attenuated inversion recovery (FLAIR) images and DWIs. High DWI signals have been attributed to spongiform change.[9] A recent report indicated a strong correlation between high-signal DWI or FLAIR and the accumulation of pathological prion protein detected by immnohistochemistry.[10] It has been reported that in the early stage of this disease, brain MRI often demonstrated marked laterality of abnormal signal intensity areas in the cerebral cortex and deep gray matter, and these abnormalities correlated well with the asymmetric clinical features and EEG findings of lateralized or focal periodic sharp waves.[11] Although the present patient showed PSD, the left dominant abnormal high intensity in cerebral cortex, including the motor cortex, might be related to the frequent occurrence of myoclonus in the right extremities. In particular, the high signal intensity of the left motor cortex might be related to the enhanced inhibitory motor system demonstrated by the long duration of the SP, thus causing negative myoclonus only on the right side. The asymmetric presentation of the cortical damage, suggested by the MRI, may simply result from a momentary asymmetrical pathological process, later evolving toward a more classical bilateral presentation. This might justify the asymmetrical presentation of electrophysiological findings and of the associated myoclonus.

In conclusion, we reported a clinically diagnosed CJD patient in the early stage who manifested asymmetric myoclonus: frequent positive–negative myoclonus on the right extremities and few positive myoclonus on the left extremities. The generation mechanism of myoclonus differed between the two sides. We suggest that the asymmetric feature of myoclonus was related to the asymmetry of the MRI signal intensity in the cerebral cortex.

LEGEND TO THE VIDEO

A 49-year-old man presents jerky movements in all extremities with the right predominance. Jerks of the right upper extremities were rhythmic and caused postural lapses.

REFERENCES

1. Tassinari CA, Rubboli G, Shibasaki H. Neurophysiology of positive and negative myoclonus. Electroenceph Clin Neurophysiol 1998;107:181–195.
2. Shibasaki H, Motomura S, Yamashita Y, et al. Periodic synchronous discharge and myoclonus in Creutzfeldt–Jakob disease: diagnostic application of jerk-locked averaging method. Ann Neurol 1981;9:150–156.
3. Shibasaki H, Neshige R. Photic cortical reflex myoclonus. Ann Neurol 1987;22:252–257.
4. Matsunaga K, Uosumi T, Akamatsu N, et al. Negative myoclonus in Creutzfeldt–Jakob disease. Clin Neurophysiol 2000;111:471–476.
5. Shibasaki H. Physiology of negative myoclonus. Adv Neurol 2002;89:103–113.
6. Schnitzler A, Benecke R. The silent period after transcranial magnetic stimulation is of exclusive cortical origin: evidence from isolated cortical ischemic lesion in man. Neurosci Lett 1994;180:41–45.
7. Chiofalo N, Fuentes A, Gálvez S. Serial EEG findings in 27 cases of Creutzfeldt–Jakob disease. Arch Neurol 1980;37:143–145.
8. Yokota T, Tsukagoshi H. Cortical activity–associated negative myoclonus. J Neurol Sci 1992;111:77–81.
9. Bahn MM, Parchi P. Abnormal diffusion-weighted magnetic response images in Creutzfeldt–Jakob disease. Arch Neurol 1999;56:577–583.
10. Haïk S, Dormont D, Faucheux BA, et al. Prion protein deposits match magnetic resonance imaging signal abnormalities in Creutzfeldt–Jakob disease. Ann Neurol 2002;51:797–799.
11. Cambier DM, Kantarci K, Worrell GA, et al. Lateralized and focal clinical, EEG, and FLAIR MRI abnormalities in Creutzfeldt–Jakob disease. Clin Neurophysiol 2003;114:1724–1728.

