Intravenous Conivaptan: Effects on the QTc Interval and Other Electrocardiographic Parameters in Healthy Volunteers

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ABSTRACT

Prolongation of the QT interval is clinically important because it may be associated with torsade de pointes, a potentially fatal arrhythmia. The objective of this study was to define the effects on electrocardiogram (ECG) of intravenous conivaptan, the first arginine vasopressin V_{1A}/V_2-receptor antagonist indicated for the treatment of euvolemic hyponatremia, on hospitalized patients without congestive heart failure. After a placebo run-in period, participants in this randomized, single-blind, placebo- and positive-controlled, parallel-group study received an intravenous 20-mg loading dose of conivaptan (day 1), followed by a 40-mg/d continuous infusion (days 1–4); a 20-mg loading dose of conivaptan (day 1), followed by an 80-mg/d continuous infusion (days 1–4); or moxifloxacin 400 mg (positive control) or placebo from day 1 to day 4. The primary ECG endpoint was QTc interval duration, which was determined by the individually corrected QT interval for each subset; secondary endpoints included QT intervals corrected with Bazett's formula and Fridericia's formula. No clinically notable changes in ECG parameters were associated with conivaptan, suggesting that conivaptan did not affect cardiac repolarization or cardiac conduction.

Keywords: | conivaptan; QT interval; electrocardiogram

INTRODUCTION

The QT interval represents the duration of cardiac repolarization; a prolonged QT interval may be associated with torsade de pointes, a potentially

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1134

fatal ventricular arrhythmia.[1] Prolongation of the QT interval or the heart rate (HR)-corrected QT interval (QTc interval) associated with noncardiac drugs is the single most common reason why drug development is delayed, drugs in development are not approved, and drugs are withdrawn after marketing.[2] According to recent US Food and Drug Administration (FDA) guidelines, robust measures must be carried out to determine the cardiac safety of all bioactive compounds before they can be considered for approval. The FDA-Health Canada Electrocardiographic Concept document requires that all bioactive compounds be tested in phase 1 trials that are powered to exclude a 5-msec QTc effect (upper confidence interval: 10 msec).[2,3]

Case reports and clinical studies of conivaptan, an arginine vasopressin V_{1A}/V_2-receptor antagonist approved by the FDA for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients, suggest that conivaptan does not produce clinically significant changes in blood pressure, HR, or the cardiac conduction system.[4-9]

Per FDA guidelines, it was necessary to specifically test the conduction system effects of conivaptan. Accordingly, this trial was conducted in healthy volunteers to define the effects of conivaptan on electrocardiogram (ECG) parameters, including waveform morphology, HR, and duration of QTc, PR, and QRS intervals.
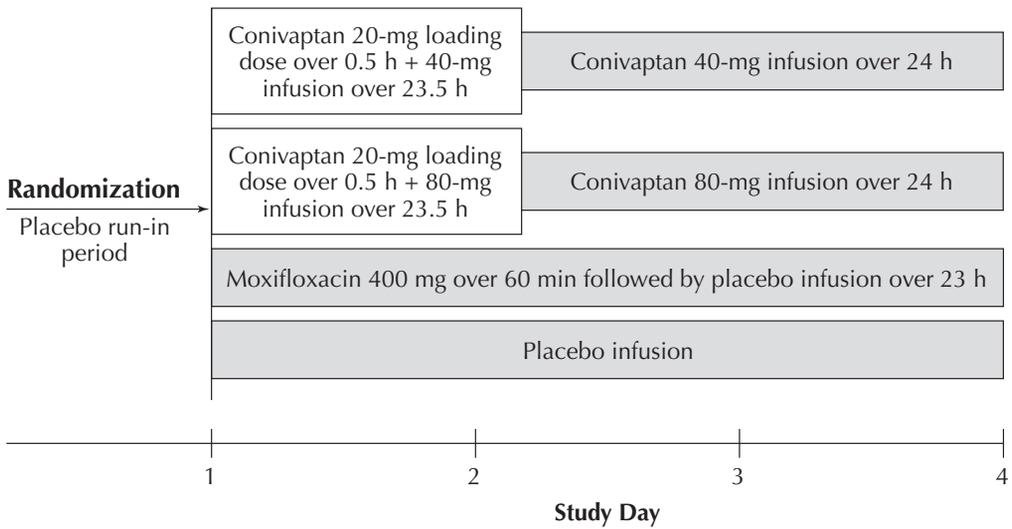
METHODS

This randomized, single-blind (subjects and ECG readers were blinded to treatment assignments), placebo- and positive-controlled, parallel-group study was conducted in accordance with FDA principles of Good Clinical Practice and International Conference on Harmonization guidelines. Participants provided written informed consent before entering the study. The study protocol and informed consent forms were reviewed and approved by an institutional review board (LeeCoast Institutional Review Board, Fort Myers, Fla) prior to screening of study participants.

