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Nasal administration of desmopressin by spray and drops

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A solution of desmopressin was administered intranasally as a spray using a metered dose pump, or as drops using a single dose pipette or rhinyle catheter. Volunteers, and patients with diabetes insipidus, were given an intranasal dose of 20 μg desmopressin by each method. The antidiuretic activity was measured by determination of urine osmolality and diuresis. Each delivery system was equally effective in producing a rapid onset of activity, a highly reproducible magnitude of effect and duration of the antidiuretic effect which lasted for more than 8 h. The pipette and spray pump offer a choice of single dose administration without preservative, or for chronic use, well-controlled, reproducible dosing, respectively.

The first examples of intranasal drug therapy were the use of the posterior pituitary hormones and other analogues such as vasopressin (Barltrop 1963), oxytocin (Hoover 1971), and desmopressin (Andersson & Arner 1972). This experience has been extended to the anterior pituitary hormones such as luteinizing hormone releasing hormone (LHRH) (Anik et al 1984) and to other hormones like insulin (Morimoto et al 1985), secretin (Ohwaki et al 1985), and growth hormone releasing hormone (GHRH) (Evans et al 1983).

However, little attention has been paid to the manner in which the drugs are given. Traditionally, preparations have been administered into the nasal cavity for their local action, often in the form of simple nose drops from a dropper bottle, with little need for accuracy of dosing and dosing instructions. The vasopressin analogue, desmopressin (DDAVP), has been used for over a decade for the treatment of diabetes insipidus. It has a potent antidiuretic effect, minimal side effects and lacks the vasopressor effects of its parent molecule (Richardson & Robinson 1985). It is administered intranasally by means of a calibrated catheter tube (rhinyle) but the technique has presented problems to the young, the very old and the partially sighted. Recently, for single dose administration, an intranasal pipette has been developed and for chronic dosing, various metered dose spray pumps have become available. With these new dosage forms it would be useful to know their effect on the clinical efficacy of systemically acting drugs. We have examined three dosage forms of nasal solutions of the peptide desmopressin on the magnitude and duration of its antidiuretic activity.

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Materials and methods

The desmopressin (DDAVP) solutions were prepared under aseptic conditions. Nasal formulations were made up containing 100 μg mL^{-1} desmopressin (Ferring Pharmaceuticals, Malmö, Sweden) in 0·9% sodium chloride (w/v) and, with the exception of the single dose pipette, 0·05% chlorobutanol (w/v).

Desmopressin was administered intranasally using a rhinyle tube, a single dose pipette or a metered dose precompression pump. The rhinyle tube was a calibrated plastic catheter designed to give a dose of 200 μL of solution. The single dose pipette, containing 200 μL of the preservative-free solution, was manufactured using the Bottlepac (Rommelag GmbH, Switzerland) principle of fill, form and seal. The nasal spray pump gave a metered dose of 100 μL solution per actuation (Pfeiffer GmbH, Radolfzell, West Germany).

Intranasal administration. A standard dose of 20 μg of desmopressin was self-administered. The rhinyle tube was first filled then one end was put into the mouth and the other introduced 5–10 mm into the nostril, delivery being accomplished by blowing. The dose from the pipette was administered after the subject's head had been tilted back and individual drops dispensed into the nostril during normal breathing, the head was turned right, left, and then back to the original position. The spray device was primed before use by activating the pump five times then the applicator tip was introduced 5–10 mm into the nostril, and the spray activated twice during normal inhalation, with the contralateral nostril open.

Protocol

Volunteers. Dosing was separated by a week interval. Nasal solutions of desmopressin given by rhinyle and pipette were administered to 5 healthy subjects, four male and one female aged 18 to 43 years. A second experiment compared rhinyle and spray in 10 healthy subjects, six male and four female, aged 18 to 43 years. Each subject was first water-loaded by drinking a volume of tap water corresponding to 1·5% of body weight. At 15 min intervals, the bladder was emptied and the urine volume measured. An equivalent amount of water was then taken by each subject. When the 15 min diuresis exceeded 150 mL 20 μg desmopressin was administered. Urine was collected at 15 min intervals for 8 h. The osmolality of each sample was determined using the freezing point depression method

(Digital Osmometer, Advanced Instruments, Mass., USA).

