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MONOGRAPH

LIXIVAPTAN

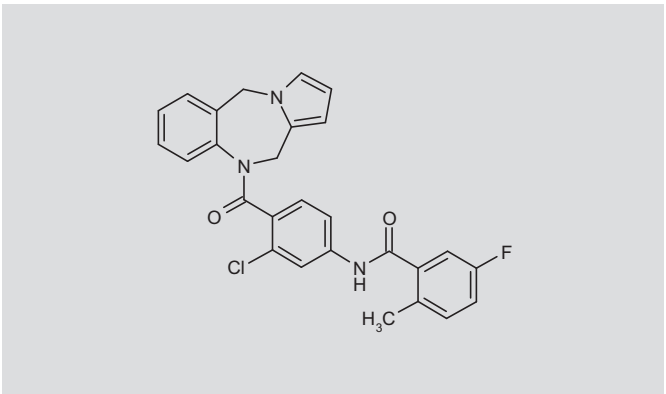
Rec INN

Vasopressin V_2 Receptor Antagonist
Treatment of Heart Failure
Treatment of Hyponatremia

VPA-985
WAY-VPA-985

N-[3-Chloro-4-(10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide

InChI: 1S/C27H21ClFN3O2/c1-17-8-9-19(29)13-23(17)26(33)30-20-10-11-22(24(28)14-20)27(34)32-16-21-6-4-12-31(21)15-18-5-2-3-7-25(18)32/h2-14H,15-16H2,1H3,(H,30,33)



$C_{27}H_{21}ClFN_3O_2$

Mol wt: 473.926

CAS: 168079-32-1

EN: 224116

SUMMARY

Hyponatremia is the most common electrolyte abnormality and has been associated with various morbidities, longer hospital stay and increased mortality. Until recently, options for treating hyponatremia were limited; however, the introduction of vasopressin antagonists has signaled the beginning of a new era in its treatment by addressing the responsible mechanism in the majority of cases: inappropriately high levels of vasopressin. By promoting aquaresis, or electrolyte-free water excretion, vasopressin antagonists could potentially play an important role in the treatment of euvolemic hyponatremia, typically encountered in the syndrome of inappropriate antidiuretic hormone secretion, and hypervolemic hyponatremia, seen in heart failure and cirrhosis. This review discusses lixivaptan, a selective, orally active, vasopressin V_2 receptor antagonist, and its potential use in the treatment of hyponatremia.

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SYNTHESIS*

Lixivaptan can be synthesized by two alternative methods:

Acylation of methyl 4-amino-2-chlorobenzoate (I) with 5-fluoro-2-methylbenzoyl chloride (II) in the presence of Et_3N gives amide (III), which is then hydrolyzed at the ester group using NaOH in boiling H_2O/EtOH to yield 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoic acid (IV). Finally, after chlorination of acid (IV) with $SOCl_2$ at reflux, the resulting acid chloride (V) (1-4) is condensed with 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (VI) by means of DIEA in CH_2Cl_2 (5). Scheme 1.

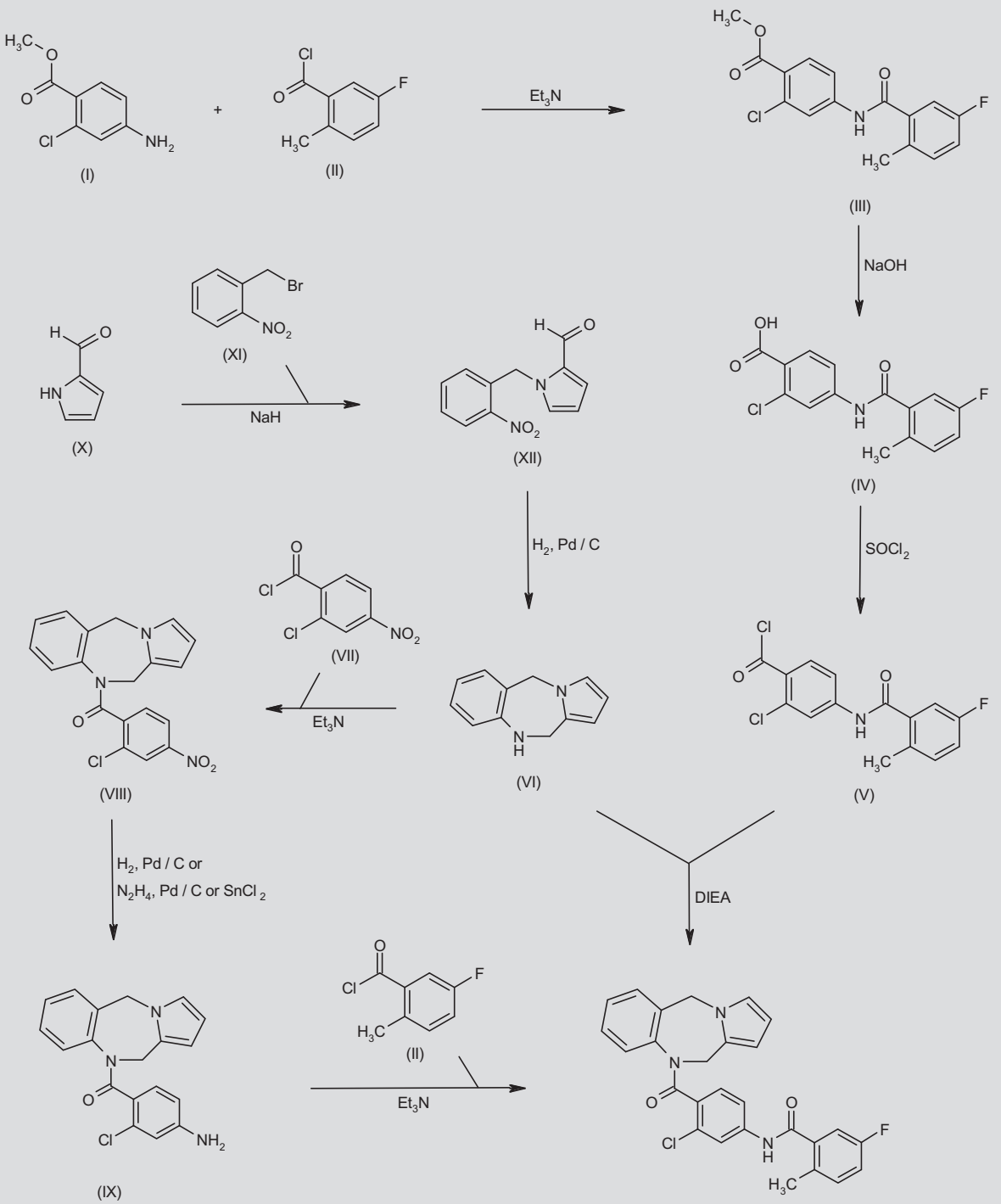
In a related method, acylation of benzodiazepine (VI) with 2-chloro-4-nitrobenzoyl chloride (VII) by means of Et_3N in CH_2Cl_2 provides the nitrobenzamide (VIII), which is reduced to the corresponding 4-amino derivative (IX) using either H_2 or hydrazine in the presence of Pd/C in EtOH or by means of $SnCl_2$. Finally, amine (IX) is acylated with 5-fluoro-2-methylbenzoyl chloride (II) using Et_3N in CH_2Cl_2 (1-4). Scheme 1.

