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Original Article

Efficacy and Safety of Dichlorphenamide for Primary Periodic Paralysis in Adolescents Compared With Adults

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ABSTRACT

Background: Primary periodic paralyses are rare, hereditary skeletal muscle diseases characterized by episodic muscle weakness. Dichlorphenamide was effective and well tolerated in two studies, including one with adolescents. This analysis describes effects of dichlorphenamide among adolescents and adults.
Methods: Patients with primary periodic paralyses in a double-blind, controlled, crossover study were randomized to dichlorphenamide or placebo for nine weeks, with a nine-week or longer between-treatment washout period. Attack rate and severity-weighted attack rate during the final eight weeks of each treatment phase were calculated for adolescents and adults separately.
Results: Seven adolescents (10 to ≤17 years) and 66 adults were enrolled; five of seven adolescents were evaluable for efficacy and six for safety. Dichlorphenamide total daily dosing among adolescents was 50 mg (n = 1) or 100 mg (n = 5), and in adults was 105.7 mg (mean; n = 61). In adolescents, the median decrease from baseline in frequency of weekly attacks was greater with dichlorphenamide (−0.96) than with placebo (−0.57), similar to findings in adults (dichlorphenamide, −0.83; placebo, −0.24). Severity-weighted attack frequency was likewise reduced more with dichlorphenamide than with placebo in adolescents and adults. The most common adverse event with dichlorphenamide in adolescents was skin rash (two of six [33%]). In adults, numbness was the most common adverse event (26 of 54 [48%]); skin rash occurred less frequently (10 of 54 [19%]).
Conclusions: Dichlorphenamide was comparably effective and tolerated among a small number of adolescents as well as adults, although types of adverse events differed between groups.

Introduction

The primary periodic paralyses (PPP) are a rare, heterogeneous group of hereditary skeletal muscle ion channelopathies (e.g., hypokalemic and hyperkalemic periodic paralyses) that lead to attacks of episodic or persistent muscle weakness.[1-3] A number of different genetic mutations affecting ion channels are associated with PPP, although some patients with PPP currently do not have identified mutations.[4-7] Patients with PPP typically experience initial symptoms during childhood or adolescence, with the number of attacks typically decreasing as the patient ages.[1,7] The frequency of attacks ranges from once in a lifetime to multiple events per week, and the duration of an attack can range from hours to days.[1,2,7]

Management of PPP is based on a patient's symptom profile, and diet and lifestyle modifications are typically the first strategy used to prevent attacks.[1,3] Pharmacologic management of PPP includes treatment to prevent attacks and treatment of acute attacks, although options are limited and most are used empirically.[3] The

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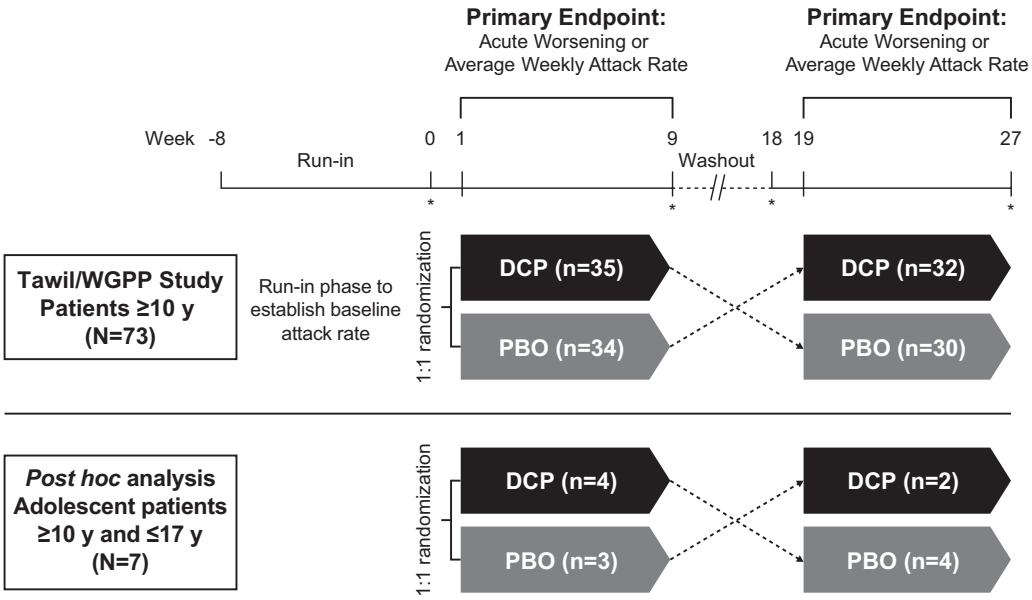

FIGURE 1. Study design. DCP, dichlorphenamide; PBO, placebo; WGPP, Working Group on Periodic Paralysis. *Safety assessments evaluated by the investigator; assessments also occurred during weekly phone calls.