Patients. Four patients with diabetes insipidus, two male and two female (mean age 44 ± 15 years) were hospitalized for 12 h and regular treatment with desmopressin interrupted. Baseline diuresis was measured every hour. Then at 0800h an intranasal dose of 20 μg desmopressin was given either by rhinyle tube or pipette, the sequence being determined by randomization. Diuresis and urine osmolality was followed at every voiding point. Twenty-four hours later the sequence was repeated using the other delivery system.

Both studies were approved by the local ethical committee and each person gave informed consent.

Statistical methods. Friedman's two-way analysis of variance by ranks and the Wilcoxon matched-pairs signed rank test were used where appropriate.

Results and discussion

Volunteers. Figs 1 and 2 combine the effect of desmopressin on urine volume and urine osmolality. It induced a rapid and prolonged antidiuresis and its effect was not influenced by the choice of intranasal delivery. Antidiuresis of <25 mL min^{-1} occurred at 25·5 ± 6·1 min (rhinyle), 28·5 ± 5·0 min (spray pump) and 26·2 ± 4·7 min (pipette) (n.s.). The maximum antidiuretic effect was 11 ± 2 mL/15 min (rhinyle), 10 ± 1 mL/15 min (spray) and 7 ± 3 mL/15 min (pipette) (n.s.). The effect persisted for at least 8 h. The effect on urine osmolality was also rapid and prolonged. Maximum osmotic concentration was reached within 2 to 3 h and was 917 ± 29 mOsm kg^{-1} (Fig. 1) and 756 ± 50 mOsm kg^{-1} (Fig. 2) (rhinyle), 772 ± 54 mOsm kg^{-1} (spray) and 950 ± 55 mOsm kg^{-1} (pipette) (n.s.).

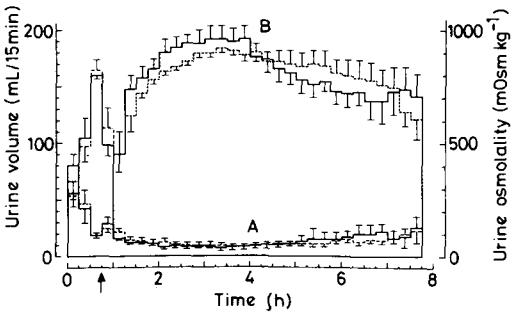

FIG. 1. The effect on (A) urine volume and (B) urine osmolality of an intranasal administration of 20 μg desmopressin (at arrow) by rhinyle tube ——, and pipette – – – each to five hydrated subjects (mean ± s.e.m.).

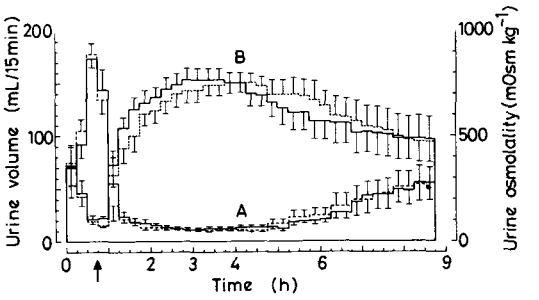

FIG. 2. The effect on (A) urine volume and (B) urine osmolality of an intranasal administration of 20 μg desmopressin (at arrow) by rhinyle tube ——, and spray – – – each to ten hydrated subjects (mean ± s.e.m.).

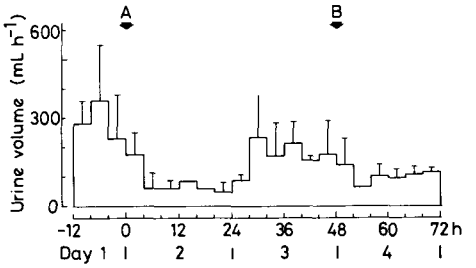

FIG. 3. The antidiuretic effect of an intranasal dose of 20 μg desmopressin by (A) pipette and (B) rhinyle tube to four patients with diabetes insipidus (mean ± s.d.).

