Hyperdopaminergic crises in familial dysautonomia

A randomized trial of carbidopa

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ABSTRACT

Objective: The purpose of this study was to determine whether carbidopa (Lodosyn), an inhibitor of dopa-decarboxylase that blocks the synthesis of dopamine outside the brain, is an effective antiemetic in patients with familial dysautonomia (FD) and hyperdopaminergic nausea/retching/vomiting attacks.

Methods: We enrolled 12 patients with FD in an open-label titration and treatment study to assess the safety of carbidopa. We then conducted a randomized, double-blind, placebo-controlled, crossover study to evaluate its antiemetic efficacy.

Results: Previous fundoplication surgery in each patient studied prevented vomiting, but all of the subjects experienced severe cyclical nausea and uncontrollable retching that was refractory to standard treatments. Carbidopa at an average daily dose of 480 mg (range 325–600 mg/day) was well tolerated. In the double-blind phase, patients experienced significantly less nausea and retching while on carbidopa than on placebo ($p < 0.03$ and $p < 0.02$, respectively). Twenty-four-hour urinary dopamine excretion was significantly lower while on carbidopa ($147 \pm 32 \mu\text{g/gCr}$) than while on placebo ($222 \pm 41 \mu\text{g/gCr}$, $p < 0.05$).

Conclusions: Carbidopa is a safe and effective antiemetic in patients with FD, likely by reducing the formation of dopamine outside the brain.

Classification of evidence: This study provides Class II evidence that carbidopa is effective in reducing nausea/retching/vomiting in patients with FD. *Neurology*® 2013;80:1611–1617

GLOSSARY

FD = familial dysautonomia.

Recurrent bouts of nausea, retching, and vomiting accompanied by tachycardia and hypertension following emotional or physiologic stresses are a common disabling feature of familial dysautonomia (FD) (Riley-Day syndrome or hereditary sensory and autonomic neuropathy type III).^{1,2} Standard antiemetics have little effectiveness during these episodes. Traditionally, patients with FD were advised to manage their episodes with benzodiazepines.³ Many quickly become tolerant and require increasing doses, which have been associated with respiratory depression. The central sympatholytic agent, clonidine, has been used with some success, but its use is limited by the unwanted side effects of sedation and hypotension.³ Metoclopramide has also been used, but it is frequently associated with tardive dyskinesia, and is therefore not suitable as a long-term therapy.⁴ Newer agents like pregabalin are only moderately effective.⁵

Because of a developmental abnormality in the afferent neurons of the baroreflex, patients with FD are unable to restrain sympathetic outflow.⁶ Vomiting/retching attacks occur during sympathetic activation when dopamine spills over into the circulation.² We hypothesize, therefore, that vomiting is due to activation of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood–brain barrier.⁷

The purpose of this study was to determine whether carbidopa (Lodosyn, Merck & Co., Inc., Whitehouse Station, NJ), an inhibitor of dopa-decarboxylase that blocks the synthesis of dopamine outside the brain,⁸ is an effective antiemetic in patients with FD. We present the results of a randomized, placebo-controlled trial conducted in patients with FD.

Supplemental data at
www.neurology.org

From the Dysautonomia Center, New York University School of Medicine, New York.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS Patients. We enrolled 12 patients homozygous for the common FD intron-20 gene mutation⁹ who complained of severe nausea and retching and had failed multiple treatment attempts (inclusion criteria). All were being followed as outpatients at the Dysautonomia Center in New York University School of Medicine. Patients younger than 12 years or with severe renal disease (serum creatinine >2.0 mg/dL) or significant electrocardiographic abnormalities were ineligible. Patients taking dopamine blockers (metoclopramide, domperidone, risperidone), monoamine oxidase inhibitors, tricyclic antidepressants, or neuroleptics were also excluded.

Standard protocol approvals, registrations, and patient consents. The study was approved by the US Food and Drug Administration's Office of Rare Disorders and ethical approval was obtained from the Institutional Review Board of New York University. The trial was registered on ClinicalTrials.gov (NCT01212484). Written informed consent (or assent) was obtained from all participants. Recruitment ran from February 2010 to September 2011.

Study design. Participants first monitored their symptoms of nausea and retching in a daily diary on a validated patient-reported outcome scale for 1 month.¹⁰ Twenty-four-hour urine collections were assayed to measure daily dopamine excretion the day before scheduled study visits, at baseline, at the end of the open-label treatment phase, and at each crossover visit. Baseline laboratory values, EKG, and blood pressures were obtained at scheduled office visits (table 1).

