

Description

This invention relates generally to antidiuretic compositions and methods for treating humans with said compositions. In particular, this invention relates to the antidiuretic compound 1-deamino-8-D-arginine vasopressin, which is commonly known as DDAVP.

DDAVP exhibits a high and specific antidiuretic activity and is useful in treating diabetes insipidus as disclosed in United States Patent US—A—3,497,491.

It has been traditionally accepted that proteins and peptides, such as DDAVP, are decomposed in the stomach and intestines without substantial, or any, absorption taking place. Thus, peptide and protein-based pharmaceuticals have been traditionally administered subcutaneously or via absorption through the mucous membranes of the nose or mouth. The above-noted United States Patent US—A—3,497,491 discloses that DDAVP is preferably administered subcutaneously or intranasally.

The present most common form for administering DDAVP requires the use of a rhinyle. A rhinyle is a graded plastic tube. The appropriate amount of a solution to be administered is drawn into this tube. Then one end is placed into the nostril and the other end is placed into the mouth. The contents of the tube may thus be aspirated intranasally. This mode of administration is difficult to carry out for some patients, particularly elderly patients. Furthermore, intranasal administration adversely affects the cilia such that virus and bacterial may more readily pass to the mucosa.

Also, DDAVP in its dry form is stable but when used in solution form the solution should be refrigerated and a preservative added to the solution.

DDAVP solutions may also be administered via a conventional pump spray. Dosage is unreliable with this device, however, and there is a fair amount of waste when the contents in the bottle are reaching an end. The so-called sublingual tablet is also objectionable since it requires a relatively long dissolving time and is dependent upon a patient's saliva secretion.

The search has continued for improved DDAVP compositions useful for oral administration to humans for gastrointestinal absorption and methods of administering these compositions. This invention was made as a result of this search.

Objects and summary of the invention

Accordingly, it is a general object of the present invention to avoid or substantially alleviate the above-described problems of the prior art.

A more specific object of the invention is to provide DDAVP compositions in a single dosage form for oral administration as lined out below.

Another object of the invention is to provide DDAVP compositions which dissolve in the gastrointestinal tract in order to allow for the gastrointestinal absorption of DDAVP.

Yet another object of the present invention is to provide DDAVP compositions in a stable form without the need for preservatives and/or refrigeration.

Still other objects and advantages of the present invention will become apparent from the following summary of the invention and description of its preferred embodiment.

According to one aspect of the present invention, there is provided an antidiuretic composition in the form of a tablet or capsule for peroral administration in unit dosage form for the treatment of a human, containing as active ingredient from 50 to 200 µg of 1-deamino-8-D-arginine vasopressin for absorption in the gastrointestinal tract of said human, and a pharmaceutically acceptable carrier.

According to a second aspect, the present invention provides a pharmaceutical package comprising an antidiuretic composition in the form of a tablet or capsule in unit dosage form for the treatment of a human, containing as active ingredient 1-deamino-8-D-arginine vasopressin for absorption in the gastrointestinal tract of said human in combination with a pharmaceutically acceptable carrier, and including instructions that a dose which includes between 50—200 µg of said active ingredient is to be orally administered in a period of between 8 and 12 hours.

The antidiuretic effect of the DDAVP used in this invention is most likely due to absorption of the intact DDAVP molecule since any enzymatic destruction of the peptide-binding or of the disulphide bridge in DDAVP leads inevitably to biological inactivation. In the present invention, the peroral doses of DDAVP used to initiate antidiuresis are only slightly higher than the amounts of DDAVP used intranasally by patients who are suffering from diabetes insipidus to control their polyuria.

In the composition of the present invention, an antidiuretically effective amount of DDAVP in oral dosage form may be used. This amount is typically from 50 to 200, and preferably from 50 to 100 micrograms of DDAVP, based upon an assumed 70 kilogram weight of a mature adult, per each oral dosage unit. This oral dosage unit should be taken two or three times daily.

The composition may be in any form for oral administration including tablets, capsules or other forms known to those skilled in this art. The tablet form is preferred.

Other ingredients well known to those skilled in this art may be used in these compositions. These ingredients include well known fillers and other inert constituents.

The present invention is further illustrated by the following Examples and Comparative Examples

Examples 1 and 2

Two tablets are prepared containing the following ingredients:

	Ingredient	Example 1	Example 2
5	DDAACP (synthesized by Ferring AB) (μ g)	50	100
	Mannitol USP XX (mgs.)	39	78
10	Lactose (Ph. Eur. II) (mgs.)	60	60
	Microcrystalline cellulose (mgs.)	60	60
	Crosslinked carboxymethylcellulose (mgs.)	2	2
15	Talcum (Ph. Eur. III) (mgs.)	8	8
	Magnesium stearate (Ph. Eur. III) (mgs.)	2	2

The microcrystalline cellulose AVICEL PH101 is a highly purified particulate form of cellulose which is commercially available from FMC Corporation, Philadelphia, Pa. The cross-linked carboxymethylcellulose is Ac-Di-Sol sodium carboxymethylcellulose which is also commercially available from FMC Corporation.

In addition to the above, small amounts of polyvinylpyrrolidone-ethanol are used as the binding agent in making the tablets.

The tablets were administered to three patients who suffer from diabetes insipidus. The administration took place for a period of more than 3 months. The dose required to keep the polyuria under control for these patients was 2 to 3 of the 100 microgram tablets every 24 hours. No side-effects were observed. The patients preferred the tablet administration to the conventional intranasal administration of DDAVP.

