



Published in final edited form as:

Arch Ophthalmol. 2010 September ; 128(9): 1215–1217. doi:10.1001/archophthalmol.2010.178.

A Pilot Study of Levodopa Dosage as Treatment for Residual Amblyopia in Children 8 to <18 Years Old

Michael X. Repka, M.D.¹, Raymond T. Kraker, M.S.P.H.², Roy W. Beck, M.D., Ph.D.², Scott C. Atkinson, M.D.³, Darron A. Bacal, M.D.⁴, Don L. Bremer, M.D.⁵, Patricia L. Davis, M.D.⁶, Matthew D. Gearinger, M.D.⁷, Stephen R. Glaser, M.D.⁸, Darren L. Hoover, M.D.⁹, Daniel M. Laby, M.D.¹⁰, David G. Morrison, M.D.¹¹, David L. Rogers, M.D.⁵, Nicholas A. Sala, D.O.¹², Donny W. Suh, M.D.¹³, and Maynard B. Wheeler, M.D.¹⁴ for the Pediatric Eye Disease Investigator Group (PEDIG)*

¹ Johns Hopkins University School of Medicine, Baltimore, MD

² Jaeb Center for Health Research, Tampa, FL

³ St. John's Clinic, Eye Specialists, Springfield, MO

⁴ Eye Physicians & Surgeons, PC, Milford CT

⁵ Pediatric Ophthalmology Associates, Inc., Columbus, OH

⁶ Progressive Eye Care, Lisle, IL

⁷ University of Rochester Eye Institute, Rochester, NY

⁸ Stephen R. Glaser, M.D., P.C., Rockville, MD

⁹ Everett and Hurite Ophthalmic Association, Cranberry TWP, PA

¹⁰ Daniel M. Laby, M.D., Sharon, MA

¹¹ Vanderbilt Eye Center, Nashville, TN

¹² Pediatric Ophthalmology of Erie, Erie, PA

¹³ Wolfe Clinic, West Des Moines, IA

¹⁴ Concord Eye Care P.C., Concord, NH

To the editor

Prior studies have evaluated levodopa as an adjunct to occlusion therapy in the treatment of amblyopia.^{1–9} Improvement in visual acuity after completion of a course of levodopa has been reported; however, regression has occurred in several studies after stopping the medication.^{4, 6} Reported side effects of levodopa were mild. They have included nausea, headache, fatigue, mood changes, emesis, dizziness, dry mouth, decreased appetite, and nightmares.

In preparation for conducting a phase 3 randomized trial, we conducted a prospective randomized pilot study to provide a preliminary assessment of the efficacy and safety of two doses of levodopa combined with daily ocular occlusion therapy of the fellow eye in older

Corresponding Author: Michael X. Repka, M.D., c/o Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; phone: (813) 975-8690, fax: (813) 975-8761, pedig@jaeb.org.

*A list of the sites participating in the study appears online

children and teenagers with residual amblyopia from strabismus, anisometropia, or both combined.

Methods

Institutional Review Boards approved the study and written consent was obtained from parents. Eligibility criteria included age 8 to <18 years, best-corrected visual acuity in the amblyopic eye between 67 and 18 letters inclusive (approximately 20/50 to 20/400) measured with the electronic early treatment diabetic retinopathy study (E-ETDRS) method,¹⁰ fellow eye best-corrected visual acuity of 78 letters or better (approximately 20/25 or better), and the presence of, or history of, strabismus and/or anisometropia. At the time of enrollment, subjects were required to have been treated with at least 2 hours per day of daily patching and while on that regimen to have had stable visual acuity (defined as less than 5 letters or one logMAR line of improvement since a previous visit at least 8 weeks earlier).

The study intervention consisted of continuing 2 hours of daily patching plus the addition of levodopa in one of two doses randomly assigned with equal probability (0.51 or 0.76 mg/kg/tid, referred to as lower dose and higher dose, respectively). The lower dose has been used in most prior studies. The study medication was administered for 8 weeks with one additional week for tapering of treatment. Levodopa was prepared in capsules combined with carbidopa 0.17 mg/kg/tid. Carbidopa was combined with levodopa to reduce side-effects associated with levodopa alone.

Follow-up visits occurred at 4 ± 1 weeks from randomization, 9 ± 1 weeks from starting levodopa treatment as the primary outcome, and 10 ± 2 weeks after stopping levodopa treatment. The assigned levodopa/carbidopa dose was continued until one week prior to the 9-week visit, at which time it was tapered over one week. Following the 9-week visit, patching alone was continued for 10 ± 2 weeks. At each visit, visual acuity was measured using the E-ETDRS method.

