Tiagabine Appears Not to Be Efficacious in the Treatment of Acute Mania

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Background: Because a GABAergic hypofunction has been implied in the pathophysiology of mania, we have tested the antimanic properties of the GABA transporter 1 inhibitor tiagabine.

Method: An open trial was conducted in 8 acutely manic inpatients with DSM-IV bipolar I disorder, 2 of them with tiagabine monotherapy and 6 with tiagabine as an add-on to previously insufficient mood-stabilizing medication. The study duration was 14 days. Changes in psychopathology were assessed by the Bech-Rafaelsen Mania Rating Scale.

Results: None of the patients showed clear-cut relief from manic symptoms during the 2-week observation period. In 2 patients, we saw pronounced side effects (nausea and vomiting in one and a generalized tonic-clonic seizure in the other).

Conclusion: The results from this open trial suggest that tiagabine seems to have no pronounced antimanic efficacy compared with standard treatments such as valproate, lithium, or neuroleptics. It also appears that rapid dosage increases for antimanic treatment can cause potentially severe side effects.

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GABAergic hypofunction has been implicated as a central pathophysiologic disturbance in bipolar disorder, especially acute mania.[1,2] This theory has been supported by the findings of decreased GABA levels in the cerebrospinal fluid of acutely manic patients,[2] as well as depressed patients.[3] One of the first findings on the mechanism of action of valproate was its ability to increase GABAergic transmission in the frontal cortex,[4] and its antimanic properties were thus attributed to this finding. Consequently, anticonvulsants that act on the GABAergic system were then considered for screening of antimanic properties.

The new antiepileptic drug tiagabine, (-)-(R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride, exerts its action by inhibiting GABA reuptake from the synaptic cleft.[5,6] Furthermore, tiagabine has demonstrated an antikindling potency,[7] which makes it a candidate for being potentially effective in bipolar disorder.[8] On the other hand, tiagabine is also capable of inducing cortical depolarizations in an in vitro slice preparation of rats,[9] presumably by increasing the level of excitatory amino acids, which, in turn, may counteract an increase in GABAergic transmission. This can paradoxically increase the risk of seizures, and, in fact, increased seizure frequencies have been observed in epileptic patients taking some anticonvulsants.[10] Tiagabine has recently been released for adjunctive use in partial seizures in the United States and several European countries. Since we still face the situation in the treatment of mania where any given drug is efficacious only in approximately 60% of all manic patients,[11] a major need still exists to expand our possibilities of treatment. Therefore, we conducted this open trial in 8 acutely manic inpatients to test tiagabine's antimanic potency.

METHOD

Eight patients of both genders (4 men, 4 women) and aged 29 to 45 years (mean ± SD = 35.9 ± 5.1 years) were recruited from inpatients of the admission wards of the Departments of Psychiatry at Munich and Freiburg, Germany. Inclusion criterion was the diagnosis of a bipolar I disorder with an acute manic episode as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[12] (DSM-IV 296.0x, 4x, or 6x). The diagnosis was based on a clinical interview. The manic syndrome was considered moderate in 5 patients (Bech-Rafaelsen Mania Rating Scale[13] [BRMAS] score ≤ 30) and severe in 3 patients (BRMAS score > 30). None of the patients had previously displayed a rapid-cycling pattern. Exclusion criteria were concomitant medical illnesses, especially hints of a neurologic disease; a history of allergic

Table 1. Demographic Characteristics of Patients With Bipolar I Disorder and Their Pre-Tiagabine Treatment[a]

Patient No.	Sex	Age	No. of Episodes, Manic/Depressed	Pre-Tiagabine Treatment
1	M	30	6/4 in the last 3 years	Valproate, 2500 mg/d
2	F	45	3/8 in the last 15 years	Clonazepam, 4 mg/d
3	M	34	2/0 in the last 6 years	None
4	F	37	4/3 in the last 17 years	Lithium, 1350 mg/d; haloperidol, 20 mg/d; perazine, 600 mg/d
5	F	29	3/0 in the last 2 years	Risperidone, 2 mg/d; levomepromazine, 100 mg/d
6	M	37	4/2 in the last 15 years	Haloperidol, 2 mg/d; perazine, 200 mg/d
7[b]	F	39	4/3 in the last 8 years	Perazine, 175 mg/d
8	M	36	7/7 in the last 13 years	Haloperidol, 10 mg/d; levomepromazine, 50 mg/d

[a]Bipolar I disorder diagnosed according to DSM-IV 296.0x, 4x, or 6x.
[b]This patient was diagnosed with bipolar I disorder, mixed episode.

reaction to tiagabine or related substances; inability to give informed consent; and age below 18 or above 65 years. These criteria were checked by a thorough medical examination including electroencephalograms (EEGs), electrocardiograms (ECGs), and blood tests.

