Letters to the Editor

Catastrophic Reactions Induced by Tetrabenazine

Dear Editor:

Tetrabenazine was introduced in 1956 as an antipsychotic. It is currently indicated to treat hyperkinetic movement disorders. It depletes vesicular storage of dopamine (DA), serotonin, and norepinephrine and antagonizes DA postsynaptic receptors (1).

Tetrabenazine induces depression in animal models (2). Depression has also been reported in 15% of patients under tetrabenazine treatment, with anxiety states in more than 10%. These side effects have been described as dose-related and usually abated after discontinuation of the drug (1).

There are no data regarding risk factors for psychiatric side effects with this drug, nor are there any data on the efficacy of antidepressants in treating tetrabenazine-induced anxiodepressive states. Could prophylactic antidepressant treatment prevent their appearance? We describe here 2 cases illustrating psychiatric side effects.

Case Report 1

Mrs H is a 55-year-old secretary. She had Sydenham’s chorea at age 3 years and developed subsequent tics. She suffered from a major depression in 1995, which was treated with sertraline and then venlafaxine 37.5 mg daily. In the neurologist’s opinion, she suffered from Tourette syndrome. He stopped her antidepressant and began treatment with tetrabenazine 25 mg twice daily. After 6 weeks her tics improved, but she began to feel anxious and depressed. She described paralyzing fears that made her unable to do most of her daily activities. She also described somatic worries and intensified agoraphobia. Tetrabenazine was withdrawn and paroxetine 25 mg daily was introduced. It was subsequently stopped because of side effects.

We saw her in psychiatric consultation 1 month after tetrabenazine washout. Because her anxiodepressive state remained unchanged, we introduced citalopram 20 mg daily. At the control visit 1 month later, she appeared less anxious. She described obsessive–compulsive symptoms that had been present for many years but that had clearly been increased by tetrabenazine and concomitant antidepressant withdrawal. We increased citalopram to 40 mg daily and added low-dose risperidone 0.75 mg daily. However, she finally improved only after a few months’ trial of high-dose venlafaxine and continued risperidone treatment.

Case Report 2

The second case is a 40-year-old man with dystonia of the right foot related to a perinatal encephalopathy. After 1 month of tetrabenazine 150 mg daily treatment, he presented with irritability, insomnia, panic attacks, depressive and guilty thoughts, and obsessional ruminations. This state was attributed to tetrabenazine treatment because he had never before reported such symptoms. We stopped tetrabenazine and began treatment with sertraline 50 mg daily. This treatment rapidly alleviated the panic attacks and obsessionality, and his mood improved.

Deficient monoaminergic states have been proposed as pathophysiological mechanisms underlying anxious and depressive disorders. Anxious and depressive symptoms have been linked to noradrenergic and serotonergic dysfunction (3–5). This hypothesis is supported by the efficacy of serotonergic antidepressants in treating anxiety, depression, and obsessive–compulsive disorders (6). The fact that a tryptophan-free diet also exacerbated anxiodepressive states in predisposed patients supports the monoaminergic depletion theory (7).

Our 2 patients had florid psychiatric symptoms precipitated or exacerbated by tetrabenazine (and in the first case, by a concomitant antidepressant withdrawal). We believe tetrabenazine treatment warrants careful psychiatric evaluation and follow-up. The target population for tetrabenazine treatment is probably at risk because of a high comorbid prevalence of psychiatric disorders. Future studies should explore the efficacy of prophylactic or curative antidepressant therapy for anxiodepressive states precipitated by tetrabenazine.

References


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Olanzapine: A Proarrhythmic Drug?

Dear Editor:

A 70-year-old woman presented with an 8-month history of auditory and visual hallucinations that had developed within 4 weeks of beginning carbidopa and levodopa (100 mg and 25 mg) 3 times daily for antiparkinsonian therapy. The patient’s history included parkinsonism for the last 9 years, essential hypertension for the last 4 years (treated with tablet
Enalapril maleate 7.5 mg once daily, bronchial asthma for the last 3 years (treated with inhaled Ipratropium bromide, Salbutamol, and long-acting Theophylline 400 mg once daily), osteoarthritis of the left knee (treated with tablet Tramadol 50 mg 3 times daily), and asymptomatic ventricular premature contractions (no active intervention) for the last 1½ years. Baseline cardiovascular parameters 3 months prior to evaluation were available: heart rate, 88/minute with occasional ectopic beats; blood pressure, 158/94 mm Hg in right upper limb; echocardiography, left ventricular diastolic dysfunction; and Holter, multiple ventricular premature contractions. The baseline ECG recording showed a pulse rate of 81/minute, PR interval of 160 msec, QR of 120 msec, and corrected QT (QTc) of 418 msec. We started her on Olanzapine 2.5 mg (half-tablet) once daily. Follow-up at 1 week showed improvement in her psychotic features. An ECG recording showed a pulse rate of 107/minute, PR interval of 160 msec, QR of 100 msec, and QTc of 428 msec. Olanzapine was immediately discontinued; all other treatment parameters were unchanged. A repeat ECG recorded 2 days after discontinuation showed pulse rate of 115/minute, PR interval of 200 msec, QR of 80 msec, and QTc of 444 msec. A final ECG, recorded 1 week after discontinuation (to ensure complete washout of olanzapine from her body), showed pulse rate of 100/minute, PR interval of 160 msec, QR of 72 msec, and QTc of 413 msec.

