Dopaminergic Therapy With Carbidopa L-Dopa for Left Neglect After Stroke: A Case Series

Jon A. Mukand, MD, PhD, Thomas J. Guilmette, PhD, Deborah G. Allen, MS, CCC-SLP, Lois K. Brown, MS, CCC-SLP, Suzanne L. Brown, OTR/L, Kelly L. Tober, OTR/L, Walter R. VanDyck, OTR/L, BCN

ABSTRACT. Mukand JA, Guilmette TJ, Allen DG, Brown LK, Brown SL, Tober KL, VanDyck WR. Dopaminergic therapy with carbidopa L-dopa for left neglect after stroke: a case series. Arch Phys Med Rehabil 2001;82:1279-82.

Objective: To evaluate the efficacy of carbidopa L-dopa (Sinemet) in reducing left spatial neglect after stroke.

Design: Case series.

Setting: Inpatient neurorehabilitation unit in a regional rehabilitation center.

Participants: A convenience sample of 4 women with right brain strokes and left neglect.

Intervention: A trial of carbidopa L-dopa to treat left neglect, if indicated by selected subtests of the Behavioral Inattention Test (BIT).

Main Outcome Measures: Baseline and posttreatment evaluation with the modified BIT and the FIMTM instrument.

Results: Three of 4 subjects had significant improvements in their modified BIT scores (8%, 12%, 27%, respectively) and their functional status on the FIM.

Conclusion: With further study, carbidopa L-dopa may be shown to reduce unilateral spatial neglect and thereby improve rehabilitation outcomes.

Key Words: Carbidopa; Cerebrovascular accident; Dopamine agonists; Left neglect; Levodopa; Rehabilitation

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UNILATERAL SPATIAL NEGLECT is often found in neurologic patients^{1,2} and is characterized by impaired attention or reactions to stimuli presented contralateral to the brain lesion. It is far more common and severe in patients with damage to the nondominant hemisphere,³ usually on the right. Unilateral spatial neglect has been associated with poor safety awareness, disrupted daily activities, and the decreased likelihood of returning to work or driving.^{4,5} Patients may dress only 1 side, ignore food on half the plate, read only 1 side of a page, or bump into objects on the neglected side. Overall, unilateral spatial neglect can be a major impediment to functional recov-

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ery in rehabilitation.⁶ Estimates of its incidence after stroke range from 12% to 90%, depending on the operational definition of this phenomenon.¹

Despite the impact of unilateral spatial neglect on the recovery of functional abilities, a standardized therapeutic program for this condition has yet to be developed.⁷ Behavioral interventions include visual scanning, perceptual retraining, imagery, and right hemispheric activation.^{5,8,9} Music therapy, vestibular stimulation, and eye patching have also produced some benefit.¹⁰ Although numerous advances have been made recently,⁸⁻¹¹ there is insufficient evidence to support 1 therapy over another.

A contributing factor to a lack of systematic therapy for unilateral spatial neglect is that its neuropathology is not well understood. Although it is believed to reflect a deficit with spatial attention, different aspects of attention and orienting responses have been implicated.¹ Neuroanatomically, unilateral spatial neglect occurs most frequently with damage to the nondominant parietal lobe, and less often with frontal, thalamic, and basal ganglia lesions.¹² Evidence from animal studies supports the role of dopaminergic pathways in the motor and perceptual components of neglect. For example, sensory inattention in rats has been reduced through the use of apomorphine, a dopamine agonist.¹³⁻¹⁵ In monkeys, hemineglect has been induced by the infusion of a dopaminergic neurotoxin in the caudate nucleus.¹⁶

Apomorphine temporarily reverses the off state in Parkinson's disease,¹⁷ and was studied in 4 patients with left neglect due to right ischemic lesions.¹⁸ It produced a transient but significant improvement in perceptual-motor and perceptual functions. The authors concluded that "dopaminergic neuronal networks may mediate, in different ways, both perceptive and premotor components of the unilateral neglect syndrome."¹⁸

A literature search revealed no reports on carbidopa L-dopa (Sinemet) for the treatment of neglect after stroke. Levodopa (L-dopa) is a metabolic precursor of dopamine and presumably treats Parkinson's disease by increasing dopamine levels in the brain. We hypothesized that increased dopaminergic activity in the brain would also reduce unilateral spatial neglect.

METHOD

Four right-handed female patients with a right brain stroke and left unilateral spatial neglect were given a shortened version of the Behavioral Inattention Test¹⁹ (BIT) before and after 1 week of carbidopa L-dopa to obtain a standardized functional assessment of unilateral spatial neglect. A modified test was used because the BIT was developed and validated with patients who stayed in the acute setting for long periods²⁰; in contrast, our patients had an average acute stay of only 6 days and could have become fatigued with the lengthy original version. Some redundancies also exist in the standard BIT (letter and star cancellation, 3 reading subtests). Also because of concerns about fatigue, the BIT was administered in the morning.