Patients who reported severe, frequent (>3/week) attacks of nausea and retching in their diaries were enrolled in an open-label dose titration and active treatment phase. During the trial, the patients continued to take the same doses of standing medications (diazepam, clonidine, clonazepam, pregabalin) that they had taken during the previous 4 weeks. Doses of carbidopa were increased in a stepwise fashion over an average of 38 days. Doses began at 12 mg and were increased in 25 mg/day increments every other day. The duration of the titration phase depended on the dosage,

but on average lasted 38 days. Adult patients were titrated up to 600 mg of carbidopa per day (divided into 3 200-mg doses every 6 hours by mouth or via gastrostomy tube, if preferred). Doses were adjusted accordingly in pediatric patients who weighed less than 50 kg using the Lack and Stuart-Taylor formula.¹¹ Patients remained on their maximum dose of carbidopa for 4 weeks to evaluate safety and tolerability.

To evaluate the efficacy of carbidopa, we used a randomized, double-blind, placebo-controlled crossover design in which each patient served as his or her own control. The order in which carbidopa or placebo was administered was determined randomly (computer generated) and none of the treating physicians, patients, or caregivers knew the identity of the drugs given. To maintain allocation concealment, we prepared identical orange capsules containing either carbidopa powder (active agent) or an identical-looking lactose powder (placebo). Patients were instructed to take equal numbers of either placebo or carbidopa capsules every 6 hours. The 2 crossover periods ran consecutively and each lasted 4 weeks.

Evaluation procedures. Table 1 provides a schedule of the main assessments during the trial. Safety measures included weight and temperature, supine/seated/standing blood pressures, complete blood counts, metabolic panels, 12-lead EKGs, and full neurologic examinations (table 1). Side effects were monitored throughout.

Primary efficacy outcome measures. Our primary research question was to determine whether carbidopa (Lodosyn) is an effective treatment for nausea/retching/vomiting attacks in patients with FD. To assess efficacy, patients were given a printed diary and asked to grade their symptoms each night for 1 month. On each diary page, nausea and retching were defined in detail and assessed individually. Daily scores were reported on a modified version of the Rhodes Index of Nausea, Vomiting and Retching,¹² which included all 5 items relating to nausea and retching. Items addressing vomiting/throwing up were omitted, as all

Table 1 Study assessments during the trial

Procedure	Baseline	Open-label	Double-blind	
			Carbidopa	Placebo
Safety measures				
Physical examination	X	X	X	X
Neurologic examination	X	X	X	X
Vitals	X	X	X	X
Complete blood count	X	X	X	X
Metabolic panel	X	X	X	X
12-Lead EKG	X	X	X	X
Blood pressure assessments	X	X	X	X
Pregnancy test	X			X
Primary efficacy measure				
4-week nausea diary	X	X	X	X
Secondary efficacy measures				
GCI: nausea severity	X	X	X	X
GCI: nausea improvement		X	X	X
24-Hour urinary catecholamines	X	X	X	X

Abbreviation: GCI = global clinical impression.

participants had antireflux surgery that prevented vomiting (Nissen fundoplication). Retching distress, nausea distress, number of nausea episodes per day, number of retching episodes per day, and the amount of time spent feeling nauseous were graded on a 5-point scale. Patients were also asked to note whether they took additional drugs to control their nausea that day.

Secondary efficacy outcome measures. Patients were asked to make global clinical assessment of symptom severity, using a 7-point scale, ranging from 1 (no nausea) to 7 (extremely ill with nausea), at scheduled office visits. Patients were also asked to rate their global impressions of improvement on a 7-point scale. Scores ranged from 1 (very much improved) to 7 (very much worse) and were made in relation to baseline (screening prior to dose titration). Twenty-four-hour urine was collected in standardized darkened collection bottles containing hydrochloric acid as a preservative. Samples were refrigerated before being assayed using quantitative high-performance liquid chromatography to assess free dopamine and norepinephrine levels (table 1).

Statistical analysis. An average daily score was calculated from the nausea diaries at baseline, during open-label active treatment, and in both crossover phases. Analysis was carried out on the individual item scores and the composite score generated from the sum of all 5 domains.¹² Datasets were first tested for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Depending on the outcome, mean unadjusted scores as well as change from baseline were compared during placebo and carbidopa using paired *t* tests, 2-way analysis of variance, or Wilcoxon signed-rank tests. Parametric and nonparametric evaluations were used as appropriate. Data were analyzed using Prism version 5.0 (GraphPad Software, Inc., 2011).