Recently, an increasing number of non-cardiac drugs have been reported to be associated with QT interval prolongation and torsades de pointes (1). The degree of QT interval prolongation increases in the presence of organic heart disease and sinus bradycardia, especially in female subjects (1). Among noncardiac drugs, new (atypical) antipsychotics can cause QT interval prolongation and potentially fatal arrhythmias (2). Sertindole (1) and risperidone (3) have been implicated to a greater degree than have clozapine or olanzapine. However, animal models have suggested that all atypical antipsychotics, including olanzapine, prolong QT interval in a concentration-dependent manner (4). Our case demonstrates a temporal relation of QT prolongation (although in the normal range) with initiation of olanzapine and reversal of this QTc prolongation to baseline level on washout of olanzapine from the body.

One may argue that the ECG recording made just prior to discontinuation of olanzapine showed less prolongation of QTc interval, compared with the ECG recording on day 2 of discontinuation. This can be explained by olanzapine’s pharmacokinetic profile (that is, its half-life of approximately 30 hours). Additionally, with regard to effects on the cardiovascular system, the patient’s relatively long-term concomitant use of multiple other medicines is not associated with any significant pharmacokinetic or pharmacodynamic interactions with olanzapine (5). Owing to ethical issues and because informed consent was not available, we did not attempt rechallenge.

Hence, based on the available information, it can be theorized that olanzapine led to QTc interval prolongation in an elderly woman with preexisting heart disease; that is, olanzapine can be a proarrhythmic noncardiac agent. We recommend that atypical antipsychotics, including olanzapine, should be initiated with caution and with careful monitoring of the cardiac parameters in elderly patients.

References

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Respiratory Symptoms in Nocturnal Panic Attacks

Dear Editor:

There is a connection between respiratory system dysfunction and panic disorder (1). Subjects with panic disorder and respiratory problems appear as a distinct subtype: nocturnal panic attacks present with a closer relation to the respiratory system (2). We describe 2 clinical cases of panic disorders (diagnosed according to DSM-IV criteria) with prominent respiratory symptoms during nocturnal panic attacks. Both were treated at the Laboratory of Panic and Respiration, Institute of Psychiatry, Federal University of Rio de Janeiro.

Case Report 1

Ms A is a 42-year-old Caucasian who, while awake, had spontaneous attacks with palpitations, shortness of breath, choking, chest pain, dizziness, and fear of losing control. All laboratory tests were within the normal range. She then developed panic attacks during sleep that were associated with her waking attacks. Her nocturnal panic attacks were more intense, occurred every night, and were accompanied by prominent respiratory symptoms (that is, shortness of breath, chest pain, tingling, severe choking, and fear of losing control and dying). An agoraphobic pattern developed, and she could only sleep seated. She presented an intense anticipatory anxiety at nightfall. Her waking panic attacks changed from a spontaneous pattern to situational attacks with nausea, diarrhoea, dizziness, and tachycardia.

She was initially treated with nortriptyline 10 mg daily. At the dosage of 75 mg daily, her nocturnal panic attacks re-mitted, but she was still presenting...
limited symptom attacks. At 100 mg daily, her panic attacks fully remitted.

Case Report 2

Mr BN is a 24-year-old Caucasian with a chief complaint of choking and shortness of breath while sleeping. He presented panic attacks during sleep, with shortness of breath, chest pain, dyspnea, choking, paresthesias, sweating, tachycardia, and severe fear of dying. His laboratory tests were within normal limits. His clinical picture was marked by intense fear of having a panic attack while sleeping. He developed an avoidant pattern of falling asleep while working at his usual daily activities during the night. A diurnal drowsiness resulted in difficulty in maintaining concentration.