From the Southern New England Rehabilitation Center, Providence, RI (Mukand, Guilmette, Allen, Brown, Brown, Tober, VanDyck); Department of Physical Medicine and Rehabilitation, Boston University, Boston MA (Mukand); Department of Physical Medicine and Rehabilitation, Tufts University School of Medicine, Boston, MA (Mukand); Department of Orthopedics and Rehabilitation, Brown University, Providence, RI (Mukand); Providence College and Brown University School of Medicine, Providence, RI (Guilmette).

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Reprint requests to Jon A. Mukand, MD, PhD, Southern New England Rehabilitation Center, 21 Peace St, Providence, RI 02907.

Subject	Age (yr)	Location of Right CVA	BIT Gain(%)	FIM-A	FIM-C	FIM-D	FIM Gain (%)
1	76	Frontoparietal hemorrhage	27	49	64	84	31
2	75	Basal ganglia infarct	8	59	69	80	16
3	66	Occipital/posteromedial temporal infarcts	12	62	66	87	32
4	70	Middle cerebral artery territory infarct	NM*	27	47	52	11

Table 1: Patient Characteristics

Abbreviations: CVA, cerebrovascular accident; FIM-A, FIM score on admission; FIM-C, FIM score at initiation of carbidopa L-dopa; FIM-D, FIM score at discharge; FIM Gain, % gain after carbidopa L-dopa.

* BIT scores were inconsistent and the gain is not meaningful (NM).

In our protocol an occupational therapist administered a subtest of the conventional section of the BIT (paper and pencil tasks) and a speech language pathologist administered a subtest of the behavioral section (functional tasks). For the former we used line-crossing, star cancellation, figure and shape copying, and line bisection (maximum score, 103). Items from the behavioral section included telephone dialing, telling and setting the time, address and sentence copying, and coin sorting (maximum score, 36). These subtests¹⁹ appear to assess fully perceptual and functional abilities while eliminating unnecessary duplication.

If a patient had functional deficits and a BIT score below 120, a trial of carbidopa L-dopa was started. The Sinemet dose was 25/100mg, half a tablet 3 times daily for 2 days and then 1 tablet 3 times daily. Patients and family members gave informed consent and were advised about possible side effects including movement disorders, psychiatric symptoms, nausea, and orthostatic hypotension. Gains in functional status were measured with the FIMTM instrument score. All patients received at least 3 hours each day of physical, occupational, and speech therapy as part of our standard stroke rehabilitation program.²¹ The ages, diagnoses, BIT gains (%) after 1 week of carbidopa L-dopa, and FIM scores (admission, premedication, discharge) are listed in table 1. Figure 1 shows BIT scores pre-and postadministration of Sinemet.

Case 1

This patient presented with dense left hemiplegia, mild lethargy, left facial weakness, and dysarthria. She had reduced sensation to light touch and pain at the left lower extremity. The functional assessment revealed poor balance and maximum assistance for mobility and activities of daily living (ADLs). Her poor attention and concentration affected her short-term memory, reading, writing, and safety. Baseline test-



Fig 1. Modified BIT scores before and after carbidopa L-dopa.

ing with the modified BIT revealed 87/103 on the conventional subtest and 21/36 on the behavioral one. After carbidopa L-dopa for 1 week, the scores improved to 101 and 36. At discharge, she required supervision or contact guard with mobility and most ADLs. She was able to read short paragraphs with only occasional verbal cues for left-sided scanning. Overall, fewer verbal cues were necessary for attention and redirection to the left side.

Case 2

This patient had left hemiplegia and hypertonicity, distractibility, and difficulty with multiple-step commands. Cues were necessary for scanning to the left with tasks such as letter cancellation, but her neglect was not as severe during functional tasks. Her BIT scores improved from 25 to 32 on the behavioral portion and 88 to 90 on the conventional items after 1 week of treatment with carbidopa L-dopa. Her balance as well as her functional status improved. At discharge she required supervision for most ADLs, except for minimal assistance with toileting and lower body functions.

Case 3

A patient with left central facial weakness, mild dysarthria, occasional diplopia, and vertical nystagmus had a dense left homonymous hemianopsia and inattention. Her functional assessment revealed minor difficulties with 3-step commands and paragraph comprehension. She could transfer with minimal assistance but needed moderate cues for safety. She required moderate assistance and cues to attend to her left side, especially with bathing and dressing. After a trial of carbidopa L-dopa, she improved with attending to the left and required fewer cues to scan to the left. Her conventional BIT score improved from 51 to 62 and the behavioral part had a slight decrease (22 to 20), but her total score showed a gain from 73 to 82 (12%). She was discharged with supervision for most of her ADLs.

