Clinical Pharmacology in Drug Development 2015, 4(2) 130–136

DOI: 10.1002/cpdd.128

Intravenous Pharmacokinetics, Local Tolerability, and Hemolysis of an SBE7-β-Cyclodextrin Formulation of the Neurokinin-1 Receptor Antagonist Vestipitant

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Abstract

Vestipitant is a potent and selective neurokinin 1 (NK-1) receptor antagonist that was investigated as a potential treatment for post-operative nausea and vomiting (PONV). A previous mannitol-based formulation of vestipitant was associated with hemolytic activity in preclinical studies. In an effort to reduce the hemolytic potential and develop an IV formulation of vestipitant that could be administered more rapidly, an IV formulation containing sulfobutylether-7-beta-cyclodextrin (SBE7-β-CD, Captisol™) was developed and tested in a phase 1 clinical study. This was a randomized, single-blind (subjects and investigator—blinded, sponsor-unblinded), placebo controlled, dose escalation study in healthy subjects in which 7 cohorts of 8 subjects per cohort received SBE7-β-CD -based vestipitant (2 mg/mL) or placebo (saline) in a 3:1 ratio (active:placebo) at different doses and infusion rates. The results demonstrated the ability to infuse up to 48 mg vestipitant in a 2 mg/mL formulation over 30 seconds with no evidence of hemolytic effects. Cohorts of subjects at lower doses and longer infusion duration (>1 minute) reported more AEs related to the infusion site than those at the higher doses and faster infusion rates.

Keywords

NK-1 receptor antagonist, vestipitant, SBE7-β-cyclodextrin, hemolysis, intravenous

Vestipitant is a potent and selective neurokinin 1 (NK-1) receptor antagonist that was being investigated as a potential treatment for post-operative nausea and vomiting (PONV) and has been evaluated for other indications including depression, anxiety, chemotherapy-induced nausea and vomiting, tinnitus, and primary insomnia.[1–3]

Preclinical studies with a mannitol-based intravenous (IV) formulation of vestipitant, demonstrated the potential for hemolysis and injection site irritation when administered at concentrations greater than 0.2 mg/mL. Thus, in order to avoid local tolerability and hemolysis effects, IV vestipitant was administered to human subjects as a 15 minute-infusion at concentrations not greater than 0.1 mg/mL. Other NK-1 inhibitors, such as fosaprepitant dimeglumine,[4] have similar infusion rate restrictions; therefore a more rapid administration would provide more treatment flexibility.

In an effort to reduce the hemolytic potential and develop an IV formulation of vestipitant that could be administered more rapidly, an IV formulation containing sulfobutyleteher-7-beta-cyclodextrin (SBE7-β-CD, Captisol™) was developed. The SBE7-β-CD formulation of IV vestipitant did not demonstrate any local tolerability findings when given in a single-dose

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Submitted for publication 9 January 2014; accepted 30 April 2014

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study in dogs up to the maximum concentration (4 mg/mL) administered compared to irritation and hemolysis observed with a mannitol formulation at 1 and 2 mg/mL, respectively. Consistently, in vitro studies indicated that up to 2 mg/mL vestipitant in a SBE7-β-CD formulation mixed with human blood did not produce hemolysis. The purpose for the current study was to evaluate the safety and tolerability and pharmacokinetics (PK) of the SBE7-β-CD formulation of vestipitant when administered over 2 minutes or less to healthy subjects.

Materials and Methods

Study Design and Participants

This study was conducted in Australia (Nucleus Network, Melbourne, Australia) according to the ethical principles of "good clinical practice" (GCP) and the Declaration of Helsinki after obtaining a written informed consent from each subject. The protocol and its amendment were approved by the Alfred Hospital Ethics Committee (Melbourne, Australia).

This was a randomized, single-blind (subjects and investigator), placebo controlled, dose escalation study in healthy subjects (ClinTrials.gov identifier: NCT01290133). The sponsor was unblinded to study treatment. The study planned to enroll eight subjects into each of seven cohorts, such that six subjects would be randomized to receive the SBE7-β-CD-based vestipitant (2 mg/mL) formulation and two subjects would receive placebo (saline injection). Each subject participated in only one cohort. Each cohort consisted of three periods for all subjects (screening, treatment, and follow-up). Safety and PK were assessed throughout the study. The doses of vestipitant and regimen designations for this study are summarized in Table 1.