All *p* values were 2-tailed and *p* < 0.05 was considered statistically significant.

RESULTS Baseline data. Twelve patients entered the trial (figure e-1 on the *Neurology*® Web site at www.neurology.org). The average age of the patients was 18 years (range 12–36 years). Eight were male. All had histories of multiple hospitalizations for uncontrollable retching attacks. Despite chronic treatment with benzodiazepines (all 12) and clonidine (11 out of 12), all enrolled patients experienced daily episodes of nausea/retching (table 2). Seven of the 12 had failed a trial of pregabalin. On average, patients had 3 attacks per day, rated them as moderately distressing, and spent 1.7 ± 1.5 hours each day feeling nauseated. Average dopamine excretion in urine was 271 $\mu\text{g/gCr}$ (range 782–552 $\mu\text{g/gCr}$).

Active open-label treatment. All 12 patients entered the dose-escalation phase. Despite symptomatic improvement, one patient withdrew because of constipation. His medical records revealed similar past episodes.

The remaining 11 patients were titrated to their maximum dose (on average 480 mg, range 325–600 mg/day). There were no changes in electrocardiographic parameters and there were no signs of renal or hepatotoxicity. One patient was hospitalized

Table 2 Clinical characteristics of the trial participants^a

Subject sex/ age, y	Pretreatment nausea attacks/week	Standing medications, mg/day	BP when well, mm Hg	BP when nauseous, mm Hg	Carbidopa dose, mg/day	Route of administration
F/16	17	Clonidine TTS#1 patch, diazepam 8 mg, clonazepam 1 mg, paroxetine 10 mg	125/68	169/117	600	Gastrostomy
F/17	15	Diazepam 8 mg	124/61	191/111	600	Gastrostomy
M/12	51	Clonidine 0.2 mg and TTS#1 patch, diazepam 6 mg, clonazepam 0.5 mg, pregabalin 75 mg, tocotrienols 300 mg	127/68	Not available	325	Gastrostomy
M/16	17	Clonidine 0.1 mg, diazepam 7.5 mg, tocotrienols 600 mg	146/77	204/153	400	Oral
M/13	37	Clonidine TTS#1 patch, diazepam 7.5 mg, clonazepam 0.1 mg, pregabalin 75 mg	129/63	170/110	400	Gastrostomy
M/36	32	Clonidine 0.2 mg, clonazepam 1 mg, diazepam 10 mg	139/78	188/110	600	Oral
F/16	13	Clonidine 0.3 mg and TTS#1 patch, diazepam 17 mg, pregabalin 75 mg	144/72	170/114	400	Gastrostomy
M/16	17	Clonidine 0.05 mg, diazepam 2 mg	123/53	Not available	450	Oral
F/19	7	Clonidine 0.2 mg, diazepam 6 mg	121/69	193/111	600	Gastrostomy
M/16	15	Clonidine 1.0 mg, diazepam 15 mg, propranolol 40 mg	128/61	188/130	150 ^b	Gastrostomy
M/20	27	Clonidine 0.05 mg, diazepam 3 mg, pregabalin 50 mg, tocotrienols 400 mg	86/56	161/106	600	Gastrostomy
M/25	11	Clonidine 0.3 mg, diazepam 10 mg, clonazepam 3.5 mg, pregabalin 25 mg, propranolol 80 mg, tocotrienols 400 mg	120/59	190/115	600	Oral

Abbreviation: BP = blood pressure.

^a Nausea episodes/week were calculated as the average number of nausea episodes reported in the baseline (pretreatment) nausea diary over 7 days. All medications are given as total daily dose of scheduled administrations and do not include “as-needed” additional doses of clonidine and diazepam.

^b Patient withdrew because of constipation during the titration, hence lower carbidopa dose.

for an unrelated respiratory complication. He opted to continue in the trial.

During the 4 weeks of open-label treatment, all but 2 patients showed an improvement (composite nausea score; baseline 14 ± 5 vs active treatment 9 ± 2 units, $p < 0.01$). On average, there was a 50% improvement in overall symptom scores. Two patients were asymptomatic. Urinary dopamine output decreased significantly compared to baseline (figure 1). Urinary dopamine levels were positively correlated with average daily symptom scores (figure 1).

