A Controlled Trial of Propoxyphene and Naltrexone in Patients with Tourette's Syndrome

Roger Kurlan, MD,* Lisa Majumdar, MD,* Cheryl Deeley, RN, MS,* Govind S. Mudholkar, PhD,† Sandra Plumb, BS,† and Peter G. Como, PhD*

To investigate the effect of drugs acting on the endogenous opioid system, we studied 10 adults with Tourette's syndrome who received propoxyphene hydrochloride (260 mg/day), naltrexone hydrochloride (50 mg/day), and placebo in a double-blinded, randomized clinical trial. Using a self-report scale (Tourette's Syndrome Symptom List), subjects noted a significant ($p < 0.04$) lessening of tics after treatment with naltrexone when compared with placebo. An improvement in performance on the Trail Making B test, a measure of attention and visuomotor sequencing and planning, occurred after receiving naltrexone when compared with placebo ($p < 0.08$) or propoxyphene ($p < 0.02$). The Trail Making B test best discriminated the treatments ($p < 0.02$, analysis of variance). No other treatment effects were observed for several other measures of tic severity, attentional ability, or obsessive-compulsive symptoms. Our findings indicate that pharmacological manipulation of the endogenous opioid system does influence symptoms of Tourette's syndrome.

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Tourette's syndrome (TS) is a hereditary disorder characterized by chronic motor and vocal tics, often accompanied by obsessive-compulsive symptoms and an attentional disorder [1]. Current evidence indicates that central dopamine receptor supersensitivity may underlie the tic disorder, although the detailed neurochemical pathology of TS remains unknown [1]. The first specific neurochemical abnormality observed in a postmortem brain of a person with TS, described by Haber and colleagues [2], consisted of a lack of dynorphin-like immunoreactivity in the dorsal part of the external segment of the globus pallidus and faint staining in the ventral pallidum [2]. Dynorphin A, a 17 amino acid peptide, has potent agonist activities at kappa and mu opiate receptors. Pharmacological manipulations of the endogenous opioid system (EOS) have produced conflicting results in patients with TS. In uncontrolled observations, the administration of an opiate antagonist medication, naloxone or naltrexone, has been reported to reduce tics [3, 4], obsessive-compulsive symptoms [3, 5], and self-mutilatory behavior [6] in patients with TS. Others have observed no effect [7] or a worsening of symptoms [4, 8]. One patient with TS was reported to experience an exacerbation of tics while jogging, an activity associated with heightened release of brain endorphins [9]. We have reported 2 patients in whom sudden withdrawal of chronic opiate therapy produced a dramatic exacerbation of TS symptoms [10, 11], and another similar patient has been subsequently observed [12]. A measured abnormal release of growth hormone and gonadotrophins in response to naloxone challenge has suggested disturbed central opioid regulation in patients with TS [13–15].

Although inconsistent, when taken together, this largely anecdotal pharmacological experience suggests that reversible overactivity of the EOS may be contributing to the symptoms of TS. In support of this idea, opiate antagonists have been observed to reduce self-injurious behavior, a symptom of TS that is associated with other conditions including mental retardation and autism [16]. The potential therapeutic effects of drugs acting on the EOS for neurological movement disorders is illustrated by the reported efficacy of propoxyphene hydrochloride and codeine for neuroleptic-induced akathisia [17].

In view of the foregoing suggestive but inconsistent evidence implicating disturbances of the EOS in patients with TS, we performed a double-blinded, placebo-controlled, clinical trial of naltrexone hydrochloride and propoxyphene in 10 adult patients with TS.

From the Departments of *Neurology and †Biostatistics, University of Rochester School of Medicine and Dentistry, Rochester, NY.

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Address correspondence to Dr Kurlan, Department of Neurology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave, Rochester, NY 14642.

Evaluations included assessments of tic severity, obsessive-compulsive symptoms, and attentional abilities. If overactivity of the EOS is indeed present in patients with TS, we hypothesized that naltrexone would improve symptoms, whereas propoxyphene, a mild opiate analgesic, would worsen them.