carbonic anhydrase inhibitors acetazolamide and dichlorphenamide (DCP) have a long history of use in patients with PPP; DCP is currently the only US Food and Drug Administration-approved agent for the treatment of patients with hypokalemic and hyperkalemic periodic paralyses and related variants.[3,8] A randomized, double-blind, controlled, crossover study, containing two substudies, in patients aged 10 to 75 years with PPP (n = 73) demonstrated that nine-week treatment with DCP decreased the frequency and severity of attacks compared with placebo.[9] A subsequent randomized, double-blind, controlled study, also with two substudies, reported that DCP reduced the median number of attacks in patients aged 18 years and older with PPP (n = 65) compared with placebo during the final eight weeks of the nine-week treatment period.[10] Given that the efficacy and safety of DCP in adolescents with PPP have not been previously described, the aim of this analysis was to characterize the efficacy and safety of DCP in the subgroup of adolescents with PPP who participated in the first randomized study.[9]

Methods

Study design and patients

The study design (Fig 1) and overall patient population have been described previously.[9] Briefly, two multicenter, randomized, double-blind, controlled, crossover substudies of patients with PPP aged 10 to 75 years (i.e., hypokalemic periodic paralysis and potassium-sensitive periodic paralysis [hyperkalemic periodic paralysis and paramyotonia congenita with periodic paralysis]) were conducted. Patients included in the study had to experience more than one weakness episode per week and less than three per day. After a run-in phase of at least eight weeks (i.e., baseline period), patients were randomly assigned to receive DCP or placebo for nine weeks, followed by a washout period of at least nine weeks and crossover to the other treatment for nine weeks. Patients receiving acetazolamide during the run-in phase were to receive DCP at a dose that was one-fifth of the acetazolamide dose (in milligrams), and patients receiving DCP at baseline received the same dose during the study. All other patients received DCP 50 mg twice daily.

Assessments

In this analysis, the attack rate (i.e., average number of attacks per week during the final eight weeks of each treatment phase) and severity-weighted attack rate (i.e., average of severity grades [range, 1 to 4] for each attack during the final eight weeks of each treatment phase) were calculated for adolescents (10 to ≤17 years of age) and adults (greater than 17 years of age).[9] Severity was graded by a modified functional scale previously used in Guillain-Barré

TABLE 1.
Demographic and Baseline Characteristics for Adolescents

Patient	Age,* y	Sex	PPP Phenotype	Prior Medications	Assigned Treatment Sequence	Disposition
1	13	Male	Hypokalemic	Potassium	PBO-DCP	Completed
2	15	Male	Hypokalemic	Potassium	DCP-PBO	Completed
3	17	Female	Potassium sensitive†	None	PBO-DCP	Completed; missing efficacy data
4	10	Male	Potassium sensitive†	Acetazolamide	PBO-DCP	Discontinuation from study; no data
5	16	Male	Hypokalemic	Acetazolamide + potassium	DCP-PBO	Completed
6	13	Male	Potassium sensitive†	None	DCP-PBO	Completed
7	16	Male	Potassium sensitive†	Acetazolamide	DCP-PBO	Completed

Abbreviations:
DCP = Dichlorphenamide
PBO = Placebo
PPP = Primary periodic paralyses
* At time of study entry.
† May include patients with hyperkalemic PPP or paramyotonia congenita.

TABLE 2.
Average Weekly Attack Rate in Adolescents

	Weekly Attack Rate			Severity-Weighted Weekly Attack Rate*		
Patient	Baseline	DCP	PBO	Baseline	DCP	PBO
1	0.88	0	0.13	2.75	0	0.25
2	1	0.13	1.25	3.63	0.13	2.38
3	NA	NA	1.71	NA	NA	2.43
4	2.63	NA	NA	4	NA	NA
5	1.25	0.29	0	2.38	0.29	0
6	1	0	0.43	1.38	0	0.43
7	2.5	0.88	3.57	3.25	1	7.71

Abbreviations:
DCP = Dichlorphenamide
NA = Not available
PBO = Placebo
* Severity graded (range, 1 to 4) by modified functional scale previously used in Guillain-Barré syndrome.[11]

syndrome.[9,11] The frequency of nine prespecified individual adverse events (AEs) was assessed in adolescents and adults.

Statistical analyses

Patients with data for both treatment phases were included in the analyses. Demographics, baseline characteristics, and AEs were evaluated descriptively. Statistical analyses of attack rates and severity-weighted attack rates were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). Ninety-five percent confidence intervals (CIs) are presented.