The decision to proceed to the next dose regimen of vestipitant was based on safety, tolerability, and preliminary PK data obtained in at least three subjects at the preceding dose regimen. In particular, laboratory evidence of hemolysis was evaluated before dose escalation to the next highest cohort was permitted. These assessments included haptoglobin, lactate dehydrogenase (LDH), serum potassium, phosphate, and total and direct bilirubin. Other hemolysis assessments included hemoglobin, red blood cell count, reticulocyte count, and urine hemosiderin. The infusion site was assessed at various times up to 36 hours post-dose using a 0–3 scale as follows: Grade 0 = none; Grade 1 = pain or itching or erythema; Grade 2 = pain or swelling, with inflammation or phlebitis; Grade 3 = ulceration or necrosis.

Eligibility included healthy males or females, between 18 and 65 years of age, inclusive, with a body weight $\geq$50 kg and body mass index (BMI) $\leq$ 31 kg/m^2. Females were of non-childbearing potential and males must have agreed to the use of contraception. Subjects had aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and bilirubin $\leq$1.5 × upper limit of normal (ULN, isolated bilirubin >1.5 × ULN was acceptable if bilirubin was fractionated and direct bilirubin was <35%) and QTcB or QTcF <450 milliseconds; or QTc <480 milliseconds in subjects with Bundle Branch Block.

Pharmacokinetic Assessments

Blood samples for PK analysis were collected at predose (0), end of infusion, 5, 30 minutes, and 1, 1.5, 2, 4, 6, 10, 18, 24, and 36 hours post dose. Concentrations of vestipitant in human plasma were determined using a high-performance liquid chromatography (HPLC) assay coupled with a triple quadruple mass spectrometer with an electrospray ionisation interface. [$^2H_3{}^{13}C$]-vestipitant

Table 1. Doses and Administration Rates

Cohort	n	Vestipitant dose	Solution volume (mL)	Infusion time (minutes)	Treatment infusion rate	Solution infusion rate (mL/min)
1	2	Placebo	6	2	—	3
	6	12 mg			6 mg/min	
2	2	Placebo	9	2	—	4.5
	5	18 mg			9 mg/min	
3	2	Placebo	12	2	—	6
	6	24 mg			12 mg/min	
4	2	Placebo	12	1	—	12
	6	24 mg			24 mg/min	
5	2	Placebo	12	0.5	—	24
	6	24 mg			48 mg/min	
6	2	Placebo	18	0.5	—	36
	6	36 mg			72 mg/min	
7	2	Placebo	24	0.5	—	48
	6	48 mg			96 mg/min	

was used as internal standard. The study sample collection procedure included whole blood sample centrifuged to obtain plasma, which was stored at −20°C until analysis. A volume of 200 μL internal standard solution (80/20 acetonitrile/2 mM ammonium formate, pH 3 v/v) was added to human plasma (50 μL) to precipitate plasma proteins. After mixing and shaking, the sample was centrifuged at 6,400*g* for 20 minutes. The supernatant was transferred to an autosampler vial. A 2 μL volume was injected onto the HPLC column (Varian Pursuit 3 C18, 50 mm × 3.0 mm ID, Agilent Technologies, Santa Clara, CA, USA) and eluted with 2 mM ammonium formate (pH 3.0):acetonitrile (20:80 for 1.7 minutes). The column outlet was connected to an Applied Biosystems/MDS Sciex (Foster City, CA, USA) API-4000 liquid chromatography tandem mass spectrometer (LC/MS/MS) instrument operated in positive mode with a TurboIonSpray sample inlet. The monitored transitions for vestipitant were m/z 492 to 221. Concentration ranges of nominally 2–4,000 ng/mL were validated (samples with concentrations outside of this range were appropriately diluted and re-assayed). During study sample analysis, bias and precision were calculated using normalized interpolated concentrations of all measured quality control samples at three concentration levels. Bias ranged between −2.8% and 0.8%, within and between run precision ranged from 1.0% to 5.8% and 3.0% to 4.6%, respectively.

Statistical Analyses

The primary objectives of this study were to describe the safety and tolerability in healthy subjects following single IV infusions of the SBE7-β-CD-based vestipitant formulation. The secondary objectives were to characterize the PK and dose proportionality of the SBE7-β-CD-based vestipitant formulation in healthy subjects.