Eligible subjects were aged 18 to 45 y, had a body mass index of 18 to 30 kg/m^2, did not smoke, and were in good health. Subjects were excluded from enrollment if they had a history of drug or alcohol abuse within 2 y prior to the study or had used any prescription medication within 14 d prior to the study or any nonprescription medications, herbal preparations, or vitamins within 48 h prior to the study. Subjects were also excluded if the screening ECG showed a PR interval >240 msec, a QRS interval >110 msec, a QTc interval >480 msec, or clinically significant ST-T wave changes, or if they had been given an investigational drug during the 30 d prior to screening, donated or lost more than 1 unit of blood within 30 d prior to screening, had an allergy to moxifloxacin, or had any clinical condition that would prevent them from completing the study or completing it safely.

After an initial screening period, each participant received a single 30-min intravenous (IV) infusion of placebo during a 1-d run-in period. Participants were then randomly assigned in a 1:1:1:1 ratio to receive IV conivaptan 40 mg/d, conivaptan 80 mg/d, moxifloxacin 400 mg/d (positive control), or placebo from day 1 to day 4 (Fig 1). On day 1, conivaptan group participants each received a 20-mg loading dose over 30 min, which was followed by a 40-mg or 80-mg dose infused over 23.5 h. From day 2 to day 4, each participant was given a continuous infusion over 24 h through a central line or an indwelling catheter by means of a pump infusion system. Participants in the moxifloxacin group were given a 60-min infusion of moxi-

floxacin from a commercially available 250-mL bag, which was followed by a 23-h infusion of 5% dextrose from day 1 to day 4. Placebo group participants each received 4 successive infusions of 5% dextrose over 24 h from day 1 to day 4. Conivaptan hydrochloride for IV administration is a sterile formulation of conivaptan 5 mg/mL in 30% propylene glycol/10% ethanol, with lactic acid added to adjust the pH. Conivaptan ampules were provided to the study site pharmacist in an open-label fashion.

Fig 1. Study design.

Randomization		
Conivaptan 20-mg loading dose over 0.5 h + 40-mg infusion over 23.5 h	Conivaptan 40-mg infusion over 24 h
Conivaptan 20-mg loading dose over 0.5 h + 80-mg infusion over 23.5 h	Conivaptan 80-mg infusion over 24 h

Randomization
Placebo run-in period

Conivaptan 20-mg loading dose over 0.5 h + 40-mg infusion over 23.5 h   Conivaptan 40-mg infusion over 24 h

Conivaptan 20-mg loading dose over 0.5 h + 80-mg infusion over 23.5 h   Conivaptan 80-mg infusion over 24 h

Moxifloxacin 400 mg over 60 min followed by placebo infusion over 23 h

Placebo infusion

1   2   3   4

Study Day

Drug plasma concentrations were determined by collecting serial blood samples over a 24-h period before dosing and after dosing on day 4 (0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 18, and 24 h post dose) to coincide with steady-state drug plasma concentrations. The method used to analyze plasma concentrations of conivaptan was validated over the linear range of 5 to 5000 ng/mL. Twelve-lead ECG data were obtained digitally using an H-12 ECG continuous recorder (Mortara Instruments, Milwaukee, Wis). Data provided through approximately 24 h of continuous recording were collected during the run-in period and on days 1 and 4 (a 15-min window was allowed for site staff to change leads, batteries, and flash memory cards between the run-in day and day 1, and on day 4). A total of 52 ECGs were obtained from each participant during the run-in period to establish a correction exponent unique for each person. The individually corrected QT interval (QTcI) was calculated from the formula QTcI=QT/RR, where RR is the interval between 2 consecutive R waves; this approach is considered the most accurate correction of QT to QTc. During the placebo run-in period and on days 1 and 4, 118 ECGs were analyzed for each participant, for a total of 18,800 ECGs from 160 participants.

ECGs were sent to a central laboratory (eResearch Technology, Philadelphia, Pa) for high-resolution measurement of cardiac intervals and morphologic assessment by a cardiologist who was blinded to study treatment. The cardiologist verified interval durations and performed a morphology analysis while noting any T-/U-wave complex abnormalities that were compatible with drug effects on cardiac repolarization.

