

NASAL ADMINISTRATION OF DESMOPRESSIN

FIELD OF THE INVENTION

5 The present invention relates to nasal administration of desmopressin, desmopressin acetate and other pharmaceutically acceptable desmopressin salts, and to optimal compositions for such administration.

10 BACKGROUND OF THE INVENTION

 Nasal administration is an attractive route for delivery of therapeutic peptides. However, the art is deficient in optimal conditions for intranasal deposition of peptide drugs which have to
15 overcome the nasal mucosal barrier, enter the systemic circulation and be delivered, in effective form, to intended peripheral target organs. In addition, most of the known peptides suitable for nasal administration are expensive, and the current trend is wasteful "over" delivery of such expensive nasal peptides. There is thus a
20 need in the art for improvements in nasal peptidal administration.

 Dispensing volumes lower than 50 μ l by nasal pump is reported as being unacceptable as dose accuracy and probability of effective delivery to target organs is not assured; on the other hand, a higher volume, over 150 μ l, is considered in the art as unsuitable
25 as this is known to lead to flooding: F. Morén, *Aerosols in Medicine*. Morén et al., Eds., page 346, Elsevier Scientific, Amsterdam (1993).

 There is a need for accurate delivery and an economical system for effective nasal administration of peptides. In
30 particular, a need exists for an accurate and optimal delivery system for effective nasal administration of desmopressin (hereinafter also "DDAVP").

OBJECTS OF THE INVENTION

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 It is an object of the invention to provide a single dose pharmaceutical composition of desmopressin, desmopressin acetate or other pharmaceutically acceptable desmopressin salts for nasal administration, which composition is an improvement, providing
40 optimal, effective delivery to peripheral targets.

 It is another object of the invention to provide an aqueous stock solution of desmopressin, desmopressin acetate or a salt

of desmopressin.

A further object is to provide a means for nasal administration of an aqueous stock solution of desmopressin, desmopressin acetate or other pharmaceutically acceptable desmopressin salts, for repeated and consistent dispensation of a volume of 5 to 75 μ l, more preferred a volume from 10 to 50 μ l, and in particular a volume of about 20 to 45 μ l.

Yet another object is to provide a method for nasal administration of desmopressin, desmopressin acetate or other pharmaceutically acceptable desmopressin salt in a convenient manner such that consistent, effective concentrations are delivered to the plasma of a patient.

An additional object of the invention is to provide a method for manufacture of a medicament for treating urinary disorders selected from the group consisting of diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis.

These and other objects will be apparent to those skilled in this art after having the benefit of this disclosure.

SUMMARY OF THE INVENTION

For purposes of this description, desmopressin (DDAVP) is 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin. The term "nasal" comprises the term "intranasal" meaning, in context, the delivery of drugs through the nasal mucosa.

The invention includes a single dose pharmaceutical composition for nasal administration comprising an aqueous solution having a volume of from about 5 to about 75 μ l, with the solution containing from about 0.1 to about 2.0 mg/ml of a compound selected from desmopressin, desmopressin acetate or a pharmaceutically acceptable salt of desmopressin. The solution can have a volume of from about 10 to about 50 μ l; from about 20 to about 45 μ l; or about 35 μ l. The compound is from about 0.1 to about 0.5 mg/ml or about 0.5 to about 2.0 mg/ml in the solution.

Also included in the invention is a means for delivery in conjunction with a nasal spray pump or a device for dropwise nasal administration for repeated dispensation of a volume from about 5 to about 75 μ l of an aqueous solution containing from about 0.1 to about 2.0 mg/ml of desmopressin, desmopressin acetate or a pharmaceutically acceptable desmopressin salt. The solution in the delivery means has a volume of from about 10 to about 50 μ l; from about 20 to about 45 μ l; or about 35 μ l.