Methods

Patients

Patients included 10 adults (8 men, 2 women; aged 33 ± 10 [mean ± SD] years) who satisfied *Diagnostic and Statistical Manual of Mental Disorders, Edition III–Revised* (DSM-IIIR) criteria for TS. Patients had no history of adverse reactions to narcotic drugs or naltrexone and no history of narcotic abuse or addiction. Patients remained on medications prescribed for the treatment of TS (haloperidol, 3 patients; clonidine hydrochloride, 1 patient; haloperidol, clomipramine hydrochloride, and clonazepam, 1 patient) during the course of the study, but dosages remained unchanged throughout the duration and for at least 2 weeks before entering the study. Patients using opiate medications were excluded. The study was approved by the Research Subjects Review Board of the University of Rochester (Rochester, NY), and patients provided informed consent.

Design

This study involving three treatments (propoxyphene, naltrexone, and placebo) was conducted in a double-blinded, randomized, block design analogous to that used by Morgan and associates [18]. In this design, patients served as the blocks and treatment periods each served as the plots. Each treatment period lasted 6 weeks, and a 2-week washout period separated treatments. The washout periods were designed to avoid opiate withdrawal symptoms, particularly in patients who were randomized to propoxyphene followed by naltrexone. Propoxyphene dosage was gradually increased to 260 mg/day (65 mg four times daily) during the first week of treatment and remained unchanged for 5 weeks. The subsequent washout period included a tapering dosage schedule over 1 week and the patient remained on placebo alone for the final week. Naltrexone was administered at the manufacturer's recommended maintenance dosage of 50 mg each morning. Thus, subjects received a medication (propoxyphene, naltrexone, or placebo) four times daily throughout the duration of the study. A 2-week placebo wash-in period, designed to ensure patient compliance with the protocol, was used before randomization.

Evaluations were performed in the Clinical Research Center of the University of Rochester and took place at the time of entry, after the 2-week wash-in period, before the initiation of each treatment period, and after completion of each period (before washout). Severity of the tic disorder was assessed by the examiner during an interview session using the Goetz Tic Rating Scale [19] and the Tourette's Syndrome Global Scale (TSGS) [20]. Additionally, patients completed the self-reporting Tourette's Syndrome Symptom List–Revised (TSSL) for the day before each evaluation [20]. The Leyton Obsessional Inventory (LOI) served as a measure of obsessive-compulsive symptoms [21]. A battery of standardized neuropsychological tests was used to assess attentional abilities and included Trail Making A and B [22], Perceptual Motor Speed [23], Symbol Digit Modalities [24], and Verbal Fluency [25] tests. Additionally, patients completed the self-report ADD-H Attentional Scale [26] at each visit. The Sickness Impact Profile [27] was used to assess overall daily functioning.

Analysis

The data from the study were subjected to a variety of exploratory analytic techniques. The changes in test scores from the evaluation just before a treatment period to the one at its conclusion were analyzed by using a variety of parametric, nonparametric, univariate, and multivariate methods.

The primary analyses consisted of the standard, randomized, block analysis of variance (ANOVA), accompanied by Tukey's one degree of freedom test for additivity (subject-by-treatment interaction) and Bonferroni multiple comparisons for the individual test score changes. The secondary analyses included Graybill's method of comparing treatments in a randomized, block design, which uses Hotelling's T^2 statistic. This test was performed to rule out the possible effect of time trends on the observed significance of treatment differences. We also performed two-by-two comparisons of the three treatments by using parametric and nonparametric methods, such as two-sample t and Mann-Whitney rank-sum tests.

Results

A total of 10 patients participated in the study. One patient was unable to complete treatment with naltrexone due to palpitations and another patient did not tolerate propoxyphene due to a skin rash. One patient did not complete propoxyphene and naltrexone treatments due to noncompliance with medications.

