Successful Long-Term Treatment of Hyponatremia in Syndrome of Inappropriate Antidiuretic Hormone Secretion with Satavaptan (SR121463B), an Orally Active Nonpeptide Vasopressin V_2-Receptor Antagonist

Alain Soupart,*† Peter Gross,‡ Jean-Jacques Legros,§ Sándor Alföldi,‖ Djillali Annane,¶ Hassan M. Heshmati,†† and Guy Decaux† **

**Department of Internal Medicine, Jolimont/Tubize-Nivelles Hospital, Tubize, †Research Unit for the Study of Hydromineral Metabolism and **Department of General Internal Medicine, Erasmus University Hospital, Free University of Brussels, Brussels, and §Department of Internal Medicine, Regional Hospital Center of Citadelle, Liege, Belgium; ‡Nephrology, Department of Medicine, University Medical Center Care Gustav Carus, Dresden, Germany; ‖Szent Imre Kórház és Rendelöintézet I, Belgyógyászati Osztály, Budapest, Hungary; ¶Department of Intensive Care Unit, Raymond Poincare Hospital, Garches, France; and ††Clinical Development, Sanofi-Aventis, Malvern, Pennsylvania*

The effects of satavaptan (SR121463B), a novel long-acting orally active vasopressin V_2-receptor antagonist, were investigated in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In the first part of this randomized, double-blind study, 34 patients first were treated with satavaptan (*versus* placebo) for up to 5 d and then during 23 d of open-label dosage-adjustment period. In the second part of the study, long-term efficacy and safety of satavaptan was assessed in an open-label trial during at least 12 mo. Mean (±SD) serum sodium (SNa) levels before treatment were 127 ± 2 mmol/L (placebo, $n = 8$), 125 ± 6 mmol/L (25 mg, $n = 14$), and 127 ± 5 mmol/L (50 mg, $n = 12$). Responders (patients SNa levels normalized or increased by at least 5 mmol/L from baseline during the double-blind period) were 79% in the 25-mg group (SNa 136 ± 3 mmol/L; $P = 0.006$), 83% in the 50-mg group (SNa 140 ± 6 mmol/L; $P = 0.005$), and 13% in the placebo group (SNa 130 ± 5 mmol/L). No drug-related serious adverse events were recorded. During the long-term treatment, 15 of 18 enrolled patients achieved 6 mo and 10 achieved 12 mo of treatment. The SNa response was maintained during this time with a good tolerance. The new oral vasopressin V_2-receptor antagonist satavaptan adequately corrects mild or moderate hyponatremia in patients with SIADH and has a good safety profile.

Clin J Am Soc Nephrol 1: 1154–1160, 2006. doi: 10.2215/CJN.00160106

Vasopressin is involved in most cases of sustained hyponatremia (1). Therefore, the use of specific blockers of vasopressin receptors is a logical approach in the treatment of patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) and may present advantages over current available therapies (2). Selective nonpeptide V_2-receptor antagonists (V_2RA) have been in development since 1992 (3–6). Oral compounds have been synthesized more recently, and, to our knowledge, publications have focused mainly on patients with SIADH that is treated with an oral V_2RA for a short period of time (<1 wk) (7–10).

In this study, we investigated the efficacy and the safety of a new oral nonpeptide V_2RA, satavaptan (SR121463B) (11), in correcting hyponatremia in patients with SIADH of various origins. After the initial phase of the study (short-term, 1 mo), we evaluated for the first time the efficacy and the tolerance of a V_2RA over a long-term period (12 mo).

Received January 13, 2006. Accepted August 21, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. Alain Soupart, Research Unit for the Study of Hydromineral Metabolism, Department of General Internal Medicine, Free University of Brussels, Hôpital Erasme, 808, route de Lennik, 1070 Brussels, Belgium. Phone: +322-555-4960; Fax: +322-555-3211; E-mail: alainsoupart@swing.be

Materials and Methods

Patients

From June 2001 to June 2003, a total of 35 patients from four countries (Belgium, Germany, Hungary, and France) were included in a randomized, double-blind, placebo-controlled study to assess the efficacy and the safety of different dosages of satavaptan in SIADH. The diagnosis of SIADH was based on several criteria: True serum hypo-osmolality; inappropriate urinary osmolality; clinical euvolemia; elevated urinary sodium excretion while on a normal salt and water intake; and normal renal, adrenal, and thyroid functions. Patients with low sodium excretion (≤20 mmol/L) as a result of low solute intake (anorexia) were included. Drug-induced SIADH was limited to carbamazepine and antidepressants. The search for the cause of SIADH (especially neoplasia and iatrogenic) was performed carefully by each investigator before considering the origin as idiopathic.