We instituted treatment with nortriptyline, with a gradual increase of the dosage. At 20 mg daily, the patient experienced a lessening in the frequency and intensity of his panic attacks, and the respiratory symptoms remitted. A complete remission of the panic attacks, agoraphobia, and anticipatory anxiety was achieved at 75 mg daily, and the patient has been without any panic attacks at 1-year follow-up.

Nocturnal panic attacks are common and often neglected. These case reports suggest major findings in regard to them: 1) the prominent respiratory symptoms; 2) the overlapping with sleep disorders symptoms; and 3) a change in the pattern of diurnal panic attacks, from spontaneous situational. A hypothesis to account of diurnal panic attacks, from spontaneous situations, respiratory symptoms; 2) a change in the pattern of diurnal panic attacks, from spontaneous situational

The test was double-blind, and 2 mixtures were used: 1) 35% CO₂ and 65% O₂, and 2) 100% atmospheric compressed air, given 20 minutes apart. Participants were asked to exhale as fully as possible, place the mask on their face, and take a fast, vital-capacity breath, inhaling either the 35% CO₂ mixture or the atmospheric compressed air. They were asked to hold their breath for 8 seconds. Immediately after, they were asked to repeat the fast, vital-capacity breath and hold it again for 8 seconds. After 20 minutes, this test was repeated with the other gas mixture. We repeated the tests in 2 weeks. During that time, no participants received any psychotropic drugs.

We defined a CO₂-induced panic attack as follows: 1) 4 or more DSM-IV panic attack symptoms, 2) at least 1 DSM-IV cognitive symptom (for example, fear of dying or losing control), 3) the sensation of a spontaneous panic attack, and 4) agreement of 2 investigators. To compare the differences between the presence of panic attacks after CO₂ challenge, we used Fisher’s exact test.

The patients were 12 women and 8 men with a mean (SD) age of 35.8 (6.9) years. In the respiratory subtype there were 6 women and 5 men with a mean (SD) age of 33.4 (9.8) years, and in the nonrespiratory subtype there were 6 women and 3 men with a mean (SD) age of 37.8 (4.3) years. There was no difference between the 2 groups in mean age (t-test, P = 0.677).

In the first CO₂ challenge test, 7/11 (63.6%) respiratory PD patients and 3/9 (33.3%) nonrespiratory PD patients had a panic attack (Fisher’s exact test, P = 0.024). In the second CO₂ challenge (after 2 weeks), 9/11 (81.8%) respiratory PD patients and 3/9 (33.3%) nonrespiratory PD patients had a panic attack (Fisher’s exact test, P = 0.011). No patient had a panic attack with atmospheric air.

Our results are similar to those of Biber and Alkin (1). Klein’s theory (3) could explain why the respiratory panic subtype

References


Carbon Dioxide Test in Respiratory Panic Disorder Subtype

Dear Editor:

Inhaling high concentrations of carbon dioxide (CO₂) has consistently been shown to provoke panic attacks in patients with panic disorder (PD) (1). Our objective was to verify the sensitivity to CO₂ challenge of PD patients with respiratory and nonrespiratory subtypes. We randomly selected 20 PD patients (diagnosed according to DSM-IV criteria) at the Laboratory of Panic and Respiration in Rio de Janeiro. The subjects signed a voluntary written informed consent, and the protocol was approved by our local ethic committee.

To participate, we required the subjects to be at least 18 years old, to report at least 3 panic attacks in the last 2 weeks, and to be free of psychotropic drugs for at least 1 week. Exclusion criteria were any other current mental or major medical disorders, pregnancy, and substance abuse within the prior 6 months. We assessed the clinical symptoms of the most severe recent panic attack before the initial test to classify the subjects as respiratory and nonrespiratory subtypes (2).

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patients had higher rates of panic attacks than those of the nonrespiratory subtype, indicating greater sensitivity to CO2. The characterization of PD subtypes through CO2 challenge may be useful in elucidating the biological features, course, and response to treatment of PD.

References

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Depression in Multiple Sclerosis Associated With Interferon Beta-1a (Rebif)

Dear Editor:

The lifetime risk of depression in those with multiple sclerosis (MS) is very high, with some estimates exceeding 50% (1). In initial trials of interferon beta-1b, there were several suicide attempts and 1 completed suicide, compared with no suicides in the placebo group (2). Since that time, there has been concern that interferon treatment can cause depressive symptoms, and the product monograph suggests that patients treated with interferon beta-1b be “informed that depression and suicidal ideation may be a side effect of treatment” (3). Some recent studies have not confirmed this association. The following case suggests a causal link between interferon beta-1a treatment of MS and major depressive disorder.

