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Open-Label, Dose-Escalation, Phase 1 Study of Safety and Single and Multiple-Dose Pharmacokinetics of Dichlorphenamide in Healthy Volunteers

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Abstract

Single-and multiple-dose pharmacokinetics and safety were investigated in this phase 1 study of dichlorphenamide, a carbonic anhydrase inhibitor approved in the United States for treatment of primary periodic paralysis. Dichlorphenamide was administered to 6 cohorts (n = 6 each) of healthy adults. Cohorts A through E received single doses of 25–400 mg followed by 50–800 mg/day in divided doses for 10 total doses. Cohort F (safety analysis only) received up to 28 titrated doses from 100–800 mg/day. Plasma for pharmacokinetics sampling was obtained predose and up to 48 hours postdose. Twenty-five of 36 enrolled subjects completed. Median time to maximum plasma concentration ranged from 1.5–3 hours, and mean half-life from 32–68 hours. Mean area under the concentration-time curve from time 0 to tau (length of the dosing interval estimated using the trapezoidal method) and maximum observed plasma concentration increased dose-proportionally after multiple doses. The incidence and severity of adverse events (AEs) were dose-related, with at least one mild AE reported among 17%, 17%, and 67% of patients in cohorts A, B, and C, respectively; and at least one mild-to-moderate AE among 100% of subjects in cohorts D, E, and F. One serious AE of rash was reported in cohort F. Eleven subjects discontinued; 10 due to AEs at 400 or 800 mg/day (cohorts E and F), including 100% of cohort F. Hypokalemia contributed to 5 of 6 discontinuations in cohort F (all 800 mg/day).

Keywords

Carbonic anhydrase, dichlorphenamide, pharmacokinetics, periodic paralysis, sulfonamide

Primary periodic paralysis (PP) is a rare disorder associated with autosomal-dominant genetic mutations in skeletal muscle voltage-gated sodium, calcium, and potassium channels.[1,2] Patients experience acute attacks of muscle paralysis lasting from minutes to hours, sometimes accompanied by stiffness (myotonia) and pain. Chronic muscle weakness and atrophy often develop progressively, even as acute attacks wane. Dietary factors, rest after exercise, cold, stress, and alterations in serum potassium levels may precipitate attacks. Management includes avoidance of triggers and modulation of blood potassium. Carbonic anhydrase inhibitors have been used for almost 50 years as empiric treatment for hypokalemic and hyperkalemic forms of PP, owing to observations that if used continuously, they can reduce attack frequency.[1,3,4]

Dichlorphenamide, a carbonic anhydrase inhibitor, was approved in 2015 by the US Food and Drug Administration for the treatment of PP based on results from 2 randomized placebo-controlled studies, each of which included substudies of hypokalemic PP and hyperkalemic PP, the two most common forms of PP.[5,6] These studies demonstrated a significant reduction in the frequency and severity of attacks with dichlorphenamide doses from approximately 100 to 200 mg/day, resulting in a labeled starting dose of 50 mg twice daily (BID) (100 mg/day) and a maximum dose of 200 mg/day.[7] The most common adverse events (AEs)

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reported more frequently among dichlorphenamide-treated subjects in the combined substudies of the hypokalemic/hyperkalemic periodic paralysis trial were paresthesia, cognitive disorder, dysgeusia, headache, fatigue, hypoesthesia, and muscle spasms.[5]

To our knowledge, the pharmacokinetics (PK) of dichlorphenamide have not been previously studied, nor are published studies available describing the effects of doses higher than 200 mg/day. Likewise, there is no published information that describes the pathways of clearance or biotransformation of dichlorphenamide. Based on one published case report and its similarity to acetazolamide, dichlorphenamide is hypothesized to have a drug-drug interaction with salicylates (such as aspirin).[8] Dichlorphenamide is a relatively weak activator of cytochrome P450 (CYP) 2C9-mediated 7-methoxy-4-(trifluoromethyl)coumarin (MFC) metabolism.[9] No other CYP interactions have been reported.