The tricyclic intermediate (VI) is prepared by alkylation of pyrrole-2-carbaldehyde (X) with 2-nitrobenzyl bromide (XI) by means of NaH in DMF to afford 1-(2-nitrobenzyl)pyrrole-2-carbaldehyde (XII), which undergoes reductocyclization to the pyrrolobenzodiazepine (VI) upon catalytic hydrogenation over Pd/C in EtOH/EtOAc (1-4). Scheme 1.

BACKGROUND

Hyponatremia is the most common electrolyte abnormality, encountered in 14-38% of hospitalized patients, depending on its definition (6-9). Traditionally, the lower limit of serum sodium (Na^+) is defined as 135 mEq/L (10). However, there is a need to redefine hyponatremia (11), as several studies have shown worsening outcome at a cut-off serum Na^+ level of 138 mEq/L (7-9, 12). Hyponatremia has been

Scheme 1. Synthesis of Lixivaptan



associated with cognitive impairment and falls (13), osteoporosis and fractures (14-16), longer hospital stay, higher costs and greater mortality (6-9, 12, 17). Multiple diseases can cause hyponatremia, so careful physical examination to assess the volume status is required for accurate diagnosis and treatment.

Classification of hyponatremia

Na^+ is the major determinant of serum osmolality, which should be maintained between 280 and 300 mOsm/kg to ensure normal cellular function. Hyponatremia is usually accompanied by hypo-osmolality, although it can be associated with normal serum osmolality (often referred to as pseudohyponatremia), as seen in conditions characterized by a marked elevation in serum lipids or proteins (18). On the other hand, hyperosmolar hyponatremia can be seen when solutes other than Na^+ are present in plasma, leading to extracellular volume expansion due to a water shift from the intracellular to the extracellular compartment. This can be seen with the use of mannitol or contrast agents, or in conditions characterized by high plasma glucose levels (10).

The most common form of hyponatremia is associated with hypo-osmolality, and is further divided into hypo-, eu- and hypervolemic hyponatremia, depending on the volume status. Hypovolemic hyponatremia is caused by greater Na^+ loss as compared with water through renal or extrarenal routes, or by the administration of hypotonic solutions when replacing fluid loss. Euvolemic hyponatremia is mainly seen with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Hypervolemic hyponatremia is seen in conditions that are associated with increase in the extracellular volume, such as heart failure (HF) and cirrhosis. Euvolemic and hypervolemic hyponatremia are usually associated with inappropriately high levels of arginine vasopressin (AVP) hormone.

Arginine vasopressin

AVP is a nonpeptide hormone that plays a major role in water homeostasis, blood volume control and osmolality (19). It is synthesized in the neurohypophyseal magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. Subsequently, it is transported down the supraopticohypophyseal tract to the posterior pituitary, where it is eventually stored (20). AVP is released into the blood circulation under the influence of specific stimuli: osmotic (due to increase in serum osmolality) and nonosmotic (unrelated to osmolality changes) (20-23).

Osmoreceptors are located in the anteroventral third ventricle of the hypothalamus (23). They detect changes in serum osmolality and either stimulate (in hyperosmolar states) or inhibit (in hypo-osmolar states) AVP release. A slight rise (as low as 1-2%) in serum osmolality stimulates the release of AVP, which increases water reabsorption by binding to the vasopressin V_2 receptors at the renal tubular cells, maintaining serum osmolality within the normal range (21, 24).

The nonosmotic stimulus of AVP release is thought to be mediated by baroreceptors. These receptors are located in the carotid sinus, walls of the great veins, atria and renal afferent arterioles. They are sensitive to changes in blood volume (20-22). Neurohormonal systems, including the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), are stimulated in conditions associated with arterial underfilling (24-26). Stimulation of the neurohormonal systems causes the release of AVP from the posterior pituitary, which stimulates water retention in an attempt to restore intravascular volume (24).

Vasopressin receptors

AVP exerts its function through multiple G protein-coupled receptors. These receptors are classified into three different subtypes: V_{1A} V_{1B} and V_2. AVP mediates its actions by binding to these receptors (27). The V_{1A} and V_{1B} receptors are linked to the phosphoinositol signaling pathway. When AVP binds to either one, an influx of calcium (second messenger) to the intracellular compartment is observed. In contrast, binding to V_2 receptors, which are mainly found in the renal collecting ducts, results in an increase in intracellular cyclic adenosine monophosphate (cAMP) through the adenylate cyclase signaling pathway, which functions as a second messenger (28-30).