The primary ECG variable was QTcI. Secondary endpoints included QTc intervals corrected with Bazett's formula (QTcB) and Fridericia's formula (QTcF),[10,11] HR, PR and QRS interval duration, and ECG morphology changes. Safety assessments included reports of adverse events, clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), physical examination findings, and vital signs.

Statistical Analysis

Forty subjects per group were necessary to detect with high probability (>80%) a 1-msec change in time-matched QTcI (confidence interval, ±5 msec). The sample size selected for this study was based on expert recommendations and similar ECG safety studies. It was not based on a specific power calculation.

The null hypothesis was based on the assumption that no relationship existed between the QTc interval change from baseline and the dose of conivaptan. Moxifloxacin was used as a positive control to demonstrate assay sensitivity to a small positive change in QTc duration (~6–10 msec) from baseline.[12] Descriptive statistics were used to summarize HR and PR, QRS, QT, QTcB, QTcF, and QTcI intervals. Each study participant who received at least 1 dose of study medication was included in the safety evaluation.

RESULTS

All of the 161 participants enrolled in this study received treatment and 160 completed the study. One participant in the conivaptan 40-mg/d group withdrew consent after receiving the first dose of study medication. This individual was replaced with another individual, who was selected according to the criteria for study enrollment. All treatment groups consisted of similar numbers of men and women, and the mean age of all participants was 33 y. Treatment groups were similar with regard to baseline ECG parameters (Table 1). There was a 4-fold difference in plasma conivaptan levels between the 2 doses at steady state (Fig 2)—a finding consistent with conivaptan's known nonlinear pharmacokinetics, of which inhibition by conivaptan of its own metabolism is likely a major factor.[9] In the group given conivaptan 40 mg/d, mean plasma levels were between 135 and 187 ng/mL; in the group that received 80 mg/d, mean plasma levels were between 562 and 717 ng/mL.

Clinically notable changes in ECG parameters from baseline to days 1 and 4 were not detected during treatment with conivaptan (Table 2). Placebo-corrected QTcI changes from baseline in the groups given conivaptan 40 and 80 mg/d were –4 msec and –3 msec, respectively, at day 1, whereas at day 4, both groups demonstrated a placebo-corrected change of –2 msec. Mean QTcI interval at day 1 in the groups given conivaptan 40 mg/d (390.8) and 80 mg/d (385.1) did not differ significantly from that in the group given placebo (392.9). Similar results were observed at day 4 (390.2, 383.8, and 390.7, respectively). No participants in any of the treatment groups

Table 1. Patient Characteristics and Baseline ECG Parameters

Patient Demographics	Conivaptan 40 mg/d (n=41)	Conivaptan 80 mg/d (n=40)	Moxifloxacin (n=40)	Placebo (n=40)
Mean age, y (SD)	35.1 (7.2)	32.2 (7.6)	33.0 (7.4)	33.0 (7.4)
Sex, n (%)				
Male	22 (54)	21 (52)	20 (50)	18 (45)
Female	19 (46)	19 (48)	20 (50)	22 (55)
Race, n (%)				
Hispanic	27 (66)	23 (58)	25 (62)	25 (62)
White	9 (22)	15 (38)	7 (18)	10 (25)
Black	5 (12)	2 (5)	8 (20)	5 (12)
HR, bpm*	73	74	75	73
PR interval, msec*	149	149	149	149
QRS interval, msec*	83	85	83	83
QT interval, msec*	371	365	366	370

*Baseline values are rounded to the nearest whole number.
ECG=electrocardiogram; SD=standard deviation; HR=heart rate; bpm=beats per minute.

Fig 2. Mean steady-state plasma conivaptan concentrations on day 4 in patients given IV conivaptan 40 mg/d or 80 mg/d.
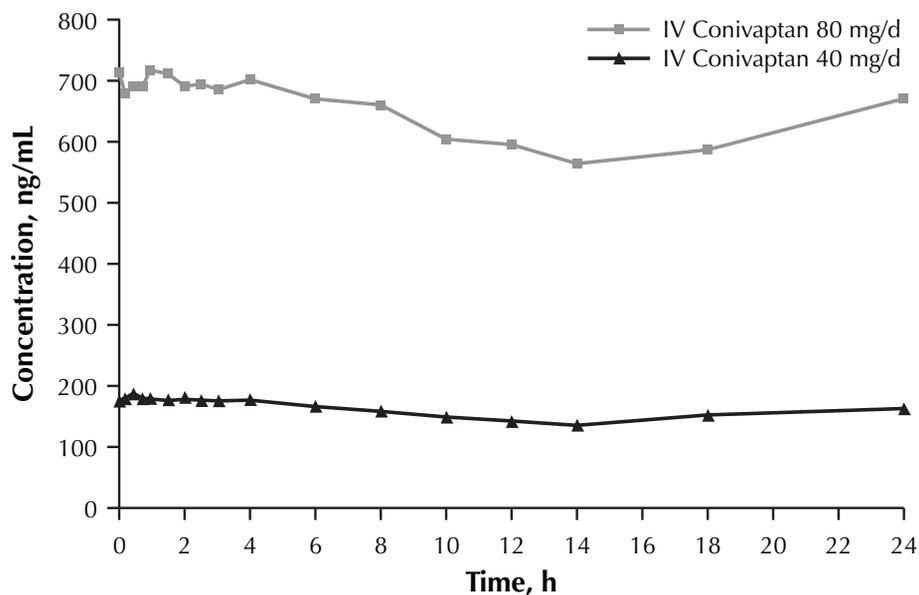
IV=intravenous.