Comparative Example

The effect of orally administering DDAVP was compared with the effect of orally administering 1-deamino-4-asparagine-8-D-arginine-vasopressin (4-Asn-DDAVP) as follows:

Ten healthy subjects of both sexes, aged 18 through 43 were treated with DDAVP and 4-Asn-DDAVP.

One to two hours after a normal breakfast, the subjects were hydrated by drinking the volume of tap water that corresponded to 2% of their body weight. Every 15 minutes, urine was collected and its volume and osmolality were measured using an Advanced Osmometer Model 3D11. In order to overhydrate themselves, the subjects substituted their loss of fluid by drinking a volume of tap water that corresponded to the amount of urine collected. After appr. 40 to 45 minutes, the diuresis increased to about 200 milliliters per 15 minute period. At that time, DDAVP or 4-Asn-DDAVP in amounts of from 20 to 200 micrograms was administered perorally in 50 milliliters of distilled water. The DDAVP and 4-Asn-DDAVP were supplied by Ferring AB in lyophilized powder form which could easily be dissolved in water. The water diuresis was followed continually up to 6 hours.

Two of the subjects were supplied with a duodenal tube which was inserted through the nose. The end of the tube was placed with the help of X-rays in the distal part of the duodenum. Overhydration and urine sampling were then carried out as described above.

Urine volumes exceeding 200 milliliters per 15 minutes were taken as an indication that endogen secretion of vasopressin had been maximally suppressed. After this, 200 micrograms of DDAVP dissolved in 10 milliliters of water were injected through a tube.

These investigations illustrate that there is a dose-dependent effect of DDAVP, both on the magnitude and duration (the effect lasted at least 6 hours) of the response. A therapeutic effect was obtained with a 20 microgram dosage of DDAVP. Those who were administered DDAVP through the duodenal tube had an immediate antidiuretic response when a corresponding increase in the osmolality and conductivity of the urine was observed. Apart from a slight feeling of tension in the stomach in connection with the initial overhydration, no side effects were experienced by any of the subjects.

In contrast to the above results with DDAVP, the oral administration of 4-Asn-DDAVP in doses of from 20 to 200 micrograms provides only a moderate, extremely short-lived, effect with only the highest dose. Moreover, a dose of 100 micrograms gave no therapeutic effect.

The principles, preferred embodiments and modes of operation of the invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since these are to be regarded as illustrative.

Claims

1. An antidiuretic composition in the form of a tablet or capsule for oral administration for



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gastrointestinal absorption in unit dosage form for the treatment of a human, containing as active ingredient from 50 to 200 µg of 1-deamino-8-D-arginine vasopressin for absorption in the gastrointestinal tract of said human, and a pharmaceutically acceptable carrier.

2. A composition according to claim 1, containing from 50 to 100 µg of 1-deamino-8-D-arginine vasopressin.

3. A pharmaceutical package comprising an antidiuretic composition in the form of a tablet or capsule for oral administration for gastrointestinal absorption, containing as active ingredient 1-deamino-8-D-arginine vasopressin for absorption in the gastrointestinal tract of said human in combination with a pharmaceutically acceptable carrier, and including instructions that a dose which includes between 50—200 µg of said active ingredient is to be orally administered in a period of between 8 and 12 hours.

Patentansprüche

1. Antidiuretisches Präparat in Form einer Tablette oder einer Kapsel zur oralen Verabreichung für gastrointestinale Absorption in Einheitsdosisform zur Behandlung eines Menschen, das als wirksamen Bestandteil 50 bis 200 µg 1-Desamino-8-D-arginin-Vasopressin für die Absorption im Magen-Darm-Trakt des Menschen und einen pharmazeutisch verträglichen Träger enthält.

2. Präparat nach Anspruch 1, das 50 bis 100 µg 1-Desamino-8-D-arginin-Vasopressin enthält.

3. Arzneimittelpackung mit einem antidiuretischen Präparat in Form einer Tablette oder einer Kapsel zur oralen Verabreichung für gastrointestinale Absorption, das als wirksamen Bestandteil 1-Desamino-8-D-arginin-Vasopressin für die Absorption im Magen-Darm-Trakt eines Menschen in Kombination mit einem pharmazeutisch verträglichen Träger enthält, wobei die Arzneimittelpackung die Anweisungen enthält, daß in einem Zeitraum von 8 bis 12 h eine Dosis, die 50 bis 200 µg des wirksamen Bestandteils enthält, per os zu verabreichen ist.

Revendications

1. Composition antidiurétique se présentant sous la forme d'un comprimé ou d'une capsule pour l'administration orale en vue de l'absorption gastrointestinale, sous forme de dose unitaire pour le traitement d'un être humain, contenant, en tant qu'ingrédient actif, de 50 à 200 µg de désamino-1 D-arginine-8 vasopressine en vue de l'absorption dans l'appareil gastro-intestinal dudit être humain, et un support pharmaceutiquement acceptable.

2. Composition selon la revendication 1, contenant de 50 à 100 µg de désamino-1 D-arginine-8 vasopressine.

3. Conditionnement pharmaceutique comprenant une composition antidiurétique se présentant sous la forme d'un comprimé ou d'une capsule pour l'administration orale en vue de l'absorption gastro-intestinale, contenant, en tant qu'ingrédient actif, de la désamino-1 D-arginine-8 vasopressine en vue de l'absorption dans l'appareil gastro-intestinal dudit être humain, en combinaison avec un support pharmaceutiquement acceptable, et comprenant des instructions suivant lesquelles une dose qui comprend entre 50 et 200 µg dudit ingrédient actif doit être administrée par la voie orale dans une période de temps se situant entre 8 et 12 heures.