Tetrabenazine Therapy of Pediatric Hyperkinetic Movement Disorders

Samay Jain, MD,[1]* Paul E. Greene, MD,[2] and Steven J. Frucht, MD[2]

[1]Department of Neurology, Movement Disorders Division, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Neurological Institute, The Center for Parkinson's Disease and other Movement Disorders, Columbia University Medical Center, New York, New York, USA

Video 

Abstract: **Tetrabenazine (TBZ), a presynaptic dopamine depletor and postsynaptic dopamine receptor blocker, is widely used for the treatment of hyperkinetic movement disorders in adults. However, reports of its use in children are limited. We review the efficacy and tolerability of TBZ therapy in 31 children with hyperkinetic movement disorders refractory to other medications. TBZ was effective in reducing the severity of movement disorders resistant to treatment with other medicines. When compared to adult patients, pediatric patients required higher doses. Side effects were similar to the adult population; however, chil-**

This article includes Supplementary Video, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat

*Correspondence to: Dr. Samay Jain, Department of Neurology, 3471 Fifth Ave., Suite 811, Kaufmann Medical Building, Pittsburgh, PA 15218. E-mail: jains@upmc.edu

Received 1 October 2005; Revised 28 February 2006; Accepted 18 April 2006

Published online 6 September 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21063

dren had a lower incidence of drug-induced Parkinsonism.

Key words: tetrabenazine; pediatric movement disorders; hyperkinetic movement disorders; pharmacotherapy

Tetrabenazine (TBZ) is a benzoquinolone that depletes presynaptic monoamines and blocks postsynaptic dopamine receptors. Developed initially in the 1950s to treat psychosis, it is now commonly used to treat severe hyperkinetic movement disorders. TBZ use has been well documented in the adult population; however, reports of its use in children are limited. TBZ is available in several countries outside the United States and is soon expected to be available in the United States, as it has been granted fast-track and orphan status by the United States Food and Drug Administration for the treatment of Huntington's disease.

Prior reports of TBZ use in children consist of case reports and small series, including posthypoxic chorea,[1] postencephalitic hyperkinesis,[1] Lesch–Nyhan syndrome,[2] Tourette's syndrome,[3] generalized dystonia,[4] and athetoid cerebral palsy.[1] Several series of pediatric and adult patients with tic disorders have also been published. We summarize our experience using TBZ in 31 pediatric patients treated over 19 years at a single institution, to describe the efficacy and tolerability of this drug in the pediatric population.

PATIENTS AND METHODS

We performed a retrospective, single-institution chart review at the Movement Disorders Division of the Neurological Institute of Columbia University Medical Center (CUMC). Use of TBZ in this population was approved by the CUMC Internal Review Board, with consent obtained from the child's parent or legal guardian. All patients were evaluated by a movement disorders specialist before starting TBZ. TBZ was typically started at 12.5 mg/day and increased by 12.5 mg/day until adequate control of movements was achieved (as assessed by the treating neurologist) or side effects prevented further dose escalation. Doses were typically given three times daily. Patients or their guardians were asked about side effects of medications, and whenever possible, patients were videotaped before and after treatment (see Video, Segment 1).

Data were retrospectively abstracted from medical records and placed in a database designed for the current study. This information included patient age, gender, age of onset of symptoms, duration of symptoms (in years), age when TBZ treatment was initiated, phenomenology of movements (i.e., chorea, tics, myoclonus, dystonia, ballism, etc.), diagnosis, medication history, weight (kg), initial dose of TBZ (mg/kg), maintenance dose of TBZ (mg/kg), maximum dose of TBZ (mg/kg), duration of treatment with TBZ (in years), and adverse effects and the reason for discontinuation of TBZ. All patients were examined by a movement disorder specialist before starting TBZ therapy (pretreatment evaluation). Response to TBZ was also assessed by a movement disorder specialist at one or more follow-up visits. However, there was only one post-treatment rating deduced from the chart narrative for each patient. If multiple follow-up visits were done, the rating used for this study was taken at best overall balance between clinical efficacy and adverse effects. The post-treatment rating was coded as either improved (reduction of involuntary movements), unchanged, or worsened (increased involuntary movements). If the status of posttreatment movements was unclear from the records, the outcome was coded as "not determined."

RESULTS

Clinical Features

A total of 31 children were treated with TBZ for hyperkinetic movement disorders from 1986 to 2005: 18 with chorea, 10 with tics, and 3 with dystonia. Clinical features of these patients are summarized in Table 1. Of those with chorea, half had chorea in isolation and half had prominent chorea plus at least one of the following: myoclonus, dystonia, tremor, athetosis, and/or ballism. The average duration of symptoms before TBZ treatment was 4 years (range, 3 weeks to 10 years). The mean age at the time of TBZ initiation was 11.0 ± 4.9 years (range, 22 months to 18 years). The underlying diagnoses included tic disorders (10 patients), cerebral palsy (2 patients), and primary generalized dystonia (2 patients). Each of the following conditions was diagnosed in 1 patient: proprionic acidemia, intraventricular hemorrhage with developmental delay, Leigh's syndrome, infantile spasms, neurofibromatosis type 1, static encephalopathy, posthypoxic injury, tardive dystonia, Lesch–Nyhan syndrome, Sydenham's chorea, withdrawal emergent syndrome, and arteriovenous malformations with developmental delay. The etiology of the involuntary movements was unknown in 5 patients.