Results

Efficacy

A total of seven adolescents and 66 adults with PPP from the overall study population (N = 73) were included in this analysis (Fig 1). The adolescents were predominantly male and were aged between 10 and 17 years (Table 1). Of these seven patients, one patient (aged 10 years) withdrew before receiving DCP and one patient (aged 17 years) provided only tolerability data. Thus, five of the seven adolescents (age range, 13 to 16 years) were evaluable for efficacy and six were evaluable for safety. The mean self-reported age of onset of PPP (not including patients with an age of onset reported as 0) was 10 years for adolescents (n = 4) and 11 years for adults (n = 55). The adolescents were almost evenly divided into those with hypokalemic periodic paralysis (n = 3) and those with potassium-sensitive PPP (n = 4). Two adolescents had received acetazolamide alone before enrolling in the study, one adolescent had received acetazolamide in combination with potassium, and two adolescents had received potassium alone. No adolescents were receiving DCP at the time of study entry. Total daily dosing of DCP was 50 mg in one adolescent and 100 mg in five adolescents. Mean daily dosing of DCP was 105.7 mg (range, 50 to 300 mg) in adults (n = 61).

For adolescents with available baseline data, the average weekly attack rate at baseline ranged from 0.9 to 2.6 (Table 2).[1] When severity of attacks was also considered, the weekly attack rate at baseline ranged from 1.4 to 4. Treatment with DCP resulted in a numerically greater median decrease from baseline in the frequency of weekly attacks in adolescents (−0.96 [95% CI, −1.63, −0.88]) compared with placebo (−0.57 [95% CI, −1.25, 1.07]); adults experienced a comparable improvement relative to placebo (median change for DCP, −0.83 [95% CI, −2.75, −0.26]; median change for placebo, −0.24 [95% CI, −0.88, 0.35]; Fig 2A). The median improvement in severity-weighted attack rate from baseline in adolescents was numerically greater with DCP (−2.25 [95% CI, −3.5, −1.38]) than placebo (−1.25 [95% CI, −2.5, 4.46]); for adults, the median change for DCP was −1.17 (95% CI, −3.38, −0.63) and for placebo was −0.55 (95% CI, −0.88, 0.58; Fig 2B).

Safety

Three adolescents reported five solicited AEs during DCP treatment, including skin rash (n = 2 patients), dizziness (n = 1 patient), itchiness (n = 1 patient), and numbness (n = 1 patient; Table 3). The most common AE reported during DCP treatment by adults was numbness (48%). Skin rash and itchiness were not reported during placebo treatment in the adolescents. No AEs were dose limiting or resulted in study withdrawal in the adolescent population. Adults also reported the following solicited events during DCP treatment that were not reported by adolescents: decrease in appetite (anorexia), diarrhea, taste changes, flank pain, and abdominal cramping. AEs reported spontaneously by adolescents during DCP treatment included lightheadedness (n = 1); nausea, persistent or recurrent lightheadedness, and slow thinking (n = 1); weakness (n = 1); and weight loss (n = 1). Adults spontaneously reported similar types of AEs (lightheadedness, n = 6; slow thinking, n = 3; weakness, n = 6) but additionally reported cognitive changes (i.e., difficulty concentrating, mental confusion, and disorientation [n = 7; 13%]), which were not reported among adolescents.

Conclusions

This analysis suggests that DCP has a similar ability to reduce the frequency and severity of attacks in adolescents with PPP as in

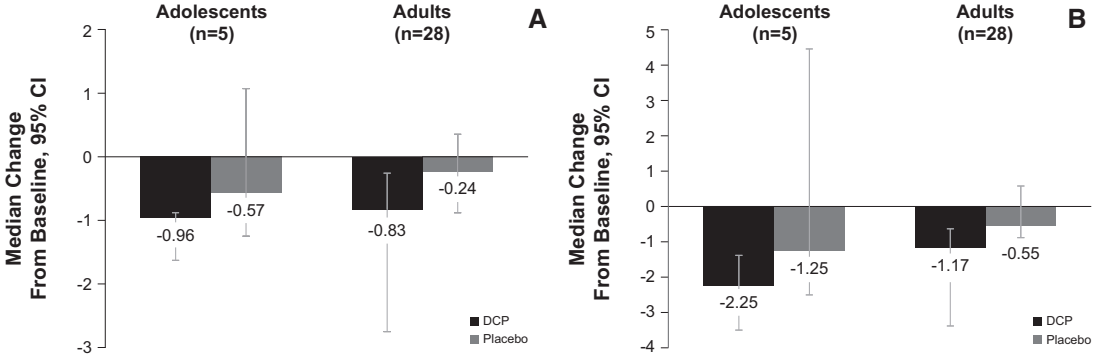

FIGURE 2. Median changes from baseline in weekly attack rate (A) and severity-weighted weekly attack rate (B) in adolescents and adults. CI, confidence interval; DCP, dichlorphenamide. Includes only patients with nonmissing data during both treatment periods.

