

Appendix 1

STUDY 1

TITLE: "An Open-Label Pharmacokinetic Comparison of Desmopressin Acetate Administered by Oral and Intranasal Routes" A dose proportionality study (protocol No. RG 84063-101)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

The objective of this study was to determine the dose proportionality of the three dose levels of oral DDAVP tablet in healthy subjects. Secondary objectives were to compare data following the administration of oral tablets to the IN formulation and to demonstrate antidiuretic activity of oral and IN DDAVP administration under steady-state conditions.

STUDY DESIGN:

This open-label, multiple-dose, pharmacokinetic and pharmacodynamic study was conducted in normal healthy male subjects at a single center. The study was a 4-way crossover Latin square design with balanced, randomized assignment of four treatment sequences. The doses administered were: DDAVP (oral) 0.1 mg (1 x 0.1 mg tablet; Treatment C), 0.2 mg (2 x 0.1 mg tablets; Treatment A), 0.4 mg (4 x 0.1 mg tablets; Treatment D), and DDAVP (IN) 0.01 mg (0.1 ml of 0.1 mg/ml solution; Treatment B), by rhinal tube.

POPULATION:

Thirty-six healthy, adult male volunteers were enrolled into the study. All subjects completed the study and were included in all analyses (all treated subjects). The demographic data for the volunteers were: mean (\pm SD) age of 31.2 (\pm 7.8) years old, mean height of 177.6 (\pm 6.8) cm, and mean weight (BW) of 72.5 (\pm 5.6) kg (Table 1).

DRUG ADMINISTRATION:

In each of the four treatment periods, DDAVP was administered every 8 hours for 8 doses, extending over 56 hours (starting at nighttime of Day 1 till the morning of Day 4), i.e., only one dose was administered at 23:00 on Day 1 and at 7:00 on Day 4, and Days 2 and 3 (7:00, 15:00, and 23:00) received a total (daily) oral dose of 0.3 mg, 0.6 mg, 1.2 mg or intranasal 0.03 mg of each period. There were 4.67 drug-free days (112 hours) between treatment periods.

Note: The meal times and what kind of meals served, were not clearly stated in the submission. However, the firm mentioned that the meals were served at the customary time and were the same time every day.

Within each study day, daily fluids were restricted to a total of 1.5 liters in 24 hr, including meals. Caffeinated beverages were not allowed at any time during the confinement periods of the study.

Note: DDAVP for IN use was supplied as a sterile, aqueous solution containing 0.1 mg/ml DDAVP (2.5 ml per vial). Each package contained one vial of DDAVP and two soft, flexible plastic nasal applicator tubes. Each nasal tube (rhinal) has four graduation marks on it that measure 0.2, 0.15, 0.1 and 0.05 ml. Instructions for IN administration of DDAVP using the rhinal tube were provided in the protocol.

SAMPLE COLLECTION:

1. Blood Samples:

Blood (5 ml each) was collected 5 min prior to the administration of the 1st, 5th, and 8th doses, and it was also collected at 0.33, 0.50, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 16 hr post dosing of the 8th dose during each treatment period. EDTA-plasma samples (1 ml each) in duplicate were obtained after the centrifugation of blood sample and were stored frozen until extracted.

2. Urine Samples:

a. Baseline: (prior to the 1st dose on Day 1 of Period I only)

To measure the baseline urine output, subjects had their 8-hour urine output and osmolality measured before the first dose of drug on Day 1 of Period I. This was done in the same way and at the same time of the day as the post-DDAVP measurements of urine output and osmolality for the 6th dose. At about 14:15 on Day 1, subjects voided to empty their bladder. Their urine's specific gravity and osmolality were recorded. Subjects were then hydrated by consuming a volume of drinking water equal to 1.5% of body weight (15 ml water/kg body weight) over a 15-min period. Urine was collected in 15-min increments for the next 8 hr and 45 min. Every 15-min, each subject was given a new container in which to void. Collections were not to be combined. The volume of each 15-min urine collection was recorded and a 10 ml portion of each 15-min collection was retained for measurement of osmolality. Subjects drank a volume of water equal to the volume of urine voided in each 15-min collection. No other fluids were allowed during the 8 hr and 45 min of urine collection.

b. On Day 3 of all Periods:

On Day 3 for all periods, dosing was every 8 hr (e.g., 07:00, 15:00, 23:00). Forty-five min prior to the 6th dose (e.g., at 14:15), subjects voided to empty bladder and water loaded (15 ml/kg) over a 10-15 min period. Urine collections were obtained every 15 minutes until 8 hours post-dose (e.g. until 23:00). During the 8 hr and 45 min urine collection, subjects drank a volume

of water equal to the volume of urine voided in each 15-min collection. No other fluids were allowed during the 8 hr and 45 min urine collection. Fluids were restricted to a total of 1.5 liters in 24 hours, including meals.