Efficacy

Ninety-four percent (29 of 31) of patients were treated with other medications before being prescribed TBZ. Upon posttreatment evaluation, 77% (24 of 31) were rated as improved, 13% (4 of 31) were unchanged, and 3% (1 of 31) worsened while taking TBZ. The outcome of 2 patients (6%) on TBZ was not determined due to

TABLE 1. *Summary of results*

Patient no.	Age (yr), sex	Movement(s)	Underlying Condition	Duration of movements	Prior medication	Maintenance dose, mg (mg/kg)	Efficacy*	Side effect
1	5, M	Chorea	Proprionic Acidemia	NA	Baclofen, lorazepam, trihexyphenidyl, risperidone, carbidopa-levodopa, dextromethorphan	187.5 (11)	I	Sedation, nausea, vomiting, agitated
2	2.5, M	Chorea	Infantile Spasms	NA	Primidone	75 (5.9)	I	Sedation
3	11, M	Chorea	Unknown	NA	Trihexyphenidyl	350 (10)	I	Sedation
4	13, M	Chorea	Cerebral palsy due to neonatal meningitis	NA	Clonazepam	125 (2.84)	I	
5	8.5, M	Chorea	Sydenham Chorea	2 yrs	Haloperidol, prednisone,	25 (0.9)	I	Sedation, irritable
6	7.5, F	Chorea	Unknown	NA	Valproic acid, lorazepam	NA	ND	
7	3.5, F	Chorea	Intraventricular hemorrhage with developmental delay	3.5 yrs	Clonazepam	75 (5)	I	
8	6, M	Chorea	Postencephalitic Chorea	NA	None	50 (2.4)	U	
9	12, M	Chorea	Withdrawal Emergent Syndrome	3 yrs	Haloperidol	75 (1.88)	I	Agitated, anxious, irritable
10	2, F	Chorea, athetosis, ballism, dystonia	Neurofibromatosis Type-1	NA	None	250 (23)	I	Sedation
11	7, F	Chorea, athetosis, dystonia	Leigh Syndrome	NA	Clonazepam	150 (4.1)	I	Depression
12	7, M	Chorea, athetosis, dystonia	Posthypoxic choreathetosis	2 mo	Haloperidol, morphine, phenobarbital, diphenhydramine, methyprednisolone, clonazepam, chloral hydrate	50 (8)	I	None
13	17, M	Chorea, athetosis, dystonia, ballism	Lesch-Nyhan	NA	Trihexyphenidyl	87.5 (1.35)	I	None
14	5, F	Chorea, dystonia	Unknown	3 wks	Benzodiazepines (unspecified)	NA	ND	None
15	7, M	Chorea, myoclonus	Cerebral palsy	4 yrs	None	81.25 (3.5)	W	Sedation
16	7, M	Chorea, tremor	Unknown	NA	Reserpine, haloperidol, carbidopa-levodopa, clonazepam, acetazolamide	125 (3.7)	I	Oculogyria
17	10, F	Hemichorea, hemiballism	Unknown	7.5 yrs	Pimizode, diazepam, carbidopa-levodopa	75 (1.26)	I	Sedation, drooling
18	14, M	Hemichorea, hemiballism	Arteriovenous malformations with developmental delay	1 mo	Valproate	150 (2.7)	I	None
19	14, F	Tics, stereotypies	Tic disorder with Mental retardation	2 yrs	Clonazepam	93.75 (1.9)	I	Sedation
20	15, F	Tics	Tourette Syndrome	8 yrs	Clonazepam	75 (1.3)	U	None
21	18, M	Tics	Tourette Syndrome	8 yrs	Haloperidol	75 (1.1)	U	Parkinsonism, depression
22	14, M	Tics	Tourette Syndrome	7 yrs	Pimozide, risperidone, clonazepam, olanzapine, sertraline, benztropine	75 (1.32)	I	Depression
23	13, M	Tics	Tourette Syndrome	4 yrs	Pimozide, clonidine, pergolide, risperidone	37.5 (0.81)	I	Sedation
24	14, M	Tics	Tourette Syndrome	10 yrs	Methylphenidate, clonidine, fluoxetine, paroxetine, fluvoxime, buspirone, sertraline, risperidone	62.5 (1.2)	I	Akathesia
25	18, M	Tics	Tourette Syndrome	10 yrs	Clonidine, haloperidol, pimizode, clonazepam	200 (2.9)	I	Sedation