had an absolute QTcI interval >500 msec. Similar results were observed for the QTcB and QTcF intervals. Placebo-corrected changes from baseline QTcI interval in the moxifloxacin group ranged from 7 to 10 msec on days 1 and 4, respectively, which demonstrated the sensitivity of study conditions to a genuine change in QTc interval. A central tendency analysis of time-matched QTc intervals indicated no effect of conivaptan on cardiac repolarization. The slope of the change from baseline in QTcI interval vs plasma conivaptan concentration linear regression line was essentially 0 (–0.0006), indicating no correlation between conivaptan plasma concentration and QTcI interval response. No sign of any effect of sex on study results was noted.

Table 2. Change From Baseline in ECG Parameters

| | Conivaptan | | | |
ECG Variable	40 mg/d (n=41)	80 mg/d (n=40)	Moxifloxacin (n=40)	Placebo (n=40)
Change From Baseline to Day 1				
QTcI, msec	–5	–4	6	–1
QTcI, mean maximum	20	19	32	24
QTcI, 30–60 msec, n (%)	5 (12)	3 (8)	20 (50)	10 (25)
QTcI, >60 msec, n (%)	0	1 (3)	1 (3)	0
QTcB, msec	–4	–2	8	–1
QTcF, msec	–5	–4	7	–1
HR, bpm	1	3	1	–1
PR interval, msec	1	–2	1	1
QRS interval, msec	–2	–2	–1	–1
Change From Baseline to Day 4				
QTcI, msec	–5	–5	7	–3
QTcI, mean maximum	16	13	30	15
QTcI, 30–60 msec, n (%)	5 (12)	3 (8)	20 (50)	4 (10)
QTcI, >60 msec, n (%)	0	0	0	0
QTcB, msec	0	5	12	1
QTcF, msec	–6	–5	7	–3
HR, bpm	7	11	5	5
PR interval, msec	–4	–8	–2	–4
QRS interval, msec	–2	–3	–2	–2

ECG=electrocardiogram; HR=heart rate; bpm=beats per minute.

Conivaptan did not affect HR. All groups demonstrated a minimal change in HR on day 1; the maximum placebo-corrected change was 4 beats per minute (bpm) in the group given conivaptan 80 mg/d. At steady state, there was a placebo-corrected increase of 6 bpm in the high-dose conivaptan group. Placebo-corrected outliers with tachycardia (25% increase from baseline to HR >100 bpm) were observed on days 1 and 4 in the group given high-dose conivaptan (33% and 43%, respectively) and in the group given moxifloxacin (23% and 15%, respectively).

Participants in each group experienced minimal changes from baseline in PR and QRS interval durations. In the group given conivaptan 80 mg/d, mean placebo-corrected changes observed on day 1 were –1 msec and –4 msec, respectively; on day 4, a change of –1 msec was observed for each measure. The only noteworthy ECG morphology change was that participants taking conivaptan had more frequent new changes in their T-wave morphology. A T-wave inversion was observed on day 1 in 3% of participants who received conivaptan 40 mg/d and in 5% of those who received 80 mg/d. On day 4, 5% of participants in each conivaptan group (placebo-corrected) had a T-wave inversion; however, similar changes were noted in 5% of patients in the placebo group and in 8% of patients in the moxifloxacin group.

The most common treatment-related adverse events were injection-site reaction, thirst, headache, pollakiuria (abnormally frequent urination), and dry mouth (Table 3). No deaths or serious adverse events were reported during this study, and no one discontinued the study because of an adverse event. No clinically significant treatment-related changes were reported in serum chemistry, hematology, or urinalysis results.