Note: In a telecon held on 11/24/92, the firm indicated that the daily fluid intake (replacement) was not restricted to 1.5 liters since during the urine collection period (every 15 min) the subject drank the same volume of water in replacing the volume of urine excreted.

ASSAY:

1. Plasma Samples:

Plasma protein was first precipitated from 1 ml plasma with 2 ml ice-cold acetone. After centrifugation, the supernatant was extracted twice with petroleum ether, and the remaining water phase was evaporated under a stream of nitrogen. Dried extracts were stored at -20°C until assayed. Prior to assay, dried extracts were dissolved in 500 µl assay buffer and the assay of DDAVP levels in plasma was performed by Ferring Pharmaceutical, Malmo, Sweden, using RIA method.

Dried extracts were dissolved in 500 µl assay buffer and the assay of DDAVP levels in plasma was performed by Ferring Pharmaceutical, Malmo, Sweden, using RIA method:

Standard curve: 2.5 to 1280 pg/ml corresponding to 0.5 to 256 pg/ml/assay tube.

Stability: Plasma sample was stable for at least 267 days at -70°C and dry plasma extract was stable for at least 43 days at -20°C.

Extraction Recovery: 78% (n = 33), 77% (n = 37), 63% (n = 37) at 5, 10, 100 pg/r. l (extraction control), respectively.

Accuracy: (% error from the predicted)

53.3% (n = 33), 2.0% (n = 37), 0.2% (n = 37) at 3, 10, 100 µg/ml (buffer control), respectively.

Precision:

1. Interassay: CV of 29.0% (n = 33), 21.3% (n = 37), 7.3% (n = 37) at 3, 10, 100 pg/ml plasma (buffer control), respectively. CV of 29.6% (n = 33), 48.9% (n = 37), 15.5% (n = 37) at 5, 10, 100 pg/ml plasma (extraction control), respectively.

2. Intraassay: CV of $18.7 \pm 6.0\%$ ($n=33$), $12.2 \pm 4.9\%$ ($n=37$), $5.4 \pm 2.9\%$ ($n=37$) at 3, 10, 100 pg/ml (buffer control), respectively.

Note: At lower concentration of 3 pg/ml, the assay method gave 53.3% error to the predicted. This value is relatively high compared to others and it would in turn give noisy baseline values.

2. **Urine Samples:**

Urine was collected in each treatment period following maximal water hydration as an index of antidiuretic activity. Urine volume and osmolality were measured and recorded before the first dose of the study and for 8 hrs in each period following the 6th dose of DDAVP administration.

DATA ANALYSIS:

1. **Pharmacokinetic Analysis:**

Pharmacokinetic analysis for DDAVP was performed using noncompartmental methods. The maximum plasma concentration (C_{max}) and the time it occurred (T_{max}) were determined from the plasma concentration-time profile. Apparent terminal elimination rate constant (k_{el}) was presumably to be determined by linear regression of the terminal phase of the log DDAVP plasma concentration versus time profile. The terminal phase was determined by inspection and was usually the last three measurable concentration time points. The terminal half-life ($T_{1/2}$) was calculated as $T_{1/2} = 0.693/k_{el}$. The $T_{1/2}$ could not be, however, accurately determined from the plasma concentration-time profiles for the lowest oral dose. Area under the DDAVP plasma concentration vs. time curve from 0 to 8 hours (AUC_{0-8}) was calculated by numerical integration using the trapezoidal rule. Trough plasma drug concentrations (C_{min}) values were taken at zero hr on Day 1 (prior to 1st dose), Day 3 (prior to 5th dose), and Day 4 (prior to 8th dose). The parameter estimates for AUC_{0-8} and C_{max} were scaled by a factor of 0.4/dose in order to compute the dose normalized values to the 0.4 mg oral dose.

2. **Pharmacodynamic Analysis:**

The pharmacodynamic variables of urine volume and osmolality were collected using a schedule with time 0.75 hr before DDAVP dosing. DDAVP dosing occurred at HOUR=0.75. All time values for the pharmacodynamic parameters (variable name HOUR) were adjusted by subtracting 0.75 so that the pharmacodynamic and the pharmacokinetic plots have the same time axis to facilitate comparison.

Note: Patient No. 20 had only 11 collections at baseline because he became ill and was unable to complete his original baseline measurements. Thus, his baseline was repeated on Day 8. This repeat baseline was used for analysis.