For all safety data, summaries of actual value and changes from baseline in the following parameters were generated: vital signs (systolic blood pressure, diastolic blood pressre, mean arterial blood pressure, and pulse rate), ECG values (ventricular rate, intervals of PR, QRS, QT, and QTc), clinical chemistry, and hematology values.

From the plasma concentration–time data, the following PK parameters were determined, as data permitted: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve ($AUC_{0-\infty}$), apparent terminal phase half-life t½, total plasma clearance (CL) volume of distribution at steady-state (Vdss), and volume of distribution based on the terminal phase (Vz). Dose proportionality of $AUC_{0-\infty}$, and C_{max} (30 seconds and 2 minutes infusion cohorts separately) for vestipitant were assessed using the following power model: $\log(\text{PK parameter}) = a + b \times \log(\text{dose})$, where a is the intercept and b is the slope.[5] The mean slope was estimated from the power model and the corresponding 90% confidence interval calculated.

Results

Demographics

A total of 55 healthy subjects were randomized into the study across 7 cohorts, in which 14 subjects received placebo and a total of 41 subjects received the SBE7-β-CD-based vestipitant formulation. Subjects were generally well-matched between the placebo and the combined vestipitant doses with respect to age, gender and race. The majority of subjects in both groups were White/Caucasian males.

Safety

The overall frequency of reported AEs was similar between the saline placebo (57%) and the combined vestipitant groups (56%) as summarized in Table 2. The most commonly reported AEs in ≥2 subjects, regardless of the dose of vestipitant received, were infusion site pain, infusion related reaction, infusion site hematoma, infusion site discomfort, headache, lethargy, procedural dizziness, dysgeusia, myalgia, and upper respiratory tract infection (Table 2). The majority of events associated with infusion site conditions were considered related to the study medication by the investigator. All AEs were mild, except for one case of moderate headache in a subject that received vestipitant 12 mg, which was considered related to the study medication.

There were no serious AEs, deaths, or withdrawals due to AEs during this study. There were no clinically significant findings in clinical laboratory tests (chemistry, hematology, urinalysis), vital signs or ECGs in this study, and no apparent dose-related trends.

Infusion Site Assessment

Infusion site inspections included, but were not limited to, evaluations for the presence of edema, induration, erythema, warmth, pain, or bruising. During the study, only Grade 1 findings (pain, itching, or erythema) were observed.

A total of 19 subjects, 3 receiving placebo and 14 receiving vestipitant, experienced at least one Grade 1 infusion site assessment finding (Table 3). There were no Grade 2 or Grade 3 findings; thus, dose escalation to the next highest cohort proceeded as planned. A total of 8 (57%) of the findings, all in patients receiving vestipitant, occurred within the first 30 minutes of infusion and all resolved. Delayed and persistent infusion site findings were generally related to bruising and were observed in both the placebo and vestipitant groups. The majority of findings in both the placebo group (3 of 3) and vestipitant group (13 of 14) were observed with infusions of 1 or 2 minutes. The 30-second infusion cohorts had no

Table 2. Summary of Adverse Events Reported in ≥2 Subjects, Regardless of Causality

Preferred term, n (%)			Vestipitant cohort						
	Total	Placebo	1 (N = 6)	2 (N = 5)	3 (N = 6)	4 (N = 6)	5 (N = 6)	6 (N = 6)	7 (N = 6)
Infusion	(N = 55)	(N = 14)	12 mg/2 min	18 mg/2 min	24 mg/2 min	24 mg/1 min	24 mg/30 s	36 mg/30 s	48 mg/30 s
Subjects with any AE	31 (56)	8 (57)	5 (83)	5 (100)	4 (67)	3 (50)	1 (17)	3 (50)	2 (33)
Subject with any related AE	25 (45)	6 (43)	4 (67)	5 (100)	4 (67)	2 (33)	1 (17)	1 (17)	0
Infusion site pain	5 (9)	0	1 (17)	1 (20)	2 (33)	1 (17)	0	0	0
Infusion related reaction	5 (9)	0	3 (50)	1 (20)	0	0	0	0	1 (17)
Infusion site hematoma	5 (9)	2 (14)	0	1 (20)	2 (33)	0	0	0	0
Headache	5 (9)	1 (7)	1 (17)	1 (20)	1 (17)	1 (17)	0	0	0
Lethargy	4 (7)	0	0	2 (40)	0	0	0	2 (33)	0
Procedural dizziness	3 (5)	0	1 (17)	1 (20)	0	1 (17)	0	0	0
Somnolence	3 (5)	2 (14)	0	0	0	0	1 (17)	0	0
Dysgeusia	2 (4)	0	0	0	0	1 (17)	1 (17)	0	0
Infusion site discomfort	2 (4)	0	0	0	0	1 (17)	0	1 (17)	0
Myalgia	2 (4)	0	1 (17)	0	0	1 (17)	0	0	0
Upper respiratory tract infection	2 (4)	0	2 (33)	0	0	0	0	0	0
Abdominal pain	2 (4)	1 (7)	0	0	0	1 (17)	0	0	0