Inclusion criteria were age 18 yr or older, stable hyponatremia (serum sodium [SNa] increase ≤4 mmol/L between two measurements of 24 h apart) between 115 and 132 mmol/L during the screening period,

ISSN: 1555-9041/106-1154

ability to give a written informed consent, and ability to follow verbal and written instructions. Exclusion criteria were cardiac failure, symptomatic liver disease or serum alanine aminotransferase or aspartate aminotransferase more than two-fold the upper limit of normal, uncontrolled diabetes (blood glucose ≥200 mg/dl), significant renal impairment (serum creatinine >150 μmol/L), inadequate hematologic function (hemoglobin <9 g/dl, neutrophils <1500/mm^3, platelets <100,000/mm^3), and hypothyroidism or adrenal deficiency. Radiotherapy and chemotherapy within 2 wk before study drug administration were not allowed. Previous and concomitant administration of some drugs were not accepted (from 1 mo before the randomization for demeclocycline or lithium and 2 d for diuretics and urea). Women who were of childbearing potential and had positive pregnancy test and women with absence of medically approved contraceptive methods were excluded.

Protocol

In the first part of the study (1 mo), after a screening period (day −6 to day −1) to confirm stable hyponatremia, patients were randomly assigned to take placebo or a once-daily dose of 25 or 50 mg of satavaptan during a double-blind period of up to 5 d. The duration of the double-blind period could have been <5 d if SNa reached values ≥135 mmol/L on two consecutive days before day 5. Patients were hospitalized during the double-blind period. The double-blind period was followed by 23 d of open-label treatment (dosage adjustment). In the initial dosage adjustment on day 6, if the last SNa on day 5 was <135 mmol/L, then patients received a dosage of satavaptan equal to the dosage of their group. If SNa was ≥135 mmol/L, then they received a dosage that was one level below the dosage of their group (in case of 25 mg, the drug was discontinued). From day 7 to the end of the open-label period, the dosage was adjusted on the basis of the results of SNa. In the second part of the study (12 mo), the long-term efficacy and the safety of the satavaptan were assessed in an open-label trial with 12.5, 25, or 50 mg once daily.

Drug was administered in the morning under fasting conditions. During the entire study, it was recommended to limit total fluid intake to 1500 ml/d. Dietary sodium intake remained unchanged throughout the study for each patient.

Treatment aim was to obtain normalization of the SNa within a range of 135 to 145 mmol/L on two separate consecutive determinations. Responders were patients who reached normal SNa levels or increasing SNa levels by at least 5 mmol/L from baseline over at least 24 h during the double-blind period.

Body weight was assessed each day during the double-blind period before dosing and on days 6, 7, 10, 14, 21, and 28 in the open-label period. Vital signs, including supine and standing systolic and diastolic BP, heart rate, and oral temperature, were assessed three times per day from day 1 to day 7 and once a day thereafter (just before dosing). Thirst index was evaluated by a visual analogue scale each day of the double-blind period and on days 6, 7, 10, 14, 21, and 28 of the open-label period (7). Electrocardiogram (standard 12-lead) was recorded at screening and on days 5, 14, and 28, before dosing.

Blood samples for SNa and osmolality measurements were collected between 7 and 9 a.m. on fasting patients before and 6 and 12 h after drug intake each day during the double-blind period and before drug intake at each visit of the open-label period. Blood samples also were collected on screening day and on days 5, 14, and 28 before dosing for standard hematology and serum chemistry.

For arginine vasopressin, renin, and aldosterone, blood samples were taken at the same time from patients in the supine position for at least 30 min. Plasma satavaptan concentration was determined just before drug intake and 3, 6, and 12 h after by use of a validated liquid chromatography tandem mass spectrometry (Department of Sanofi-Synthelabo Research, Malvern, PA). Urine samples were collected daily (collections from 8 a.m. to 2 p.m., and from 2 p.m. to 8 a.m.) for urinary volume, electrolyte, and osmolality determinations.

Free water clearance (FWC) was calculated using the following formula: (urinary flow rate) × (1 − urinary osmolality/serum osmolality). Effective FWC (EFWC) was calculated using the following formula: (urinary flow rate) × (1 − urinary sodium + potassium/SNa).

Written informed consent was obtained from each patient. The study protocol was approved by the local ethics committee of the participating centers.

Statistical Analyses

Data are provided as mean ± SD or SEM as appropriate. All statistical tests were two sided at the 5% significance level. Comparison of data between treatment groups was done by using ANOVA for continuous data and Fisher exact test for qualitative variables.