TABLE 3.
Solicited Adverse Events Reported by Adolescents and Adults Receiving Dichlorphenamide

AE, n (%)	Adolescents (n = 6)	Adults (n = 54)
Skin rash	2 (33)	10 (19)
Numbness (paresthesia)	1 (17)	26 (48)
Dizziness	1 (17)	9 (17)
Itchiness (pruritus)	1 (17)	7 (13)
Decrease in appetite (anorexia)	0	11 (20)
Diarrhea	0	11 (20)
Taste changes	0	7 (13)
Flank pain	0	4 (7)
Abdominal cramping	0	2 (4)

Abbreviation:
AE = Adverse event

adults. Median decreases from baseline in the weekly attack rate and the severity-weighted weekly attack rate in adolescents receiving DCP were comparable with results in adults receiving DCP. Although the number of adolescents evaluated was small, this is the first report to specifically examine the efficacy and tolerability of DCP in adolescents with PPP. The only other randomized clinical study of patients with PPP receiving DCP limited participation to those aged at least 18 years.[10]

Although DCP treatment was generally well tolerated in both adolescents and adults, too few AE reports were made among the small number of adolescents receiving DCP to determine whether the drug is tolerated differently in adolescents than in adults, but available data suggest that there may be some differences. For example, a greater percentage of adolescents experienced skin rash compared with adults, whereas only adults reported cognitive disturbances. In this study, AEs were primarily captured through solicited inquiries of specific prespecified events, with spontaneous AE reports recorded as “other events”; severity was not captured. To determine the tolerability profile of DCP in adolescents more completely and accurately, it will be important in future studies to capture AE reports spontaneously along with additional information on severity and steps taken in response, as was done in another study of adults in PPP.[10]

A strength of the current study is the crossover design,[9] with patients receiving both DCP and placebo. The crossover minimizes interindividual variability and allows patients to serve as their own control.[12] Indeed, the Small Population Clinical Trials Task Force of the International Rare Diseases Research Consortium recommends consideration of crossover study design for studies of rare diseases.[13] Limitations of this analysis are its *post hoc* nature, the small number of adolescents enrolled, and the solicitation method used to capture AEs. In addition, there was no genetic confirmation of the diagnosis of PPP in any of the patients. Furthermore, although the duration of DCP treatment is comparable with that of another study (nine weeks),[9,10] this study did not include an extension phase, so potential long-term benefits and risks of DCP in adolescents are unknown. In conclusion, this analysis provides evidence that efficacy and tolerability of DCP are similar in adults and a small number of adolescents, although AE profiles differed between adolescents and adults. The findings of this analysis can serve as an impetus for further, larger studies of DCP among adolescents with PPP.

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References

1. Venance SL, Cannon SC, Fialho D, et al. The primary periodic paralyses: diagnosis, pathogenesis and treatment. Brain. 2006;129(Pt 1):8–17.
2. Fontaine B, Vale-Santos J, Jurkat-Rott K, et al. Mapping of the hypokalaemic periodic paralysis (HypoPP) locus to chromosome 1q31-32 in three European families. Nat Genet. 1994;6:267–272.
3. Statland JM, Fontaine B, Hanna MG, et al. Review of the diagnosis and treatment of periodic paralysis. Muscle Nerve. 2018;57:522–530.
4. Cannon SC. Channelopathies of skeletal muscle excitability. Compr Physiol. 2015;5:761–790.
5. Sampedro Castañeda M, Zanoteli E, Scalco RS, et al. A novel ATP1A2 mutation in a patient with hypokalaemic periodic paralysis and CNS symptoms. Brain. 2018;141:3308–3318.
6. Matthews E, Labrum R, Sweeney MG, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. Neurology. 2009;72:1544–1547.
7. Charles G, Zheng C, Lehmann-Horn F, Jurkat-Rott K, Levitt J. Characterization of hyperkalemic periodic paralysis: a survey of genetically diagnosed individuals. J Neurol. 2013;260:2606–2613.
8. KEVEYIS® (Dichlorphenamide) Tablets, for Oral Use. Trevose, PA: Strongbridge US Inc.; 2017.
9. Tawil R, McDermott MP, Brown Jr R, et al. Randomized trials of dichlorphenamide in the periodic paralyses. Working Group on Periodic Paralysis. Ann Neurol. 2000;47:46–53.
10. Sansone VA, Burge J, McDermott MP, et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. Neurology. 2016;86:1408–1416.
11. Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome study group. Neurology. 1985;35:1096–1104.
12. Gupta S, Faughnan ME, Tomlinson GA, Bayoumi AM. A framework for applying unfamiliar trial designs in studies of rare diseases. J Clin Epidemiol. 2011;64:1085–1094.
13. Day S, Jonker AH, Lau LPL, et al. Recommendations for the design of small population clinical trials. Orphanet J Rare Dis. 2018;13:195.