TABLE 1. (*Continued*)

Patient no.	Age (yr), sex	Movement(s)	Underlying Condition	Duration of movements	Prior medication	Maintenance dose, mg (mg/kg)	Efficacy*	Side effect
26	18, M	Tics	Tic Disorder	9 yrs	Clonazepam, risperidone, clonidine	125 (1.56)	I	None
27	8, F	Tics	Tourette Syndrome	5 yrs	Haloperidol, clonidine,	33 (1.32)	I	None
28	16, M	Tics	Tourette Syndrome	10 yrs	Clonidine, clonazepam	100 (1.16)	I	Sedation, akathesia
29	11, M	Dystonia	Idiopathic Torsion Dystonia	6 yrs	Trihexyphenidyl, carbidopa-levodopa, reserpine, carbamazepine	112.5 (3.125)	U	None
30	13, M	Dystonia	Generalized Dystonia	NA	Trihexyphenidyl, diazepam, carbidopa-levodopa, carbamazepine, valproic acid, clonazepam, baclofen	100 (2.17)	I	None
31	17, M	Dystonia	Tardive dystonia	1 yr	Reserpine, clonazepam	50 (0.77)	I	Akathesia

*Efficacy rating: I, improved; U, unchanged; W, worse; ND, not determined.
NA, not available.

insufficient information in the medical record. In patients with more than one movement disorder, it was chorea that improved more often than other movements, although upon several occasions, there was a reduction in more than one type of movement. At least one follow-up evaluation was completed in 90% (28 of 31) of patients. There were 8 patients who were able to taper all other medications for involuntary movements and achieve TBZ monotherapy, 3 patients reduced but did not stop other medications, and 18 patients continued other medications. The average total dose of TBZ was 107 mg/d (3.7 mg/kg per day), and the average duration of treatment was 1.8 years.

Tolerability

Nineteen patients (61%) experienced at least one side effect while taking TBZ. Side effects included sedation (10 patients, 35%), behavioral changes (6 patients, 19%), depression (3 patients, 10%), worsening movements (2 patients, 6%), nausea (1 patient, 3%), and Parkinsonism (1 patient, 3%). Behavioral changes included restlessness, irritability, anxiety, and agitation. In all cases, a reduction in dose ameliorated side effects. No tardive movement disorders were observed as a result of treatment. TBZ was stopped due to behavioral changes in 10 patients (32%), sedation in 3 patients (10%), lack of improvement or increasing movements in 2 patients (6%), major depression in 1 patient (3%), and spontaneous remission in 1 patient (3%).

DISCUSSION

We report our single-institution experience with TBZ in pediatric hyperkinetic movement disorders that were resistant to other medications. We are aware of several limitations to our study. The open label, retrospective review with subjective rating of improvements susceptible to observer bias limits our ability to conclude that TBZ definitely helped these patients. This statement is compounded by the fact that the most common conditions treated were tics disorders, which have a natural history of waxing and waning. However, TBZ was subjectively effective in a wide range of disorders, and most children were able to tolerate doses higher than those reported in the adult population. Although side effects were common, most children were able to continue treatment and derive benefit from the drug.