Another aspect of the invention is a method for delivery of consistent plasma levels of nasally administered desmopressin, desmopressin acetate or a pharmaceutically acceptable desmopressin salt, at from about 10 to about 50 μ l of an aqueous solution containing desmopressin, desmopressin acetate or a pharmaceutically acceptable desmopressin salt in the range of from about 0.1 to about 2.0 mg/ml in the solution. The method is useful for treating urinary disorders such as diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 depicts the graphical results of research associated with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, single doses of pharmaceutical compositions in the form of aqueous solutions having a volume of from 5 to 75 μ l and containing from 0.1 to 2.0 mg/ml of desmopressin, desmopressin acetate or a molarly corresponding amount of a pharmaceutically acceptable salt thereof, are provided.

The compositions of the present invention are useful for the management of various urinary disorders such as those associated with diabetes insipidus, incontinence and enuresis, in particular, nocturnal enuresis.

The aqueous solution preferably has a volume of 10 to 75 μ l. More preferred is a volume of from 15 to 50 μ l, and in particular, a volume of about 20 to 45 μ l. Independent of the preferred volumes for the aqueous solution, it is preferred for the concentration of desmopressin to range from 0.1 to 0.5 mg per ml, or from 0.5 to 2.0 mg per ml.

According to the invention, a sealed container specific for use with a nasal spray pump or a device for dropwise nasal administration is provided, for repeated dispensation of a volume of 5 to 75 μ l, more preferred a volume from 10 to 50 μ l, and, in particular, a volume of about 20 to 45 μ l, of an aqueous stock solution of desmopressin, desmopressin acetate or other pharmaceutically acceptable desmopressin salt.

The sealed container dispenses single, consistent doses of a stock solution containing from 0.1 to 0.5 mg per ml or from 0.5 to 2.0 mg per ml of desmopressin acetate or a molarly corresponding

amount of desmopressin or other suitable, pharmaceutically acceptable salt of desmopressin. The spray pump or the device for dropwise administration may be integrated with the container and be disposable. The spray pump is preferably of the precompression type and designed for delivery of a volume within the range of from 5 to 75 μ l.

The single dose composition and the stock solution according to the invention may contain osmotic-pressure controlling agents such as sodium chloride; preservatives such as chlorbutanol or benzalkonium chloride; a buffering agent such as sodium phosphate or sodium citrate buffers designed to maintain a pH from about 4 to about 6, preferably of about 5; and absorption enhancing agents such as bile salts, monolauryl ethers of macrogols and fusidate derivatives.

Other pharmaceutically acceptable solutions and compositions in sealed containers for use with a spray pump or a device for dropwise nasal administration for dispensation of a single dose of a pharmaceutical composition of desmopressin, desmopressin acetate or other pharmaceutically acceptable desmopressin salts in molar ranges equivalent to those herein described are well within the scope of this disclosure.

Also disclosed is the manufacture of a medicament for treating urinary disorders selected from the group consisting of diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis, the medicament comprising a compound selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable desmopressin salt, the medicament comprising from about 10 to about 75 μ l of an aqueous solution containing said compound in the range of from about 0.1 to about 2.0 mg/ml of said solution.

The invention is based on the finding that intranasal administration of desmopressin acetate at a concentration of about 1.5 μ g/ μ l gives rise to essentially the same desmopressin concentration profile in plasma independent of the amount administered over a range from 25 to 100 μ l for adults and is equally effective as such a range of administration. This pattern extends to even lower volumes for adults, such as a volume of 10 to 15 μ l, and for children, to a volume below 10 μ l, such as a volume of about 5 to 7 μ l.

Presently available metering spray pumps on the market are not useful for reproducible dispensation of volumes below about 50 μ l. This is due to lack of incentive for developing and

marketing such pumps because the volume/concentration/desmopressin plasma level relationship according to the invention is being disclosed uniquely for the first time by this description.

5 The following example demonstrates the independence of the effect of plasma desmopressin from the administered volume of a desmopressin solution of given desmopressin acetate concentrations.

EXAMPLE

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A stock solution containing 0.3 mg desmopressin acetate per ml in distilled water was prepared. Varying doses of this stock solution were administered to six healthy male volunteers.

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Administration was in the form of nasal spray by using metered spray pumps provided with nebulizer heads.