findings in the placebo group and only one finding in the vestipitant group.

Female subjects reported AEs at a higher overall rate (90%, 18 of 20) than males (37%, 13 of 35), regardless of treatment assignment or dose. However, no female subjects were recruited into the 30-second infusion cohorts. In the 1 and 2 minute infusion placebo groups, 2 of 5 females (40%) and 1 of 3 males (33%) had findings. In the 1 and 2 minute infusion vestipitant groups, 11 of 15 females (73%) and 2 of 8 males (25%) had findings (Table 3).

Hemolysis

Overall, there was no pattern in the data indicative of potential hemolysis, either individually or by treatment. The average changes from baseline in parameters of hemolysis were variable in the vestipitant treatment groups, with some regimens having a decrease and some with an increase in a non-dose dependent manner. However, all average changes were well within the expected sample variability of 0.1 g/L and less than the decrease observed after footstrike hemolysis

Table 3. Number of Subjects (by Cohort) with ≥1 Grade 1 Infusion Site Finding[a]

Dose/infusion time	Cohorts							
	1	2	3	4	5	6	7	
	12 mg/2 min	18 mg/2 min	24 mg/2 min	24 mg/1 min	24 mg/30 s	36 mg/30 s	48 mg/30 s	Total (%)
Placebo (N = 2 each)	1 of 2	1 of 2[b]	0 of 2	1 of 2	0 of 2	0 of 2	0 of 2	3 of 14 (21%)
Female	1 of 2	1 of 2[b]	NA	0 of 1	NA	NA	NA	2 of 5 (40%)
Male	NA	NA	0 of 2	1 of 1	0 of 2	0 of 2	0 of 2	1 of 9 (11%)
Vestipitant (N = 6 each)[c]	4 of 6	4 of 5	3 of 6	2 of 6	0 of 6	1 of 6	0 of 6	14 of 41 (34%)
Female	4 of 4	4 of 5[b]	1 of 2	2 of 4	NA	NA	NA	11 of 15 (73%)
Male	0 of 2	NA	2 of 4	0 of 2	0 of 6	1 of 6	0 of 6	3 of 26 (12%)

NA, not applicable.

[a]All Infusion Site Findings were Grade 1–no Grade 2 or Grade 3.

[b]Includes 1 subject whose findings were also observed pre-dose.

[c]Only 5 subjects received vestipitant in Cohort 2.

(0.085 g/L decrease)[6] and generally similar to placebo subjects.

One placebo subject had an infusion site hematoma. Laboratory findings were consistent with evidence of hemolysis and included a 0.20 g/L decrease in haptoglobin, a 121 U/L increase in LDH, and a 1 mmol/L increase in potassium (end of infusion sample).

Pharmacokinetics

Pharmacokinetic profiles and parameters are summarized in Figure 1 and Table 4, respectively. Peak plasma vestipitant concentrations (C_{max}) were generally observed in the end of infusion sample for treatment groups that received the SBE7-β-CD-based vestipitant formulation over 2 minutes (12, 18, and 24 mg), although it was highly variable. As infusion duration was reduced, t_{max} was delayed slightly, and C_{max} was frequently observed in the PK sample obtained subsequent to the end of infusion PK sample. When vestipitant was infused over 30 seconds (24, 36, and 48 mg), median t_{max} values of 4.8–5.4 minutes were observed. Accordingly, the observed C_{max} was variable and inconsistent between cohorts.