Results

Short-Term Study (First Part)

In the double-blind phase, nine patients received placebo, 14 patients received 25 mg/d, and 12 patients received 50 mg/d of satavaptan. Thirty-four patients completed the double-blind portion of the study. One patient in the placebo group discontinued the treatment on the second day because of an adverse event. Twenty-two patients completed the open-label portion of the study. Thirteen patients discontinued the open-label period for various reasons (*e.g.*, adverse event, death, lack of efficacy, personal reason).

There were no significant differences in the baseline characteristics of the patients between groups (Table 1). In the patients with drug-induced SIADH, all cases were related to carbamazepine that was prescribed for epilepsy or chronic pain (the drug was continued during the study). Patients presented with moderate hyponatremia (range 114 to 131 mmol/L). The low urinary sodium that was observed in some patients may be attributed to the low caloric and solute intake of the patients.

Efficacy. Figure 1 represents the course of the SNa throughout the double-blind period. SNa reached 136 ± 3 mmol/L ($n = 14$; range 131 to 141 mmol/L) in the 25-mg group ($P = 0.011$ *versus* placebo), 140 ± 6 mmol/L ($n = 12$; range 133 to 156 mmol/L) in the 50-mg group ($P < 0.0001$ *versus* placebo), and 130 ± 5 mmol/L ($n = 8$; range 120 to 134 mmol/L) in the placebo group. There was a trend for a higher increase in SNa in the 50-mg group (dosage-related effect). Serum osmolality also was significantly higher at the end of the double-blind period in the treated patients compared with placebo (data not shown).

A total of nine patients who were treated with satavaptan (five in the 25-mg group and four in the 50-mg group) presented with an increase in SNa concentration >8 mmol/L within 24 h after the first dose. The increase in SNa ranged from 9 to 16 mmol/L. Per protocol, to avoid brain myelinolysis, the rate of correction of SNa should not exceed 12 mmol/L during the first 24 h and 18 mmol/L during the first 48 h. In three patients (two in the 25-mg group and one in the 50-mg group), the increase was >12 mmol/L per 24 h (14 to 16 mmol/L per 24 h). In the 25-mg group, the mean gradient of increase was 7

Table 1. Summary of demographic data and of disease characteristics at baseline[a]

Characteristics	Placebo ($n = 9$)	Satavaptan	
		25 mg ($n = 14$)	50 mg ($n = 12$)
Age (yr)			
mean ± SD	62.0 ± 18.9	71.1 ± 10.8	68.9 ± 14.0
range	34 to 85	55 to 93	45 to 96
Gender (male/female)	2/7	7/7	4/8
SIADH origin (*n* [%])			
malignant tumor	1 (11.1)	2 (14.3)	2 (16.7)
carbamazepine	2 (22.2)	3 (21.4)	2 (16.7)
miscellaneous	3 (33.3)	4 (28.6)	3 (25.0)
idiopathic	3 (33.3)	5 (35.7)	5 (41.7)
SNa (mmol/L)			
mean ± SD	126 ± 3	125 ± 6	127 ± 5
range	120 to 130	114 to 131	115 to 131
Serum creatinine (μmol/L)			
mean ± SD	64.4 ± 23.0	74.3 ± 19.9	55.0 ± 14.5
range	40.0 to 120.0	40.0 to 100.0	30.0 to 70.0
Blood urea nitrogen (mmol/L)			
mean ± SD	3.9 ± 2.4	4.5 ± 2.5	4.2 ± 1.4
range	1.4 to 8.5	2.0 to 10.5	2.0 to 5.9
Serum uric acid (μmol/L)			
mean ± SD	158 ± 63	214 ± 132	170 ± 53
range	80 to 270	80 to 580	100 to 270
Serum osmolality (mOsm/kg H_2O)			
mean ± SD	257 ± 10	258 ± 14	264 ± 12
range	237 to 270	230 to 277	241 to 284
Urinary sodium (mmol/L)			
mean ± SD	69 ± 36	45 ± 27	77 ± 64
range	19 to 124	11 to 103	6 to 176
Urinary potassium (mmol/L)			
mean ± SD	27 ± 15	28 ± 18	31 ± 24
range	10 to 60	9 to 72	4 to 74
Urinary osmolality (mOsm/kg H_2O)			
mean ± SD	428 ± 198	432 ± 168	451 ± 206
range	184 to 848	257 to 794	187 to 657

[a]SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNa, serum sodium.

mmol/L during the first 24 h (5 mmol/L after the first 6 h). In the 50-mg group, the mean gradient of increase was 6 mmol/L during the first 24 h (4 mmol/L after the first 6 h). Also, one patient (50-mg group) had an increase in SNa >18 mmol/L within 48 h (increase of 19 mmol/L).

