High-dose oral baclofen: Experience in patients with multiple sclerosis

Article abstract—We reviewed a 10% random sample of charts from an outpatient clinic for multiple sclerosis to determine the frequency with which baclofen was prescribed for spasticity in high doses (>80 mg/d). About 20% of patients had taken high-dose baclofen, and 15% were still receiving a high dose. Taking a high dose was not associated with discontinuing treatment.

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Spasticity, a frequent problem in multiple sclerosis (MS), can limit daytime function and interfere with sleep. Severe spasticity can result in fibrous contractures predisposing to pressure sores.[1] Baclofen is the treatment of choice for spasticity of spinal origin,[2] but not all patients respond to baclofen in the manufacturer's recommended dosage range of 40 to 80 mg/d. Some patients experience adverse effects while others derive insufficient benefit. Some clinicians will prescribe beyond the recommended maximum when a satisfactory effect does not occur within the usual dosage range.[1] However, there are no published data on how frequently high doses of baclofen are given, what the range of dosage is, or whether patients on high doses are more likely to discontinue treatment because of adverse effects.

To gather some data concerning baclofen use in the management of spasticity in MS, we completed a chart review for a 10% random sample of all patients actively followed at a large MS outpatient center. Our purpose was to generate estimates of the frequency of baclofen usage at various dosage levels. Of particular interest were those patients at or above the recommended maximum dosage of 80 mg/d. Since it was a simple chart review, we did not design this study to address directly safety and efficacy issues.

Methods. A chart review was completed for a 10% random sample of all patients with MS (n = 1,120) actively followed at the Medical Rehabilitation Research and Training Center for MS of the Albert Einstein College of Medicine. Demographics and history of baclofen use, if any, were recorded. Specifically, the highest dose, current dose, duration of therapy (both overall and at the highest dose), and the reason for stepdown or discontinuation were recorded.

Results. *Demographics.* A total of 112 charts were analyzed. The mean age was 45.2 years (SD, 13.5; range, 18 to 75). The mean duration of MS was 12.9 years (SD, 9.6; range, 5 months to 50.5 years). Women comprised 66% of the sample. As a predominantly female, middle-aged sample with a several-year history of MS, this sample closely parallels the patient population at the Center.

Analysis of baclofen use. The average duration of therapy with any dose of baclofen was 43.7 months (SD, 37.6 months; range, 1 to 132 months). The average duration at the highest recorded dose was 15.8 months (SD, 16.4 months; range, 1 to 63 months).

Table 1 presents data on baclofen prescription in terms of the history of baclofen use. While 59% (n = 66/112) were currently taking baclofen, 66% (n = 74/112) had taken it at some time while a patient at the Center. Thus, the majority of patients treated at this Center receive baclofen on an ongoing basis. Of those still taking baclofen, the majority (n = 45/66 or 68%) were receiving baclofen at the highest dose they had ever gotten.

As expected, use of high-dose baclofen was frequent, with 15% of patients currently on baclofen receiving more than 80 mg (≤80 mg, 85%; >80 mg, 15%; mean, 59.7 mg; SD, 44.5 mg; range, 5 to 270 mg). When the maximum dosage recorded was considered and patients who had discontinued were included, the percentage of patients who had received more than 80 mg rose to 20% (≤80 mg, 80%; >80 mg, 20%; mean, 65.6 mg; SD, 49.2 mg; range, 15 to 280 mg). For those patients currently receiving >80 mg (n = 10), the mean dose of baclofen was 141 mg (SD, 50.7), and for those who had ever taken >80 mg (n = 15), the mean dose was 137 mg (SD, 60.2). Table 2 gives the distribution of baclofen dosage for the entire sample.

Of the eight patients who had discontinued baclofen, none were taking more than 60 mg (<80 mg, 100%; mean, 27.5 mg; SD, 18.3 mg; range, 5 to 60 mg). The most common reasons for stopping baclofen (table 3) were lack of benefit as observed by the patient or physician (n = 4) and weakness (n = 3). One patient discontinued treatment because of urinary incontinence and one because of nausea. No reason was recorded for another patient. Two patients had two reasons for discontinuing baclofen. Only two patients sought advice from their physician before stopping the drug.