3. Statistical Analysis:

Statistical analyses were performed using General Linear Models. Analysis of variance (ANOVA) for a crossover design was used to test for differences in the raw and dose normalized mean parameters among all treatments at an alpha level of 0.05. The mixed effects model uses groups, periods, and treatments as fixed effects and subjects between groups as a random effect. The 90% CI about treatment mean differences estimated from this model were expressed as percent of the reference mean. In an ANOVA of untransformed parameters from all treatments, relative bioavailabilities (F_{rel}) were compared between the 0.01 mg intranasal dose and each oral dose. The ANOVA to compare dose normalized AUC_{0-8} and C_{max} excluded data from the intranasal dose.

Study 1

Table 1

Baseline Demographics of All Treated Subjects by Treatment Sequence

	Treatment Sequence (Total Daily Dose)					TOTAL
	0.03 mg IN 0.3 mg PO 1.2 mg PO 0.6 mg PO	1.2 mg PO 0.03 mg IN 0.6 mg PO 0.3 mg PO	0.3 mg PO 0.6 mg PO 0.03 mg IN 1.2 mg PO	0.6 mg PO 1.2 mg PO 0.3 mg PO 0.03 mg IN		
N =	9	9	9	9	36	
Sex						
Male	9	9	9	9	36	
Age (years)						
Mean	33.1	29.1	31.7	31.0	31.2	
S.D.	8.3	5.6	9.7	8.1	7.8	
Min	21.0	21.0	18.0	20.0	18.0	
Max	44.0	36.0	44.0	45.0	45.0	
Race						
Caucasian	7	7	7	8	29	
Black	1	1	0	1	3	
Hispanic	1	1	2	0	4	
Weight (kg)						
Mean	71.7	69.8	72.5	76.0	72.5	
S.D.	6.7	5.2	5.2	4.1	5.6	
Min	62.0	62.3	64.2	71.5	62.0	
Max	82.4	76.5	78.0	83.5	83.9	
Height (cm)						
Mean	177.1	175.3	177.0	181.2	177.6	
S.D.	8.7	6.0	5.8	6.2	6.8	
Min	163.8	165.1	170.2	170.2	163.8	
Max	188.0	182.9	185.4	190.5	190.5	

Extracted from Appendix E, Table 6.

Subject demography listings and summaries are presented in Appendix E, Tables 2-8.

RG-84063-101; December 23, 1991

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STUDY 2

TITLE: "An Open-Label Pharmacokinetic Comparison of Desmopressin Acetate Administered by Oral and Intravenous Routes" A Formulation Uniformity study (protocol No. RG 84063-102)

INVESTIGATOR AND LOCATION:

STUDY DESIGN:

This open-label, single-dose, pharmacokinetics study was conducted in normal healthy male subjects at a single center. The study was a 3-way crossover Latin square design with balanced, randomized assignment of three treatment sequences. The doses administered were: DDAVP IV 0.002 mg (0.5 ml of 0.004 mg/ml solution; Treatment A) and DDAVP oral 0.2 mg (1 x 0.2 mg tablet; Treatment B), and 0.2 mg (2 x 0.1 mg tablets; Treatment C).

POPULATION:

Thirty-six healthy, adult male volunteers were enrolled into the study. All subjects completed the study and were included in all analyses (all treated subjects). The demographic data for the volunteers were: mean age of 27.3 (\pm 5.8) years old, mean height of 177.1 (\pm 6.9) cm, mean BW of 73.8 (\pm 7.1) kg (Table 1).

DRUG ADMINISTRATION:

Subjects fasted from 23:00 on the night preceding dosing, until 2 hours after morning dosing. A light standardized breakfast was served and the lunch and dinner were served at the customary time and were the same time every day.

The oral doses were given with 150 ml of water. Within each study day, daily fluids were restricted to a total of 1.5 liters in 24 hr, including meals. Caffeinated beverages were not allowed at any time during the confinement periods of the study.

SAMPLE COLLECTION:

Blood (7 ml each) was collected 5 min prior to the administration and also collected as follows:

Post IV dosing

0.0833, 0.167, 0.25, 0.333, 0.5, 0.75,
1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16 hr

Post oral dosing

0.333, 0.5, 0.75, 1, 1.25, 1.5,
2, 3, 4, 6, 8, 12, 16 hr

EDTA-plasma samples (at least 1 ml) in duplicate were obtained after the centrifugation of blood sample and were stored frozen until extracted.

SAMPLE ASSAY:

Plasma samples were first precipitated followed by extraction and evaporation procedures, and dried extracts were stored at -20°C until reconstituted prior to assay.

The assay of DDAVP levels in plasma was performed by Ferring Pharmaceutical, Malmö, Sweden, using RIA method. Please see a more detailed assay description and validation in the sample assay section of Study 1.

Standard curve: 2.5 to 1280 pg/ml corresponding to 0.5 to 256 pg/ml/assay tube.

Stability: Plasma sample was stable for at least 267 days at -70°C and dry plasma extract was stable for at least 43 days at -20°C.