Of the 11 patients who completed the open-label treatment phase, one withdrew because his nausea had improved and he was unwilling to take placebo. A second patient was withdrawn in the first arm of the randomization because of severe anemia, a common complication in FD. Drug accountability logs showed that he was on active carbidopa, but did

not comply with the dosing regimen. A third patient withdrew at the end of the first randomization. He thought, as his symptoms were improved, he was taking active agent and did not want to be randomized to placebo. He was correct.

Randomized data. Eight patients completed both arms of the double-blind, randomized, placebo-controlled phase. Three were randomized first to carbidopa and 5 were randomized first to placebo. There were no significant baseline differences in clinical characteristics, nausea scores, or dopamine levels between the patients who received carbidopa first and the patients who received placebo first (Class II level of evidence).

There was less dopamine in the urine of patients when they were taking carbidopa than when they were taking placebo ($p < 0.05$, table 3). Figure 2 shows change from baseline in nausea/retching subscale and composite scores during the randomized period. The composite and subscale scores fell more on carbidopa than on placebo, indicating a greater improvement in symptoms while on active study drug (table 3 and figure 2). When randomized to carbidopa, patients rated their nausea and retching as less distressing ($p < 0.01$ and $p < 0.05$, respectively), they reported fewer episodes of nausea ($p < 0.02$) and retching ($p < 0.02$), and they spent less time feeling unwell ($p < 0.05$). On the clinical global impressions scale, patients rated their nausea as less severe ($p < 0.02$) on carbidopa compared with placebo. Compared to baseline, they reported no change while on placebo, while feeling much improved on carbidopa ($p < 0.002$, see table 3 for details). According to the daily nausea diaries, patients required additional doses of benzodiazepines and clonidine less often when randomized to carbidopa ($p < 0.01$, table 3). Interestingly, 2 patients reported missing days of school while taking placebo; none missed school while randomized to carbidopa.

Effect on blood pressure. Supine and standing blood pressures were similar at baseline and the end of active open-label treatment. During the double-blind phase, standing systolic blood pressure was lower on carbidopa compared with placebo ($p < 0.02$, table 3). Diastolic and mean pressures were similar. Urinary norepinephrine levels tended to be lower on carbidopa than at baseline (table 3).

Generalized weakness, a common complaint in patients with FD, was reported as an adverse event by one patient while randomized to carbidopa and while randomized to placebo.

DISCUSSION This is the first double-blind, placebo-controlled clinical trial of a specific symptomatic therapy in patients with FD. The results

Figure 1 Open-label phase

(A) Bar chart shows mean (unadjusted) composite nausea scores at baseline and during the open-label treatment phase. (B) Line graph shows 24-hour dopamine (DA) excretion at baseline and on carbidopa (open-label). (C) Scatterplot shows the significant relationship between nausea scores and dopamine excretion during the open-label phase ($y = 0.0199x + 6.9212$, $R^2 = 0.19134$).

Table 3 Outcome variables during the trial^a

Procedure	Baseline	Open-label	Double-blind		p
			Placebo	Carbidopa	
Safety measures					
Physical/neurologic examination	No change	No change	No change	No change	—
10-Minute supine SBP, mm Hg	131 ± 8	127 ± 7	128 ± 11	123 ± 5	NS
3-Minute standing SBP, mm Hg	88 ± 7	95 ± 6	96 ± 8	72 ± 5	<0.02
Primary efficacy measures					
Composite daily score	13.3 ± 1.5	8.9 ± 0.7	9.7 ± 2.5	6.9 ± 2.2	<0.0001
Retching distress	3.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.4	1.6 ± 0.3	<0.002
Time spent nauseous in 24 hours	1.7 ± 0.2	1.0 ± 0.3	1.6 ± 0.4	0.9 ± 0.3	<0.03
Nausea distress	3.0 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	1.8 ± 0.3	<0.05
Episodes of daily nausea	3.0 ± 0.6	1.5 ± 0.6	2.0 ± 1.0	1.2 ± 0.8	<0.03
Episodes of daily retching	2.6 ± 0.5	1.3 ± 0.5	2.3 ± 1.0	1.4 ± 0.8	<0.02
Use of PRN medications, d	Not done	Not done	15 ± 4	9 ± 3	<0.01
Secondary efficacy measures					
GCI: nausea severity	4 ± 0.5 (moderate)	3 ± 0.5 (mild)	4 ± 0.8 (moderate)	2 ± 0.5 (borderline)	<0.02
GCI: nausea improvement	—	3 ± 0.4 (much/slight)	4 ± 0.4 (no change)	3 ± 0.4 (much/slight)	<0.002
24-Hour urinary DA, µg/gCr	271 ± 41	147 ± 32	222 ± 41	127 ± 29	<0.05
24-Hour urinary NE, µg/gCr	32 ± 9	12 ± 2	13 ± 2	11 ± 3	NS

Abbreviations: DA = dopamine; GCI = global clinical impression; NE = norepinephrine; NS = not significant; SBP = systolic blood pressure.