The mean values of the change scores together with their standard errors are summarized in the Table. A negative value of the change score for a variable indicates a reduction in the test score and, hence, an improvement in the corresponding symptom; a positive change score indicates worsening of the symptom. Using the TSSL, patients reported a significant ($p < 0.04$) lessening of tics after treatment with naltrexone (mean score decreased 4.9 ± 3) when compared with placebo (score increased 7 ± 4.1). All but 2 patients reported an improvement in tic severity by TSSL ratings after naltrexone therapy. An improvement in performance on Trail Making B occurred after naltrexone treatment (mean time decreased 13.7 ± 3.1 seconds) when compared with placebo (time decreased 4.5 ± 3.5 seconds, $p < 0.08$) or propoxyphene (time decreased 0.3 ± 3.1 seconds, $p < 0.01$). All patients showed an improvement in performance on Trail Making B after naltrexone treatment. By ANOVA, Trail Making B was the measure that best discriminated the treatments ($p < 0.02$). No subject-by-treatment time trend effects or other significant treatment effects were observed for

Mean Change Scores and Their Standard Errors

	Placebo	Propoxyphene	Naltrexone
Goetz scale			
Tic character	−0.4 ± 0.6	−0.7 ± 1.2	−1.5 ± 0.5
Tic frequency	0.4 ± 1.7	0.5 ± 2.1	−0.4 ± 0.8
Tic intensity	−0.2 ± 0.3	−0.4 ± 0.5	−1.1 ± 0.5
TS Global Scale	5.0 ± 4.1	−3.7 ± 3.9	4.9 ± 3.8
TS Symptom List	7.0 ± 4.1	−3.8 ± 4.1	−4.9 ± 3.1[a]
ADD-H Scale	0.6 ± 1.2	−2.4 ± 2.1	0.8 ± 3.1
Leyton Obsessional Inventory	3.8 ± 4.5	−0.9 ± 2.0	−7.4 ± 6.4
Trail Making A	−4.2 ± 4.7	−5.8 ± 5.0	3.6 ± 1.8
Trail Making B	−4.6 ± 3.5	−0.3 ± 3.1	−13.7 ± 3.1[b,c]
Perceptual Motor Speed	0.6 ± 1.2	−2.9 ± 3.8	−2.7 ± 4.1
Verbal Fluency	−2.0 ± 2.7	2.3 ± 2.3	−0.1 ± 1.5
Symbol Digit Modalities	0.3 ± 1.2	0.8 ± 0.9	−0.4 ± 1.7
Sickness Impact Profile	5.5 ± 11.5	−34.3 ± 31.4	−7.6 ± 7.6

[a] $p = 0.04$, for naltrexone vs placebo.
[b] $p = 0.01$, for naltrexone vs propoxyphene.
[c] $p = 0.02$, by analysis of variance for the three treatments for this variable.

For the units of the tests, see references provided in the text.
TS = Tourette's syndrome.

examiner ratings of tic severity, or ratings of obsessive-compulsive symptoms or attentional abilities.

Discussion

The small sample size of our study and the known variability of symptoms in patients with TS require careful interpretation of the results. Naltrexone, an opioid antagonist, however, appears to have some effects in ameliorating tics and attentional disturbances in patients with TS as assessed in our controlled trial. Although significant, these effects were mild and evident only with a patient self-report scale of tic severity (TSSL) and a neuropsychological test of attention, visuomotor sequencing, and planning (Trail Making B). As the symptoms of TS characteristically wax and wane, it is not unexpected that a patient self-report of tic severity may be more sensitive to change than examiner ratings performed during an isolated and rather brief time period. The worsening of symptoms as reported on the TSSL after placebo treatment could be related to the expected fluctuation in symptom severity, may be largely responsible for the measured improvement after naltrexone therapy, and further supports careful interpretation of our findings. Similarly, because several attentional, concentration, cognitive, and motor skills are involved in performance on the Trail Making B test, this may be a particularly sensitive measure of drug effects in patients with TS. A worsening of performance after propoxyphene therapy when compared with placebo was also observed with the Trail Making B test. No patient reported side effects of propoxyphene, such as drowsiness, which might have impaired performance on this test. We are unaware of any other studies assessing the effect of opiate or opiate antagonist medications in normal subjects or other populations on this neuropsychological test.

