Niaprazine in the Treatment of Autistic Disorder

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greater perceptive capabilities than indicated by other neuroimaging techniques. Moreover, the FDG-PET studies showed the relative hypermetabolism in the caudate and lentiform nuclei, consistent with an active seizure disorder in this patient that was not clinically observed, albeit supported by the EEG findings.

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Niaprazine in the Treatment of Autistic Disorder

ABSTRACT

Niaprazine is a histamine H_1-receptor antagonist with marked sedative properties. It has been employed in subjects with behavior and sleep disorders. No data concerning the use of niaprazine in subjects with autistic disorder are reported in the literature. The authors performed an open study to assess niaprazine efficacy in a sample of 25 subjects with autistic disorder and associated behavior and sleep disorders. Niaprazine was administered at 1 mg/kg/day for 60 days. A positive effect was found in 52% of patients, particularly on hyperkinesia, unstable attention, resistance to change and frustration, mild anxiety signs, heteroaggressiveness, and sleep disorders. Statistical comparison between responders and nonresponders showed no influence on niaprazine effect by age over or under 12 years, presence of neurologic signs, epilepsy, or abnormalities seen on brain imaging. Niaprazine was more efficacious in subjects with a mild or moderate degree of mental retardation. No side effects were observed. Because of its sedative effects and good tolerability, niaprazine can be used as a first-choice drug to improve behavior and sleep disorders in patients with autistic disorder. (*J Child Neurol* 1999;14:547–550).

Autistic disorder is characterized, according to *Diagnostic and Statistical Manual of Mental Disorders-IV* (*DSM-IV*) criteria, by qualitative impairment in social interaction and communication; restricted, repetitive and stereotyped patterns of behavior, interests, and activities; and onset before 3 years of age.[1]

Clinical experience shows many cases with associated problems such as mood disorders, aggressiveness, hyperkinesia, and sleep disorders, especially in adolescence.[2,3] These symptoms associated with the typical features of autistic disorder make the rehabilitation and social integration of these patients more difficult. Niaprazine is a histamine H_1-receptor antagonist that has sedative properties.[4] It induces a selective dose-dependent depletion of noradrenaline and dopamine and gives a slight biphasic effect on serotonin levels in experimental animals.[5] In children niaprazine is used as a sedative agent in the treatment of sleep and behavior disturbances.[6–10] The side effects indicated in the product information sheet are somnolence, dizziness, hypotonia, and hypertonia.

The purpose of the present study was to ascertain the efficacy of niaprazine in subjects with autistic disorder associated with severe mood disorders, aggressiveness, and hyperkinesia in order to verify if the disappearance of these signs could improve contact, communication, and behavioral disorders. Clinical and laboratory factors were investigated to establish when niaprazine can be used as a first-choice drug. Undesirable side effects also were evaluated.

Subjects and Method

This study was carried out on a group of 25 subjects with autistic disorder diagnosed on the basis of *DSM-IV* criteria,[1] admitted to the Department of Child Neurology and Psychiatry of the University of Bologna between January 1996 and September 1997. The group included 23 boys and 2 girls with a mean age of 9 years, 9 months (range, 2 years, 5 months to 20 years, 9 months).

Six patients received previous and concomitant monotherapy, fixed for almost 1 month and for the duration of niaprazine treatment, including haloperidol (1 patient), sodium valproate (2), phenobarbital (2), and carbamazepine (1), respectively. The main criterion of inclusion was the continuous presence for almost 1 year of severe mood disorders, aggressiveness, and hyperkinesia. We excluded all patients with a nosographically defined congenital or acquired encephalopathy, but admitted subjects with slight nonspecific cerebral abnormalities of unknown etiology seen on computed tomographic (CT) scan or magnetic resonance imaging (MRI).

For every subject the following clinical and laboratory data were evaluated: (1) age (over or under 12 years); (2) neurologic examination; (3) mental retardation and its degree of severity (*DSM-IV*)[1]; (4) epilepsy or febrile convulsions; (5) cerebral CT scan or MRI.

Niaprazine was administered in an open trial of 1 mg/kg/day three times daily. Final dose was reached over a period of 15 days to avoid drowsiness.

To assess niaprazine's effects on the basis of parent interview we used the Behavioral Summarized Evaluation scale for autistic disorder,[11] which we modified to include the following 10 signs: tendency to be alone, unstable attention, resistance to change and frustration, mood disorders, mild anxiety signs, autoaggressiveness, heteroaggressiveness, hyperkinesia, stereotyped motor activity, sleep disorders. The intensity of signs was evaluated by a score from 0 to 4: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.