Case 4

This patient was admitted with severe hypertension (220/ 114), dense left hemiplegia, left facial weakness and ptosis, lethargy, left neglect, and anxiety. She needed maximal assistance of 2 people for bed mobility and transfers, and was dependent for her ADLs. BIT testing revealed scores of 1/36 and 32/103. After a trial of carbidopa L-dopa, her BIT score improved from 33 to 46, but because she had no significant functional gains the medication was discontinued after a week. Retesting off carbidopa L-dopa yielded a score of only 28, which was lower than her baseline score. In view of these inconsistent results and the lack of functional progress, the medication was not resumed. On discharge, she required maximal assistance for all ADLs, mobility, and reading.

DISCUSSION

The beneficial response of 3 patients (fig 1, table 1) to carbidopa L-dopa provides further support for the dopaminergic theory of unilateral spatial neglect that has been studied in animals¹³⁻¹⁶ and with apomorphine in humans.^{17,18} At present, apomorphine is not available in the United States, but other dopaminergic options include ropinirole (Requip) and pramipexole (Mirapex).

The dopamine agonist bromocriptine has also been effective for the treatment of unilateral spatial neglect in humans, although in a small study.²² Dopaminergic therapy with bromocriptine has also benefited akinetic mutism, a condition that may be described as severe bilateral neglect.²³ Bromocriptine has some early side effects that are problematic in patients with stroke, including dizziness, drowsiness, and fainting. In studies conducted for the treatment of Parkinson's disease, adverse reactions included nausea, dyskinesias, hallucinations, and confusion. In addition, a recent case report²⁴ described an adverse effect of bromocriptine on left neglect. None of our patients developed any side effects related to carbidopa Ldopa.

It is uncertain why carbidopa L-dopa has not been studied as an agent for improving unilateral spatial neglect. This dopamine agonist improves cognitive functions, presumably by increasing the level of arousal,²⁵ and it may be difficult to differentiate this effect from that on unilateral spatial neglect. Clinicians may resist using carbidopa L-dopa for this reason, but it could be at the expense of a beneficial effect on cognition as well as neglect. In fact, the 3 patients in our series who responded favorably to the medication all had cognitive deficits to some extent. Future studies should include detailed cognitive testing before and after carbidopa L-dopa.

Although our findings are encouraging, it is important to note the limitations of the present study: the absence of control subjects, of blinded staff, and of a large sample size. A larger randomized controlled study should address the issues of dosage, duration of treatment, and refined criteria for a carbidopa L-dopa trial, eg, a BIT threshold. Such a study would determine if BIT and FIM scores have improved due to spontaneous recovery, to the medication, or to both. A larger study could also assess if the modified BIT is helpful in screening candidates for carbidopa L-dopa. Based on the absent response of the fourth patient, who had severe left neglect and a very low BIT score, it seems reasonable to suggest a BIT threshold above which a medication trial of carbidopa L-dopa is indicated. Conversely, patients with high BIT scores may respond to nonpharmacologic treatments and may not require carbidopa L-dopa. Improved BIT scores after carbidopa L-dopa should be correlated with the FIM or a more detailed instrument that focuses on activities affected by unilateral spatial neglect. This approach would help determine if the medication should be continued, as in the fourth patient. If neglect and functional status improve, one may consider a trial period off carbidopa L-dopa. In any event, the medication should be stopped after 6 months to avoid the long-term complication of dyskinesias.

The present series of cases also confirms earlier findings that unilateral spatial neglect may occur after a variety of lesions. Patients who responded to carbidopa L-dopa had lesions in the right frontoparietal and right subcortical areas as well as the territory of the posterior cerebral artery (temporal and occipital lobes). The patient who did not respond had a large right middle cerebral artery stroke. Therefore, it appears that patients should neither be included nor excluded from a trial of carbidopa L-dopa based solely on the anatomic location of the cerebrovascular accident.

CONCLUSION

Unilateral spatial neglect is thought to be multifactorial, and current hypotheses focus on deficits with perceptual, attentional, and representational functions. A deafferentation hypothesis ascribes unilateral spatial neglect to a combination of deficits such as hemianopsia and disorientation for person, place, or time; finally, there is an interhemispheric hypothesis that blames the undamaged left hemisphere for excessive attention to the right side.²⁶ Therefore, carbidopa L-dopa should not be used without other approaches such as right hemisphere activation,⁵ imagery,⁸ and scanning.⁹

Because today's health care climate is oriented to short hospitalizations, it is important to accelerate the patient's recovery process and to gain the maximal benefit from the inpatient therapeutic environment. Carbidopa L-dopa may eventually be shown to reduce unilateral spatial neglect, which may enhance the recovery process and reduce the length of the inpatient stay. Additional benefits may be fewer complications of stroke, such as falls, fractures, depression, and social isolation, all of which are important for the patient's quality of life.