^ap Values are for comparison between carbidopa and placebo during the double-blind phase (2-way analysis of variance). Scores are mean (unadjusted) ± SD. A reduction of patient-reported outcome scores indicated an improvement in symptoms. Baseline n = 12, open-label n = 11, placebo n = 8, carbidopa n = 8. Baseline characteristics were similar in the patients first assigned to placebo and those first assigned to carbidopa (Class II evidence: data not presented).

showing that blocking dopamine synthesis outside the brain significantly reduces the severity and frequency of the nausea/retching crises strongly support the hypothesis that excessive dopamine is the likely cause of retching and nausea in these patients. Except in patients with Parkinson disease who are taking levodopa, carbidopa has never before been used as an antiemetic.

Carbidopa was well-tolerated in our current trial. All adverse events (anemia, constipation, weakness, respiratory complications) occur frequently in patients with FD and a relationship with carbidopa was unlikely.

Carbidopa was first successfully used to prevent the side effect of nausea and vomiting in patients with Parkinson disease treated with levodopa in 1969.¹³ It remains an adjunct therapy to levodopa. This is the first time it has been used in patients with FD.

Previous trials to assess the antiemetic efficacy of pregabalin,⁵ tocotrienols,¹⁴ benzodiazepines,¹⁵ and bethanechol¹⁶ in patients with FD were all uncontrolled and without validated endpoints. Unlike clonidine and benzodiazepines, agents traditionally used to manage the hyperdopaminergic vomiting attacks in FD, treatment with carbidopa was not associated with sedative effects. Improving symptoms without

depressing respiration has obvious benefits for this population, in whom respiratory drive from chemoreceptors is severely impaired.¹⁷

The present study has several limitations. The best dose could not be determined from the trial design. While we saw no evidence of central effects, it is possible that at high doses, carbidopa might cross the blood–brain barrier, and we do not know whether lower doses than those studied are as effective in FD. Free dopamine in urine does not take into account the amount that is conjugated or metabolized and therefore likely underestimates its synthesis. Nevertheless, it is believed to be clinically useful.¹⁸ In this study, samples were collected in standardized bottles with preservative, protected from ultraviolet light, and refrigerated to help stabilize the dopamine compound, and we did see a significant reduction in dopamine excretion with carbidopa. We could not measure the concentration of dopamine in the area postrema, a known vomiting center,⁷ but we did find a significant correlation between free dopamine in the urine and symptom severity (figure 1). Finally, because FD is a very rare disorder, our study includes a small number of patients.

As carbidopa reduces the bioavailability of dopamine,⁸ it is conceivable that it could also inhibit the

Figure 2 Double-blind phase

Bar charts show change in symptom scores from baseline during the randomized, double-blind, placebo-controlled phase. Greater reduction in scores indicated symptomatic improvement (2-way analysis of variance). * $p < 0.01$, ** $p < 0.05$, *** $p < 0.02$.

synthesis of norepinephrine, which is synthesized from dopamine.¹⁹ Carbidopa's effects on blood pressure warrant further investigation. It could potentially be useful as an antihypertensive to lessen surges in sympathetic outflow and may mitigate hypertensive damage to the end organs.²⁰

Although the severity and duration of the nausea and retching were improved, some patients continued to experience (milder) symptoms while taking carbidopa. In those patients, despite high doses of carbidopa, plasma dopamine levels remained within the normal range. Perhaps this is due to phenotypic variability in the expression of the enzymes involved in catecholamine synthesis and metabolism in FD.^{21,22} Combining carbidopa with domperidone, a dopamine receptor blocker, might prove useful in patients who continue to be symptomatic. Alternative treatment approaches with cognitive behavioral therapy or psychotherapy have been useful in some cases.²³

AUTHOR CONTRIBUTIONS

Dr. Norcliffe-Kaufmann contributed to the study concept and design, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Mr. Jose Martinez contributed to the study procedures and assigned patients to the interventions. Dr. Axelrod contributed to the acquisition of data. Dr. Kaufmann was involved in the study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, and was the study supervisor.

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