This phase 1 study was undertaken to investigate the PK of dichlorphenamide in healthy subjects after single doses up to 400 mg and multiple doses up to 400 mg BID (800 mg/day).

Methods

The study was conducted at BioPharma Services Inc. (Columbia, Missouri) in accordance with US Food and Drug Administration guidelines and Good Clinical Practice as established by the International Conference on Harmonisation and the principles of the World Medical Association Declaration of Helsinki (2013). The study protocol and informed consent forms were reviewed by the Chesapeake IRB, Columbia, Maryland. All study subjects provided written informed consent prior to performance of any study procedures.

Study Design

This was a phase 1, open-label, dose-escalation study of single and multiple doses of dichlorphenamide tablets administered orally to healthy volunteers. The study consisted of 5 single- and multiple-dose cohorts (6 subjects each in cohorts A through E) and one dose-titration cohort (cohort F, n = 6) (Table 1). During the single-dose phase, subjects who met eligibility criteria received a single oral dose of dichlorphenamide on day 1. In the multiple-dose phase, the same subjects received the prior-assigned dose of dichlorphenamide twice daily except on the last treatment day, when they received a single morning dose of dichlorphenamide. Each subject in cohorts A through E received a total of 10 doses (1 in the single-dose phase and 9 in the multiple-dose phase). Subjects in dose-titration cohort F were to receive dichlorphenamide twice daily on days 1 through 14, for a total of 28 doses. All subjects ingested a morning dose with 8 ounces of water after at least a 10-hour fast; subjects in cohorts A through E fasted an additional 4 hours. The evening dose was taken with 8 ounces of water without regard to meals.

Table 1. Dose Administration in Single- and Multiple-Dose Cohorts and Dose-Titration Cohort

Cohort	Single Doses (No. Doses × mg)	Multiple Doses[a] (No. Doses × mg)	Maximum Exposure per Subject (mg)
A	1 × 25	9 × 25	250
B	1 × 50	9 × 50	500
C	1 × 100	9 × 100	1000
D	1 × 200	9 × 200	2000
E	1 × 400	9 × 400	4000
	Study Days	No. Doses × mg	Maximum Exposure per Subject (mg)
F	1	2 × 50	
	2–3	4 × 100	
	4–6	6 × 200	8100
	7–14	16 × 400	

[a]In the multiple-dose phase, subjects in cohorts A through E received the prior assigned dose of dichlorphenamide twice daily except for the last dose, when a single morning dose was received.

Study Subjects

Nonsmoking adults aged 18 to 65 years with a body mass index of 18.5 to 29.9 kg/m^2 were eligible if they were determined to be healthy based on medical history and physical examination, electrocardiogram (ECG), vital signs, and clinical laboratory testing at screening. Women were required to be surgically sterile for at least 6 months, postmenopausal for at least 1 year, or agree to use a medically acceptable method of contraception for 30 days prior to and after the study. Subjects were excluded for any clinically significant medical condition, including clinically significant gastrointestinal pathology, which could interfere with absorption, distribution, metabolism, or excretion of study drug. Use of any prescription medication within 14 days (except for nonhormonal contraceptives); use of any enzyme-modifying drugs, including strong inhibitors of CYP enzymes (eg, cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, HIV antivirals) and strong inducers of CYP enzymes (eg, barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s wort, rifampicin) in the previous 30 days; or use of any over-the-counter medications within 14 days prior to first drug administration (except for spermicidal/barrier contraceptive products) was prohibited. Consumption of caffeine or methylxanthine-containing products or alcohol within 48 hours or grapefruit-containing products with 10 days of the study was prohibited. Subjects

were excluded for hypersensitivity or idiosyncratic reaction to dichlorphenamide, sulfonamides, the excipients of dichlorphenamide, and/or related substances.