Of the 24 patients who had ever reduced their dosage from their maximum recorded levels (table 3), the most common reason was weakness (n = 15). For eight of these, dosage reduction was suggested by their physi-

Table 1. History of baclofen use

	No.	%
Baclofen ever used	74/112	66
Baclofen still being used	66/112	59
Baclofen dose ever >80 mg	15/74	20
Baclofen dose still >80 mg	10/66	15
Baclofen discontinued	8/74	11
Baclofen dose ever reduced	24/74	32

Table 2. Distribution of baclofen dosage

Dose range	Highest dose (N = 74) No.	%	Current dose (N = 66) No.	%
<20	12	16	11	16
21-40	17	24	22	33
41-60	15	20	10	15
61-80	15	20	13	20
81-100	6	8	3	5
101-120	4	5	2	3
>120	5	7	5	8

Table 3. Reasons for discontinuing or ever reducing baclofen dose

	Discontinued*	Reduced
Lack of benefit	4	1
Weakness	3	15
Nausea	1	1
Urinary incontinence	1	1
Drowsiness	0	2
Confusion	0	1
Not stated	1	3
Total	10*	24

* Two of eight patients had two reasons for discontinuing baclofen.

cian. Two additional patients reduced the dose because of drowsiness, one each because of nausea, urinary incontinence, and lack of additional benefit, and three for unstated reasons. In one patient, the dose was reduced by the physician because of an episode of possible confusion reported by the family.

Relationships between baclofen use and patient characteristics were examined. Compared with women, there was a nonsignificant trend for men to be more likely to have received baclofen (men = 78.9%; women = 59.5%; $p = 0.064$). Otherwise, there were no sex differences. Patients who had received baclofen were significantly older (48.5 years versus 38.7 years; $p > 0.001$) and had MS longer (14.9 years versus 9.2 years; $p > 0.01$) than those who had never taken baclofen, probably because spasticity is more likely to appear or to get worse as the disease progresses. However, there was no relationship between age or duration of illness and either the highest dose recorded or the current dose.

Discussion. Baclofen is an effective drug for the treatment of spasticity of spinal origin.[3] Adverse effects are generally mild and transient.[4] Unfortunately, physicians tend to underutilize baclofen because the recommended maximum is 80 mg/d.[5,6] As patients may suffer serious complications because of inadequate spasticity relief,[1] it is important to alleviate at least some of the more serious manifestations of severe spasticity, such as lower limb flexor spasms. Although high-dose baclofen has never been studied prospectively, our experience suggests that MS patients can readily tolerate relatively large doses.

There are several references to long-term, high-dose baclofen treatment for spasticity. Jones and Lance[7] summarized their experience with 113 patients with spasticity treated with baclofen for up to 6 years. Baclofen dosage ranged from 30 to 200 mg daily with the mean varying from 60 to 110 mg depending on the cause of spasticity. Treatment was abandoned in only four patients because of intolerable side effects, and another 20% required a reduction in dosage. Pedersen et al[8] treated patients with up to 100 mg of baclofen daily for more than 3 years. Adverse effects were transient but more frequent at higher doses. Pinto et al[9] identified patients who had taken up to 225 mg daily for up to 30 months and emphasized that many patients need more than 100 mg daily and that side effects are only infrequently a persisting problem.

The present study did not attempt to collect objective evidence indicating that doses of baclofen in excess of 80 mg/d are safe or result in increased benefit. However, the results of this retrospective study do suggest that doses in excess of 80 mg/d are used rather frequently in clinical practice and should be considered when more aggressive management of spasticity is indicated. Our study also suggests that adverse effects may only rarely be important as obstacles in determining the best dose.

Recently, considerable interest has been generated by reports of the efficacy of intrathecal baclofen.[10] While a welcome addition to the management of refractory spasticity, this treatment is expensive, invasive, and prone to complications. We hope that patients being considered for intrathecal baclofen will first be given an adequate trial with oral baclofen or other oral antispastic medications such as diazepam and dantrolene sodium.

This brief chart review confirmed that use of high-dose baclofen is fairly frequent in a large MS center. The results also suggested that high dosages are not associated with discontinuation of the medication, although there is a reduction of dose from highest recorded levels for a significant proportion of patients using >80 mg (n = 5/15). On the basis of these data, no conclusions can be drawn concerning the safety or efficacy of high doses of baclofen. However, given that high dosing is frequent enough in MS, the results do strongly suggest that patient needs and response to therapy, and not some arbitrary maximum, should determine the optimal dose.