The V_{1A} receptors are mainly located on the vascular smooth muscle cells; however, they are also found in many other tissues, such as the liver, platelets, uterus, kidney, adrenal gland and brain. Their stimulation results in vasoconstriction, glycogenolysis, platelet aggregation, myocyte hypertrophy, stress and anxiety, depending on the location (31, 32). The V_{1B} receptors are mainly located in the anterior pituitary gland. Their activation plays a major role in the regulation of adrenocorticotropic hormone (ACTH) secretion during stress and in resting conditions (33).

The antidiuretic effect of AVP is mediated by the V_2 receptors located on the principal cells of the renal collecting ducts. By binding to V_2 receptors, intracellular cAMP increases through the adenylate cyclase signal transduction pathway. This in turn leads to the insertion of aquaporin-2 (AQP-2) water channels into the luminal membrane of the principal cells. The AQP-2 channels increase the permeability of the renal collecting ducts and lead to water reabsorption (34, 35). Thus, AVP plays a major role in maintaining body water homeostasis and osmolality.

Role of vasopressin in hyponatremia

Under normal physiological circumstances, serum Na^+ and osmolality are maintained within their narrow normal range to ensure normal cellular physiology. Two major mechanisms are involved in this regulation: fluid intake (controlled by thirst) and renal water excretion (regulated mainly by AVP) (19).

The inappropriately elevated AVP levels observed in hyponatremic animals with cirrhosis (36) and HF (37) suggest that AVP plays an important role in the development of hyponatremia. Similar findings were reported in hyponatremic patients with liver cirrhosis, HF and SIADH (38-41). In all these conditions, AVP secretion was inappropriately stimulated rather than suppressed, as it should have been under normal physiological situations. This stimulation of AVP release is driven by a nonosmotic mechanism and thought to be mediated by baroreceptors, as described earlier.

SIADH is a condition characterized by euvolemic hyponatremia as a result of nonphysiological secretion or lack of suppression of AVP, which results in enhanced water reabsorption, leading to dilutional hyponatremia (42). HF and liver cirrhosis are characterized by hyper-

volemic hyponatremia. They are associated with decreased arterial filling secondary to low cardiac output or peripheral vascular resistance that is sensed by baroreceptors, leading to stimulation of AVP release. This nonosmotic mechanism of AVP release results in renal water reabsorption despite low osmolality, leading to hyponatremia (24, 36, 37).

Treatment of chronic hyponatremia represents a challenge among this patient population. Current treatment options, including fluid restriction (6), diuretics (43), demeclocycline (44), lithium (45) and urea (46), are limited because of noncompliance, electrolyte imbalance, nephrotoxicity, narrow therapeutic/toxic ratio and poor palatability, respectively.

Vasopressin receptor antagonists

Given the central role of AVP in the pathophysiology of hyponatremia through binding to AVP receptors, an interest in producing vasopressin receptor antagonists to treat hyponatremia developed as early as the 1960s. Vasopressin receptor antagonists were first recognized by Manning and Sawyer in the early 1970s (47) and were first synthesized as peptide compounds. These antagonists had limitations to their clinical use secondary to their short half-lives, poor oral bioavailability and partial agonist activity in humans (48, 49). In 1992, the first nonpeptide V_2 receptor antagonist, OPC-31260, was discovered by Yamamura et al. (50). The nonpeptide antagonists are more orally bioavailable and have longer half-lives than the peptide compounds, rendering them a better and practical choice for the treatment of hyponatremia (50, 51).

Several vasopressin receptor antagonists have been developed in the last few decades. Conivaptan is an intravenous dual V_{1A}/V_2 receptor antagonist that was approved by the FDA for the treatment of euvolemic hyponatremia in December 2005 and for hypervolemic hyponatremia in February 2007 (52). Tolvaptan is the first oral and selective V_2 receptor antagonist that was approved by the FDA for the treatment of euvolemic and hypervolemic hyponatremia in 2009 (53). Lixivapatan (VPA-985) is a potent, selective, competitive, orally active, nonpeptide V_2 receptor antagonist (1, 54) that was originated by Wyeth (now Pfizer) and is currently licensed to Cardiokine and Biogen Idec (55).

PRECLINICAL PHARMACOLOGY

In vitro studies showed that lixivaptan is a potent, competitive V_2 receptor antagonist with no partial agonist activity. It is approximately 100-fold more selective for the human V_2 over V_{1A} receptors, has no activity at V_{1B} receptors and has weak affinity for oxytocin receptors (1, 54).

In an initial study published in 1998, lixivaptan inhibited the binding of AVP to native V_2 receptors in membranes isolated from rat and dog renal medulla, with K_i values of 0.48 and 0.82 nM, respectively. In membranes of cultured murine fibroblasts expressing the human V_2 receptor, the K_i was 0.6 nM. The dissociation constant (k_d) of AVP increased from 0.79 nM to 1.04 nM in the presence of lixivaptan, while the maximum binding remained unchanged, suggesting that lixivaptan competitively inhibits AVP binding to V_2 receptors (54).

cAMP is the second messenger that is generated by AVP binding to V_2 receptors (1, 54). Lixivaptan had no effect on basal cAMP generation but inhibited AVP-induced cAMP generation (IC_{50} = 6 nM at 1 nM AVP stimulation) (54).

In vivo, lixivaptan was tested in a rat model of HF to assess its effect on renal and cardiovascular functions. The animals received 10 mg/kg/day of lixivaptan for 8 weeks. Different parameters were measured at the beginning of the study and at 4 and 8 weeks, including: echocardiographic and hemodynamic parameters, urine volume, urine osmolality and urine electrolytes. Organ weight and histology were performed at the end of the study (after 8 weeks). Lixivaptan was associated with increased aquaresis and decreased urine osmolality. In addition, a decrease in cardiac hypertrophy and lung weight and a reduction in the degree of HF were observed (56).