Study Assessments

Subjects had a physical examination and clinical laboratory testing (chemistry, hematology, and urinalysis) at the screening visit and the last study day. At screening, tests were made for HIV and hepatitis B and C viruses, and a 12-lead ECG was obtained. Vital signs (blood pressure, heart rate) were obtained at screening, at baseline, and on each study day. AEs were recorded when reported. In women, a serum pregnancy test was obtained at screening and a urine pregnancy test at baseline. Drug and alcohol screenings were run at screening and baseline.

Pharmacokinetic Analysis

Plasma clinical samples in potassium-EDTA were stored at –70°C for a maximum of 62 days. Dichlorphenamide was extracted using solid-supported liquid-liquid extraction. Chlorfenamide (Enamine Ltd., Ringoes, New Jersey; 97% purity) was used as the internal standard. Stock reference solutions of chlorfenamide and dichlorphenamide (TLC PharmaChem, Aurora, Ontario, Canada; 98.6% purity), for calibration and quality control, were screened for potential interference at the retention times/mass transitions of 268.9/77.9 daltons and 304.9/78.0 daltons, respectively. Both solutions were free of any significant interference. The compounds were identified and quantified by reversed-phase liquid chromatography (Venusil ASB C18; Bonna-Agela Technologies Inc, Wilmington, Delaware) with tandem mass spectrophotometric detection validated over a nominal concentration range of 1-1000 ng/mL (BioPharma Services Inc.). Assay coefficients of variability (ie, precision) within- and between-run were 3.8%-8.7% and 3.4%-9.7%, respectively; and accuracy was 102.1%-109.3% and 97.3%-104.8%, respectively, over the nominal range. Dilution integrity tests up to 10 times the upper limit of quantitation yielded a precision estimate of 6.9% and accuracy of 108%. There was no significant degradation of dichlorphenamide or chlorfenamide over the storage durations and conditions of the assays. Sample analysis was performed by an analyst blinded to randomization, and for each subject, all samples were analyzed in the same batch.

Based on measured concentrations through 48 hours postdose, the following parameters were estimated after single doses: maximum observed plasma concentration (C_{max}); time to maximum plasma concentration (T_{max}); area under the concentration-time curve from time 0 until the last measurable concentration or last sampling time t ($AUC_{0\text{-}t}$), whichever occurred first (estimated using the trapezoidal method); AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$), calculated as [$AUC_{0\text{-}t} + C_{last}/\lambda$], where C_{last} is the last measurable concentration and λ is the terminal elimination rate constant estimated by linear regression analysis of the terminal portion of the log-transformed (Ln) concentration versus time plot; and half-life ($T_{1/2}$). For the multiple-dose phase, the following parameters were estimated: average plasma concentration (C_{avg}), C_{max}, minimum observed plasma concentration (C_{min}), plasma concentration immediately before a dose (C_{pd}), T_{max} and AUC from time 0 to tau (length of the dosing interval [AUC_{τ}] estimated using the trapezoidal method). Fluctuation, expressed as a percentage and defined as the range of concentrations divided by the average steady-state concentration [$100*(C_{max}–C_{min})/(C_{avg})$] was also derived, as was swing, expressed as a percentage and defined as the range of concentrations divided by the minimum observed concentration at steady state, calculated as [$100*(C_{max}–C_{min})/C_{min}$]. For cohorts A through D, sampling times were predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hours postdose for the single-dose phase; and predose on days 3–7 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose for the multiple-dose phase. For cohort E, sampling times were predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hours postdose for the single-dose phase; and predose on days 4-8 and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose. Subjects from cohort F were evaluated for safety and tolerability only and were not sampled for PK.

Table 2. Baseline Demographics

Characteristic	Subjects (N = 36)
Age (years), mean ± SD	38.1 ± 12.1
Male, n (%)	23 (63.9)
Hispanic/Latino, n (%)	2 (5.6)
Race, n (%)	
White	12 (33.3)
Black	22 (61.1)
American Indian/Alaska Native	1 (2.8)
Multiple races	1 (2.8)
Body mass index (kg/m^2), mean ± SD	26.0 ± 3.1
Weight (kg), mean ± SD	77.4 ± 12.7

SD, standard deviation.