All subjects were observed and submitted to Behavioral Summarized Evaluation before (T^0) niaprazine administration and after 60 days (T^{60}) of treatment. The parents were interviewed at the same times to collect information on the evolution of general behavior and single Behavioral Summarized Evaluation signs.

Statistical analysis was carried out as follows: (1) the Wilcoxon sign rank test was used for each patient to evaluate the overall improvement of all signs between T^0 and T^{60}. All patients with an improvement of signs represented by a statistically significant loss of score were defined as "responders," the others as "nonresponders;" (2) each sign was compared with the same statistical test between T^0 and T^{60} in responders and nonresponders; (3) the influence of age (over or under 12 years), neurologic examination, degree of mental retardation, epilepsy or febrile convulsions, and cerebral CT scan or MRI on the efficacy of treatment of niaprazine was evaluated by the Fisher exact test; (4) Kendall tau test was used to confirm the effect of niaprazine in the whole sample with different degrees of mental retardation. Finally, side effects, heart rate, blood pressure, and laboratory findings regarding liver, kidney, and blood functionality were determined during treatment with niaprazine.

Table 1. Comparison* of Signs at Start and End of Treatment

Signs	*P*
Tendency to be alone	>.05
Unstable attention	<.001
Resistance to change and frustration	<.001
Mood disorders	>.05
Mild anxiety signs	<.05
Autoaggressiveness	>.05
Heteroaggressiveness	<.05
Hyperkinesia	<.00001
Stereotyped motor activity	>.05
Sleep disorders	<.001
Signs considered globally	<.00001

*Wilcoxon sign rank test.

Results

Eight patients were age 12 years or older, and 17 were younger than age 12 years. Neurologic examination showed mild nonspecific signs in 16 (64%) subjects such as hypotonia in 13 (52%), hyperlaxity in 8 (32%), clumsiness in 4 (16%), and macrocrania in 1 (4%); each patient could have more than one sign. All patients had mental retardation: mild in 2 (8%), moderate in 4 (16%), severe in 9 (36%), and profound in 10 (40%). Ten patients had epilepsy, febrile convulsions, or both. CT scan or MRI revealed brain abnormalities in seven (28%) cases, including subcortical atrophy (2), hypoplasia of the cerebellar vermis (2), Arnold-Chiari malformation type 1 (1), focal cortical atrophy (1), and periventricular leukomalacia (1).

At T^0 all 25 patients showed a tendency to be alone, unstable attention, resistance to change and frustration, mild anxiety signs, and hyperkinesia of varying intensity; 24 (96%) cases showed stereotyped motor activity; 21 (84%) had mood disorders; 20 (80%) showed heteroaggressiveness; and 19 (76%) demonstrated autoaggressiveness. In 23 (92%) patients sleep disorders were present: difficulties in falling asleep in 20 (80%) and nocturnal or early awakenings in 11 (44%).

At T^{60} a general evaluation of signs for each patient in relation to niaprazine treatment showed a significant decrease of the Behavioral Summarized Evaluation score ($P < .05$), indicating a clinical improvement in 13 (52%) subjects previously defined as responders and in the other 12 (48%; nonresponders) no significant amelioration. The comparison between T^0 and T^{60} in responders and non-

Table 2. Comparison* Between Responders and Nonresponders in Relation to Clinical and Brain Imaging Findings

Findings	*Responders (n = 13)*	*Nonresponders (n = 12)*	*P*
Age 12 years or older	4 (30.8%)	4 (33.3%)	> .05
Abnormal neurologic examination	8 (61.5%)	8 (66.7%)	> .05
Mild or moderate mental retardation	6 (46.2%)	0	< .05
Epilepsy or febrile convulsions	5 (38.5%)	5 (41.7%)	> .05
Abnormal CT scan or MRI	2 (15.4%)	5 (41.7%)	> .05

*Fisher exact test.
CT = computed tomographic; MRI = magnetic resonance imaging.

responders for each single symptom (Table 1) revealed a statistically significant decrease of score for unstable attention ($P < .001$), resistance to change and frustration ($P < .001$), mild anxiety signs ($P < .05$), heteroaggressiveness ($P < .05$), hyperkinesia ($P < .00001$), and sleep disorders ($P < .001$) (Table 1).

No statistical differences were found for other signs (mood disorders, autoaggressiveness, stereotyped motor activity); however, a reduction of Behavioral Summarized Evaluation score between T^0 and T^{60} was also noted for the latter. A statistical evaluation of the 10 signs considered globally indicated a highly significant improvement at T^{60} ($P < .00001$).

