Comorbid Bipolar Disorder in Tourette’s Syndrome Responds to the Nicotinic Receptor Antagonist Mecamylamine (Inversine)

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Background: We have previously proposed that the therapeutic effect of transdermal nicotine in Tourette’s syndrome may involve nicotinic receptor inactivation resulting from a prolonged continuous exposure to nicotine. In vitro studies with nicotine and preliminary positive experience with mecamylamine (Inversine), a nicotinic receptor antagonist, in the clinical treatment of Tourette’s syndrome patients, further supports the receptor inactivation hypothesis.

Methods: We retrospectively documented an unexpected therapeutic response to mecamylamine (2.5–7.5 mg/day) in two Tourette’s syndrome patients who were subsequently found to have comorbid bipolar disorder as defined by DSM-IV criteria.

Results: In patient 1, the mood-stabilizing effect of mecamylamine was noticed by the patient during the course of mecamylamine treatment and brought to our attention, whereas for patient 2, manic symptoms were only apparent clinically following cessation of mecamylamine treatment.

Conclusions: The clinical observations presented here suggest that nicotinic antagonists might be potential therapeutic agents for the treatment of bipolar disorder. Double-blind, placebo-controlled studies are now necessary to investigate these observations under more rigorous conditions.

Key Words: Mecamylamine, bipolar disorder, nicotine, mood stabilizer, nicotinic receptor antagonist, Tourette’s syndrome

Case Reports

Patient 1 was a female 35-year-old, who has TS with severe motor and vocal tics, obsessions, and compulsions since the age of 6 years. She is the mother of three children, her oldest child, a girl aged 12 years, also has TS. A variety of medications were tried, including sertraline for several years to limit her premenstrual syndrome (PMS) and anxiety. Attempts to control her tics with short trials of transdermal nicotine and then later with haloperidol in our clinic both resulted in adverse side effects, which required discontinuation. On follow-up at our clinic 1 year later, she was tense and unhappy, with multiple and severe tics, almost continual eye blinking, grimacing, nose twitching, sniffing, and a compulsive need for everything to be “just right” in her home. At that time she was receiving sertraline, 50 mg twice daily, which she had been taking for several years for PMS and anxiety.

Within the first week of adding mecamylamine 5 mg daily, she responded with a distinct reduction of tics, which, although still present, were reduced in intensity. Three weeks later, she reported feeling more relaxed with decreased anxiety and a reduction in the occurrence of inappropriate mood swings. Moreover, she reported that her urges to have rage outbursts during stressful situations were reduced while taking mecamylamine. Mecamylamine (5 mg/day) was continued for 1 month with no appreciable change in blood pressure or heart rate; how-
ever, she did complain of constipation during her menses and mild frontal headaches, but both symptoms resolved when her dose of mecamylamine was decreased to 3.25 mg/day. When her prescription for mecamylamine ran out each month, she requested that the mecamylamine be continued. Sertaline was gradually discontinued without a worsening of symptoms.

At a 6-month follow-up visit, her tics had returned, but when asked why she wanted to continue receiving mecamylamine, she said she had noticed that mecamylamine “evens me out.” She stated that since starting mecamylamine, she no longer has the “ups and downs” that used to trouble her. Moreover, her family noticed a big difference in her mood in that she “no longer gets angry about little things” and that she “is much easier to get along with.” She also reported that she missed the “ups” when she used to get lots of housework done; but more importantly, she did not miss the subsequent “downs” when she used to get depressed and not feel like doing anything for days. After receiving mecamylamine daily for 7 months, she reported in a check-up call that she recently had discontinued taking the mecamylamine because, although she appreciated her mood being less volatile, she missed her “highs.”

Patient 2 was a male 16-year-old in the ninth grade whose overall cognitive functioning was in the high-average range but with deficits in visual–motor function. He developed motor and vocal tics at 10 years of age, within 6 months after starting on methylphenidate and dextroamphetamine for attention deficit disorder and academic difficulties. With 0.1 mg of clonidine three times a day, his tics were said by his parents to be “under control.” For two subsequent years, however, he had received no medication for motor and vocal tics. By the end of eighth grade, he had failed math, received C and D grades in his other subjects and had marked difficulty with any visual–motor function. His handwriting was slow and labored; he resisted any written work, became frustrated with it, and felt that he was doomed to failure. On his visit to our clinic, his tics were clearly evident: eye blinking, mouth grimacing, gross body tics, quick and jerky movements of his shoulders, head tics, and sniffing. He complained that he was “active in his head” and easily distracted. During the summer he was attempting to learn math so that he could retake an examination required before entering high school in the fall; however, he had difficulty writing down the steps needed to answer the math problems (as is required in the examination), although he can “get the steps in his head.” He was impatient, frustrated, and inclined to give up.