Extraction Recovery: 68% (n=24), 65% (n=25), 63% (n=26) at 5, 10, 100 pg/ml (buffer control), respectively.

Accuracy: (% error from the predicted)

4.3% (n=25), 1.0% (n=25), 0.1% (n=25) at 3, 10, 100 pg/ml (buffer control), respectively.

Precision:

1. Interassay: CV of 40.2% (n=25), 8.6% (n=25), 5.4% (n=25) at 3, 10, 100 pg/ml plasma (buffer control), respectively and CV of 18.0% (n=24), 22.0% (n=25), 13.4% (n=26) at 5, 10, 100 pg/ml plasma (extraction control), respectively.

2. Intraassay: CV of 19.4 ± 5.9% (n=25), 11.6 ± 4.1% (n=25), 5.1 ± 1.8% (n=25) at 3, 10, 100 pg/ml (buffer control), respectively.

DATA ANALYSIS:

1. Pharmacokinetic Analysis:

Pharmacokinetic analysis for DDAVP was performed using the noncompartmental methods and the PK parameters, e.g., C_{max} , T_{max} , K_{el} , $T_{1/2}$, and AUC_{0-16} were similarly obtained as those reported in Study 1.

2. Statistical Analysis:

Statistical analyses were also similarly performed using the General Linear Models. The ANOVA of untransformed parameters from all treatments were performed between the 0.002 mg IV dose and each oral dose. The ANOVA to compare dose normalized AUC_{0-16} and C_{max} excluded data from the IV dose.

Oral Desmopressin Acetate,

Study 2

Table 1

Baseline Demographics of All Treated Subjects by Treatment Sequence

Treatment Sequence (Total Daily Dose)							
	0.002 mg 1V/0.2 mg PO/2 X 0.1 mg PO	0.002 mg 1V/2 X 0.1 mg PO/0.2 mg PO	0.2 mg PO/0.002 mg 1V/2 X 0.1 mg PO	0.2 mg PO/2 X 0.1 mg PO/0.002 mg 1V	2 X 0.1 mg PO/0.002 mg 1V/0.2 mg PO	2 X 0.1 mg PO/0.2 mg PO/0.002 mg 1V	TOTAL
N =	6	6	6	6	6	6	36
Sex							
Male	6	6	6	6	6	6	36
Age (years)							
Mean	26.3	26.8	25.2	33.2	24.3	28.0	27.3
S.D.	5.0	5.7	4.7	6.3	5.1	5.9	5.8
Min	21.0	20.0	18.0	28.0	19.0	18.0	18.0
Max	35.0	36.0	30.0	42.0	31.0	36.0	42.0
Race							
Caucasian	5	2	4	5	4	5	25
Hispanic	1	3	1	1	0	1	7
Black	0	1	0	0	1	0	2
Oriental	0	0	1	0	1	0	2
Weight (kg)							
Mean	73.0	73.7	73.6	78.3	68.9	75.0	73.8
S.D.	7.3	6.2	7.6	4.5	4.0	8.9	6.8
Min	64.4	67.0	64.6	70.0	62.0	66.6	62.0
Max	84.6	80.8	84.4	81.6	73.4	88.2	88.2
Height (cm)							
Mean	174.8	174.1	177.8	182.9	174.0	177.0	177.1
S.D.	8.4	4.7	7.5	5.3	7.2	6.8	6.9
Min	162.6	170.2	170.2	172.7	167.6	170.2	162.6
Max	185.4	180.3	190.5	188.0	182.9	188.0	190.5

Extracted from Appendix E, Table 6.

RG-84063-102; December 24, 1991

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Desmopressin Acetate
0.1 and 0.2 mg Tablets
NDA 19-955
Reviewer: M. Daniel Gordin
1-D

Rorer Pharmaceutical
Fort Washington, PA
Submission Date
May 10, 1989
September 11, 1989

Review of a Dissolution Study

DEC 12 1989

Background:

Desmopressin acetate (DDAVP) is a synthetic vasopressin analogue (1-desamino-8-D-arginine-vasopressin-acetate-trihydrate) proposed for use in the treatment of central cranial diabetes insipidus, polyuria, In this submission, the sponsor is presenting results of dissolution studies performed on the DDAVP tablet.

Dissolution Procedure:

Results:

Twelve lots of DDAVP tablets were tested for dissolution (Attachment I). The lots with asterisk were lots used in the clinical studies; however, these lots were manufactured using a different formula using a lower povidone and higher starch content than what is used in the current formulation. The data presented is the percent dissolution for one time point showing at least dissolved at 30 minutes.

Recommendation:

The dissolution data filed May 10, 1989 and September 11, 1989 to NDA 19-955 is incomplete.