Seventy-seven percent of children with hyperkinetic movements improved with TBZ, including 14 of 18 with chorea, 8 of 10 with tics, and 2 of 3 with dystonia. To our knowledge, this is the second largest reported series of pediatric patients.[5] A summary of previously published pediatric patients appears in Table 2. Most studies do not report dose adjusted for weight; thus, direct comparison with our results is difficult. Of note, most studies that did not show benefit with TBZ used total doses of 75 mg/d or less, below our average total dose of 107 mg/d (3.7 mg/kg per day). Furthermore, in some studies, physicians did not attempt higher doses even if side effects were not reported. We also report conditions not previously treated with TBZ, including proprionic acidemia, intraventricular hemorrhage, Leigh's syndrome, neurofibromatosis type 1, posthypoxic injury, and arteriovenous malformations. Hyperkinesias diminished with TBZ in all of these conditions. There was one patient with infantile spasms in which chorea improved, in contrast to

TABLE 2. *Previous reports of pediatric TBZ treatment*

Age range, yrs	Sex (no. pts)	Movement	Condition(s)	Dose, mg/d	Effective	Side effects (if reported)	Source (no. pts)
3-19	NA	Athetosis	Athetoid cerebral palsy	50-100	Y	Drowsiness Salivation Slurred speech Anxiety	Heggarty and Wright[10] (30)
1.8-10	M (4) F (1)	Chorea	Cerebral palsy acute encephalopathy trisomy 21 infantile spasms	100-275 (9-17 mg/kg/d)	Y	-	Chatterjee and Frucht[1] (5)
10-12	M(1) F(1)	Chorea	Sydenham chorea	50-75	Y	-	Hawkes and Nourse[11] (2)
2-10	NA	Chorea, dystonia, ataxia, dysarthria, self-mutilation	Lesch-Nyhan syndrome	NA	Hyperkinesia: Y in 4/5 self-mutilation: Y in 2/5	-	Jankovic et al.[2] *(5)*
4	M	Choreoathetosis	Lesch-Nyhan syndrome	10	N	-	Watts et al.[12] (*1*)
8	F	Dystonia	Dystonia musculorum	75	N Insomnia Depression Myoclonus Feeling of unreality	Drowsiness	Swash et al.[13] (*1*)
13	M	Dystonia	Tardive dystonia	NA	Y	-	Burke et al.[14] (*1*)
8	M(1)	Dystonia	Autosomal-dominant dystonia musculorum deformans	150	Y	-	Jankovic and Penn[15] (*1*)
12-15	M(2)	Dystonia	Sporadic idiopathic progressive generalized dystonia	75 mg/d with pimozide and benzhexol	Y in 1/2	-	Marsden et al.[4] (2)
5-14	M (5)	Status dystonicus	Primary torsion dystonia Athetoid cerebral palsy	37.5-75 mg/d with pimozide, haloperidol, benzhexol, diazepam and/or baclofen	Y in 1/5	Depression	Manji et al.[16] (5)
NA	NA	Infantile Spasms	Infantile Spasms	45 mg/m^2/d	N	-	Hrachovy et al.[6] (12)
10-14	M(6)	Tics	Tourette Syndrome	25-100	Y	Drowsiness Depression Nausea Nervousness Transient OCG	Jankovic et al.[17] (6)
3-17	M(52) F(24)	Tics (n = 53) Dystonia (n = 12) Chorea (n = 10) Myoclonus (n = 3)	NA	6.25-150 (avg: 49.3 mg/d)	Y	Drowsiness Nausea Depression Akathisia Insomnia	Voung et al.[5] (76)

ND, not determined.

the experience of Hrachovy and colleagues[6] with 12 similar patients. However, there was also an increased frequency of seizures in this patient. This finding could be linked to TBZ, as norepinephrine depletion has been linked to lowering the seizure threshold.[7] In 6 patients, TBZ treatment alone likely accounted for a reduction of involuntary movements, as these patients were able to stop all other mediations and maintain benefit. In those who were taking multiple medications, fewer than half (11 of 23) were on another dopamine depletor or dopamine receptor blocker. In addition to antagonizing dopamine receptors, TBZ prevents monoamines from being stored in secretory vesicles, which depletes dopamine levels at the synaptic cleft. This dual mechanism suppressing dopaminergic activity may be why TBZ suppressed movements in situations when other dopaminergic antagonists did not. As reported in other studies with pediatric TBZ treatment, the concomitant use of other medications did not seem to affect the dose of TBZ.[5]