There were greater than dose proportional increases in $AUC_{0-\infty}$ for plasma vestipitant over the dose range studied, with a slope estimate from the power model of 1.33 (90% CI: 1.12, 1.53), where 1.00 would represent dose-proportional increases. Dose proportionality assessment of C_{max} could not be reliably assessed due to the highly variable estimates described above.

Discussion

Several NK-1 receptor antagonists have been demonstrated to be effective for the treatment of PONV and chemotherapy-induced nausea and vomiting (CINV).[7–9] Approved medications are available as oral and IV formulations. Fosaprepitant dimeglumine must be infused over 20–30 minutes (single dose regimen) or over 15 minutes (3-day regimen) for CINV, and cannot be administered as a bolus infusion.[4] Vestipitant has been in development as an oral agent for many indications including PONV and CINV. An IV formulation (mannitol based) was created to provide better flexibility for use in patients in settings where oral administration is contraindicated or not tolerated. However, this formulation could only be administered by a slow (15 minutes) infusion at concentrations not greater than 0.1 mg/mL to avoid any potential risk of hemolysis. Preclinical data demonstrated the potential for hemolysis or local irritation when administered at concentrations greater than 0.2 mg/mL. While the infusion duration of this mannitol-based vestipitant formulation was similar to that for fosaprepitant,[4] the goal was to develop a formulation allowing for much more rapid (bolus) infusion while minimizing infusion site reactions and eliminate the potential for hemolysis. Such a formulation is more adapted to acute setting of PONV such as rescue treatment post-surgery.

To achieve this goal, a new formulation of vestipitant was developed using SBE7-β-CD. It is hypothesized that the use of SBE7-β-CD in the vestipitant formulation

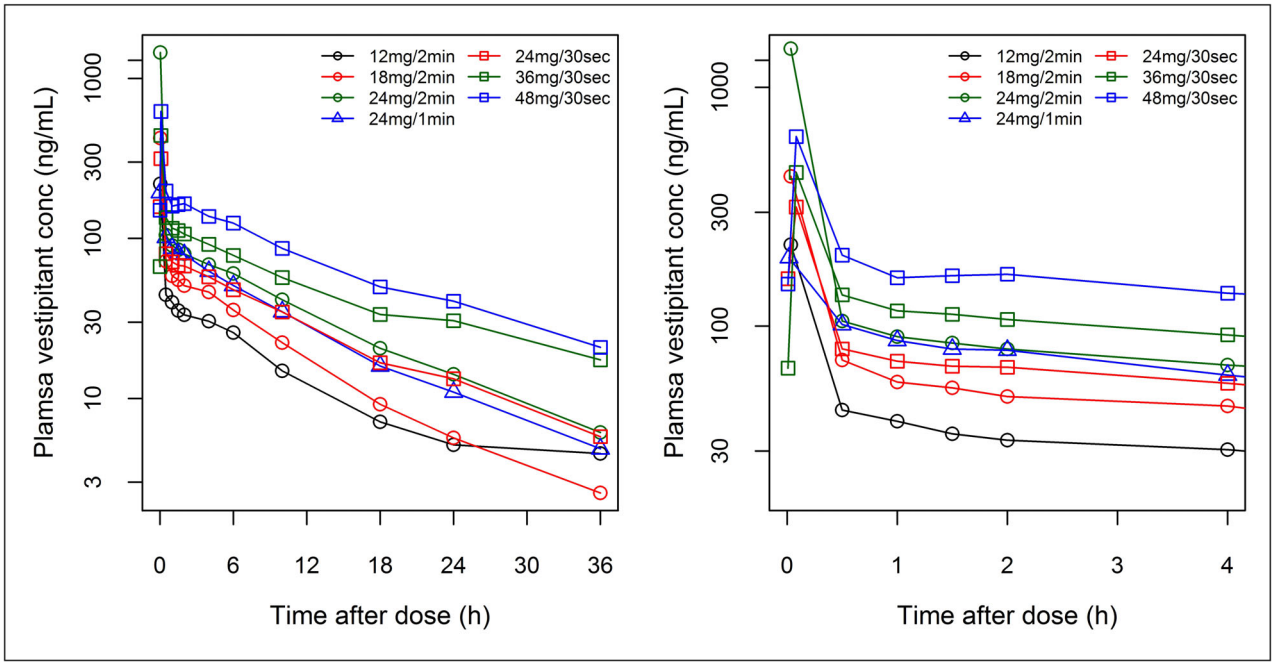

Figure 1. Mean plasma vestipitant concentration–time profiles by cohort with full (left panel) and expanded (right) time scales.