PHARMACOKINETICS AND METABOLISM

In a trial involving patients with HF, lixivaptan was administered at doses ranging from 10 to 400 mg. Rapid absorption was observed, with a t_{max} of ≤ 1 hour. The maximum concentration (C_{max}) and area under the curve (AUC) values increased in a dose-dependent manner, with a subsequent biexponential decline in the plasma drug concentration. The mean clearance value was 0.97 L/h/kg and the $t_{1/2}$ was 9.8 hours (Table I) (57).

In patients with cirrhosis and ascites, lixivaptan was given at daily doses ranging from 25 to 300 mg. There were no significant differences in the mean dose-adjusted plasma concentrations, C_{max} and AUC. Lixivaptan was rapidly absorbed, with mean t_{max} occurring within 1 hour. The rate of drug clearance, volume of distribution and $t_{1/2}$ of lixivaptan were similar across dose levels, although interindividual variability was observed within dose groups (Table I) (58).

In a single-ascending-dose trial in healthy male volunteers, lixivaptan displayed linear pharmacokinetics when given at oral doses ranging from 50 to 500 mg, with a $t_{1/2}$ of 8-10 hours (59). Another study showed that its effects increased in a dose-related manner (Table I) (60).

Studies involving rats, dogs and humans showed that the major metabolic pathways of lixivaptan were oxidation of the pyrrole and diazepine rings by liver microsomes (cytochrome P450 CYP3A4). The metabolites were identified in the urine, plasma and feces (61).

SAFETY

Lixivaptan as a single oral daily dose was well tolerated among healthy volunteers. Thirst, lightheadedness and dehydration were the most common side effects reported with its use, which could be attributed to body water loss and fluid restriction (59, 62). Due to its potential to overly correct hyponatremia, frequent monitoring of the serum Na^+ level is needed (63).

When studied in patients with HF, no serious adverse events were reported. Tachy- and bradyarrhythmia are two potentially serious adverse effects that were considered to be possibly related to treatment in patients with HF; however, both resolved without intervention. The most common adverse events were diarrhea, dizziness, headache, orthostatic tachycardia, dry mouth and flatulence. No clinically relevant changes in vital signs, electrocardiogram or chemistry values were detected (64).

Table I. *Human pharmacokinetic studies.*

Lixivaptan dose	Pharmacokinetic data	Subjects	Study design
50-500 mg	Lixivaptan displayed linear pharmacokinetics (59) t_{max} < 1 hour Dose-proportional increase in C_{max} and AUC $t_{1/2}$ 9.8 hours (8-10 hours)	Healthy volunteers (n = 10)	Single-ascending-dose trial
10-400 mg	Dose-dependent increase in C_{max} and AUC (57) $t_{max} \leq 1$ hour $t_{1/2}$ 9.8 ± 2.3 hours	Heart failure (n = 42)	Single-ascending-dose trial

	Healthy volunteers (60)				Cirrhosis (58)					
	CL_{H2O}	UF	U_{osm}	S_{osm}	t_{max}	C_{max}	AUC	$t_{1/2}$		
25 mg					0.44±0.13	83±57	499±291	14.61±9.30		Randomized, double-blind, placebo-controlled, ascending-dose studies
50 mg	4.5±1.8	6.7±2.0	98±28	287±2.5	0.50±0.00	210±43	953±755	12.49±3.66		
100 mg	7.6±1.4	10.4±2.4	77±14	294±1.9	1.00±0.71	719±28	4,391±2,213	9.05±1.78		
200 mg	9.0±0.8	11.9±1.0	70±6.5	287±5.6	0.75±0.29	1,208±489	8,775±4,431	22.56±25.69		
300 mg					0.88±0.25	1,877±713	14,884±7,807	21.62±12.51		
400 mg	8.7±1.6	11.4±1.2	64±37	290±30						
50-400 mg	t_{max} 2 hours									

$CL_{H2O,}$ free water clearance; UF, urine flow; $U_{osm,}$ urine osmolality; $S_{osm,}$ serum osmolality; $t_{max,}$ time to maximum plasma concentration; $C_{max,}$ maximum plasma concentration; $t_{1/2,}$ half-life; AUC, area under the concentration–time curve.

In a multicenter, randomized, placebo-controlled trial in hospitalized patients with hyponatremia (33 patients with cirrhosis, 6 with HF and 5 with SIADH), 12 patients discontinued therapy at a mean time of 5.3 days. The main reason for these discontinuations was dehydration (n = 6), manifested by systemic postural hypotension. Other reasons for trial discontinuation were ruptured umbilical hernia (n = 2), spontaneous bacterial peritonitis (n = 1), upper gastrointestinal bleeding (n = 1), inability to obtain blood samples (n = 1) and failure to store the drug properly (n = 1). Thirst scores were increased in patients treated with 250 mg twice daily throughout the trial period. A total of two patients developed worsening encephalopathy that resolved with lactulose therapy, and one patient died due to aspiration pneumonia. Seven patients had their lixivaptan withheld because of an increase in the serum Na^+ (serum Na^+ had risen to > 142 mEq/L or by > 8 mEq/L from the previous measurement). There was no significant change in the serum creatinine level with lixivaptan use (63).

Among patients with cirrhosis and ascites (n = 27), lixivaptan was well tolerated, with no premature withdrawals. No serious adverse events occurred during the hospitalization period. One patient with end-stage liver disease developed a viral syndrome associated with myositis 10 days after the last dose of lixivaptan. This was considered to be possibly related to lixivaptan. However, all the symptoms resolved without specific treatment. Another patient developed transient abdominal pain and elevated serum amylase levels that returned to normal after 3 days. No clinically significant changes in blood pressure, heart rate or electrocardiogram values were associated with lixivaptan treatment (58).