Statistical Analysis

Descriptive statistics of all PK parameters were calculated, and a 95% confidence interval (CI) was calculated for slopes examining PK proportionality. During PK and statistical analyses, drug concentrations below the quantifiable limit (BQL) were considered as zero,

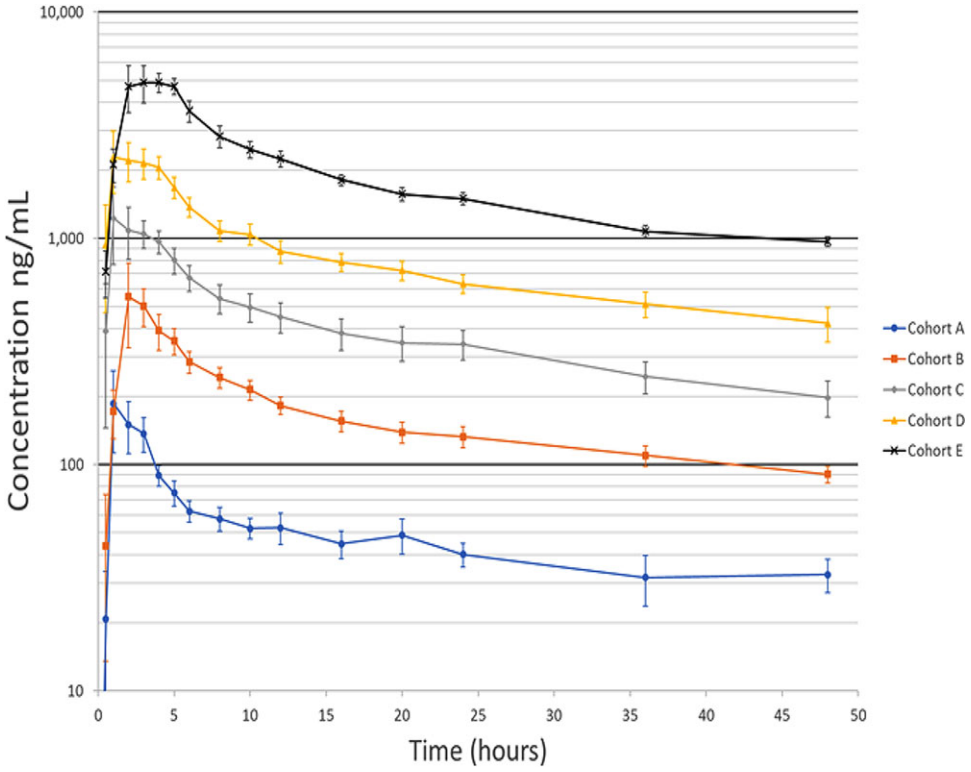

Figure 1. Mean (±SEM) plasma dichlorphenamide concentrations after single-dose administration, log-normal scale.

Table 3. Pharmacokinetic Results After Single-Dose Administration of Dichlorphenamide

Parameter	Cohort A 25 mg (n = 6)	Cohort B 50 mg (n = 6)	Cohort C 100 mg (n = 6)	Cohort D 200 mg (n = 6)	Cohort E 400 mg (n = 6)
$AUC_{0\text{-}t}$ (ng·h/mL), mean ± SD	2327 ± 731	7897 ± 2055	19,119 ± 7317	38,132 ± 8249	88,243 ± 12,616
$AUC_{0\text{-}\infty}$ (ng·h/mL), mean ± SD	5908 ± 3959	14,734 ± 4555	28,901 ± 13,317	66,456 ± 26,211	142,007 ± 16,279
C_{max} (ng/mL), mean ± SD	298 ± 77	709 ± 490	1512 ± 909	3030 ± 1209	6318 ± 1279
$T_{1/2}$ (h), mean ± SD	68.4 ± 35	51.4 ± 24	31.9 ± 11	41.0 ± 17	38.6 ± 8.0
T_{max} (h), median (range)	1.5 (1.0–3.1)	2.5 (2.0–5.0)	2.0 (1.0–4.0)	2.0 (0.5–4.0)	3.0 (2.0–5.0)