Ninety-three percent of our patients had been treated with other medications without success before TBZ, suggesting that their movements were particularly difficult to control. Indeed, this finding may account for the relatively high dose required to control movements (over 100 mg/d [3.7 mg/kg] compared to adult studies, which averaged 70 mg/d[8]). The higher dose may also explain the fact that 63% of children experienced at least one side effect. In both pediatric and adult patients, side effects are dose-dependent.[3,8] As in adults, sedation was the most common side effect in children and behavioral changes (excluding depression) were the second most common side effect.[3] Parkinsonism is a common side effect in adults,[3] whereas only one of our patients experienced this side effect and no child in another larger pediatric study exhibited this adverse effect.[5] It has been hypothesized that older patients are more susceptible to Parkinsonism from TBZ because dopamine function declines with age.[8] Age-related changes in the dopaminergic system may also account for the higher doses of TBZ needed and tolerated in our pediatric population when compared to adults. Both postmortem and functional neuroimaging studies have demonstrated age-related dopaminergic loss.[9] The availability of D1-like and D2-like receptors in the striatum declines at a rate of approximately 5% to 10% per year, with age-dependent loss of cortical and thalamic dopamine receptors.[9] This decrease in dopaminergic function may explain why adults require lower doses of TBZ to control hyperkinetic movements and more commonly experience parkinsonian side effects.

In conclusion, we found TBZ to be effective in a wide range of pediatric hyperkinetic movement disorders. We believe TBZ use in children is a relatively safe and effective treatment for hyperkinetic movement disorders that do not respond to other medications. TBZ is a reasonable option in carefully selected children when other drugs have failed. We recommend starting a low dose (12.5 mg/d) with gradual escalation on a three times a day schedule until either the movements improve or side effects occur. Children tolerated higher doses of TBZ better than reported for adults, much like observations with trihexyphenidyl.[4] Higher doses may be needed in the pediatric population compared to adults to achieve effective control.

LEGEND TO THE VIDEO

Three patients are shown before and after TBZ treatment. Patient 3 had generalized chorea and ballismus, which was markedly improved with TBZ treatment. In Patient 10, continuous generalized chorea is present with opisthotonic posturing. Protective padding was placed around her crib to prevent self-injury. After treatment with TBZ, chorea resolved. Patient 17 had severe left hemichorea and hemiballismus, which prevented ambulation. After medications failed to control her movements, she underwent a right thalamotomy, which improved her chorea to the extent that she could walk. However, prominent left arm chorea remained. Further improvement was seen with TBZ treatment.

REFERENCES

1. Chatterjee A, Frucht SJ. Tetrabenazine in the treatment of severe pediatric chorea. Mov Disord 2003;18:703–706.
2. Jankovic J, Caskey TC, Stout JT, Butler IJ. Lesch-Nyhan syndrome: a study of motor behavior and cerebrospinal fluid neurotransmitters. Ann Neurol 1988;23:466–469.
3. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997;48:358–362.
4. Marsden CD, Marion MH, Quinn N. The treatment of severe dystonia in children and adults. J Neurol Neurosurg Psychiatry 1984;47:1166–1173.
5. Voung K HC, Mejia N, Jankovic J. Safety and efficacy of tetrabenazine in childhood hyperkinetic movement disorders. Mov Disord 2004;19(Suppl. 9):S422.
6. Hrachovy RA, Frost JD Jr, Glaze DG. Treatment of infantile spasms with tetrabenazine. Epilepsia 1988;29:561–563.
7. Weinshenker D, Szot P. The role of catecholamines in seizure susceptibility: new results using genetically engineered mice. Pharmacol Ther 2002;94:213–233.
8. Paleacu D, Giladi N, Moore O, Stern A, Honigman S, Badarny S. Tetrabenazine treatment in movement disorders. Clin Neuropharmacol 2004;27:230–233.
9. Kaasinen V, Rinne JO. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neurosci Biobehav Rev 2002;26:785–793.
10. Heggarty H, Wright T. Tetrabenazine in athetoid cerebral palsy. Dev Med Child Neurol 1974;16:137–142.
11. Hawkes CH, Nourse CH. Tetrabenazine in Sydenham's chorea. Br Med J 1977;1:1391–1392.