In a randomized, double-blind, multicenter trial involving patients (n = 60) with cirrhosis and hyponatremia, the sensation of thirst increased significantly in the 200-mg lixivaptan group, but not in the 100-mg lixivaptin or placebo groups. Serious adverse events leading to discontinuation of therapy were observed in 11 patients (4 in the placebo group). These were considered to be drug-related in five patients in the lixivaptan group. Renal impairment was reported in six patients (two from the placebo group), with no statistically significant difference. No significant effects of lixivaptan were observed on systolic and diastolic blood pressure and heart rate (65).

In addition, a phase I trial was designed as a double-blind, randomized, repeat-dose, single-site, 4-arm, parallel-group trial to determine the effects of lixivaptan on electrocardiogram. Healthy volunteers (expected n = 300) were randomized to receive lixivaptan at therapeutic or supratherapeutic doses, moxifloxacin (positive control) or placebo. The primary outcome was prespecified as the change in the corrected QT interval duration from baseline electrocardiogram over 7 days. At the time of publication, the trial had been completed but data were not available (66).

The coadministration of lixivaptan and furosemide in healthy volunteers was well tolerated. Adverse events included mild dizziness, mild abdominal pain, moderate nausea and one episode of syncope. The combination was no more kaliuretic than furosemide alone and did not increase the risk of developing hypo- or hypernatremia (67).

CLINICAL STUDIES

In a study involving healthy volunteers, lixivaptan was administered for 14 days as daily oral doses ranging from 50 to 400 mg/day (Table II) (60). Maximum free water clearance, maximum urine flow, minimum urine osmolality and maximum serum osmolality were measured. The t_{max} was found to be 2 hours. Lixivaptan significantly lowered urine osmolality as compared with placebo (98 ± 28, 77 ± 14, 70 ± 6.5 and 64 ± 37 mOsm/L, respectively, on lixivaptan 50, 100, 200 and 400 mg compared with 667 ± 91 mOsm/L in the placebo group). It was also associated with significantly higher free water

Table II. *Phase I clinical trials.*

Study design	Target population (number of patients)	Intervention and dosage	Relevant findings	Refs.
Randomized, double-blind, placebo-controlled, single-ascending-dose	Healthy male volunteers with overnight fast and fluid restriction	Oral lixivaptan administration at 1-500 mg	Significant and dose-dependent increase in urine output and free water clearance at 12 and 24 hours after lixivaptan administration Decrease in urine osmolality over 24 hours with lixivaptan administration No changes in urinary Na^+ excretion during the 24 hours after lixivaptan administration	59
Randomized, double-blind, placebo-controlled, single-ascending-dose	Healthy volunteers (n = 38)	Oral lixivaptan administration at 50, 100, 200 and 400 mg/day for 14 days	Dose-dependent reduction in urine osmolality from 667 mOsm/L in the placebo group to 98, 77, 70 and 64 mOsm/L, respectively, in the 50, 100, 200 and 400 mg lixivaptan groups Increase in the free water clearance and urine flow was seen with lixivaptan No effects on urinary Na^+ excretion and creatinine clearance	60
Placebo-controlled, single-ascending-dose	Healthy volunteers with overnight fast and fluid restriction continued until 4 hours post-dose (n = 10/dose group)	Oral lixivaptan administration at 5, 50, 100, 200 and 400 mg	Increase in mean urine flow ranged from 3.8 to 11.3 mL/min in the lixivaptan groups compared to 2.1 mL/min in the placebo group Dose-dependent reduction in urine osmolality with lixivaptan groups with values returning to baseline over 2- to 24-hour period after the dose Lixivaptan increased free water clearance and serum Na^+ levels at 12 and 8 hours after dose, respectively No changes in urine Na^+ excretion were noticed among all groups	62
Randomized, open-label, placebo-controlled, crossover assignment	Healthy volunteers with overnight fast and fluid restriction (n = 12)	Single oral doses of either 75 mg lixivaptan, 40 mg furosemide, or both, with a 1-week washout period between doses	Lixivaptan and furosemide coadministration was no more kaliuretic than furosemide alone Lixivaptan and furosemide coadministration provided greater diuresis than either agent alone No increase in risk of developing hyponatremia or hypernatremia was noted	67
Two-period, randomized, open-label, placebo-controlled, crossover assignment	Healthy volunteers (n = 34)	Administration of single oral doses of 50 mg lixivaptan with 40 mg furosemide	AVP levels increased with furosemide as compared to lixivaptan (41.2 ± 97.19 and 2.9 ± 6.62 pg/mL, respectively) at 6 hours after administration At 24 hours after dose, a small increase in AVP levels (1.3 pg/mL) was observed with lixivaptan, while levels returned to baseline with furosemide Urine volume increase was similar with either agent Lixivaptan was associated with transient increases in serum Na^+ levels with no significant changes in other electrolytes as compared to furosemide, which reduced serum concentrations of all electrolytes tested	80

AVP, arginine vasopressin.

clearance as compared with placebo (4.5 ± 1.8, 7.6 ± 1.4, 9.0 ± 0.8 and 8.7 ± 1.6 mL/min, respectively, on lixivaptan 50, 100, 200 and 400 mg compared with −1.4 ± 1.8 mL/min in the placebo group). Moreover, lixivaptan was associated with significantly higher urine flow as compared with placebo (6.7 ± 2.0, 10.4 ± 2.4, 11.9 ± 1.0 and 11.4 ± 1.2 mL/min, respectively, on lixivaptan 50, 100, 200 and 400 mg compared with 1.5 ± 0.7 mL/min in the placebo group). An increase in serum osmolality was also noticed but did not reach statistical significance (287 ± 2.5, 294 ± 1.9, 287 ± 5.6 and 290 ± 2.8 mOsm/L, respectively, on lixivaptan 50, 100, 200 and 400 mg compared with 282 ± 2.8 mOsm/L in the placebo group).