Age (above or below 12 years), the presence of neurologic signs, epilepsy or febrile convulsions, and cerebral lesions detected by CT scan or MRI did not show a statistically significant influence on niaprazine effect in responders or nonresponders. However, mental retardation showed different results: all six patients with mild or moderate mental retardation were responders (Table 2; $P < .05$). The Kendall tau test confirmed a positive correlation between mild or moderate mental retardation and more favorable effects of niaprazine ($\tau = 0.512$; $P < .001$).

All patients completed the niaprazine treatment (T^{60}) without side effects. No changes were observed in heart rate, blood pressure, or laboratory test results. Fifteen patients continued the niaprazine therapy beyond the end of the trial because of its favorable effects on behavior and sleep disorders.

Discussion and Conclusions

At present, no pharmacologic treatments are able to cure autistic disorder because etiologic factors are often unknown and when documented they are disparate and often permanent. For this reason pharmacologic therapies are oriented mainly to improving the signs that increase disability.

Many drugs are employed with this aim including neuroleptics and antidepressants, but these substances are not free of major side effects, so that it is difficult to use them in children.[2,12,13] Also, treatment with vitamin B_6 and magnesium in some cases can reduce hyperkinesia or agitation.[14,15] No study on the use of niaprazine in autistic disorder has yet been reported.

Ceccarelli et al[8] and Ottaviano et al,[10] in double-blind trials versus placebo in children with sleep disorders, stressed a reliable positive effect of niaprazine on the sleep parameters considered.

Besana et al[6] and Franzoni et al,[9] in placebo-controlled double-blind trials, noted that niaprazine was always associated with an improvement, not only of sleep disorders but also of behavior abnormalities. The same results were obtained by Gallet in an open study.[7]

No important side effects were observed in children. In a few patients a moderate diurnal drowsiness occurred, which was eliminated by reducing the daily dosage.[6-9] Even if niaprazine did not change the core symptoms of autistic disorder, in our sample it was effective in 52% of cases, particularly on hyperkinesia, unstable attention, resistance to change and frustration, mild anxiety signs, and heteroaggressiveness. These symptoms hamper the development of residual and potential cognitive and relational abilities of patients with autistic disorder and further compromise patient rehabilitation and integration.

In the same patients niaprazine was also effective on sleep disorders, confirming the hypnoinducing property of the drug reported in the literature.[8,10] Niaprazine was more effective in patients with less severe degrees of mental retardation (mild or moderate). A general improvement in the residual and potential abilities still present in patients with less-severe mental retardation when the described signs are eliminated can favor social integration and rehabilitation.

Niaprazine was equally effective with the same dosage in children and adolescents. The presence of neurologic signs, epilepsy, or cerebral lesions did not influence the efficacy of treatment. Another important quality of niaprazine is its good tolerability. In fact, no side effects were observed during or at the end of the trial.

All patients concluded the trial and 60% continued the treatment. Niaprazine therefore can be considered a first-choice drug for the sedative treatment of children and adolescents with autistic disorder, showing particular efficacy on hyperkinesia, unstable attention, resistance to change and frustration, mild anxiety signs, heteroaggressiveness, and sleep disorders. However, it is advisable to administer niaprazine in gradually increasing doses, reaching the maximum over a 15-day timespan to avoid drowsiness.

With this medication regimen, the possibility of performing rehabilitation and pedagogic intervention with higher intensity and a longer duration will improve the cognitive and relational capacities of patients.

It will be useful in the future to perform long-term follow-up studies to establish whether the maintenance of niaprazine treatment further improves the safety and social integration of subjects with autistic disorder.

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Rett Syndrome: Photographic Evidence of Rapid Regression

ABSTRACT

Rett Syndrome is known to occur in females, around the second year, with loss of hand use, onset of stereotypes and acquired microcephaly. Such regression is often very rapid, but this has never been documented. In one of our patients, photographs taken at different times clearly demonstrate the rapid progression of first symptoms. Moreover, in the present case, the occurrence of a febrile illness, which preceded the onset of the neurological picture, support the hypothesis that environmental factors may trigger the onset of Rett Syndrome in genetically predisposed subjects. (*J Child Neurol* 1999;14:550–552).

Rett syndrome continues to be an incompletely understood disease and the diagnosis is still based solely on clinical signs. It has been identified in female patients of all ages. Its most characteristic signs are acquired microcephaly, hand apraxia, ad the onset of

Figure 1. The patient on her second birthday.