$AUC_{0\text{-}t}$, AUC from time 0 until the last measurable concentration or last sampling time t, whichever comes first; $AUC_{0\text{-}\infty}$, AUC from time 0 to infinity; C_{max}, maximum observed plasma concentration; $T_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; SD, standard deviation.

except when they occurred between 2 non-BQL concentrations, in which case, they were considered missing. Dose-proportionality assessments (power model) were made for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} after single-dose administration and for AUC_{τ} and C_{max} after multiple-dose administration. SAS Version 9.4 (SAS Institute, Cary, North Carolina) was used for statistical analyses.

Results

Thirty-six subjects were enrolled between February 16, 2016, and April 30, 2016, and 25 subjects completed the study. One subject (cohort A) was withdrawn for noncompliance, and 10 subjects were withdrawn for AEs (1 in cohort D, 3 in cohort E, and 6 in cohort F). Thus, the PK analysis included 30 subjects for single-dose administration and 25 for multiple-dose administration. Baseline demographic characteristics were consistent with a population of healthy subjects (Table 2).

Pharmacokinetics

After single-dose administration, a dose-related increase in plasma dichlorphenamide concentration was observed (Figure 1). The median T_{max} was 1.5-3 hours across the range of dose administration (Table 3), and $T_{1/2}$ was in the range of 32-68 hours after single-dose administration. Mean $AUC_{0\text{-}t}$ and C_{max} increased slightly greater than dose-proportionally—the slope for $LnAUC_{0\text{-}t}$ and LnC_{max} was 1.29 (95%CI, 1.18-1.40) and 1.11 (95%CI, 0.97-1.26), respectively.