Information about adverse effects of treatment was solicited during phone calls conducted after 1, 2, and 6 weeks and at each visit during treatment. An adverse event was defined as any untoward medical occurrence in a study subject, and reported even if considered unrelated to the study treatment. Subjects and study personnel were masked to treatment assignment. The entire protocol is available at www.pedig.net.

Results

Thirty-three subjects were randomized with 16 assigned to the lower dose group and 17 assigned to the higher dose group. Mean age was 11 ± 2 years, with 22 (67%) less than 12 years of age; 19 (58%) were female and 31 (94%) were white. Mean best-corrected visual acuity in the amblyopic eye was 56 ± 9 letters in the lower dose group (about 20/80) and 51 ± 12 letters in the higher dose group (about 20/100). Further details on the baseline characteristics appear in supplemental Table 1 (journal website).

The 4-week and 9-week visits were completed by all subjects. Mean time after starting levodopa treatment to completion of the primary outcome visit was 8.4 weeks (range 6.3 to 13.4 weeks). The long-term outcome visit 10 weeks after stopping levodopa was completed by all but 1 subject in the lower dose group. Mean time from stopping levodopa was 9.8 weeks (range 8.0 to 13.6 weeks).

Adherence to the medication regimen was evaluated by counting capsules in the returned medication bottles; 14 of 16 (88%) in the lower dose group and 15 of 17 (88%) in the higher

dose group had taken 90% or more of the prescribed doses. Eleven of 16 (69%) subjects in the lower dose group and 15 of 17 (88%) of subjects in the higher dose group were judged by the investigator to have adhered with the prescribed patching regimen. Three of the 4 subjects not compliant with at least 90% of prescribed doses, were also judged to not be compliant with patching. However, the small number of subjects precludes any further analysis.

The mean improvement in amblyopic eye visual acuity from baseline to the 9-week primary outcome visit was +4 (± 4) letters in the 16 subjects in the lower dose group and +6 (± 6) letters in the 17 subjects in the higher dose group (mean difference between groups = -2 letters, 95% confidence interval -6 to +1, Table 2). An improvement of 10 or more letters was noted in 2 (13%) and 5 (29%) of the lower and higher dose subjects, respectively. At the 9-week outcome examination, on average the fellow eye improved 0 letters in the higher dose group and 1 letter in the lower dosage group

At the visit 10 ± 2 weeks after stopping the levodopa treatment, the mean change in amblyopic eye visual acuity from baseline was +5 (± 4) letters in the lower dose group and +4 (± 5) letters in the higher dose group. .

Levodopa/carbidopa was not discontinued by any subject during the 9 week dosing regimen. Adverse events were reported for 8 of 16 subjects (29 events) in the lower dose group and 11 of 17 subjects (26 events) in the higher dose group (Supplemental Table 3 on journal website). None of the adverse events were considered serious. Headaches were reported by 6 subjects, a cold/upper respiratory infection/cough by 6, rash by 4 and nausea/vomiting by 3.

Comment

We enrolled a small cohort to gain experience with the drug, define the treatment dose for a future trial, and develop study procedures. The results suggested that levodopa/carbidopa therapy for residual amblyopia in older children and teenagers is well tolerated and may improve visual acuity. There was a suggestion of partial regression of the improvement in visual acuity after treatment was discontinued. No serious adverse effects were noted. Headache and nausea were infrequent. Without a patching-only control group, no conclusions about the efficacy, safety, or frequency of side effects associated with this treatment can be made. A placebo controlled trial is necessary to determine whether levodopa can successfully augment occlusion therapy in the treatment of amblyopia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported through a cooperative agreement from the National Eye Institute EY11751 and conducted under an FDA investigational New Drug registration 103,617. The trial was registered at www.clinicaltrials.gov, NCT# NCT00789672.

References

1. Leguire LE, Walson PD, Rogers GL, Bremer DL, McGregor ML. Longitudinal study of levodopa/carbidopa for childhood amblyopia. *J Pediatr Ophthalmol Strabismus*. 1993; 30(6):354-60. [PubMed: 8120739]