The available information on the effects of lixivaptan in heart failure is derived from one published study (Table III) (64); however, other major studies have been completed but not yet published (Table IV) (68, 69).

A randomized, double-blind, placebo-controlled study was designed to investigate the effect of lixivaptan in patients with chronic symptomatic HF New York Heart Association (NYHA) functional class II or III, with left ventricular ejection fraction (LVEF) ≤ 35% documented within 3 months of study enrollment. Forty-two patients were enrolled and completed the study (64). One day before the study (day −1), all patients received a single-blind placebo dose (baseline). On day 1, patients received placebo (n = 12) or lixivaptan at doses of 10, 30, 75, 150, 250 or 400 mg (n = 5 per dose group). Multiple serum, urinary and neurohormonal tests were performed on both days. On day 1, there was a dose-related increase in urine volume with all lixivaptan doses above 10 mg 4 hours post-dose. Also, urine flow rate was significantly greater at 2 hours with all lixivaptan doses ≥ 30 mg compared to placebo ($P < 0.001$). In addition, urine volume increased from 1.8 L with placebo to 3.9 L

Table III. *Phase II clinical trials.*

Study design	Target population (number of patients)	Intervention and dosage	Relevant findings	Refs.
Randomized, double-blind, placebo-controlled	Hospitalized patients with stable hyponatremia (n = 44)	Administration of oral lixivaptan twice daily at doses of 25, 125 and 250 mg for up to 7 days	Lixivaptan was associated with increased net fluid volume, free water clearance, serum Na^+ concentration, and serum osmolality Lixivaptan was associated with reduction in urine osmolality, lower body mass and higher AVP levels	63
Randomized, double-blind, placebo-controlled, single-ascending-dose	Chronic symptomatic HF patients with NYHA functional class II or III (n = 42)	Single oral dose of lixivaptan of 10, 30, 75, 150, 250 or 400 mg	Lixivaptan was associated with a dose-dependent increase in urine volume, urine flow, serum osmolality and serum Na^+ concentration Lixivaptan was associated with a dose-dependent reduction in urine osmolality and higher solute-free water excretion	64
Post hoc analysis of a randomized, double-blind, placebo-controlled	Hyponatremic patients due to cirrhosis (n = 60)	Lixivaptan at 50 or 100 mg twice daily for a total of 7 days	Hyponatremia corrected in 27% of patients receiving 50 mg lixivaptan and 50% of patients receiving 100 mg lixivaptan as compared with 0% of patients receiving placebo, with mean correction time of 4.8 and 5.7 days with 50 and 100 mg lixivaptan, respectively Significant dose-dependent reduction in urine osmolality, increase in urine volume and free water clearance after 7 days were associated with lixivaptan administration as compared with placebo	65
Randomized, double-blind, placebo-controlled, single-ascending-dose	Chronic symptomatic HF patients with NYHA functional class II or III (n = 21)	Single oral dose of lixivaptan of 30, 75, 150 or 250 mg	Significant reduction in urinary AQP-2 excretion observed with all lixivaptan doses at 2 hours after administration as compared with placebo and baseline AQP-2 excretion continued to be lower 8 hours after administration of 30 and 75 mg ($P < 0.05$), and 250 mg lixivaptan ($P < 0.001$) as compared with placebo and baseline	70
Randomized, double-blind, placebo-controlled, multiple-dose	Hyponatremic patients (n = 112)	Lixivaptan 50 or 100 mg twice daily for a total of 7 days	Lixivaptan was associated with a significant reduction in urinary osmolality and a significant increase in serum Na^+ concentrations from a baseline of 128 mEq/L to 132 and 134 mEq/L with 50 and 100 mg, respectively No changes in urinary electrolyte excretion	71
Substudy, multicenter, randomized, double-blind	Patients with stable hyponatremia due to SIADH or cirrhosis (n = 11)	Oral lixivaptan twice daily at a dose of 50 or 100 mg	In the SIADH group, lixivaptan was associated with normalization of serum Na^+ concentration after 1 day of treatment, reduction in Na^+ and uric acid excretion, a reduction in the fractional excretion of Na^+, and no changes in plasma renin, aldosterone, AVP, atrial natriuretic factor, blood pressure and pulse rate In the cirrhosis group, lixivaptan was associated with normalization of serum Na^+ concentration after approximately 2 days of treatment, slight increase in Na^+ and K^+ excretion, significant increase in urea excretion, increase in the fractional excretion of Na^+ and AVP level, and no changes in plasma renin, aldosterone, atrial natriuretic factor, blood pressure and pulse rate	74
Double-blind, placebo-controlled	Hyponatremia due to carbamazepine or oxcarbazepine (n = 8)	Single oral dose of 75 mg of lixivaptan	Lixivaptan safely corrected the hyponatremia with low plasma AVP levels throughout the trial	75

HF, heart failure; SIADH, syndrome of inappropriate antidiuretic hormone; AVP, arginine vasopressin.

with the 400-mg lixivaptan dose in the first 24 hours after dosing ($P < 0.01$). Reductions in urinary osmolality were noticed to be dose-dependent among all patients who received lixivaptan ($P < 0.001$ compared to placebo), with no significant differences in urinary excretion of Na^+, potassium, chloride, magnesium or urea nitrogen. In addition, at doses ≥ 75 mg, lixivaptan was associated with higher serum osmolality after 2 hours as compared to placebo ($P < 0.05$). Similarly, higher serum Na^+ concentrations were recorded at 2 hours post-administration with doses of 150 and 250 mg ($P < 0.05$). Plasma AVP concentration was measured at different times during the study, and a significant increase in the AVP was noticed early at 2 hours after lixivaptan administration at a dose of 400 mg as compared to placebo and at 4 hours with doses of 150, 250 and 400 mg as compared to placebo. Compared to baseline, this increase in AVP was significant after administration of lixivaptan at doses ≥ 250 mg within 2-8 hours. The average AVP concentration did not rise above 3.5 pg/mL and did not exceed 6.6 pg/mL in any individual patient. There was no significant difference in plasma renin, aldosterone, atrial natriuretic peptide, endothelin-1 and norepinephrine as compared to placebo or baseline.