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The following dosages were administered to each nostril of each human volunteer: 75 µg in 25 µl, 150 µg in 50 µl, 210 µg in 70 µl, and 300 µg in 100 µl. The combined results are summarized by the graph depicted in Fig. 1. Whereas individual variations were present in the desmopressin plasma profile, the dose volume/plasma profile relationship was essentially the same for all tested individuals.

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Fig. 1 shows that, within the dosage range investigated, the plasma level effect is not dependent on the administered volume of a desmopressin solution of a given desmopressin acetate concentration (1.5 µg/µl). This relationship also holds for a broader range of concentrations, such as from 0.1 µg/µl to 2 µg/µl, and for desmopressin and pharmaceutically acceptable salts of desmopressin other than the acetate.

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Various modifications and alterations to the present invention may be appreciated based on a review of this disclosure. These changes and additions are intended to be within the scope and spirit of this invention as defined by the following claims.

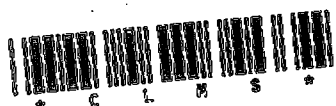
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C l a i m s

1. A single dose pharmaceutical composition for nasal administration comprising:
 - 5 an aqueous solution having a volume of from about 5 to about 75 μ l; and
 - said solution containing from about 0.1 to about 2.0 mg/ml of a compound selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable salt of desmopressin.
- 10 2. The composition of claim 1, wherein said solution has a volume of from about 10 to about 50 μ l.
- 15 3. The composition of claim 1, wherein said solution has a volume of from about 20 to about 45 μ l.
4. The composition of claim 1, wherein said solution has a volume of about 35 μ l.
- 20 5. The composition of claim 1, wherein said compound is from about 0.1 to about 0.5 mg/ml in said solution.
- 25 6. The composition of claim 1, wherein said compound is from about 0.5 to about 2.0 mg/ml in said solution.
7. A means for delivery in conjunction with a nasal spray pump or a device for dropwise nasal administration for repeated dispensation of a volume from about 5 to about 75 μ l of an aqueous solution containing from about 0.1 to about 2.0 mg/ml of desmopressin, desmopressin acetate or a pharmaceutically acceptable desmopressin salt.
- 30 8. The means of claim 7, wherein said solution has a volume of from about 10 to about 50 μ l.
- 35 9. The means of claim 7, wherein said solution has a volume of from about 20 to about 45 μ l.
- 40 10. The means of claim 7, wherein said solution has a volume of about 35 μ l.



11. A method for delivery of consistent plasma levels of a peptide compound, comprising nasal administration of said compound which is selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable desmopressin salt, at
5 from about 10 to about 75 μ l of an aqueous solution containing said compound in the range of from about 0.1 to about 2.0 mg/ml of said solution.
12. The method of claim 11, wherein said volume is in the
10 range of from about 10 to about 50 μ l.
13. The method of claim 11, wherein said volume is in the range of from about 20 to about 45 μ l.
14. The method of claim 11 for treating urinary disorders selected from the group consisting of diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis.
15. The manufacture of a medicament for treating urinary disorders
20 selected from the group consisting of diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis, the medicament comprising a compound selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable desmopressin salt, the medicament comprising from about
25 10 to about 75 μ l of an aqueous solution containing said compound in the range of from about 0.1 to about 2.0 mg/ml of said solution.