2. Leguire LE, Walson PD, Rogers GL, Bremer DL, McGregor ML. Levodopa/carbidopa treatment for amblyopia in older children. *J Pediatr Ophthalmol Strabismus*. 1995; 32:143–51. [PubMed: 7636693]
3. Leguire LE, Narius TM, Rogers GL, Bremer DL, McGregor ML. Long-term follow-up L-dopa treated amblyopic children. *Invest Ophthalmol Vis Sci*. 1996; 37(supp 3):S941.
4. Leguire LE, Komaromy KL, Nairus TM, Rogers GL. Long-term follow-up of L-dopa treatment in children with amblyopia. *J Pediatr Ophthalmol Strabismus*. 2002; 39(6):326–30. [PubMed: 12458842]
5. Gottlob ISWS, Reinecke RD. Visual acuities and scotomas after 3 weeks' levodopa administration in adult amblyopia. *Graefes Arch Clin Exp Ophthalmol*. 1995; 233(7):407–13. [PubMed: 7557504]
6. Mohan K, Dhankar V, Sharma A. Visual acuities after levodopa administration in amblyopia. *J Pediatr Ophthalmol Strabismus*. 2001; 38(2):62–7. [PubMed: 11310708]
7. Procianoy E, Fuchs FD, Procianoy L, Procianoy F. The effect of increasing doses of levodopa on children with strabismic amblyopia. *J AAPOS*. 1999; 3(6):337–40. [PubMed: 10613576]
8. Leguire LE, Rogers GL, Walson PD, Bremer DL, McGregor ML. Occlusion and levodopa-carbidopa treatment for childhood amblyopia. *J AAPOS*. 1998; 2(5):257–64. [PubMed: 10646745]
9. Bhartiya P, Sharma P, Biswas NR, Tandon R, Khokhar SK. Levodopa-carbidopa with occlusion in older children with amblyopia. *J AAPOS*. 2002; 6(6):368–72. [PubMed: 12506278]
10. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol*. 2003; 135(2):194–205. [PubMed: 12566024]

The Pediatric Eye Disease Investigator Group

Clinical Sites that Participated in this Protocol

Sites are listed in order by number of patients enrolled into the study. Personnel are listed as (I) for Investigator, (C) for Coordinator, and (V) for Visual Acuity Examiner.

We have obtained written permission from all persons named in the acknowledgment.

Columbus OH - Pediatric Ophthalmology Associates, Inc. (5)

Don L. Bremer, (I); David L. Rogers, (I); Rae R. Fellows, (C); Amy J Wagner, (C); Laura J. Shenberger, (V)

Concord NH - Concord Eye Care P.C. (5)

Maynard B. Wheeler, (I); Caroline C. Fang, (C)

Erie PA - Pediatric Ophthalmology of Erie (4)*

Nicholas A. Sala, (I); Rhonda M. Hodde, (C)

Lisle IL - Progressive Eye Care (4)

Patricia L. Davis, (I); Katie R. Hulett, (C)

Cranberry TWP PA - Everett and Hurite Ophthalmic Association (3)

Darren L. Hoover, (I); Pamela A. Huston, (C)

*Center received support utilized for this project from an unrestricted grant from Research to Prevent Blindness Inc., New York, New York.

Milford CT - Eye Physicians & Surgeons, PC (3)

Darron A. Bacal, (I); Donna Martin, (C); Kelly D. Moran, (C); Jennifer A Coyne, (V)

West Des Moines IA - Wolfe Clinic (3)

Donny W. Suh, (I); Autumn Swallow, (C); Amy J. Dix (c); Lisa M Fergus, (V); Rhonda J. Countryman (v); Susan K. Hayes (v)

Sharon MA - Daniel M. Laby, M.D. (2)

Daniel M. Laby, (I); Beth G Harper, (C); Ricky Laby, (C)

Nashville TN - Vanderbilt Eye Center (1)

David G. Morrison, (I); Lisa A. Fraine, (C)

Rochester NY - University of Rochester Eye Institute (1)*

Matthew D. Gearinger, (I); Doreen M. Francis, (C); Lynne M. Addams, (V); Dan A. Castillo, (V)

Rockville MD - Stephen R. Glaser, M.D., P.C. (1)

Stephen R. Glaser, (I); Monica Pacheco, (I); Tracey L. Coussens, (C); Noga Senderowitsch, (C)

Springfield MO - St. John's Clinic - Eye Specialists (1)

Scott Atkinson, (I); Pearlina K. Hamlet, (C); Crystal L. Trythall, (C)

PEDIG Coordinating Center

Raymond T. Kraker, Roy W. Beck, Nicole M. Boyle, Christina M. Cagnina-Morales, Debora A. Cagnina, Danielle L. Chandler, Laura E. Clark, Elise R. Diamond, Quayleen Donahue, Brooke Fimbel, Nicole C. Foster, Heidi A. Gillespie, Brett M. Kaminski, Elizabeth L. Lazar, Stephanie V. Lee, Lee Anne Lester, B. Michele Melia, Pamela S. Moke, Michael J. Philips, Diana E. Rojas, Sydney L. Shrader