The number of responders at the end of the double-blind period was significantly higher in both satavaptan groups compared with placebo. Responders were 79% (11 of 14 patients) in the 25-mg group ($P = 0.006$ *versus* placebo), 83% (10 of 12 patients) in the 50-mg group ($P = 0.005$ *versus* placebo), and 13% (one of eight patients) in the placebo group. For responder patients, the median time to reach response in SNa levels was significantly lower in the 25-mg group (63 h; $P = 0.010$) and the 50-mg group (30 h; $P = 0.002$) in comparison with the placebo group (>120 h).

At the end of the double-blind period, SNa concentrations were significantly correlated to trough plasma satavaptan concentrations ($P < 0.0001$, $r = 0.694$). The correlation remained statistically significant (but weaker) when one outlier patient with high SNa (156 mmol/L) was removed from the analysis ($P = 0.038$, $r = 0.243$). For both dosages, a large interindividual variability was observed in plasma satavaptan concentrations. Maximal concentrations were observed 3 h after dosing, and mean plasma concentrations increased with dosage and duration of administration with stabilization on day 5 (data not shown). Overall, plasma satavaptan concentrations were lower in nonresponders than in responders. A decrease in exposure to satavaptan was observed in patients who received carbamazepine, a widely known CYP3A inducer. Among the five nonresponders who were on active treatment, two patients (one in the 25-mg group and one in the 50-mg group) received carbamazepine during the study. However, three patients who were

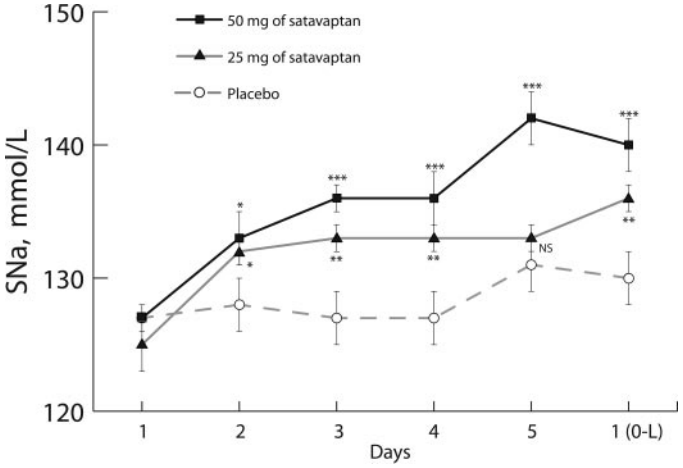

Figure 1. Mean (±SEM) serum sodium (SNa; mmol/L) during the double-blind period in the placebo, 25-mg, and 50-mg groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

on carbamazepine were responders (two in the 25-mg group and one in the 50-mg group). In three nonresponders, the lack of increase in SNa despite a large increase in diuresis and a decrease in urinary osmolality probably was due to an increase in water intake (likely patients with "reset osmostat").

At the end of the double-blind period, the 6-h postdose diuresis was increased by 573 ± 423 ml in the 25-mg group ($P = 0.002$ *versus* placebo), 488 ± 392 ml in the 50-mg group ($P = 0.009$ *versus* placebo), and 10 ± 179 ml in the placebo group. At the end of the double-blind period, the 6-h postdose urinary osmolality was 225 ± 100 mOsm/kg H_2O in the 25-mg group, 179 ± 112 mOsm/kg H_2O in the 50-mg group, and 350 ± 160 mOsm/kg H_2O in the placebo group. The decrease was significant in the 50-mg group ($P = 0.044$ *versus* placebo). The 6-h postdose urinary electrolyte excretion (sodium and potassium) was not significantly modified by satavaptan.

Figure 2 shows the 6-h postdose FWC in the three groups during the double-blind period. It was increased from baseline in a dosage-related manner in the satavaptan groups. A peak was observed the first day. Mean change from baseline at the end of the double-blind period was significantly higher for the 50-mg dose ($P = 0.008$ *versus* placebo) and close to significance for the 25-mg dose ($P = 0.058$ *versus* placebo). A very similar pattern was observed for EFWC (Figure 3).

At the end of the double-blind period, there was no significant change from baseline in body weight, thirst index, fluid intake, plasma arginine vasopressin, plasma renin, and serum aldosterone in both satavaptan-treated groups compared with placebo (Table 2). For body weight, a trend for a higher decrease *versus* placebo was observed at 24 h postdose in the 50-mg group.