Table IV. *Phase III clinical trials*

Study design	Target population (number of patients)	Intervention	Endpoints	Refs.
Randomized, double-blind, placebo-controlled	Hyponatremic HF patients with NYHA class III/IV (n = 650)	Administration of lixivaptan at 50 mg/day to 100 mg twice daily or matching placebo for 60 days	The primary endpoint is the change in the serum Na^+ concentration at day 7 of treatment Other endpoints include assessment of dyspnea, body weight, cognitive function and days of hospital-free survival	68
Multicenter, randomized, double-blind, placebo-controlled parallel-group efficacy and safety trial	Chronic HF patients with clinical evidence of volume overload (n = 150)	Lixivaptan dose of 100 mg/day for 8 weeks or placebo	The primary outcome is to assess the efficacy and safety of oral lixivaptan in patients with HF and volume expansion	69
Randomized, double-blind, placebo-controlled	Euvolemic hyponatremic patients (n = 200)	Oral lixivaptan 25 mg daily, which can be titrated up to 50 or 100 mg	Assess the safety, tolerability and effectiveness of lixivaptan in achieving and maintaining increased serum Na^+ concentration, improvement in serum Na^+, percentage of subjects achieving normal serum Na^+, percentage of subjects requiring fluid restriction and the change from baseline in serum Na^+ level	76, 77
International, multicenter, observational, open-label, extension trial	Chronic hyponatremia (euvolemic and hypervolemic) (n = 150)	Administration of oral lixivaptan over 28 weeks	Assess the safety of long-term oral lixivaptan use	78

HF, heart failure.

A subanalysis using a quantitative Western blot was performed to assess the effect of lixivaptan on urinary AQP-2 expression. Urine samples from 21 patients who received lixivaptan at doses of 30-250 mg were collected. A statistically significant reduction in urinary AQP-2 excretion was noted with lixivaptan as compared to placebo and baseline. This reduction was noticed at 2 hours and continued up to 8 hours after dose administration among all groups. The decrease in urinary AQP-2 excretion correlated with the increased aquaretic effect of lixivaptan ($r = 0.77$), while weaker correlations with urinary osmolality and urinary output were observed (Table II) (70).

The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) study is a randomized, double-blind, placebo-controlled phase III trial that was recently completed. It is designed to evaluate the effects of lixivaptan in patients hospitalized with HF NYHA class III/IV who have a serum Na^+ concentration ≤ 135 mEq/L (68). Patients (target n = 650) were randomized in a 1:1 ratio to receive lixivaptan or placebo for 60 days. Patients were assigned to receive oral lixivaptan (starting dose 50 mg/day) or matching placebo within 48 hours of hospitalization. Doses of lixivaptan could be titrated up to a maximum dose of 100 mg twice daily. Adjustments were based on serum Na^+ and volume status changes to avoid complications from rapid correction of serum Na^+. The primary endpoint was the change in the serum Na^+ concentration at day 7 of treatment. Other endpoints included assessment of dyspnea, body weight, cognitive function and days of hospital-free survival. Results of the study have not been published at the time of this publication.

Another multicenter, randomized, double-blind, placebo-controlled, parallel-group study was designed to assess the efficacy and safety of oral lixivaptan in patients with HF and volume expansion (69). The study was initiated in January 2010 with an estimated enrollment of 150 patients and has been completed. Inclusion criteria required a history of chronic HF, defined as receiving standard HF treatment, including diuretics, for a minimum of 30 days, documentation of LVEF within 12 months prior to screening and clinical evidence of volume overload at the time of the inclusion. Patients will be randomized to receive a dose of 100 mg/day of lixivaptan or placebo in a 2:1 ratio for 8 weeks. The results of this study have not yet been published.

Multiple trials were conducted to evaluate the effects of lixivaptan on hyponatremia, not only in HF patients but also in cirrhosis and/or SIADH.

In a randomized, double-blind, placebo-controlled, multiple-dose, multicenter phase II trial, 112 patients (60 liver cirrhosis, 15 HF, 33 SIADH, 4 other causes) with dilutional hyponatremia were enrolled from June 1997 to March 1999 (Table III) (71). Lixivaptan was administered at 50 or 100 mg twice daily for a total of 7 days or until normalization of serum Na^+ concentration. All patients were placed on 1 L daily fluid restriction. There was a significant reduction in urine osmolality with lixivaptan 100 mg twice daily ($P < 0.05$) and a significant increase in serum Na^+ concentrations with doses of 50 and 100 mg ($P < 0.05$). No changes in urinary electrolyte excretion were noticed with lixivaptan administration.

A subanalysis of the previous trial was conducted in patients with cirrhosis (n = 60) (Table III) (65, 71). Normalization of serum Na^+ concentration (defined as serum Na^+ level ≥ 136 mEq/L) was achieved in 27% and 50% of patients, respectively, in the lixivaptan 50 and 100 mg twice a day groups, but in none of the patients in the placebo group ($P < 0.05$ and $P < 0.001$, respectively). Treatment with lixivaptan was associated with a significant reduction in urine osmolality and body weight. Thirst sensation increased significantly in the 100-mg twice daily group but not in the 50-mg twice daily or placebo groups. Serious adverse events were similar among the three groups.