National Eye Institute - Bethesda, MD

Donald F. Everett

PEDIG Executive Committee

Jonathan M. Holmes (Chair), Darron A. Bacal (2009), Roy W. Beck, Eileen E. Birch, Stephen P. Christiansen, Susan A. Cotter, Donald F. Everett, Darren L. Hoover, Pamela A. Huston, Raymond T. Kraker, Katherine A. Lee (2008–2009), Noelle S. Matta (2008–2009), David G. Morrison, Michael X. Repka, Robert P. Rutstein (2009), Nicholas A. Sala (2009), Mitchell M. Scheiman (2008), David K. Wallace

PEDIG Data and Safety Monitoring Committee

Marie Diener-West (Chair), John D. Baker, Barry R. Davis, Velma Dobson, Donald F. Everett, Dale L. Phelps, Stephen W. Poff, Richard A. Saunders, Lawrence Tychsén.

Table 2

Best-corrected Amblyopic Eye Visual Acuity

| Amblyopic Eye Visual Acuity | Baseline (Randomization) | | Visit 1 (4±1wks after starting levodopa) | | Visit 2 (9±1wks after starting levodopa) | | Visit 3 (10±2wks after stopping levodopa) | |
|---|--------------------------|---------------------------|--|---------------------------|--|---------------------------|---|---------------------------|
| | Lower Dose Group N=16 | Higher Dose Group N=17 | Lower Dose Group N=16 | Higher Dose Group N=17 | Lower Dose Group N=16 | Higher Dose Group N=17 | Lower Dose Group N=15 | Higher Dose Group N=17 |
| <20/100 (<47 letters) | 2 (13%) | 5 (30%) | 2 (13%) | 4 (24%) | 2 (13%) | 5 (30%) | 2 (13%) | 5 (30%) |
| 20/100 (47 to 52 letters) | 2 (13%) | 0 | 2 (13%) | 1 (6%) | 2 (13%) | 0 | 0 | 1 (6%) |
| 20/80 (53 to 57 letters) | 4 (25%) | 6 (35%) | 1 (6%) | 3 (18%) | 1 (6%) | 1 (6%) | 3 (20%) | 2 (12%) |
| 20/63 (58 to 62 letters) | 4 (25%) | 5 (29%) | 4 (25%) | 5 (29%) | 3 (19%) | 5 (29%) | 4 (27%) | 3 (18%) |
| 20/50 (63 to 67 letters) | 4 (25%) | 1 (6%) | 4 (25%) | 3 (18%) | 4 (25%) | 3 (18%) | 2 (13%) | 6 (35%) |
| 20/40 (68 to 72 letters) | 0 | 0 | 3 (19%) | 1 (6%) | 3 (19%) | 2 (12%) | 1 (7%) | 0 |
| 20/32 (73 to 77 letters) | - | - | 0 | 0 | 1 (6%) | 1 (6%) | 3 (20%) | 0 |
| Mean (SD) letter score | 56.2 (8.8) ~20/80 | 50.5 (12.2) ~20/100 | 59.1 (9.2) ~20/63 | 54.3 (12.9) ~20/80 | 59.9 (9.7) ~20/63 | 56.5 (12.7) ~20/80 | 60.6 (11.1) ~20/63 | 53.9 (11.4) ~20/80 |
| Change from Baseline (Randomization) | | | | | | | | |
| ≥15 letters worse | - | - | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 to 14 letters worse | - | - | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 to 9 letters worse | - | - | 0 | 0 | 0 | 1 (6%) | 0 | 1 (6%) |
| Within ±4 letters | - | - | 11 (69%) | 9 (53%) | 9 (56%) | 5 (29%) | 7 (47%) | 8 (47%) |
| 5 to 9 letters better | - | - | 5 (31%) | 7 (41%) | 5 (31%) | 6 (35%) | 6 (40%) | 7 (41%) |
| 10 to 14 letters better | - | - | 0 | 1 (6%) | 2 (13%) | 4 (24%) | 2 (13%) | 1 (6%) |
| ≥15 letters better | - | - | 0 | 0 | 0 | 1 (6%) | 0 | 0 |
| Mean (SD) letter change | - | - | 2.9 (2.8) | 3.8 (3.6) | 3.8 (3.5) | 6.1 (5.6) | 4.9 (3.7) | 3.5 (4.7) |
| 95% confidence interval | - | - | 1.4 to 4.4 | 2.0 to 5.7 | 1.9 to 5.6 | 3.2 to 8.9 | 2.9 to 7.0 | 1.1 to 5.9 |