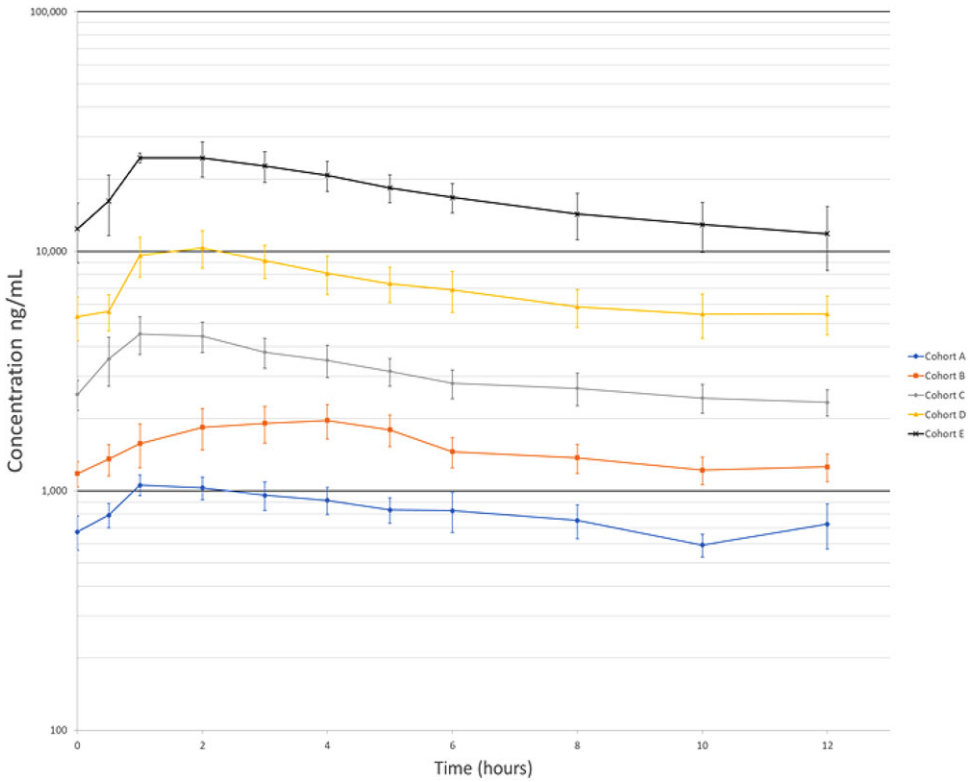

Figure 2. Mean (±SEM) plasma dichlorphenamide concentrations after multiple-dose administration, log-normal scale.

Table 4. Pharmacokinetic Results After Multiple-Dose Administration of Dichlorphenamide

Parameter	Cohort A 25 mg BID (n = 5)	Cohort B 50 mg BID (n = 6)	Cohort C 100 mg BID (n = 6)	Cohort D 200 mg BID (n = 5)	Cohort E 400 mg BID (n = 3)
AUCτ (ng·h/mL), mean ± SD	10,038 ± 3283	18,329 ± 6593	37,468 ± 13,298	84,960 ± 34,245	207,577 ± 62,626
C_{max} (ng/mL), mean ± SD	1148 ± 239	2219 ± 959	4867 ± 1886	10,736 ± 4030	26,577 ± 5391
C_{min} (ng/mL), mean ± SD	726 ± 348	1258 ± 410	2341 ± 722	5479 ± 2273	11,837 ± 6116
C_{avg} (ng/mL), mean ± SD	837 ± 274	1527 ± 549	3122 ± 1108	7080 ± 2854	17,298 ± 5219
T_{max} (h), median (range)	2.0 (0.5–3.0)	3.0 (0.5–5.0)	1.5 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)
Fluctuation (%), mean ± SD	58.6 ± 42	56.7 ± 22	80.5 ± 26	75.8 ± 17	90.9 ± 28
Swing (%), mean ± SD	75.3 ± 61	69.7 ± 33	108.2 ± 39	99.1 ± 25	146.9 ± 65

AUC_τ, AUC from time 0 to tau (length of dosing interval); C_{max}, maximum observed plasma concentration; C_{min}, concentration at end of dosage interval; C_{avg}, average concentration over the dosing interval; T_{max}, time to maximum plasma concentration; SD, standard deviation.

After multiple-dose administration, a dose-proportional increase in plasma dichlorphenamide concentration was observed over the range from 25–400 mg (Figure 2); the slope for $LnAUC_\tau$ and LnC_{max} was 1.09 (95%CI, 0.92–1.26) and 1.13 (95%CI, 0.95–1.31), respectively. Median T_{max} ranged from 1–3 hours (Table 4).

Accumulation ratios of $AUC_\tau/AUC_{0\text{-}t}$ were considerably greater than 1, as were C_{max} for both single- and multiple-dose phases, indicating accumulation with repeated dosing. Fluctuation and swing both appeared to increase with dose.

Safety/Tolerability

Increased exposure to dichlorphenamide resulted in more subjects stopping study drug. All 6 subjects in cohort F, who were assigned to receive 400 mg BID for up to 14 days following dose titration, withdrew from the study (Table 5). Five of the six subjects reached the highest dose level of 800 mg/day, but the longest exposure was only 13 doses at this level. In cohort E, the most common reasons for early study withdrawal were related to symptoms of lightheadedness, while in cohort F, hypokalemia associated with symptoms suggesting excessive diuresis prompted withdrawal.