Case Report
A 42-year-old Caucasian woman diagnosed in March 2001 with clinically definite relapsing and remitting MS started on interferon beta-1a therapy the same month. The Center for Epidemiological Studies Depression Rating Scale (CES-D) score (4,5), obtained prior to initiation of interferon beta-1a, was 4. A second rating, obtained in September 2001, was 28. The patient described a 5-month history of sustained depressed mood, crying spells, sleep disturbance (early morning awakening), hostility, amotivation, apathy, no libido, poor concentration and short-term memory, and a depressed cognitive shift (that is, feelings of hopelessness and guilt). Regarding psychiatric history, the patient had never seen a psychiatrist or mental health professional prior to the consultation in December 2001. However, she did acknowledge a remote history of bulimia nervosa in her teens. Medical history and family history were not contributory to her depression. The patient was started on citalopram in November 2001, and 6 weeks after initiation of the antidepressant she noticed a decrease in sadness and hostility. Her sleep also improved. A CES-D was repeated in December 2001 and her score was 23.

The 5 point reduction in CES-D scores was modest, but there was a significant clinical reduction in depressive symptomatology, and she was able to continue with interferon beta-1a treatment. It has been shown that patients with MS who have depression often discontinue therapy (6); this patient felt well enough to continue with her prescribed disease-modifying therapy.

An analysis of depression data from the PRISMS clinical trial showed no evidence of increased depressive symptomatology associated with interferon beta-1a (the median change in CES-D score after 6 months of treatment was 0) (7). While the PRISMS trial provides evidence that depression must be a rare event during interferon treatment, clinicians should maintain an index of suspicion. If significant depressive symptoms arise, pharmacotherapeutic treatment appears to be an option. In our case, there was a beneficial response to selective serotonin reuptake inhibitor (SSRI) therapy (citalopram). Recent studies have shown that prophylactic treatment with paroxetine is an effective strategy to minimize depression induced by treatment with interferon alfa-2b for malignant melanoma (8). It is also evident that swift detection and treatment can reduce the impact of major morbidity associated with MS.

References

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Atypical Antipsychotics and Glycemia: A Case Report

Dear Editor:

Recently, there have been numerous case reports of glucose intolerability and diabetic ketoacidosis (DKA) associated with olanzapine. These cases are confounded by factors such as polypharmacy and comorbid medical illness. We report the case of a young healthy man on olanzapine monotherapy who developed DKA, and hyperglycemia when rechallenged.
Case Report

The patient is a 33-year-old, adopted Aboriginal man with chronic schizophrenia and multiple unsuccessful trials of antipsychotics. He had no history of diabetes. His fasting blood sugar on admission was 6.5 mmol/L. A trial of risperidone was discontinued after 6 weeks, owing to poor response. We initiated olanzapine as monotherapy, titrated to 30 mg daily. He was receiving no other regular medications. The patient was malnourished on admission, weighing 60.7 kg. This increased to 69.7 kg before the onset of DKA. Three months after starting olanzapine, he was noted to be pale and short of breath. Investigation revealed a blood sugar level 37.5 mmol/L, blood pH of 7.05, and urine ketones of 7.8. He was transferred to intensive care with DKA. It was difficult to wean the patient from intravenous insulin until olanzapine was discontinued. His insulin requirements decreased daily until glycemic control was possible with diet.

One month after the episode of DKA, the patient was becoming increasingly psychotic. Olanzapine was restarted, and 2 days later, his blood sugar measurements increased. Olanzapine was discontinued, and 24 hours later, blood sugars normalized. Blood sugar measurements became unstable, and Glyburide (sulfonylureas) 2.5 mg taken orally twice daily was added. An adequate trial of quetiapine yielded limited improvement. A trial of Clozaril (clozapine) was indicated. Two weeks after the initiation of Clozaril, blood sugar increased. Despite an increased dosage of Glyburide, blood sugar measurements continue to be unstable.

A Medline search using the term “olanzapine and diabetes” yielded 4 articles (1–4) and 4 letters (5–8). These reported 10 cases of new-onset diabetes and 8 cases of DKA after the introduction of olanzapine, including 1 death from DKA (3). Previous case reports have several confounding variables, including polypharmacy, obesity, and multiple medical problems. In our case, the patient was slim (body mass index 23), olanzapine was his only regular medication, and he was healthy.