Table 3. Incidence of Treatment-Emergent Adverse Events Observed in ≥5% of Study Participants

	Conivaptan		Moxifloxacin	Placebo
	40 mg/d (n=41)	80 mg/d (n=40)	(n=40)	(n=40)
Adverse Event	n (%)	n (%)	n (%)	n (%)
Thirst	10 (24.4)	16 (40)	0	1 (2.5)
Headache	6 (14.6)	4 (10)	7 (17.5)	0
Pollakiuria	4 (9.8)	8 (20)	0	0
Dry mouth	4 (9.8)	3 (7.5)	1 (2.5)	2 (5.0)
Infusion-site erythema	2 (4.9)	4 (10.0)	0	0
Infusion-site pain	7 (17.1)	15 (37.5)	0	1 (2.5)
Infusion-site phlebitis	0	4 (10.0)	0	0
Infusion-site swelling	5 (12.2)	13 (32.5)	1 (2.5)	1 (2.5)

DISCUSSION

Despite our improved understanding of the mechanisms of drug-induced QT interval prolongation, reliable measurements of drug-induced changes in the QT interval are complicated by patient variability, drug pharmacokinetics, and measurement and interpretation of the QT interval. For example, interpretation of the QT interval is influenced by variables such as cardiac cycle length (ie, RR interval), autonomic nervous system activity, age, sex, circadian rhythm, and plasma electrolyte concentrations.[13]

Owing to the variability of the RR interval, several formulas have been used to normalize the QT interval for cycle length to obtain a QTc. The most commonly used formulas include Bazett's formula ($QTcB=QT/RR^{1/2}$) and Fridericia's formula ($QTcF=QT/RR^{1/3}$). These formulas are less than ideal, however, because the correlation between RR and QTc intervals is significantly less than zero. Consequently, the most appropriate method of calculating the QTc interval must include an accurate assessment of the population under study; this can be achieved through assessment of the QT/RR relationship for each patient (QTcI).[13]

Findings from this trial suggest that conivaptan is not associated with significant cardiac electrophysiological effects when administered intravenously to healthy individuals. No clinically notable changes in ECG parameters (HR, waveform morphology, and QTc, PR, and QRS intervals) were associated with therapeutic and supratherapeutic concentrations of conivaptan.

Typically, prolongation of the absolute QTc interval to >500 msec is thought to increase the risk of torsade de pointes.[14,15] According to the FDA, however, no consensus has been reached about the optimal upper limit of the absolute QTc interval or the optimal change from baseline; therefore, multiple analyses that consider different signal values (eg, absolute QTc interval >450 msec, >480 msec, or >500 msec and a QTc interval increase from baseline >30 or >60 msec) have been recommended to address this uncertainty.[3] No participants had an absolute QTcI interval >500 msec at day 1 and day 4, and only 1 participant given conivaptan 80 mg/d had an increase >60 msec at day 1, which was also observed in 1 participant in the moxifloxacin group. At day 1, the total number of participants with an increase in QTcI interval between 30 and 60 msec was lower among the groups given conivaptan 40 mg/d (5) and 80 mg/d (3) than among the group given placebo (10). At day 4, the numbers of participants with an increase in QTcI interval between 30 and 60 msec were similar among the 3 groups (5, 3, and 4, respectively). These results suggest that conivaptan is unlikely to have a proarrhythmic effect in that it has no effect on ventricular repolarization. The findings of this trial are supported by combined data from phase 3 trials in which conivaptan did not significantly affect ECG results in patients with euvolemic or hypervolemic hyponatremia.[7,8]

Although the ability to assess the risk of torsade de pointes during treatment with a particular drug has improved, this risk cannot be assessed or quantified accurately; therefore, the potential benefits of therapy must be weighed against the risks.[14] Unusual drug reactions may occur as a result of changes in physiology conferred by disease, genetics, or reduced repolarization reserve.[14] Furthermore, although the risk of torsade de pointes is proportional to the degree of QT interval prolongation, a number of concomitant risk factors have been implicated in its actual development (eg, female sex, hypokalemia, congestive heart failure, increased QT dispersion, clinically significant bradycardia [<50 bpm], severe hypomagnesemia, ion channel polymorphisms, endocrine disorders, altered nutritional states, cerebrovascular disease).[13,14]

CONCLUSION

Results from this study indicate that conivaptan does not prolong the QTc interval in healthy individuals. In addition, these results suggest that conivaptan does not affect cardiac repolarization or cardiac conduction.

FINANCIAL DISCLOSURES

SUPPORT

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