12. Watts RW, McKeran RO, Brown E, Andrews TM, Griffiths MI. Clinical and biochemical studies on treatment of Lesch-Nyhan syndrome. Arch Dis Child 1974;49:693–702.
13. Swash M, Roberts AH, Zakko H, Heathfield KW. Treatment of involuntary movement disorders with tetrabenazine. J Neurol Neurosurg Psychiatry 1972;35:186–191.
14. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology 1982;32:1335–1346.
15. Jankovic J, Penn AS. Severe dystonia and myoglobinuria. Neurology 1982;32:1195–1197.
16. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. Brain 1998;121(Pt. 2):243–252.
17. Jankovic J, Glaze DG, Frost JD Jr. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology 1984; 34:688–692.

Increase in Body Weight after Pramipexole Treatment in Parkinson's Disease

Hatice Kumru, MD, Joan Santamaria, MD,* Francesc Valldeoriola, MD, Maria J. Marti, MD, and Eduardo Tolosa, MD

Neurology Service, Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

Abstract: **Body weight changes occur during the clinical course of Parkinson's disease (PD) and with surgical treatment, but the effect of dopaminergic treatment on weight is unknown. Body mass index (BMI), Hamilton depression scale score (HDS), and Unified Parkinson's Disease Rating Scale III (UPRS-III) were measured before and 3 months after starting pramipexole in 28 PD patients. Pramipexole produced a significant weight increase, as well as motor and mood improvement ($P < 0.001$). HDS and BMI changes were mildly related ($P = 0.05$). A direct effect of pramipexole on limbic D_3 receptors involved in the control of feeding may be responsible for weight gain in PD.** © 2006 Movement Disorder Society

Key words: Parkinson's disease; pramipexole; weight gain

The cardinal symptoms of Parkinson's disease (PD) include a combination of tremor, bradykinesia, rigidity, and postural instability. Other nonmotor symptoms and signs may complicate its course.[1] Patients with PD, for instance, have lower weights than their matched controls. This decrease in weight starts years before the diagnosis and it is not caused by reduced energy intake.[2] It has been related to increased energy expenditure caused by rigidity or dyskinesia, difficulties in feeding or in access to food.[2–6] On the other hand, an increase in weight occurs in PD patients after pallidotomy,[4,6] after pallidal stimulation,[6] or subthalamic deep brain stimulation (DBS).[3] This weight gain after surgery has been attributed to a decrease in energy expenditure—mainly due to reduction in dyskinesia, tremor, or rigidity, and to a lack of adjustment between decreased energy expenditure and energy intake. The effect of dopaminergic treatment on body weight in PD, however, is not well known. A recent report has described a significant loss of weight 2 years after starting levodopa in previously untreated PD patients.[7] However, because this decrease was not present the first year of treatment, it is unclear if it was related with L-dopa treatment or to progress of the disease itself.

While doing research on the effect of pramipexole on somnolence in patients with PD, we observed that weight gain occurred often in these patients. In this work, we describe the effect of pramipexole on body weight and its relation to the motor and mood changes that occur during treatment.

PATIENTS AND METHODS

A total of 28 patients with PD (8 female, 20 male; mean age, 63.2 ±8.8 yr and mean PD duration, 6.8 ±4.8 yr) being on stable medical treatment and without receiving dopamine agonists at least during the last month and needing additional antiparkinsonian medication were included. Concurrent medications that patients were taking were as follows: L-dopa/carpidopa (number of patients [n] = 27, mean daily dose of 558.8 ±271.4 mg), entacopone (n = 5), selective serotonin reuptake inhibitors (n = 7), amitriptyline (n = 2), clomipramine (n = 2), selegiline hydrochloride (n = 3), amantadine (n = 1), benzodiazepines (n = 3). These drugs were unchanged throughout the study period.

Clinical assessments included the Unified PD Rating Scale (UPDRS) score subscale III for motor evaluation, Hoehn & Yahr scale (H&Y), Schwab &England daily living scale (S&E), and the UPDRS IV for evaluation of dyskinesia. At the same visit, the Hamilton depression scale (HDS) was completed. Because the HDS does not contain a subjective evaluation by the patient of his/her mood state, we also used the ninth question of the Pittsburgh Sleep Quality Index (PSQI)[8] to evaluate possible changes in mood not detected by the HDS: "How much

*Correspondence to: Dr. Joan Santamaria, Neurology Service, Hospital Clinic de Barcelona, c/ Villarroel, 170, Barcelona, 08036 Spain. E-mail: jsantama@clinic.ub.es

Received 28 November 2005; Revised 6 March 2006; Accepted 9 May 2006

Published online 13 September 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21086