During the open-label adjustment period, mean SNa remained in the normal range (SNa 137 ± 4 mmol/L at the end of the open-label), whereas the majority of the patients (27 [79%] of 34 double-blind completer patients) received 25 mg/d of the compound.

Safety. No clinically relevant changes were observed for respiratory rate and oral temperature. For BP, at the end of the

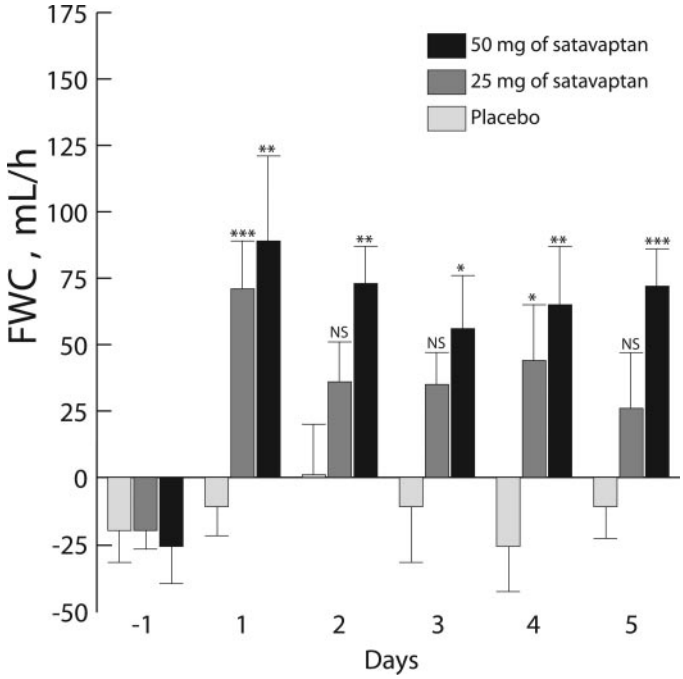

Figure 2. Mean (±SEM) free water clearance (FWC; ml/h, 0 to 6 h postdose) during the double-blind period in the placebo, 25-mg, and 50-mg groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

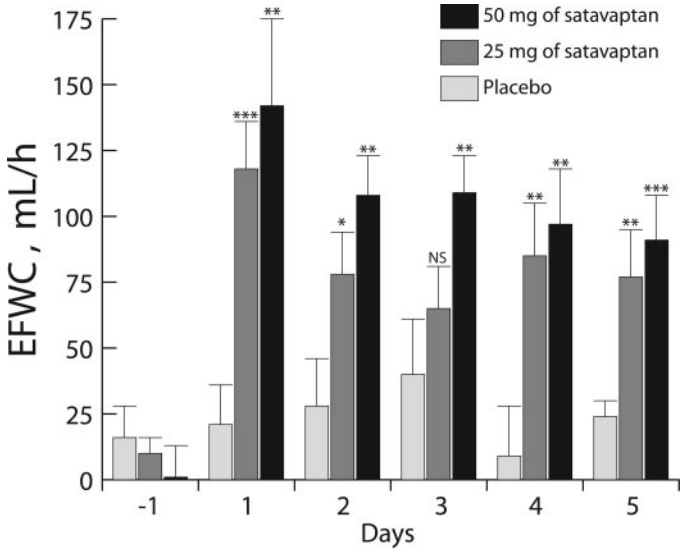

Figure 3. Mean (±SEM) effective free water clearance (EFWC; ml/h, 0 to 6 h postdose) during the double-blind period in the placebo, 25-mg, and 50-mg groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

double-blind period, a moderate decrease in standing systolic and diastolic BP was observed in the 50-mg group compared with placebo (decrease of 6 ± 23 mmHg *versus* increase of 2 ± 12 mmHg and decrease of 8 ± 14 mmHg *versus* decrease of 4 ± 12 mmHg, respectively). No other clinically relevant changes were observed in supine BP in the 50-mg group or in supine or standing BP in the 25-mg group, compared with placebo. Or-

Table 2. Changes from baseline in body weight, thirst index, fluid intake, AVP, renin, and aldosterone at the end of the double-blind period[a]