Table 5. Withdrawals Due to Adverse Events

Subject (Sex)	Cohort	Total Doses Received	Total Doses (at Final Strength)	Final Dose (mg)	AEs Reported	Maximum Severity of AEs
23 (F)	D	1	1	200	Lethargy, lightheadedness	Mild; withdrew due to "side effects"
25 (M)	E	1	1	400	Lightheadedness, paresthesia (left side), tinnitus, dizziness, memory loss/mental impairment	Mild; withdrew due to "side effects"
26 (F)	E	1	1	400	Numb lips, pressure behind eyes, dizziness/lightheadedness, tingling hands and feet, lethargy	Mild; withdrew due to "side effects"
29 (M)	E	1	1	400	Near-fainting episode after first dose, nausea, non–clinically significant drop in blood pressure	Moderate near-fainting, nausea, hypotension; withdrew due to these effects
31 (M)	F	25	13	400	Hypokalemia, weight loss, insomnia, irritability, constipation, disorientation, foggy-headed, dyspnea, heart fluttering with exercise, paresthesia, throat tightening/scratchiness	Mild; hypokalemia, weight loss, and scratchy throat prompted discontinuation
32 (M)	F	19	6	400	Hypokalemia, tachycardia, buzz in head, irritability, facial swelling, facial urticaria	Mild; clinically significant hypokalemia along with tachycardia led to discontinuation
33 (M)	F	23	10	400	Hypokalemia, weight loss	Mild; hypokalemia deemed clinically significant
34 (F)	F	16	3	400	Hypokalemia, fall, gait instability, itching, menstrual, thumb numbness, cramps, erythema arms, euphoria	Mild except moderate gait instability; hypokalemia and fear of falling led to discontinuation
35 (M)	F	25	12	400	Hypokalemia, headache, euphoria, weight loss, lost filling	Mild; dismissed for worsening hypokalemia
36 (F)	F	11	4	200	Toothache, headache, fingertips/foot tingling, ear numbness, forgetfulness, rash on feet	Moderate toothache, others mild; withdrew due to the tooth pain

Table 6. Incidence of Treatment-Emergent Adverse Events (TEAEs)

	Cohort					
	A (n = 6)	B (n = 6)	C (n = 6)	D (n = 6)	E (n = 6)	F (n = 6)
Total TEAEs reported	1	3	16	36	42	50
Treatment-related AEs reported	0	2	14	33	39	40
Subjects reporting at least 1 TEAE, n (%)	1 (16.7)	1 (16.7)	4 (66.7)	6 (100)	6 (100)	6 (100)
Subjects reporting at least 1 moderate TEAE, n (%)					1 (16.7)	2 (33.3)
Subjects reporting at least 1 serious TEAE, n (%)	0	0	0	0	0	1 (16.7)
Subjects discontinuing due to TEAE, n (%)	0	0	0	1 (16.7)	3 (50.0)	6 (100)
TEAEs of any severity reported by more than 10% of all subjects						
Paresthesia	0	0	2 (33.3)	2 (33.3)	4 (66.7)	2 (33.3)
Oral paresthesia	0	0	0	1 (16.7)	1 (16.7)	0
Dizziness	0	0	0	4 (66.7)	3 (50.0)	0
Dyspnea	0	0	0	3 (50.0)	1 (16.7)	1 (16.7)
Blood potassium decreased	0	0	1 (16.7)	0	1 (16.7)	2 (33.3)
Dysgeusia	0	0	0	3 (50.0)	1 (16.7)	0

Cohort C received the maximum approved dose of 200 mg/day; cohorts D through F received more than the approved daily dose.

In total, 148 treatment-emergent AEs (TEAEs) were reported across 24 patients (Table 6). The majority were reported as mild (n = 140) or moderate (n = 7) and 128 were considered treatment-related. One serious TEAE of rash was experienced by 1 subject in cohort F, requiring brief hospitalization for treatment. A dose relationship in the frequency of TEAEs was evident, increasing notably in subjects receiving more than the approved maximum dose of 200 mg/day (100 mg BID). Likewise, severity was also dose related. Only mild TEAEs were reported across cohorts A through D, while moderate TEAEs were reported among subjects in cohorts E and F. The most commonly affected system organ classes, by incidence of subjects reporting at least 1 TEAE, were nervous system (50% of subjects) and gastrointestinal (28% of subjects). Within the nervous system class, the most commonly reported TEAEs were paresthesia (including oral) in 12 subjects (33%) and dizziness in 7 subjects (19%).

