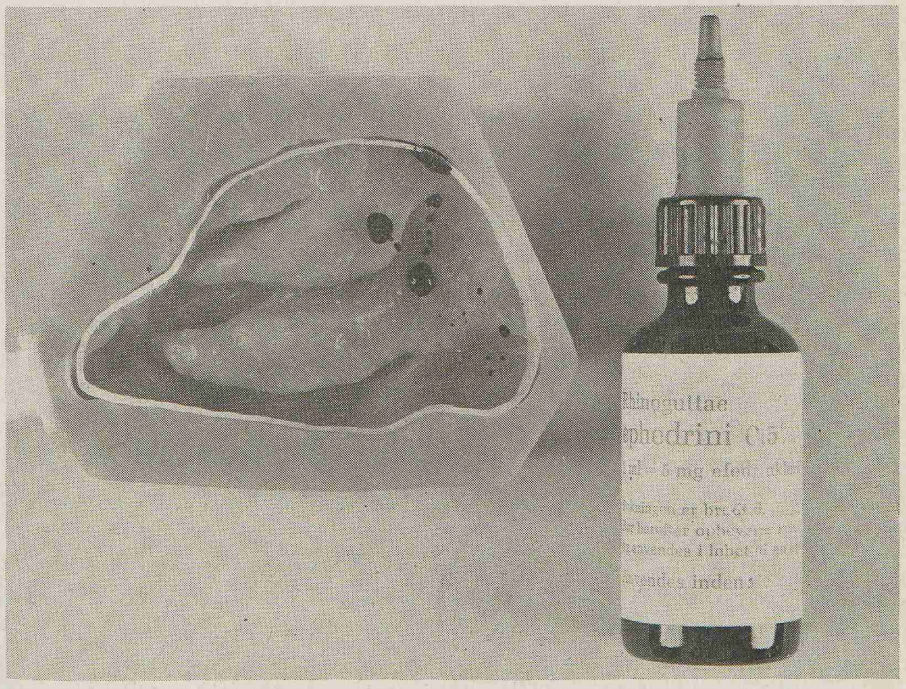

Figure 8. 2–3 drops from a drop-bottle, delivered "on hanging head" are distributed on a very small surface of the nasal cast. Refer to text for interpretation.

DISCUSSION

Differences between our artificial nose and a living, human nose will certainly affect the aerosol distribution. First, the artificial nose is an imprint of a cadaver nose with a blood volume, different from that of the living nose. Therefore, especially the turbinates had a smaller volume in the artificial nose than in most living noses. While the width of the artificial nasal cavity in the upper part was approximated to that of a living nose (2 mm), the width in the lower part (4–6 mm) was larger than that of most noses. Second, the large (18 × 22 mm) entry to the artificial nose and the rigid walls could not imitate the conditions in the living nose, in which especially the narrow, but yielding internal ostium, positioned $1\frac{1}{2}$ cm behind the outer nostril, and its relationship to the aerosol adaptor used, can be of decisive importance for intranasal drug distribution. These two factors tend to give a better drug distribution in the model than in the living nose. But two other factors work in the opposite direction. First, parts of the drug, especially dry particles, delivered from a pressurized aerosol, will be distributed to posterior parts of the nose by ciliary activity. Second, droplets will certainly spread more efficiently on a moist nasal mucosa than on a dry plastic surface.

Although we realise that the artificial nose with regard to these factors differs from the living nose, we found that the study of the artificial nose gave some results, which with due precautions can be applied to the living nose, and which allow us to draw some conclusions of practical relevance.

In contrast to the freon vapour which reached all parts of the artificial nose, it was striking that the chief part of toluidine blue and certainly also of beclomethasone dipropionate delivered from a pressurized aerosol, was concentrated to a narrow band, especially marked on the septal wall. As an even intranasal drug distribution on the lateral wall is wanted, we will as a consequence of the results now recommend the patients to hold the canister strictly in the saggital plane, and instead of one puff into each nostril four times a day, to take one puff in the upper and one in the lower part of the nose twice daily. In this way it should be possible to treat a swollen inferior turbinate as well as a polyp in the upper part of the nose.

Obviously there was no marked difference between the toluidine blue distribution with the large valve and with the small valve aerosol. In order to keep the freon dosage low, the small valve aerosol seems to be the best choise for intranasal use, but with the Beconase used, it is difficult in the living nose to hit the lower part of the nasal cavity, especially the inferior turbinate, which often causes nasal blockage. This could be achieved, if the direction of the adaptor was not upwards, but at right angles to the canister. Therefore, a change of the Beconase canister seems necessary in order to get an optimal drug distribution.

In general the distribution of dye from a plastic-bottle nebulizer was good when

the bottle was squeezed vigorously, but the varying dose, delivered from this type of nebulizer, makes it unsuitable for potent drugs, such as corticosteroids. A better delivery system is the automized pump, which both gives a constant dose and a very good mucosal distribution. As dryness in the anterior part of the nose may follow the use of freon-propelled beclomethasone diproprionate, it can be worthwhile to make an attempt with this drug in a solution, delivered, from an automized pump.

While the freon-propelled dye by and large was unaffected by nasal air-flow, this was not so with the solutions, delivered from a nebulizer or a pump. Therefore, simultaneous inhalation is of importance for these delivery systems. In addition, it may be of value to finish the medication with a quick, sniff-like inhalation to remove the larger droplets from the anterior part of the nose and with that to prevent skin irritation beneath the nostrils due to overspill of fluid.

In previous studies we have used intranasal allergen provocation to investigate the inhibitory activity of topically applied drugs (Mygind et al., 1977). While the allergen in these studies was delivered from a deVilbiss nebulizer with one puff in the upper and one puff in the lower part of the nose, the freon-propelled drug was given merely in one direction. This dissimilarity of mucosal distribution may have been in disfavour of the drug, and the present study has taught us that it is essential in such studies to investigate the distribution pattern of drug as well as of allergen.

The distribution of a few drops from a drop-bottle, which was very poor in the plastic cast, is certainly far better in a living nose with the moist surface. However, the results suggest that a large volume of a weak solution is preferable for a small volume of a concentrated solution. This may be of particular importance when the aim of a topical vasoconstrictor therapy is to increase patency of the orifices of the paranasal sinuses, as already emphasised by Proetz (Proetz, 1953) in his excellent book "Applied physiology of the nose".

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We want to thank Mr. P. Vang Jensen, Rigshospitalet, who made the nasal cast, and Mr. D. Rhodes, Allen and Hanburys, who manufactured the pressurized aerosols, containing toluidine blue.

ZUSAMMENFASSUNG

Mit Verwendung eines Abgusses der menschlichen Nasenhöhle haben wir die intranasale Verteilung von Heilmitteln, die mittels Aerosols und Verstäuber eingeführt wurden, untersucht. Es stellte sich heraus, dass ein Dosier-Aerosol in jeder Nasenhälfte zwei Mal benützt werden sollte um eine akzeptable Heilmittelverteilung zu erreichen, und ausserdem dass eine automatische Pumpe einem Plastikflaschenverstäuber vorzuziehen ist.

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