Patients. Both delivery systems were equally effective in reducing each patient's water turnover to normal (<100 mL h^{-1}) for up to 24 h in some cases (Fig. 3). The antidiuretic effect was rapid in onset.

In this study no apparent differences were observed between each of the three methods of intranasal delivery of desmopressin. A similar biological response was found in the time to onset, magnitude and duration of its antidiuretic activity.

The intranasal pipette and spray pump offers several advantages over the rhinyle catheter: the pipette may be useful for single dose administration and, as it does not need to contain a preservative, it can be used for patients with known nasal allergy. For example, preservatives such as chlorbutanol are known to cause allergic rhinitis (Itabashi et al 1982). The spray pump is useful for multidose and chronic administration and is an effective system for delivering accurate and reproducible doses.

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Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide

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Buccal absorption of morphine sulphate and morphine-3-glucuronide at various buffer pH values (4 to 10) over 5 min has been investigated in seven and four normal healthy volunteers, respectively. Increasing pH caused an increase in buccal absorption of both. The maximum mean absorption was 37% at pH 10 for morphine and 19% at pH 8 for morphine-3-glucuronide.

The method of buccal absorption was established by Beckett & Triggs (1967) as an example of an in-vivo model of passive drug transfer through a lipid membrane, and although later work has shown that absorption occurs into, rather than across, the buccal membrane (Davis & Johnston 1979), the technique has proved useful in predicting the influence of urinary pH on drug excretion (Muhiddin & Johnston 1981; Muhiddin et al 1984). We investigated the extent of buccal absorption of morphine sulphate and its major metabolite morphine-3-glucuronide in normal volunteers and the influence of pH upon it.

Materials and methods

Eleven volunteers gave their informed consent to participate in the study which had been approved by the local ethics committee.

Buffers. Three different buffer types were used, McIlvaine (citric acid/phosphate) for the pH values of 4, 5, 6, 7, Sørensen (phosphate) for pH 8 and Sörensen (glycine/NaOH) for pH values of 9 and 10 (Documenta Geigy 1975).

Method. Standard samples were prepared from a stock solution of 1000 μg mL^{-1} morphine sulphate and of morphine-3-glucuronides separately in distilled water, and were then diluted to 25 mL in the appropriate buffer to reach a final concentration of 20 μg mL^{-1}, 5 mL of which was kept refrigerated as standard (A). Drug free buffer, 10 mL, was used to rinse the subject's mouth for 10 s before each absorption and then 20 mL buffer containing drug was taken into the subject's mouth and agitated by movement of the cheeks and tongue for 5 min. The solution was then expelled into a plastic container, after which the subject rinsed his mouth for 30 s and these solutions were combined. The end volume was measured and an aliquot stored at −20 °C until analysis. The order in which each subject received the buffer was randomized and a minimum of 24 h elapsed between each buffer. The subjects fasted and refrained from smoking for at least 2 h before each test.

Buccal absorption of morphine sulphate was measured in seven subjects, and that of morphine-3-glucuronide in four subjects.

The estimations of morphine sulphate and morphine-3-glucuronide in the buccal fluids were carried out by centrifuging 2 mL of the buccal samples in plastic tubes for 10 min, and injecting 100 μL aliquots into the chromatograph.

Chromatographic conditions. The chromatographic system consisted of a Rheodyne model syringe loading sample injector with a 50 μL loop (model 7125 Rheodyne, Berkeley CA, USA). The column was 10 μm micro bond pack C18 30 × 3·9 mm, the solvent delivery system was a Spectroflow 400 pump (Kratos Analytical Instruments) and the solvent flow rate was 1·5 mL min^{-1}. A spectroflow monitor SF 770 UV-detector at wavelength 210 nm. (Schoeffel Instrument-Corp) was used to measure morphine, and a FS 970 fluorometer at an excitation wavelength of 210 nm (Kratos) was used for morphine-3-glucuronide. A computing integrator (Pye Unicam CD4) was used to derive the chromatographic data.

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