In another multicenter, randomized, placebo-controlled trial, 44 hospitalized patients (33 with cirrhosis, 6 with HF and 5 with SIADH) were studied on a constant Na^+ intake and received lixivaptan at doses of 25, 125 and 250 mg twice daily or placebo over a 7-day inpatient study period. Serum Na^+ concentration and urine output were monitored closely. Lixivaptan was held for elevated serum Na^+ (> 142 mEq/L or > 8 mEq/L from the previous concentration) or increased urine output (urine output > 3 L within 8 hours of the drug administration or > 4 L within 24 hours). During the study, lixivaptan was held in 7 patients (1, 1 and 5, respectively, in the 25-, 125- and 250-mg groups). Compared with placebo, lixivaptan produced a significant aquaretic response with dose-related increases in free water clearance ($P < 0.05$) and serum Na^+ ($P < 0.05$), without significant changes in orthostatic blood pressure or serum creatinine levels. Lixivaptan at doses of 125 and 250 mg was associated with higher AVP levels at the end of the study as compared with baseline, placebo and the 25-mg group ($P < 0.05$). Urinary Na^+ excretion, plasma renin activity, norepinephrine, aldosterone and orthostatic mean arterial pressures and heart rate were the same in all groups (72).

A substudy of a multicenter, randomized, double-blind, parallel-group phase II clinical trial looked into the effects of lixivaptan on 24-hour solute excretion in patients with hyponatremia (6 with SIADH and 5 with cirrhosis and ascites) (73, 74). Lixivaptan was given at a dose of 50 or 100 mg twice daily. All patients were on water restriction (< 1 L/day). Creatinine, urea, uric acid, Na^+, potassium and osmotic clearance were closely followed, as were various hormones (plasma renin [PR], aldosterone, antidiuretic hormone [ADH] and atrial natriuretic factor [ANF]). In patients with cirrhosis, lixivaptan normalized serum Na^+ concentration within 2 days of treatment, with a mild increment in Na^+ and potassium excretion, as well as a significant increase in urea clearance ($P < 0.05$). AVP levels increased significantly ($P < 0.05$), whereas PR, aldosterone and ANF remained unchanged. In the SIADH group, lixivaptan normalized serum Na^+ concentration after 1 day of treatment, with a reduction in Na^+ and uric acid excretion. The fractional excretion of Na^+ decreased with lixivaptan treatment compared to placebo ($P < 0.05$), indicating increased Na^+ tubular reabsorption. No significant change was noted in plasma renin, aldosterone, AVP, ANF, pulse rate and blood pressure (Table III) (74).

In a double-blind, placebo-controlled clinical trial, lixivaptan was administered as a single oral dose of 75 mg to eight patients with drug-induced (carbamazepine or oxcarbazepine) hyponatremia. There were statistically significant increases in serum Na^+, urine volume and free water clearance. Patients were noted to have low plasma AVP levels. Plasma AVP levels remained low throughout the study, and most patients were asymptomatic and did not experience thirst. Lixivaptan was also associated with insignificant changes in blood pressure (Table III) (75).

Two randomized, double-blind, placebo-controlled, multicenter, parallel-group phase III trials were conducted to evaluate the efficacy, safety and tolerability of lixivaptan in patients with euvolemic hyponatremia (primarily SIADH). Both studies have been completed but results have not yet been published (Table IV) (76, 77).

An international, multicenter, observational, cross-sectional, open-label extension trial is currently ongoing to assess the safety of long-term lixivaptan use in patients with chronic euvolemic and hypervolemic hyponatremia who were previously enrolled in one of the three phase III trials (CK-LX3401, 3405 and 3430) (Table IV) (78).

DRUG INTERACTIONS

Certain anticonvulsant drugs, such as carbamazepine and oxcarbazepine, are widely used in the treatment of patients with epilepsy, neuralgia, intellectual disability and other psychiatric disorders. Their use can be associated with hyponatremia in a frequency varying from 4.8% to 40% (79). The mechanism of hyponatremia associated with the use of carbamazepine is thought to be related to stimulation of the vasopressin V_2 receptor–protein G complex and increased AQP-2 expression in the renal collecting duct (80). A clinical trial has suggested the safety and efficacy of coadministration of lixivaptan with carbamazepine or oxcarbazepine in correcting hyponatremia (75).

Concurrent administration of lixivaptan and furosemide may be clinically indicated, so a trial was designed to evaluate the effects of coadministration of both drugs in healthy volunteers. A single 75-mg dose of lixivaptan was administered in combination with a single 40-mg dose of furosemide. Coadministration of both drugs did not alter the pharmacokinetics of either (67).

In another study, 30 healthy volunteers were randomized to receive a single oral dose of 50 mg of lixivaptan or 40 mg of furosemide. At 6 hours post-dose, there was a noticeably higher increase in AVP levels with furosemide as compared to lixivaptan (41.2 ± 97.19 and 2.9 ± 6.62 pg/mL, respectively). However, at 24 hours post-dose, AVP levels returned to baseline in patients receiving furosemide (0.8 ± 5.93 pg/mL), while the lixivaptan group exhibited a small increase in AVP levels (1.3 ± 4.63 pg/mL). Urine volume increases were similar in both groups. Lixivaptan administration was associated with an increase in serum Na^+ levels without significant changes in other electrolytes. In contrast, furosemide reduced serum concentrations of all electrolytes tested (Table II) (80).

CONCLUSIONS

The limited published data indicate that lixivaptan, a selective V_2 receptor antagonist, is safe and effective in correcting hyponatremia in euvolemic or hypervolemic patients. The evidence that it is effective in removing fluid without activation of the neurohormonal system is particularly attractive for its potential use in patients with hypervolemic hyponatremia. Publication of the completed clinical trials will shed more light on its future application in

clinical practice. Confirmation of its efficacy and safety in patients with decompensated HF or fluid overload without activation of the neurohormonal system or causing electrolyte imbalance paves the way for the exploration of its potential role in improving outcomes.

SOURCES

Cardiokine, Inc. (US) (licensed from Wyeth Pharmaceuticals, now Pfizer, in 2004); codeveloped with Biogen Idec (US).

DISCLOSURES

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