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Pick's disease: A case clinically resembling amyotrophic lateral sclerosis

Article abstract—A 50-year-old woman with a progressive neurologic illness clinically resembling amyotrophic lateral sclerosis had Pick's disease verified at autopsy. This case represents another example of Pick's disease in which the early manifestations were not those of dementia. This patient also showed some unusual histopathologic features, including degeneration of the substantia nigra and occasional "compound Pick bodies."

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Pick's disease is a rare form of dementia that is usually indistinguishable clinically from Alzheimer's disease. However, there are a few reported cases in which the initial manifestations have been those of motor neuron disease[1-3] or aphasia.[4] Still other cases, identified at autopsy, were apparently asymptomatic.[5] In this report, we describe an unusual patient with Pick's disease whose initial illness was dominated by motor deficits. Furthermore, this patient's brain displayed some unusual histopathologic features, including degeneration of the substantia nigra without formation of Lewy bodies and the presence of occasional "compound Pick bodies."[6]

Case report. A 50-year-old right-handed bank teller presented to West Virginia University (WVU) in October 1984 complaining of left arm pain and weakness that had been progressive over the previous 11 months. She had a remote (at age 17) history of rheumatoid arthritis but no history of hypertension, diabetes, heart disease, smoking, alcohol abuse, or drug abuse. There was no family history of neurologic or psychiatric diseases, including dementing disorders.

The patient was alert, oriented, and appropriate, although a bit anxious. Her speech was fluent and grammatically correct. She had decreased fine motor function in the left hand and decreased strength in the left arm, more distally than proximally. Tone was increased in the left arm. The reflexes were 3+ in the left upper extremity and left knee, but the ankle jerks were absent. The plantar reflexes were flexor. The remainder of her neurologic examination was normal, and the cytologic and chemical profile of her CSF was normal.

Prior to her initial visit at WVU, the patient had a proximal median nerve release for pronator teres syndrome. This was followed by increasing left antecubital pain. Studies at two teaching institutions in neighboring states were negative, including neuroimaging by CT and MRI. Diagnostic considerations included amyotrophic lateral sclerosis or a possible microangiopathy of the spinal cord and brainstem with a lesion above the level of the neck, either deep in the peduncle or internal capsule and thalamus.

In December 1985, the patient displayed pseudobulbar crying, decreased cough, and slight impairment of vertical eye movements. Nerve conduction studies were normal, while needle EMG showed a few fibrillations (without fasciculations), and enlarged and polyphasic motor unit potentials in several muscles in the left arm. In January 1986, she was unable to move her left arm, and had increasing weakness of all other extremities, difficulty swallowing, orbicularis oculi weakness bilaterally, and hyperactive reflexes bilaterally. By March 1986, she began having difficulty walking, with frequent falls. Her speech became dysarthric, hyperactive reflexes persisted, and a left Babinski sign was present.

When last seen in January 1987, she was unable to communicate due to her severe dysarthria, and she could not move any extremities except her right foot. She followed commands and answered yes-no questions correctly by signaling with her right extremity. Muscle tone was increased, and she had marked facial weakness and marked impairment of vertical eye movements.

Following this, her locked-in status prevented further assessment of mental functions. On June 3, 1990, she presented to a local hospital with fever, tachypnea, and tachycardia, and died on June 5, 1990.

Neuropathologic findings. The brain weighed only 879 grams and showed severe atrophy of the frontal lobes and rostral portions of the temporal lobes, with relative preservation of the parietal and occipital lobes (figure 1). Coronal sections confirmed the lobar atrophy and showed massive dilatation of the frontal horns (figure 2). The basal ganglia also showed moderate atrophy. Transverse sections of the brainstem showed atrophy of the crus cerebri and mild depigmentation of the substantia nigra. The cerebellum was unaffected.

Histologically, there was severe neuronal loss and gliosis in the atrophic portions of the cortex. Some of the neurons within the neocortex contained argentophilic Pick bodies. Sections of the hippocampi showed a severe reduction in the number of pyramidal layer neurons. Some of the remaining hippocampal neurons (figure 3A) and many of the