Table 4. Summary of Key Pharmacokinetic Parameters after Single Dose IV Infusion of the Captisol™-based Vestipitant Formulation

Vestipitant dose	Nominal infusion time (minutes)	Solution volume (mL)	N	$AUC_{(0-\infty)}$ [a] (ng h/mL)	C_{max} [a] (ng/mL)	t_{max} [b] (h)	$t_{1/2}$ [a] (h)	CL [a] (L/h)	Vdss [a] (L)	Vz [a] (L)
12 mg	2	6	6	488 (33.3) [510 ± 166.7]	192 (68.5) [219 ± 104.9]	0.03 (0.03–0.05) [0.04 ± 0.008]	8.52 (39.2) [9.1 ± 3.59]	24.6 (33.3) [25.7 ± 8.28]	267 (27.6) [275 ± 75.0]	302 (23.4) [308 ± 65.7]
18 mg	2	9	5	689 (24.8) [705 ± 168.2]	382 (59.7) [424 ± 186.3]	0.03 (0.03–0.03) [0.03 ± 0.000]	7.25 (18.6) [7.3 ± 1.38]	26.1 (24.8) [26.8 ± 6.53]	236 (20.0) [239 ± 48.6]	273 (17.7) [277 ± 46.1]
24 mg	2	12	6	1,402 (18.7) [1,422 ± 255.8]	1,131 (104.0) [1,454 ± 991.0]	0.03 (0.03–0.03) [0.03 ± 0.000]	9.84 (24.0) [10.1 ± 2.73]	17.1 (18.7) [17.4 ± 3.32]	194 (19.0) [197 ± 36.5]	273 (30.3) [283 ± 79.8]
24 mg	1	12	6	974 (34.1) [1,022 ± 367.9]	152 (103.3) [225 ± 275.0]	0.26 (0.02–0.50) [0.26 ± 0.265]	7.74 (23.1) [7.9 ± 1.91]	24.5 (34.9) [26.6 ± 7.85]	262 (35.1) [274 ± 85.4]	243 (15.2) [245 ± 37.3]
24 mg	0.5	12	6	1,045 (31.5) [1,088 ± 340.1]	372 (47.0) [407 ± 200.0]	0.08 (0.01–0.09) [0.07 ± 0.031]	10.2 (34.8) [10.8 ± 4.11]	23.0 (31.5) [23.9 ± 7.07]	303 (22.1) [309 ± 64.4]	339 (19.7) [345 ± 70.3]
36 mg	0.5	18	6	1,982 (50.0) [2,185 ± 1113.4]	449 (31.4) [466 ± 137.3]	0.08 (0.02–0.08) [0.07 ± 0.028]	13.1 (35.2) [13.7 ± 4.64]	18.0 (52.1) [19.7 ± 8.58]	315 (21.8) [321 ± 69.4]	340 (24.1) [348 ± 81.4]
48 mg	0.5	24	6	2,928 (25.8) [3,001 ± 668.7]	581 (41.1) [622 ± 262.3]	0.09 (0.08–0.10) [0.09 ± 0.006]	13.6 (19.6) [13.8 ± 2.90]	16.4 (25.8) [16.9 ± 4.86]	284 (20.2) [289 ± 58.3]	322 (25) [330 ± 83.7]

[a]Geometric mean (%CV) [arithmetic mean ± SD].
[b]Median (min–max), [arithmetic mean ± SD].

serves to disrupt the surface active properties of vestipitant by reducing the fraction of free drug in solution, resulting in the reduction of its hemolytic potential.