Parameters	Placebo (n = 8)	Satavaptan	
		25 mg (n = 14)	50 mg (n = 12)
Body weight (kg)			
baseline (mean ± SD)	60.6 ± 9.9	59.5 ± 12.4	56.9 ± 12.5
change from baseline (mean ± SD)	−1.2 ± 2.0	−0.4 ± 1.4	−1.3 ± 1.7
P value (*versus* placebo)	—	0.298	0.930
Thirst index (mm)			
baseline (mean ± SD)	51 ± 25	50 ± 14	56 ± 13
change from baseline (mean ± SD)	−3 ± 24	4 ± 17	6 ± 30
P value (*versus* placebo)	—	0.534	0.466
Fluid intake (ml/24 h)			
baseline (mean ± SD)	1570 ± 612	1558 ± 551	1539 ± 925
change from baseline (mean ± SD)	−211 ± 550	−113 ± 706	275 ± 926
P value (*versus* placebo)	—	0.776	0.185
AVP (ng/L)			
baseline (mean ± SD)	1.5 ± 1.9	1.4 ± 2.2	3.6 ± 9.1
change from baseline (mean ± SD)	−0.7 ± 1.3	1.0 ± 1.7	2.6 ± 6.7
P value (*versus* placebo)	—	0.391	0.100
Renin (ng/ml per h)			
baseline (mean ± SD)	0.6 ± 0.6	0.9 ± 1.1	1.7 ± 4.4
change from baseline (mean ± SD)	0.4 ± 0.7	0.3 ± 1.4	0.5 ± 3.1
P value (*versus* placebo)	—	0.966	0.932
Aldosterone (ng/L)			
baseline (mean ± SD)	144 ± 158	93 ± 79	65 ± 66
change from baseline (mean ± SD)	−31 ± 54	14 ± 145	−2 ± 68
P value (*versus* placebo)	—	0.344	0.554

[a]AVP, arginine vasopressin.

thostatic hypotension (systolic BP standing − supine ≤−20 mmHg) was observed in eight (67%) patients in the 25-mg group, five (50%) patients in the 50-mg group, and four (44%) patients in the placebo group during the double-blind period.

Electrocardiogram at the end of the double-blind period showed an increase in mean heart rate from baseline in the 25-mg group (6 ± 14 bpm) and in the placebo group (6 ± 23 bpm) but not in the 50-mg group (decrease of 2 ± 10 bpm). No trend to prolonged QTcB interval (>450 ms in men and >470 ms in women) was observed.

During the double-blind period, four (15%) patients who were treated with satavaptan (in both groups) and two (22%) patients who were treated with placebo experienced at least one adverse event, including a serious adverse event (Table 3). None of the adverse events was considered by the investigators to be related to study treatment. During the overall exposure to satavaptan (double-blind + open-label treatment), 18 (51%) patients experienced at least one adverse event, including a serious adverse event. In only one patient were the adverse events (polyuria, nausea, moderate rigors, and confusion) considered by the investigator to be related to study treatment (patient on 25 mg of satavaptan during the open-label period). Serious adverse events, observed in seven (20%) patients, were sepsis (leading to death), respiratory failure (with recovery), bronchitis (with recovery), gastrointestinal hemorrhage (leading to death), vasculitis (leading to death), pneumonia (leading to death), and malignant brain neoplasm (leading to death). None of the serious adverse events was considered by the investigators to be related to study treatment. Overall, three (9%) patients withdrew from study treatment as a result of serious adverse events (worsening of preexisting vasculitis on placebo during the double-blind period, gastrointestinal hem-

Table 3. Adverse event distribution during the double-blind period

Adverse Events	Placebo (n = 9)	Satavaptan	
		25 mg (n = 14)	50 mg (n = 12)
Urinary tract infection	0	1	1
Vomiting	0	1	0
Pruritus	0	1	0
Stomatitis	1	0	0
Vasculitis[a]	1	0	0
Cryoglobulinemia	1	0	0

[a]Serious adverse event.

orrhage on 25 mg of satavaptan during the open-label period, and respiratory failure on 25 mg of satavaptan during the open-label period).

Hypernatremia (SNa >145 mmol/L) developed in two patients during the double-blind period (one on 25 mg of satavaptan and one on 50 mg of satavaptan) and in five patients during the open-label period (four on 25 mg of satavaptan and one on 50 mg of satavaptan). The SNa values were 146 and 156 mmol/L during the double-blind period (the first patient, who was on 25 mg of satavaptan, had vomiting of mild intensity with spontaneous resolution, and the second patient, on 50 mg of satavaptan, was asymptomatic) and from 146 to 161 mmol/L during the open-label period (one patient on 25 mg of satavaptan with a SNa of 146 mmol/L experienced nausea, rigors, and confusion, and the other four patients were asymptomatic).

Among the nine patients who had rapid correction of SNa during the double-blind period (increase in SNa >8 mmol/L within 24 h after the first dose), one patient experienced vomiting of mild intensity (25 mg of satavaptan). No significant changes in other laboratory parameters (renal, hepatic, or hematologic testings) were noticed in satavaptan-treated patients compared with placebo.