Henderson and others reported a naturalistic study of 82 patients started on clozapine (9). Over the 5 years of the study, 30.5% developed diabetes mellitus (DM), and 1 patient had 2 episodes of DKA. Wirshing and others summarized the case reports of 9 patients in the literature who developed DM or DKA while taking clozapine and described 4 further cases from their own practice (2). Our case demonstrated a particular sensitivity to olanzapine and clozapine, whereas his blood sugar measurements appeared to stabilize while taking risperidone and quetiapine. There are 4 reported cases of risperidone and DM (10,11). There are also currently 2 reported cases of new-onset DM and 1 case of DKA that developed while taking quetiapine (12,13).

Important factors to consider in our case are as follows: 1) the difficulty in normalizing blood sugar after the resolution of DKA, until olanzapine was discontinued; 2) the patient’s decreased need for insulin until blood sugars returned to normal after 1 month; 3) the return of hyperglycemia 48 hours after the reintroduction of olanzapine; 4) the normalizing of blood sugars 24 hours after discontinuing olanzapine; and 5) the reemergence of poor glycemic control after the introduction of clozapine.

This case suggests a link between the use of atypical antipsychotics and glucose intolerance. We believe that recording baseline fasting blood sugar and regular monitoring of blood sugars should be part of routine management for patients on atypical antipsychotics.

References


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Olecranon Bursitis as a Complication of Tardive Dyskinesia

Dear Editor:

Tardive dyskinesia (TD) is associated with numerous complications. Medical complications include disturbances of gait and posture, dysphagia, dysarthria, and loosening of natural and artificial teeth (1). Respiratory irregularities, aspiration pneumonia (2), and rib fractures (3) have also been described. Psychosocial complications include suicide, occupational impairment, social stigmatization (1), and impaired sexual intercourse (4). This report describes an unusual case of olecranon bursitis (OB) as a complication of TD.

A 56-year-old man, treated for refractory schizophrenia since age 19 years, with paranoid delusions, auditory hallucinations, thought disorder, and episodes of...
aggression was managed for many years on fluphenazine decanoate. Subsequently, his daily medication for 6 years consisted of haloperidol 60 mg, chlorpromazine 1250 to 1800 mg, lithium 900 mg, procyclidine 15 mg, and diazepam 20 mg. Because he developed a bluish skin discoloration (5), chlorpromazine was replaced by loxapine 300 mg daily. Other medications remained unchanged. He remained on this combination for 4 years. In December 1997, in addition to his psychosis, he manifested parkinsonism and akathisia. Olanzapine was prescribed and loxapine reduced. In May 2000, he showed prominent TD affecting the extremities and, to a lesser degree, the buccal-oral region. When seated, his TD arm movements resulted in his rubbing both elbows against the arms of the chair.

At the end of July, he presented to the emergency room with a swollen, red, painful left elbow and lesser involvement of the right elbow. There were abrasions over both elbows and his white cell count was elevated. A tentative diagnosis of septic OB was made. The left elbow was drained, and he was treated with oral cephalaxin. The fluid showed an increase in neutrophils but no bacterial growth. His daily psychiatric medication at this time consisted of loxapine 50 mg, olanzapine 20 mg, procyclidine 15 mg, and quetiapine 50 mg. He returned 3 days later with persistent symptoms and was admitted for a 2-day course of IV cefazoline, as well as oral antibiotics. The condition improved, but in September 2000 there was persistent swelling, with draining of a yellow, odorless fluid from the left olecranon bursa. Dyskinetic movement of his arms continued, resulting in repeated trauma to the elbows when seated. Because of persistent bursitis, he underwent a bursectomy at the end of October.

Postoperatively, there was incomplete healing with persistent drainage. In December 2000, a culture of the discharge revealed a coagulase-negative staphylococcal infection. Over the ensuing months, he received repeated courses of antibiotics for recurrent infection. The skin over the elbows was noted to be scraped. By the end of September 2001, the wound had healed. His medication at this point was clopioxol depot 250 mg every 2 weeks and daily valproic acid 1500 mg, loxapine 90 mg, procyclidine 10 mg, propranolol 30 mg, and oxazepam 30 mg. The improvement in the wound was associated with a marked decrease in dyskinetic arm movements.

As far as we know, OB as a complication of TD has not been previously described. In a series of 20 patients with septic OB, Ho and others noted that 1 patient had schizophrenia together with diabetes mellitus (6). There was, however, no recent trauma to the elbow. Laupland and others reported that 2/118 patients with septic OB had a comorbid psychiatric illness (type and details not given) (7). Neither report mentioned the presence of TD. In our patient, direct observation of his TD movements and the presence of abrasions over his elbows point to a cause-effect relation between TD, OB, and recurrent infections. His movement disorder also resulted in delayed postoperative healing and recurrent infections that only resolved with lessened TD.

References

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