An IV vestipitant (2 mg/mL) formulation containing SBE7-β-CD was developed and tested in healthy subjects. The results indicated the ability to infuse up to 48 mg vestipitant in a 2 mg/mL formulation over only 30 seconds. There was no evidence of hemolysis among 41 subjects who received vestipitant during the study. However, infusion site observations were different between vehicle and the different vestipitant doses and infusion rates. Cohorts of subjects at the lower doses and longer infusion duration ($\geq$1 minute) reported more AEs related to the infusion site than those at the higher doses and faster infusion rates. Of the subjects that had infusion site findings, all 3 placebo (saline) events and 13 of the 14 vestipitant events occurred in the longer infusion duration cohorts[1–4] (Table 3). One possible explanation for this observation could be that when subjects have a longer duration infusion, they have more time and opportunity to pay extra attention to the IV site and the infusion process (1–2 minutes vs. 30 seconds). Subjects then have the potential to notice minor discomforts that might have been overlooked had their attention been elsewhere. An alternate explanation could be due to a gender difference in reactivity to study drug since a higher numbers of females enrolled at the earlier cohorts of the study and reported greater number of infusion related AEs (Table 3). A third possibility is due to the shorter infusion time in the later cohorts, limiting the time local tissue is exposed to agents with the potential to cause damage. Limiting local venous exposure to agent is consistent with experimental studies with amiodarone.[10] The placebo group (saline) observations and those at higher doses of vestipitant in the later cohorts may not be consistent with a significant local tissue effect. However, the higher overall vestipitant infusion site observations could be consistent with this possibility. Regardless, the root cause of the differences observed in the AEs at the infusion site cannot be definitively determined based on these data and due to the complex etiology of IV formulation adverse effects.[11] In any case, the data indicate that rapid infusion of vestipitant formulation with SBE7-β-CD was better tolerated than the original formulation containing mannitol.

Decreases in haptoglobin levels have been shown to be a sensitive marker for detection of initial and potentially transient hemolysis. A study comparing running and bicycling, at equivalent metabolic loads, looked at decreases in haptoglobin as a marker. The study demonstrated that mild hemolysis due to footstrike correlated well with increased levels of free hemoglobin and indicated that haptoglobin can be a sensitive marker for hemolysis.[6,11] A decrease of just $\geq$0.1 g/L of

haptoglobin would be outside the range of within-subject variability and could represent hemolysis.[6] For our clinical study evaluating the SBE7-β-CD-based formulation of vestipitant, haptoglobin levels were examined along with other laboratory and clinical evaluations for hemolysis. Only one subject who had received placebo (saline) exhibited laboratory changes indicative of hemolysis. In this case, haptoglobin levels decreased by 0.20 g/L, which was the second largest decrease observed in any subject in the study and was of a greater magnitude than the expected within-subject variability of 0.1 g/L, as noted. Although at least one decrease from baseline >0.1 g/L was observed in 3/14 (21%) placebo subjects and 9/34 (26%) vestipitant subjects, only the one placebo subject with the decrease by 0.20 g/L also had a 121 U/L increase in LDH and a 1 mmol/L increase in potassium along with observation of a hematoma at the infusion site, consistent with hemolysis.

Single dose administration of the SBE7-β-CD-based formulation of IV vestipitant (2 mg/mL) resulted in greater than dose proportional increases in AUC, an observation consistent with the increases in half-life and reductions in clearance observed with increasing dose. While variable between cohorts, Vdss is generally consistent across the dose range studied, suggesting this parameter is unlikely to be responsible for the greater-than-dose-proportional AUC observed. Plasma C_{max} and t_{max} was highly variable in this study, most likely a result of the inherent variation in obtaining a PK sample soon after a rapid IV infusion of a drug that distributes rapidly. The highly variable plasma concentrations in the end of infusion PK sample (which did not always reflect the t_{max}/C_{max}), also may reflect inadequate mixing of vestipitant in the plasma compartment immediately after the infusion. The effects of dose and infusion duration on vestipitant PK are confounded in this study, and with the exception of impacting C_{max}, infusion duration does not appear to have a significant impact on the disposition of vestipitant.

In summary, the results of this study demonstrated that a SBE7-β-CD formulation of vestipitant allowed for a rapid infusion of this NK-1 antagonist with no evidence of hemolytic effects.

Acknowledgments

The authors wish to acknowledge Kasie Fang and Kristen Jurusik, from GlaxoSmithKline department of Drug Metabolism and Pharmacokinetics, for their project support through conducting sample bioanalysis.

Declaration of Conflicting Interests

All authors, except for P.H., are employees of GlaxoSmithKline. P.H. was the principal investigator of the study involved with the study conduct. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. Editorial support (development of the first draft, assembling tables and figures, collating author comments, and referencing) was provided by Guissou Dabiri, PhD, and was funded by GSK.

Funding

Funding for this study was provided by GlaxoSmithKline (NCT01290133).

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