Long-Term Study (Second Part)

Eighteen patients (12 women and six men) who initially were included in the short-term study (1 mo) were able to be included in this long-term study (at least 12 mo). Mean (±SD) age was 68 ± 14 yr, and the origin of SIADH was malignancy (n = 2), drug (n = 4), miscellaneous (n = 4), and idiopathic (n = 8). Three dosages of satavaptan were available during this period (12.5, 25, and 50 mg, administered once daily). The dosage was adjusted as a function of the SNa values in patients who were on controlled water intake (≤1500 ml/d). Table 4 shows the evolution of the SNa during the open-label long-term extension.

Ten patients now are treated for at least 12 mo without drug escape. No adverse event related to satavaptan was noted during this period.

Discussion

This is the first study to use an oral V_2RA on a long-term basis to treat patients with SIADH-related hyponatremia. Satavaptan has a great selectivity and high affinity for renal V_2 receptors with the advantage of having a long half-life (14 to 17 h) (11,12).

Three other compounds with selectivity for V_2 receptors (or V_{1a} + V_2) and oral bioavailability are currently in development (or recently approved): OPC41061 (tolvaptan), VPA985 (lixivaptan), and YM087 (conivaptan: V_{1a} + V_2). Few published studies with these V_2RA have been conducted in patients with cirrhosis (with or without hyponatremia) (7,9,13) and patients with congestive heart failure (with or without hyponatremia) (14,15) showing that these V_2RA are effective in increasing FWC in various water-retention disorders. In SIADH, most of the publications are focused on short-term studies (<1 wk) (7–10). In our study, the number of responders to satavaptan at the end of the double-blind was comparable with both 25-mg (79%) and 50-mg (83%) dosages, the lowest SNa observed being 131 mmol/L. The normalization of the natremia after oral administration of satavaptan is the result of the rapid and marked increase in the renal free water excretion. During the first month of treatment, mean SNa remained normal and the majority (79%) of the patients were controlled with the dosage of 25 mg/d.

Excessive correction of hyponatremia is a hazardous situation with major risks for brain damage (myelinolysis) and neurologic sequelae (16). Careful approach of patients with sustained hyponatremia implies a limited correction below 12 mmol/L per 24 h (and <18 mmol/L per 48 h) and even less than 8 to 10 mmol/L per 24 h for patients with additional risk factors for myelinolysis (16,17). In our study, the mean daily increase in SNa was lower than 8 mmol/L in the first 24 h of correction with satavaptan. Few patients (n = 3) in the active treatment group had a correction level above 12 mmol/L per 24 h (maximum daily increase observed 16 mmol/L per 24 h) after the first dose of satavaptan. None of them presented neurologic complications. The maximum SNa increase and aquaresis were observed 3 to 6 h after dosing, but SNa continued to increase further. Like with the other therapies, excessive correction with V_2RA could produce osmotic demyelination (18,19). Good control and limited correction are achievable by use of titrated doses of V_2RA during the initial phase of correction, especially in patients with severe hyponatremia (<115 to 120 mmol/L). Indeed, most of published cases of myelinolysis were reported in patients with initial SNa <115 mmol/L (20), which was not the case in our study.

The efficacy of satavaptan to control the natremia remained excellent during the entire study period. Under a state of relative water control (<1500 ml/d), mean SNa values remained within the normal range during the open-label period.

These encouraging data over the efficacy of satavaptan are

Table 4. Evolution of SNa during the open-label long-term extension

SNa (mmol/L)	Time (mo)			
	Baseline[a]	6	8	12
No. of patients	18	15	13	10
Mean ± SD	135 ± 4	138 ± 3	138 ± 5	140 ± 3
Range	121 to 146	133 to 145	127 to 145	136 to 145

[a]End of short-term (1-mo) study.

strengthened by the good tolerance to the treatment that was observed in our patients. Only a slight increase in thirst was noted in both dosage groups. Some patients regained weight during treatment probably because their general status improved after correction of the hyponatremia, leading to a better food intake. The most frequently observed change in vital signs was orthostatic hypotension, usually asymptomatic and explained by the aquaretic activity of the compound. Only one patient presented symptoms that potentially were related to the compound (polyuria, nausea, rigors, and confusion), and no patients discontinued the study in relation to the treatment, even in the patients who were treated for 12 mo.

Although evolution of the symptoms related to hyponatremia was not significantly evaluated in the design of this study, patients subjectively felt better when treated with satavaptan. Additional studies are in progress to evaluate these particular points.

Conclusion

Treatment of patients with SIADH and mild or moderate hyponatremia with satavaptan, a new oral V_2RA, corrects SNa with a good safety profile. This effect was confirmed for the first time on a long-term basis.