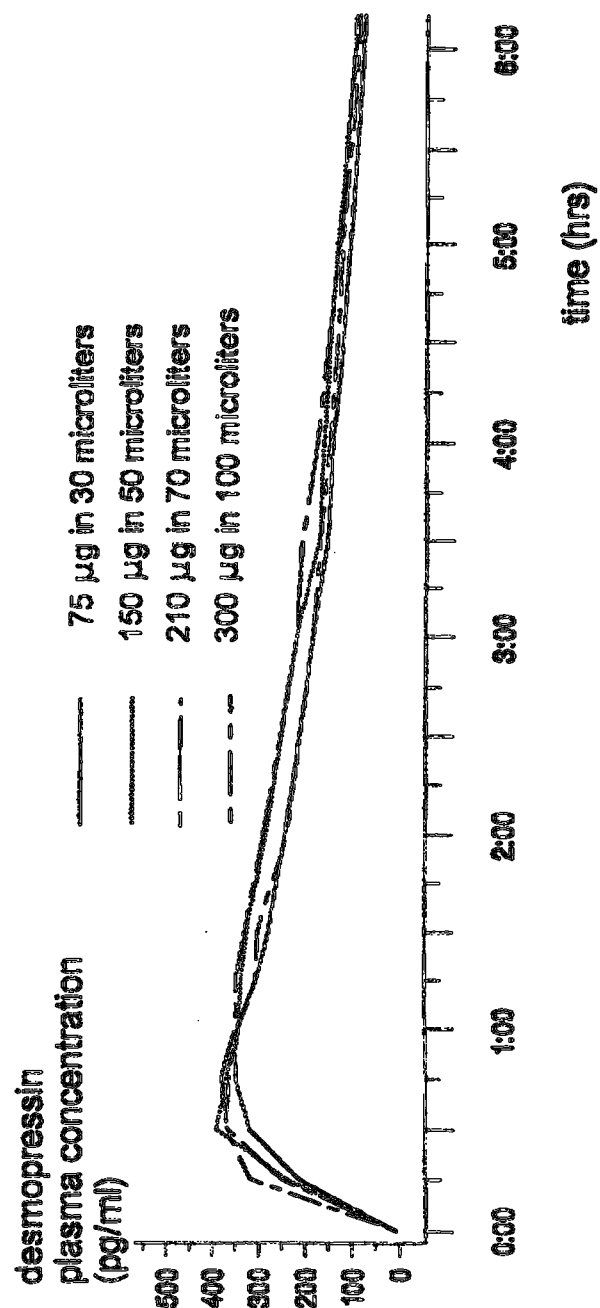
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Fig. 1

Nasal administration of an aqueous solution of desmopressin acetate



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11. A use of a peptide compound comprising nasal administration of said compound which is selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable desmopressin salt, at from about 10 to about 75 μ l of an aqueous solution containing said compound in the range of from about 0.1 to about 2.0 mg/ml of said solution, for delivery in consistent plasma levels.
12. The use of claim 11, wherein said volume is in the range of from about 10 to about 50 μ l.
13. The use of claim 11, wherein said volume is in the range of from about 20 to about 45 μ l.
14. The manufacture of a medicament for treating urinary disorders selected from the group consisting of diabetes insipidus, urinary incontinence, general enuresis and nocturnal enuresis, the medicament comprising a compound selected from the group consisting of desmopressin, desmopressin acetate and a pharmaceutically acceptable desmopressin salt, the medicament comprising from about 10 to about 75 μ l of an aqueous solution containing said compound in the range of from about 0.1 to about 2.0 mg/ml of said solution.

REPLACEMENT SHEET

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(21) International Application Number: PCT/SE97/01010 (22) International Filing Date: 10 June 1997 (10.06.97) (30) Priority Date: 08/667,047 20 June 1996 (20.06.96) US (71) Applicants: FERRING B.V. [NL/NL]; P.O. Box 3129, NL-2130 KC Hoofddorp (NL); FERRING AB [SE/SE]; P.O. Box 30047, S-200 61 Malmö (SE). (72) Inventor: BENGTSSON, Bengt; Pedalgatan 22, S-224 60 Lund (SE). (74) Agent: CONIMAR AB; (Gerhard Miksche), P.O. Box 2086, S-141 02 Huddinge (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BH, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NASAL ADMINISTRATION OF DESMOPRESSIN (57) Abstract A pharmaceutical composition for single, effective and consistent plasma level, nasal administration comprises an aqueous solution having a volume of from about 5 to about 75 μ l and from about 0.2 to about 2.0 mg/ml of desmopressin acetate, a molarly corresponding amount of desmopressin or a pharmaceutically acceptable salt of desmopressin. The composition is useful for the management of urinary disorders such as diabetes insipidus, incontinence, and nocturnal enuresis.		