Except for 1 patient, all patients had previously received a mood-stabilizing treatment for at least 10 days without showing any clinical benefit. In 6 patients, these drugs were kept at the same dosage during the trial with close monitoring of serum concentrations to reduce the chance of effects of dosage adjustments; however, in 1 patient, this treatment was discontinued by the patient's request (patient 5). Thus, 2 of 8 patients had tiagabine monotherapy during the trial. Patient diagnoses, characteristics, and pre-tiagabine treatment are depicted in Table 1. The preset observation period was 2 weeks in each patient, with a possible prolongation if a partial response was observed. This duration was chosen because tiagabine in clinical practice would only be considered a real benefit if the latency of antimanic response were in a similar time range as clinical standards, e.g., valproate loading therapy or neuroleptics.[14]

Patients were informed about all procedures and possible side effects. After giving informed written consent, oral tiagabine treatment was started with 20 mg on day 1, and further increased in steps of 5 mg/day when tolerated by the patient (i.e., when side effects were absent), up to a maximum of 40 mg/day in 2 patients. On day 7, plasma drug levels were determined in 5 patients to ensure compliance, with blood drawn 12 hours after the last dose. However, dosage was adapted during the trial in response to clinical efficacy or side effects, not in response to plasma drug levels. The affective symptomatology was rated with the BRMAS on a daily basis at 9 a.m., before the first medication of the day.

RESULTS

All patients except patients 1 and 3 finished the 14-day observation period. Table 2 shows the individual and mean daily dosage of tiagabine; the corresponding plasma levels of tiagabine, if measured; concomitant treatments, if any; and the results of the BRMAS ratings (for each patient and mean ± SD; mean calculated with last observation carried forward in the dropouts, patients 1 and 3).

Three of 8 patients (patients 5, 6, 8), who had only a moderate manic syndrome, appeared slightly improved. However, none of the severely manic patients (patients 1, 2, 3) seemed to profit from tiagabine. The mean BRMAS score in all 8 patients decreased only from 28.9 to 27 after 2 weeks of treatment. Plasma drug levels were within the range that is currently considered as effective in epileptology.

Side Effects

The most severe side effect, which led to discontinuation after 10 days, occurred in patient 1. He experienced a generalized, tonic-clonic epileptic seizure after receiving 30 mg/day of tiagabine for 3 days, despite concomitant valproate treatment (2500 mg/day in a slow-release formulation). The seizure was witnessed both by a psychiatric nurse and psychiatrist and occurred 2 hours after taking the morning medication (10 mg of tiagabine, 1000 mg of valproate). The seizure was sudden, without aura, and lasted for approximately 3 minutes, with a loss of consciousness and responsiveness to pain, but without fecal or urinary incontinence or tongue lacerations. Afterward, the patient appeared somnolent and confused for another 2 hours, and an EEG recorded 6 hours later still showed a postictal slowing. The patient had retrograde amnesia of the event. He had no previous history of epilepsy, and the magnetic resonance imaging scan gave no hint of an organic genesis. He also had no history of drug or alcohol abuse, nor did he take or discontinue benzodiazepines recently. There were no signs of hepatic dysfunction, which may inhibit tiagabine metabolism,[15] nor did he receive any comedication that is capable of inhibiting cytochrome P450 (CYP) 3A4 and therefore increasing the concentration of tiagabine.[16] After discontinuation of tiagabine, no more seizures or EEG abnormalities were observed.

After initial good tolerance of tiagabine, 1 patient (patient 5) experienced severe nausea and vomiting when the dosage was increased from 30 to 40 mg/day after the end of the observation period. The nausea was reversible after discontinuation.

CONCLUSION

Any conclusions drawn from this trial are clearly limited by its clinically oriented, open nature. Moreover, the

Table 2. Dosage and Plasma Drug Levels of Tiagabine and Treatment Outcome[a]

Patient No.	Tiagabine Dosage, mg/d (day 4)	Plasma Level, ng/mL	Comedication	BRMAS Score Day 0	Day 3	Day 7	Day 10	Day 14
1	30	...	Valproate, 2500 mg/d	39	37	36	37	*
2	30	...	Clonazepam, 4 mg/d	41	39	38	37	38
3	30	...	None	37	36	39	*	*
4	20	70	Lithium, 1350 mg/d	20	23	25	23	23
5	30	120	None	23	14	18	18	18
6	40	142	Haloperidol, 2 mg/d; Perazine, 200 mg/d	25	24	20	20	18
7	25	43	Perazine, 175 mg/d	18	22	15	18	20
8	40	170	Haloperidol, 10 mg/d	28	21	18	20	23
Mean ± SD	30.6 ± 6.8			28.9 ± 9.0	27.0 ± 9.1	26.1 ± 10.0	26.5 ± 9.4	27.0 ± 9.3