Mecamylamine (5 mg/day) was prescribed, and the patient was told to take it after dinner. His mother, a nurse, reported that 2 hours after taking 5 mg of mecamylamine he started to study math. This time, he was patient, felt his “mind is clearer,” was more relaxed, and worked on math problems for 3 hours without distraction. His tics subsided in intensity and frequency. The following morning, he felt restless, and tics started to return, though not as disturbing as previously. He had eye blinking and gross, jerky body movements. He was prescribed 5-mg mecamylamine at breakfast and 2.5 mg after dinner daily. Twelve days later, the patient reported that with the medication, he was not “hyper” and could concentrate on his schoolwork. The tics, although occasionally present, had subsided. His blood pressure was unchanged at 114/80. After 8 weeks of treatment, the patient’s mother reported that he was “doing well,” had entered high school and wanted to continue therapy. He continued on mecamylamine 5-mg for several months without adverse side effects and sustained improvement in school; however, when the patient discontinued the medication because he felt he could do without it, his ability to focus in school rapidly decreased and he began skipping school and staying out late with friends. When he came to our clinic 45 days after discontinuing the medication, throat clearing and neck straining tics were present along with restlessness and anxiety. He reported being disorganized and unable to focus because of “racing thoughts” that also were causing him problems sleeping. Mecamylamine (2.5 mg bid) was restarted and 1 week later his mother called to report that his symptoms had improved.

Based on these clinical observations, a MINI International Neuropsychiatric Interview for DSM-IV (Sheehan et al 1998) was conducted on each patient. In both cases, the patients’ symptoms met criteria for bipolar disorder with past manic episodes.

Discussion

In patients comorbid for bipolar disorder, mecamylamine (3.25–7.5 mg/day; 0.03 to 0.1 mg/kg p.o.) appeared to reduce anxiety, tic severity, distractibility, and mood instability. At these doses, which reflect approximately one fifth the average dose used to treat hypertension, mecamylamine produced few side effects even after months of daily use. Mild constipation was the most common side effect observed at these doses when used chronically for smoking cessation in adults (Rose et al 1994).

The improvement in attention and reduced distractibility observed in Patient 2 seemed paradoxical when considering previous studies reporting mild cognitive impairment with higher doses of acute mecamylamine (20 mg) administration in both young and elderly adults (Newhouse et al 1994). A recent study, however, demonstrated biphasic effects of mecamylamine where low doses (0.01 mg/day)
to 0.1 mg/kg subcutaneously) improved, whereas higher doses impaired, cognitive executive function in rats and aged primates (Terry et al 1999).

An association between TS and manic symptoms has been reported previously (Burd and Kerbeshian 1984; Comings and Comings 1987; Kerbeshian and Burd 1989; Kerbeshian et al 1995). Moreover, Berthier et al (1998) recently reported that one third of their clinically referred adult Tourette’s syndrome patients had comorbid bipolar disorder.

The apparent mood modulating effect of mecamylamine in the two patients with comorbid bipolar disorder reported here was striking and unexpected. In patient 1, the mood stabilizing effect of mecamylamine was noticed by the patient during the course of mecamylamine treatment and brought to our attention, whereas for patient 2, manic symptoms were only apparent clinically following cessation of mecamylamine treatment.

With regard to possible neuropharmacologic mechanisms, mecamylamine readily crosses the blood-brain barrier and functions primarily as a potent, long-acting, noncompetitive antagonist of nAChRs (Martin et al 1989). Recent evidence suggests that a number of psychotherapeutic medications, including several antidepressants (Fryer and Lukas 1999) and mood stabilizers, including carbamazepine (Picard et al 1999) and valproic acid (Yamamoto et al 1997) can inhibit or modulate nicotinic receptors at clinically relevant concentrations.

Although mecamylamine was originally used to treat hypertension, more recent studies suggest that it may be useful for treating tobacco (Rose et al 1998), cocaine (Reid et al 1999) and alcohol dependency (Blomqvist et al 1997). Because psychostimulant and alcohol abuse are common comorbid problems associated with poorer prognosis in bipolar disorder (Tohen et al 1998), mecamylamine might be especially useful in this population. Although neither of the two patients reported here had a history of tobacco or drug use, there is strong evidence suggesting that changes in nAChR function can alter mood. For example, clinically significant symptoms of mania and depression have been reported following smoking cessation in some individuals (Labbate 1992).

Studies characterizing the effects of smoking on mood throughout the day in normal smokers suggest that although mood improves immediately after smoking, mood impairments (i.e. irritability and depression) occur between cigarettes (Parrott 1995). This repetitive cycle of shifting mood suggests a role for nAChRs in mood regulation and may partially explain the high prevalence of smoking in bipolar disorder (Gonzalez-Pinto et al 1998).

The present clinical observations suggest that nicotinic antagonists might be potentially useful therapeutic agents for the treatment of bipolar disorder. Double-blind, placebo-controlled studies are now necessary to investigate these observations under more rigorous conditions.

The authors are inventors on a patent owned by the University of South Florida, which covers the use of nicotinic receptor antagonists for the treatment of nicotine-responsive neuropsychiatric disorders. The authors are also scientific consultants for Layton BioScience, Inc., which owns the tradename and marketing rights to mecamylamine (Inversine).

References

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