The Division of Biopharmaceutics recommends the following studies be conducted to help establish a dissolution method and specifications for both 100 mcg and 200 mcg DDAVP tablets: 1) a pH solubility profile along with stability information in different pH's and 2) dissolution studies on the 100 and 200 mcg tablets utilizing SGF without enzymes, SIF without enzymes, water and other media as appropriate using 12 dosage units per lot involving more than one time point (e.g. 5, 10, 15, 30, and 60 minutes) for those lots used in the pivotal bioavailability and clinical studies.

The sponsor should also provide for those batches/lots that are tested the following information: tablet formulation, site of manufacturing, size of each batch/lot, size of a full-scale production batch/lot, indicate whether the batch/lot was made on production size equipment, and the specific bio-study(ies) and/or clinical study(ies) the batch/lot was studied in.

Please convey the Recommendation to the sponsor.

M. D. Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt December 11, 1989

FT Initialed by John P. Hunt *JPH 11/2/89*

cc: Orig, HFD-510, HFD-426 (Gordin), HFD-344 (Turner), Drug, Chron,
and HFD-19 (FOI).

\510\DDVAP.Dis 12/12/1989

DESMOPRESSIN ACETATE
100 and 200 mcg DDAVP Tablets
NDA 19-955
Reviewer: M. Daniel Gordin
3-S
PC

Rorer Pharmaceutical.
500 Virginia Drive
Fort Washington, PA 19034
Submission Date:
February 6, 1989

Review of a New Drug Application

DEC 12 1989

BACKGROUND:

Anti-diuretic hormone (ADH) is an endogenous hormone involved in the conservation of renal water. The endogenous circulating plasma levels of ADH in normal subjects can range from 1-5 pg/ml and in diabetes insipidus patients, without an operating feedback mechanism, plasma levels increase and can range from 10-12 pg/ml.

DDAVP (desmopressin acetate) is a peptide, synthetic analogue of 8-arginine vasopressin monoacetate (salt) trihydrate and is intended for anti-diuresis and enuresis leading to renal water conservation. DDAVP in intranasal and injectable dosage forms has been used in the U.S. for a number of years. DDAVP Intranasal (10 and 20 mcg) is approved for the treatment of diabetes insipidus and DDAVP Injection for diabetes insipidus, Hemophilia A and von Willebrand's disease under NDA #17-922 and #18-938, respectively.

TITLE: CROSS-OVER STUDY OF THE PHARMACOKINETICS OF DDAVP GIVEN BY NASAL OR ORAL ROUTE.

OBJECTIVE:

1. To describe the biological response to and pharmacokinetics of DDAVP when given by nasal and peroral routes of administration.

SUBJECTS:

10 children with diabetes insipidus (7 boys and 3 girls). Age: 4.5 to 19 years. Etiology: histiocytosis (n=3), craniopharyngioma (n=2), hypothalamic dysgerminoma (n=1) and isolated idiopathic DI (n=4). All the children had previously been treated by intranasal DDAVP.

STUDY PREPARATIONS:

1. 100 mcg/ml IN (an IN solution identical to the commercially available preparation)
2. 200 mcg DDAVP tablets (No Lot Number)

STUDY DESIGN:

The treatment by intranasal or oral DDAVP was discontinued for 36 hours prior to the study. All children received the different doses according to the following order: Day 1 - 10 ug IN; Day 2 - 20 ug IN; Day 4 - 200 ug tablet; Day 5 - 400 ug tablet DDAVP (Table 1/appendix). (Note: It is not clear from the sponsor's report if they mean a 1x400 mcg tablet or 2x200 mcg tablets.) This order of rising doses was chosen so as to minimize the washout period between doses which was one day. All children ate normal breakfast and fluid intake ad libitum was permitted through the study.

BLOOD AND URINE COLLECTION:

- 1- Blood: 5 ml at 0, 20, 40 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dosing.
- 2- Plasma and Urine for osmolality: at 0, 1, 2, 4, 6, 8 and 12 hours post-dosing. (Note: Plasma osmolality results were not submitted.)

ANALYTICAL METHODOLOGY:

Urine osmolality (U-OSM) was measured by an Advanced Osmometer. Plasma-DDAVP was measured by a RIA procedure with the following assay validation:

- 1- %Recovery: 50 pg/ml 106.6% ± 11.8% (S.D.)
150 pg/ml 90.5% ± 8.9% (S.D.)
- 2- Sensitivity: 5 pg/ml.
- 3- Intra-Assay Variation: C.V. of 4.5% ± 2.1%.
- 4- Inter-Assay Variation: C.V. of 5.9%.
- 5- Cross-Reactivity: At 50% inhibition of binding of various structural analogues with antiserum ADA 6 as follows:

<u>Analogue</u>	<u>Cross-Reactivity (%)</u>
8-D-AVP	100
1-dNH ₂ -8-D-ornithine vasopressin	9.1
4-Asn-DDAVP	53.9
oxytocin	< 0.001
arginine vasopressin	0.008
6-monocarba-DDAVP	36.3
4-Val-DDAVP	100

PHARMACOKINETICS AND STATISTICAL ANALYSIS:

The following pharmacokinetic parameters were calculated or obtained from the plasma levels-time profiles of each patient: C_{max}, t_{max}, AUC_{0-12hr}, AUC_{0-infinity}, elimination rate constant and the elimination half-life of DDAVP. All effects were analyzed with SAS using a two-way ANOVA (factors=Subject, Treatment). Three-way

analyses were also performed on the major PK parameters: AUC, C_{max} , t_{max} and elimination half-life.