[a]Abbreviation: BRMAS = Bech-Rafaelsen Mania Rating Scale. Symbols: ... = not measured, * = dropout; for calculating means, last observation was carried forward.

trial allowed for comedications with potentially antimanic effects after initial loading with 20 mg/day and individual titration of tiagabine. Furthermore, observers were not blind to treatment. However, this constellation usually favors a positive outcome for the substance tested. In our case, none of the patients showed a marked amelioration of manic symptoms during the 2-week observation period.

Two of 3 patients with moderate mania and minor improvement (patients 5, 6, 8) were also taking haloperidol or haloperidol plus perazine which, in our opinion, may have accounted for the slight improvement. Discontinuation of tiagabine after 14 days in patients 6 and 8 (due to lack of efficacy or by patient's choice) and after 3 weeks in patient 5 (due to vomiting) led to no worsening of mania; on the contrary, further gradual improvement continued.

On the other hand, patients 1 and 4 also had no improvement on valproate or lithium treatment during the observation period. From their history, it was known that previous manic episodes were usually long lasting and treatment resistant. Retrospectively, however, all patients included cannot be considered as nonresponsive to antimanic treatment in general, although they did not respond sufficiently to their respective first-line treatment at the time of inclusion in the trial. Continuous treatment with different drugs after finishing this open pilot study led to a complete remission of mania in all patients within 10 weeks.

Recently, Kaufman[17] reported on 3 patients (2 with bipolar disorder, 1 with schizoaffective disorder) receiving low doses (8–12 mg/day) of tiagabine as an add-on therapy to previous unsuccessful treatment with anticonvulsants, atypical neuroleptics, and antidepressants. Two patients were experiencing mixed states with predominantly depressed and psychotic features, and 1 patient had bipolar depression with comorbid attention-deficit disorder. Adding tiagabine led to a marked symptom reduction in 4 to 6 weeks. Considering Kaufman's data with our data, it may be suggested that tiagabine can be of potential use for treating refractory depressive symptoms in bipolar and schizoaffective disorder in which the possibility of slow dose titration and prolonged observation periods is given. However, in states where efficacious treatment depends on a rapid onset of action, such as in severe mania, tiagabine appears insufficient for treatment and may cause potentially dangerous adverse events.

Rapid dosage increase in one of our patients led to a severe side effect, namely, a generalized epileptic seizure. It is known from in vitro observations that tiagabine can induce cortical depolarization waves.[9] The phenomenon of anticonvulsant-induced seizures in epilepsy patients has been described.[10] For tiagabine, cases of nonconvulsive status epilepticus (NCSE) have also been described.[18,19] The product safety database, updated December 1998, includes 13 (of 2531) cases of NCSE, of which 8 had a preexisting spike-wave EEG. However, our observation of provocation of a generalized tonic-clonic seizure by rapid dosage increase of tiagabine in a patient without a history of epilepsy appears unique so far. Besides the rapid dosage increase, drug interactions with valproate may play a causative role. The seizure occurred at a time when peak concentrations both of tiagabine and valproate can be expected. Valproate is metabolized primarily by β-oxidation and only a small fraction by the microsomal P450 pathway using CPY2D6. However, since valproate binds extensively to plasma proteins, primarily albumin, it can displace tiagabine from its protein-binding sites and thus increase the free and active tiagabine.

These findings, which do not favor antimanic treatment with the presumably exclusively GABAergic-acting substance tiagabine, raise the general question of the impact of GABA on mania. In addition, it has recently been reported that valproate, which was thought to act mainly on GABA turnover, possibly exerts ameliorating effects on mania through serotonergic action.[20] This is of interest, since clozapine, with its strong impact on serotonergic transmission, appears capable of reducing the expression of GABA-mediated, spontaneous inhibitory potentials in the amygdala, a brain region that is considered crucial in the regulation of mood.[21] Nevertheless, strong antimanic and mood-stabilizing properties of clozapine are well documented.[22,23] Therefore, we suggest that, when selecting substances for screening of antimanic properties, GABAergic transmission should not be the sole focus, but that actions on other systems, especially the serotonergic system, should also be considered.

Drug names: clonazepam (Klonopin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), risperidone (Risperdal), tiagabine (Gabitril).

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