Our results confirm in a controlled clinical trial that an opioid antagonist medication has some beneficial influence on the symptoms of TS, thus supporting a role for the EOS in the pathogenesis of this condition. As previously mentioned, the prevailing idea regarding the neurochemical mechanism of tics in patients with TS relates to supersensitivity of central dopamine receptors as suggested by the observation of low cerebrospinal fluid levels of the dopamine metabolite homovanillic acid together with observed clinical improvement after treatment with dopamine receptor antagonists and clinical worsening with dopaminergic drugs such as amphetamines [1]. The occurrence of tardive tics after chronic neuroleptic use, a form of tardive dyskinesia, also implicates supersensitivity dopamine receptors in the development of tic disorders [28]. Recent evidence suggests that the EOS may be involved in the modulation of dopamine receptor function. Chronic administration of opiates produces striatal and mesolimbic dopamine supersensitivity in animals [29], and naloxone influences rotational behavior in rats with unilateral striatal denervation supersensitivity [30]. Further support for an EOS-dopaminergic interaction is provided by the morphine-dependent rodent in which naloxone-precipitated opiate withdrawal is associated with characteristic jumping behavior and elevation of dopamine levels in the caudate nucleus [31]. The presence of opiate receptors on limbic dopaminer-

gic nerve terminals provides a neurophysiological basis for this interaction [32]. Thus, our observed clinical effect of naltrexone on the symptoms of TS could be mediated by influences on dopamine receptor sensitivity.

Conversely, the apparent overactivity of the EOS in patients with TS may represent a secondary effect of disordered dopaminergic function. Dopamine enhances met-enkephalin release [33]. Chronic administration of neuroleptic drugs in animals results in mesolimbic behavioral supersensitivity, a state that is associated with increased limbic and basal ganglia opioid levels and that is inhibited by naloxone [34]. Recent evidence indicates that dopamine receptors mediate control over the biosynthesis of certain striatonigral opiate peptides [35].

The noradrenergic system, also linked to the pathogenesis of TS, has functional relationships with the EOS as well. The locus ceruleus, which provides the main noradrenergic innervation to limbic and cortical structures, contains a high density of opioid receptors [35a]. Opiate withdrawal, which exacerbates symptoms of TS [10–12], is believed to resemble locus ceruleus stimulation, in many respects [36]. Clonidine, an α_2 adrenergic blocking agent that is used to treat TS, blocks symptoms of opiate withdrawal [36]. The drug also increases the release of beta endorphins in the brain [36]. A recent study of postmortem brains from patients with TS revealed reduced concentrations of adenosine 3,5-monophosphate (cyclic AMP) in cerebral cortex [37]. As mu and delta opiate receptors inhibit cyclase activity [38, 39], overactivity of the EOS might at least partially explain these neurochemical findings.

Dynorphin, the opioid peptide that is reduced in the basal ganglia of postmortem brains from patients with TS [2], is a proposed endogenous ligand for the kappa opiate receptor [40]. Naltrexone is a competitive antagonist at kappa, mu, and sigma receptor subtypes, whereas propoxyphene acts primarily at mu sites. It is possible that more robust influences on the symptoms of TS might be evident with drugs acting more specifically at the different opioid sites. Furthermore, our ability to detect more significant drug effects may have been limited by a relatively small sample size.

Our findings that naltrexone produces a mild improvement in tic severity and attentional ability in patients with TS supports the role of the EOS in the pathogenesis of this disorder. Given the limited clinical effect and the possible side effects of the drug, particularly hepatotoxicity, long-term use of this agent in the treatment of patients with TS does not seem warranted. Studies using a larger sample size and, perhaps, drugs acting at more specific opioid receptor subtypes, however, may produce further clues toward identifying rational therapeutic agents.

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