RESULTS:

A- PHARMACOKINETICS:

The individual plasma levels and individual pharmacokinetic parameters of DDAVP following IN and peroral administration are presented in Tables 1 A-D and Tables 2 A-F respectively (appendix). The ANOV. tables for pharmacokinetic parameters are found in the appendix Tables 3 A-F.

Table 1. The mean pharmacokinetic parameters (\pm SD) obtained after the administration of 10 and 20 ug intranasally and 200 and 400 ug orally.

Parameter	Dose/Route			
	10/IN	20/IN	200/PO	400/PO
C_{max} (pg/ml)	41.4	76.2	33.2	103.9
\pm SD	31.6	69.9	30.7	176.4
t_{max} (hr)	0.68	0.66	0.81	0.81
\pm SD	0.39	0.22	0.36	0.32
AUC(0-12hr)	111.0	181.0	69.7	218.5
(pg.hr/ml) \pm SD	108.8	192.6	58.7	351.8
AUC(0-inf)	135.0	226.2	147.6	245.9
(pg.hr/ml) \pm SD	115.8	186.7	151.7	367.1
Kel. (hr ⁻¹)	0.35	0.23	0.34	0.47
\pm SD	0.16	0.11	0.22	0.27
$t_{1/2}$ (hr)	2.52	4.19	2.96	2.47
\pm SD	1.39	2.84	2.04	2.92
max. osm.	756	828	733	809
(mOsm/kg) \pm SD	201	198	156	77
time to max. osm.	253	373	315	345
(min) \pm SD	111	126	127	77

An aim of this study was to determine the validity of using 200 and 400 mcg DDAVP tablets as replacement therapy for 10 mcg and 20 mcg DDAVP IN administration.

Table 2. Statistical analysis using the Agency's Two One-sided Test Procedure (90% Confidence Interval Approach) for 200 ug oral to 10 ug IN.

	<u>90% CI</u>	
Cmax	-96 - 257	fail
AUC(inf)	-14 - 233	fail

Table 3. Statistical analysis using the Agency's Two One-sided Test Procedure (90% Confidence Interval Approach) for 400 mcg oral to 20 mcg IN

	<u>90% CI</u>	
Cmax	40 - 232	fail
AUC(inf)	34 - 182	fail

B- PHARMACODYNAMICS:

Urine osmolality is an indirect measure of the effectiveness of DDAVP i.e. the higher the value, the more concentrated the urine and the more renal water conserved. The mean urine osmolality response following 10 mcg and 20 mcg IN and 200 mcg and 400 mcg oral doses of DDAVP are shown in Figure 1 with individual urine osmolality for the individual patients presented in Tables 4 A-D.

If the submitted data is accurate, then the urine osmolality (U-OSM) increased rapidly in a similar way for all doses (IN and PO) during the first four hours. The maximum U-OSM was higher after 20 ug IN and 400 ug PO. A difference was observed in the duration of effect. After 12 hours the mean U-OSM was still above 350 mOsmol/kg with 20 ug IN and 400 ug PO, while after 10 ug IN and 200 ug PO the mean U-OSM was 167 and 221 mOsmol/kg, respectively. Plasma osmolality remained stable during 12 hours for the four doses. Free water clearance (FWC) (Figure 2/appendix) indicated no difference between doses or routes of DDAVP administration and remained negative for approximately 7-8 hours (Tables 5 A-D/appendix).

COMMENTS:

1. The firm stated that the reference IN solution was identical to the commercially available 100 ug/ml Minirin preparation which indicates that the commercially available IN product may not have been used in this study. The preparation may be identical in concentration to the marketed IN solution but may have different excipients.

2. As the results indicate, there is large inter- and intra-subject variabilities in the plasma levels (up to 200%) as well as in the pharmacokinetic parameters (C_{max} , t_{max} and AUC) of DDAVP obtained after both the intranasal and the oral routes of administrations. On the other hand, the inter- and intra-subject variabilities in urine osmolality were much less (maximum about 25%).

3. In some subjects plasma levels of DDAVP were detectable at zero time (before administration). This could be due to endogenous compounds interference and/or to an inadequate washout period between administrations.