References

- Hartman-Maeir A, Katz N. Validity of the Behavioral Inattention Test (BIT): relationships with functional tasks. Am J Occup Ther 1995;49:507-16.
- Denes G, Semenza C, Stoppa E, Lis A. Unilateral spatial neglect and recovery from hemiplegia. Brain 1982;105:543-52.
- Heilman KM, Bowers D, Valenstein E, Watson RT. Hemispace and hemispatial neglect. In: Jennerod M, editor. Neurophysiological and neuropsychological aspects of spatial neglect. Amsterdam: Elsevier; 1987. p 115-50.
- Lorenze EJ. Dysfunction in visual perception with hemiplegia: its relation to activities of daily living. Arch Phys Med Rehabil 1962;43:514-7.
- Lin K. Right hemispheric activation approaches to neglect rehabilitation poststroke. Am J Occup Ther 1996;50:504-15.
- Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Arch Phys Med Rehabil 1999;80:379-84.
- Halligan PW, Donnegan CA, Marshall JC. When is a cue not a cue? On the intractability of the visuospatial neglect. Neuropsychologia 1992;26:161-6.
- Smania N, Bazoli F, Piva D, Guidetti G. Visuomotor imagery and rehabilitation of neglect. Arch Phys Med Rehabil 1997;78: 430-6.
- Wiart L, Bon Saint Come A, Debelleix X, Petit H, Joseph PA, Mazaux JM, et al. Unilateral neglect syndrome rehabilitation by trunk rotation and scanning training. Arch Phys Med Rehabil 1997;78:424-9.
- Beis J-M, Andre J-M, Baumgarten A, Challier B. Eye patching in unilateral spatial neglect: efficacy of two methods. Arch Phys Med Rehabil 1999;80:71-6.
- Niemeier JP. The lighthouse strategy: use of visual imagery technique to treat visual inattention in stroke patients. Brain Inj 1998; 12:399-406.
- Hier DB, Mondlock J, Caplan LR. Behavioral abnormalities after right hemisphere stroke. Neurology 1983;33:337-44.
- Marshall JF, Gotthelf T. Sensory inattention in rats with 6-hydroxydopamine-induced degeneration of ascending dopaminergic neurons: apomorphine-induced reversal of deficits. Exp Neurol 1979;65:398-411.
- Corwin JV, Kanter S, Watson RJ, Heilman KM, Valenstein E, Hashimoto A. Apomorphine has a therapeutic effect on neglect produced by unilateral dorsomedial prefrontal cortex lesions in rats. Exp Neurol 1986;94:683-98.

- 15. King V, Corwin JV. Neglect following unilateral ablation of the caudal but not the rostral portion of medial agranular cortex of the rat and the therapeutic effect of apomorphine. Behav Brain Res 1990;37:169-84.
- Miyashita N, Hikosaka O, Kato M. Visual hemineglect induced by unilateral striatal dopamine deficiency in monkeys. Neuroreport 1995;6:1257-60.
- Stibe CM, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet 1988;1: 403-6.
- Geminiani G, Bottini G, Sterzi R. Dopaminergic stimulation in unilateral neglect. J Neurol Neurosurg Psychiatry 1998;65:344-7.
- Wilson B, Cockburn J, Halligan P. The behavioral inattention test. Suffolk (Engl): Thames Valley Test Co; 1987.
- Kalra L, Dale P, Crome P. Improving stroke rehabilitation. A controlled study. Stroke 1993;24:395-8.

- Mukand J, Baker N, Fink J, Fitzsimmons C, Halpin H, Kulik T, et al. Pioneering "best practices" for stroke. Adv Directors Rehabil 1998;7:49-52.
- Fleet WS, Valenstein E, Watson RT, Heilman KM. Dopamine agonist therapy for neglect in humans. Neurology 1987;37:1765-70.
- Ross ED, Stewart RM. Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. Neurology 1981;31:14-9.
- Barrett AM, Crucian GP, Schwartz RL, Heilman KM. Adverse effect of dopamine agonist therapy in a patient with motor-intentional neglect. Arch Phys Med Rehabil 1999;80;600-3
- Horvath TB, Meares RA. L-dopa and arousal. J Neurol Neurosurg Psychiatry 1974;37:416-21
- Shinsha N, Ishigami S. Rehabilitation approach to patients with unilateral spatial neglect. Top Stroke Rehabil 1999;6:1-14