No clinically relevant changes in vital signs or ECG findings were reported for any subject. Clinical laboratory evaluations done poststudy in cohorts A through E revealed 2 subjects with clinically significant reductions in serum potassium: 1 in cohort C (2.8 mmol/L) and 1 in cohort E (2.5 mmol/L); no other clinically significant analyte changes were noted in those cohorts. Clinical laboratory evaluations made at multiple study time points in cohort F revealed below-normal serum potassium in 5 of 6 subjects, with the lowest recorded value of 2.8 mmol/L.

Discussion

This is the first reported study of the PK of dichlorphenamide. Single doses of drug were associated with increases in $AUC_{0\text{-}t}$ and C_{max} that were somewhat greater than dose-proportional, while dose-proportional increases in AUC_{τ} and C_{max} were apparent over a range of 50-800 mg/day in 2 divided doses daily. Maximal plasma concentration was generally reached within 3 hours of a dose, and drug was cleared from plasma in an apparent first-order process, with $T_{1/2}$ in the range of 40-50 hours after single doses.

The incidence and severity of TEAEs was dose-related, with an apparent threshold above 200 mg/day, which is the maximum approved dose for treating PP. None of the subjects receiving dichlorphenamide at total doses of 200 mg/day or less (cohorts A through C) experienced a moderate, severe, or serious TEAE, and none withdrew from the study. In contrast, TEAEs reported among subjects receiving a total of 400 mg/day or greater (cohorts D through F) prompted several study withdrawals, owing to symptoms and laboratory and vital signs suggestive of excessive diuresis and kaliuresis, including lightheadedness, dizziness, gait instability, hypotension, and clinically significant hypokalemia. An attempt to mitigate intolerance of high doses using a dose-titration strategy (cohort F) failed. Indeed, none of the subjects assigned to receive up to 14 days of treatment with dichlorphenamide at a total daily dosage of 800 mg in cohort F completed the study, and 5 of 6 were withdrawn in part due to hypokalemia.

Diuresis and kaliuresis are long-known effects of acute renal carbonic anhydrase inhibition by acetazolamide and other systemic carbonic anhydrase inhibitors.[10] Indeed, acetazolamide was originally developed as a diuretic for control of heart failure.[11,12] However, relatively less is known regarding the diuretic and kaliuretic effects of dichlorphenamide, and prior to the current study no studies of multiple daily dosing exceeding 200 mg/day had been published. The effects of acetazolamide on kidney water and electrolyte excretion has been observed to be dose-related and to diminish with continued use over a period of days to weeks.[12,13] Subjects in the current study who were most affected by potassium losses (ie, subjects receiving the highest tested dose regimen of 400 mg BID) were exposed for a week or less before withdrawing from the study. Therefore, further study would be needed to determine if the kidneys would adapt to continued administration of higher dichlorphenamide doses, as observed with acetazolamide. In the absence of such evidence, the current toxicity observations are instructive for the proper use of dichlorphenamide, reinforcing recommended adherence to the maximum approved dose of 200 mg/day, usually given in twice-daily doses.

Conclusions

In summary, this study demonstrated approximately linear dose-exposure (AUC and C_{max}) relationships with dichlorphenamide over a range of doses that includes the approved dose of 200 mg/day (100 mg BID). The results also confirmed dose and exposure relationships to AEs; the drug was intolerable for extended use at 800 mg total daily dose in this short-term study. These findings support dosing of dichlorphenamide up to 200 mg/day.

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Declaration of Conflicting Interest

Dr Cohen is an employee of Strongbridge Biopharma and owns stock in the company.

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