4. The relative bioavailability (without dose normalization) of the orally administered 200 ug DDAVP to the intranasal route (10 ug) was found to be very variable in the range of 20% - 750% and of the 400 ug given orally to 20 ug given intranasally in the range of 18% - 500%. This is a firm indication to the large inter- and intra-subject variability in the first-pass metabolism of DDAVP in the G.I. tract and probably in the liver.

5. For the 200 and 400 mcg doses as a replacement therapy for the IN doses, the statistical analysis using the Agency's Two One-sided Test Procedure (90% Confidence Interval Approach) indicates that the 200 mcg and 400 mcg oral doses are not equivalent to the 10 mcg and 20 mcg intranasal doses respectively, by AUC and C_{max} .

Studies 2-4 were journal articles in which individual data, assay validations, and the formulation of the DDAVP tablets employed in the studies were not submitted by the sponsor. Only the design and results of the studies will be summarized.

Study 2

Title: Absorption after Peroral and Intranasal Administration

The objective of this study was to compare the plasma concentrations and antidiuretic effect of DDAVP following intranasal and peroral administration.

This was randomized, cross-over design involving three treatment of: 20 mcg intranasal; 100 mcg peroral; and 200 mcg peroral. Subjects (6 healthy males, ages 22-34 years) were hydrated prior to treatment. Urine volume, osmolality, urine and plasma DDAVP levels were measured at regular intervals (unspecified times) up till 6 hours after administration. DDAVP levels were measured by RIA. The results of mean urine volumes, plasma concentrations following IN and PO administrations are presented in Figure 3, 4,

and 5 (Appendix). The urine osmolalities 3 hrs after dosing indicate a fairly consistent effect between IN and oral administration.

mOsm/kg (mean ± SD)

20 mcg IN	790 ± 55
100 mcg po	835 ± 39
200 mcg po	794 ± 81

If the data is accurate, the plasma DDAVP concentrations remain fairly consistent up to 6 hrs; however, large inter-individual difference in plasma concentrations are observed.

Study 3

Title: Pharmacokinetics of DDAVP in Man

The objective of this study was to determine the pharmacokinetics of DDAVP after an intravenous infusion.

Eight healthy volunteers of both sexes, aged 22-27, participated. DDAVP was dissolved in 0.9% NaCl and was administered as a bolus injection of 5 mcg followed by an intravenous infusion at a rate of 1538 pg/min/kg body weight for 3.5 hours. Blood samples were obtained at unspecified intervals.

Results:

The result of plasma concentration of DDAVP following intravenous infusion is presented in Figure 6 (appendix). The average total body clearance rate, the apparent volume of distribution, and plasma half-life for DDAVP were 2.6 ml/min/kg, 0.206 l/kg, and 55 minutes respectively.

Study 4

Title: Dose-response and Pharmacokinetics of DDAVP

The objectives of this was to investigate the dose-response relationship and pharmacokinetics of DDAVP tablets in healthy volunteers and adults with diabetes insipidus and to determine the antidiuretic effect of DDAVP given orally to children with diabetes insipidus.

Three patients groups were used: 5 healthy volunteers; 7 adults with diabetes insipidus (ages 21-52, 4 males, 3 females); and 4 children with diabetes insipidus (ages 11-16, 3 males, 1 female). Subjects were water loaded for maximal diuresis and DDAVP administered in unspecified randomized order on separate occasions at least 3 days apart. The subjects received the following doses:

Healthy subjects - 50, 100, and 200 mcg tablet orally;
Adult with diabetes insipidus - 200 mcg tablet orally;
Children with diabetes insipidus - 50 and 100 mcg tablet orally.

Urinary volumes and osmolality were measured at unspecified hourly intervals for 6-8 hrs. In adults only plasma levels for DDAVP were obtained at unspecified hourly interval. Plasma levels for DDAVP were determined by RIA.

Results:

The results of urine flow rate and osmolality, plasma DDAVP concentrations, in adults and children are presented in Figures 7, 8, 9, and 10.

If the data is accurate, there was a decrease in urine flow rate and an increase in urinary osmolality. The duration of action lasted for 6 hours. Children required doses of 100 mcg orally to achieve similar duration of action.

In children, the C_{max} for DDAVP for 50 and 100 mcg oral doses occurred at 1 hour and average levels were 1.7 and 3.2 pmol/l respectively. For the 200 ug dose in adults, C_{max} occurred at 2 hour and the average level was 7.0 pmol/l.

Comments:

1. Dr. Robert Young, Scientific Investigations, informed the Division of Biopharmaceutics that the original data and records for the pivotal study 1. could not be validated; therefore, it seems problematic that the sponsor will be able to address the deficiencies cited on pages 8 and 9 for this study.