Acknowledgments

The study was sponsored by Sanofi-Aventis.

This study was designed by H.M.H., G.D., and Dr. J.G. Verbalis.

We thank F. Coste for supervising the clinical operations; M. DeUbeda and I. Remoissenet for data collection; S. Turpault for pharmacokinetics measurements; and C. Smolens, D. Lei, and A. Boddy for statistical analysis.

References

1. Anderson RJ, Chung HM, Kluge R, Schrier RW: Hyponatremia: A prospective analysis of its epidemiology and the pathogenic role of vasopressin. *Ann Intern Med* 102: 164–168, 1985
2. Soupart A, Decaux G: Therapeutic recommendations for management of severe hyponatremia: Current concepts on pathogenesis and prevention of neurologic complications. *Clin Nephrol* 46: 149–169, 1996
3. Thibonnier M, Coles P, Thibonnier A, Sholam M: The basic and clinical pharmacology of nonpeptide vasopressin receptor antagonist. *Annu Rev Pharmacol Toxicol* 41: 175–202, 2001
4. Gross P, Reimann D, Henschkowski J, Damian M: Treatment of severe hyponatremia: Conventional and novel aspects. *J Am Soc Nephrol* 12[Suppl]: S10–S14, 2001
5. Verbalis JG: Vasopressin V2 receptor antagonists. *J Mol Endocrinol* 29: 1–9, 2002
6. Saito T, Ishikawa S, Abe K, Kamoi K, Yamada K, Shimizu K, Saruta T, Yoshida S: Acute aquaresis by the nonpeptide arginine vasopressin (AVP) antagonist OPC-31260 improves hyponatremia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Clin Endocrinol Metab* 82: 1054–1057, 1997
7. Wong F, Blei AT, Blendis LM, Thuluvath PJ: A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: A multicenter, randomized, placebo-controlled trial. *Hepatology* 37: 182–191, 2003
8. Decaux G: Long-term treatment of patients with inappropriate secretion of antidiuretic hormone by the vasopressin receptor antagonist conivaptan, urea, or furosemide. *Am J Med* 110: 582–584, 2001
9. Decaux G: Difference in solute excretion during correction of hyponatremic patients with cirrhosis or syndrome of inappropriate secretion of antidiuretic hormone by oral vasopressin V2 receptor antagonist VPA-985. *J Lab Clin Med* 138: 18–21, 2001
10. Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long WA, Smith N: Efficacy and safety of oral conivaptan. A V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab* 91: 2145–2152, 2006
11. Serradeil-Le Gal C, Lacour C, Valette G, Garcia G, Foulon L, Galindo G, Bankir L, Pouzet B, Guillon G, Barberis C, Chicot D, Jard S, Vilain P, Garcia C, Marty E, Raufaste D, Brossard G, Nisato D, Maffrand JP, Le Fur G: Characterization of SR121463A, a highly potent and selective orally active vasopressin V2 receptor antagonist. *J Clin Invest* 98: 2729–2738, 1996
12. Serradeil-Le Gal C: An overview of SR121463, a selective non-peptide vasopressin V2 receptor antagonist. *Cardiovasc Drug Rev* 19: 201–214, 2001
13. Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, Djian J; the VPA Study Group: Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: A randomized double-blind multicenter trial. *Gastroenterology* 124: 933–939, 2003
14. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayah M, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C: Acute and chronic therapeutic impact of a vasopressin antagonist in congestive heart failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA* 291: 1963–1971, 2004
15. Gheorghiade M, Gottlieb SS, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, Orlandi C; Tolvaptan Investigators: Vasopressin V2 receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol* 97: 1064–1067, 2006
16. Decaux G, Soupart A: Treatment of symptomatic hyponatremia. *Am J Med Sci* 326: 25–30, 2003
17. Sterns RH, Cappuccio JD, Silver SM, Cohen EP: Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. *J Am Soc Nephrol* 4: 1522–1530, 1994
18. Verbalis JG, Martinez AJ: Correction of chronic hyponatremia with a vasopressin receptor antagonist is associated with brain myelinolysis in rats [Abstract]. *Clin Res* 37: 586A, 1989
19. Soupart A, Silver S, Schroeder B, Sterns R, Decaux G: Comparison of mortality and brain composition in hyponatremic rats treated with vasopressin V1–V2 receptor antagonists or water diuresis [Abstract]. *J Am Soc Nephrol* 14: 747A, 2003
20. Cluitmans FH, Meinders AE: Management of severe hyponatremia: Rapid or slow correction? *Am J Med* 88: 161–166, 1989