2. In two teleconferences (October 31, 1989 and December 6, 1989) with Ms Kathy Hanlan, Korer Pharmaceutical, it was conveyed that they intend to submit a protocol for a new bioavailability study.

The following issues are concerns raised by the presently filed studies which will need to be addressed (To be sent to the firm):

a) If the formulations between the clinical and the proposed market tablet formulations are different, then a bioequivalency study(ies) comparing these formulations (if different) will be needed.

b) A dose proportionality study may be required depending on the to be recommended doses in labelling.

c) Since this drug will be given on a chronic basis, a possible multiple dose study may be required.

d) The intravenous administration of DDAVP may be required as the reference to determine the absolute bioavailability of 100 and 200 mcg DDAVP tablets.

e) A food effect study, information on DDAVP metabolism, and protein binding may be required

f) Due to the large inter-subject variability observed from DDAVP plasma levels, pharmacodynamic data i.e. urine/plasma osmolality results, may be needed to help assess items a-e above.

Deficiencies:

(To be sent to the firm):

1. The following deficiencies from the pivotal bio-study by needs to be addressed

a. The cross-reactivity of the RIA antibody indicates significant cross-reactivity with 8-D-AVP, 4-Asn-DDAVP, 6-monocarba-DDAVP, and 4-Val-DDAVP which may seriously affect the accurate measure of plasma DDAVP. The firm did not indicate if these are metabolic products of DDAVP and if present as plasma "contaminates" how they were treated prior to measuring plasma levels for DDAVP i.e. a plasma extraction prior to the RIA assay and if so, its effectiveness. In some subjects, DDAVP plasma levels were detectable at zero time (before administration). This could be due to endogenous compounds interference and/or to an inadequate washout period between administrations. Also, cross-reactivity to endogenous ADH needs to be provided. In addition, the firm states that the sensitivity of the RIA was down to 5 pg/ml; however, this was not substantiated by repeated measure test with %CV data. Therefore, the assay validation for the measure of DDAVP plasma levels is not acceptable due to incomplete validation.

b. In this study, it is indicated that 200 and 400 mcg oral doses were given. Does this mean 2x100 mcg tablets and 2x200 mcg tablets were given or were 1x200 mcg tablet and 2x200 mcg tablets given? The sponsor needs to clarify this issue.

c. The sponsor did not indicate 1) if the tablet formulation(s) used in this study was the same as those used in clinical safety and efficacy studies 2) if they or it are the to-be-marketed formulations 3) whether full-scale production lots were used and 4) the comparative formulation content information for the

two proposed market tablet strengths and the tablet(s) used in the study if different.

d. In analyzing the plasma drug concentrations, the procedure for fitting the plasma DDAVP drug concentrations and the data associated with the validity of best-fits were not submitted.

e. In the study design used, doses to the subjects were not randomized which results in the inability to measure sequence effects in terms of pharmacokinetic parameters and pharmacodynamic effects.

f. Dose proportionality analyses to include ratio comparisons for AUC and Cmax within each subject per route of administration and an ANOVA and Two One-Sided Tests Procedure analyses on dose normalized data (i.e. for AUC and Cmax) were not submitted.

g. For the 200 and 400 mcg doses for replacement for the IN doses, statistical analyses using the Agency's Two One-sided Test Procedure (90% Confidence Interval Approach) indicate that the 200 mcg and 400 mcg oral doses are not equivalent to the 10 mcg and 20 mcg intranasal doses respectively, by AUC and Cmax.

h. Statistical analyses for the pharmacodynamic data in the measure of urine osmolality as well as comparing dose and route of administration for baseline and nonbaseline adjusted data were not submitted.

2. Studies 2-4 were journal articles in which individual data, assay validations, and the formulation of the DDAVP tablets employed in the studies were not submitted by the sponsor and, therefore, not validated.

Recommendation:

The Division of Biopharmaceutics finds NDA 19-955 that was filed February 6, 1989 Not Approvable at this time due to the lack of key information as outlined in the Deficiencies section of this review. The accuracy and validation of the reported information cannot be assessed.

Please forward the Recommendation, Comments No. 2 a-f (pp 7-8), and the Deficiencies No. 1 a-h and No. 2 (pp 8-9) to the sponsor.

In a teleconference (October 31, 1989 and December 6, 1989) with Ms Kathy Hanlan, Rorer Pharmaceutical, it was conveyed that Rorer intends to submit a new bioavailability protocol for review. The Division of Biopharmaceutics looks forward to reviewing the protocol when officially submitted to the Agency.

M. D. Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt December 11, 1989

FT Initialed by John P. Hunt December 12, 1989

cc: Orig, HFD-510, HFD-426 (Gordin), HFD-344 (Turner), Drug, Chron,
and HFN-19.

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