Mirtazapine and Breast-Feeding

To the Editor: Postpartum depression occurs in approximately 10% of childbearing women, and for many of them, treatment with an antidepressant may be necessary. The benefit of breast-feeding for the infant and the mother is well established; clinicians are therefore asked to make a careful risk-benefit decision on the use of antidepressants. The literature on antidepressants and breast-feeding consists mainly of case series of selective serotonin reuptake inhibitors and tricyclics, whereas information on newer antidepressants is scarce (1). We describe what we believe to be the first reported data on mirtazapine treatment in a breast-feeding woman.

Ms. A, a 27-year-old woman, was admitted to a psychiatric hospital 3 weeks after delivery of her daughter. She was suffering from a severe depressive episode with suicidal thoughts. Ms. A had a history of a first depressive episode at age 18 that was not treated. At the time of admission to the mother-child unit, Ms. A was breast-feeding her child and had so far not received antidepressive treatment. A routine diagnostic assessment, including a physical examination, laboratory studies, and a cerebral computerized tomography scan were normal. Treatment with sertraline, 150 mg/day for 11 weeks, was not effective. Therefore, Ms. A was switched to mirtazapine, 30 mg/day at 9:00 p.m. She fed her infant six times a day. Concentrations of mirtazapine were determined in breast milk and in the serum of mother and infant by using mass spectrometry after Ms. A provided written informed consent and the study was approved by the local ethics committee for measurement of her and her infant’s serum levels of the drug. Samples were taken after reaching steady state before breast-feeding, the first time at 7:00 p.m. (22 hours postdose) and a second time at 12:00 a.m. (15 hours postdose).

At 7:00 p.m., the maternal plasma level of mirtazapine was 7 ng/ml (therapeutic range=5–100 ng/ml); the same level was found in the foremilk (the early portion), whereas in the hindmilk (the later portion), a concentration of 18 ng/ml was detected. On the next day at 12:00 a.m., the maternal plasma concentration was 25 ng/ml; in the foremilk, a concentration of 28 ng/ml and in the hindmilk, 34 ng/ml were found. The infant’s plasma concentration was 0.2 ng/ml. The body weight of the infant was 6.8 kg at this time.

Ms. A was discharged in remission after 6 weeks of mirtazapine treatment. The psychomotor development of the infant was normal, as rated by an experienced neuropsychiatrist. No adverse events related to the mother’s mirtazapine intake could be detected; especially, there was no sedation or abnormal weight gain.

The results of this case report demonstrate that mirtazapine is excreted into the milk of a nursing mother. No accumulation of mirtazapine in the milk was found. Measured serum concentration in the infant was below therapeutic concentration. We would like to add this information to still incomplete evidence on the safety of antidepressants and breast-feeding.

Reference


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Bradycardia at Low Doses of Risperidone

To the Editor: Risperidone is a selective antagonist of dopamine and serotonin receptors and is widely used for the treatment of schizophrenia. The cardiac side effects of risperidone relate to a prolonged QT interval, orthostatic hypotension, and tachycardia. Recently, an article described a case of symptomatic bradycardia secondary to risperidone in a young man undergoing alcoholic withdrawal (1) but only after increases to moderately high levels of risperidone. We describe here the dramatic finding of acute sinus bradycardia with frequent premature ventricular complexes in a pattern of bigeminy in a geriatric patient taking an initial low starting dose of risperidone. He had normal sinus rhythm before the addition, and the bradycardia and ventricular bigeminy resolved after termination of risperidone, suggesting that risperidone was the etiological agent in the arrhythmia.

Mr. A was an 80-year-old widowed white man with a history of coronary artery disease and cerebrovascular disease who was transferred to our clinic from an outside facility for treatment of dementia not otherwise specified. He was originally hospitalized for an inability to care for himself, with confusion, delusions, and poor orientation. At the outside facility, an ECG revealed a normal sinus rhythm at 74 bpm, a P-R interval of 171, a QRS interval of 81 msec, and a QT/QTc of 362/402. His CBC, liver function tests, thyroid function tests, and basic metabolic panel were all normal. Mr. A was not taking any medication initially; during the stay, the following medications were given to him: risperidone, 0.75 mg/day (for agitation and delusions), and donepezil, 10 mg/day. Five days afterward, Mr. A was admitted to our facility, and a diagnosis of dementia not otherwise specified was made. As part of our evaluation, we also performed an ECG and repeated the tests and studies. All laboratory values and studies, including calcium, phosphate, and magnesium were normal, except for borderline diabetes. Of interest was that his ECG now displayed marked sinus bradycardia with frequent premature ventricular contractions in a bigeminy pattern. His ventricular rate, including bigeminy, was 70 bpm. Discounting the confounding premature ventricular contractions, his heart rate was 38 bpm. His P-R interval was 180 msec, his QRS interval was 80 msec, and his QT/QTc was 481/451 msec. Pending evaluation by the cardiology service and because of Mr. A’s increased agitation and delusional status, we increased his risperidone to an oral dose of 1.5 mg at bedtime. Seven days after being admitted to our service and 12 days after drug initiation, we discontinued risperidone. An ECG revealed a normal sinus rhythm, with a rate of 67 bpm within 1 day of discontinuation. Throughout this time, Mr. A reported no syncope or palpitations. All major laboratory values and studies were normal before, during, and after the addition of risperidone.

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Current research suggests that risperidone acts in a fashion similar to a class III antiarrhythmic, causing concentration-dependent blockade of the rapid component of the delayed rectifier K+ current (I_{Kr}) in ventricular monocytes and possibly explaining the QTc prolongation in some patients (2). As an atypical antipsychotic, risperidone is an attractive agent because of the relatively low side effect profile and decreased extrapyramidal effects. However, it is important to note that death secondary to risperidone overdose and symptomatic cardiac side effects have been noted but at moderate to high levels of risperidone (6–24 mg/day) (3). Geriatric patients may be more susceptible to the cardiac side effects of risperidone, perhaps because of cardiac comorbidities or metabolic differences. Although our patient reported no symptoms of syncpe or palpitations, it was difficult to assess his ability to report such symptoms because he was demented. We emphasize that elderly patients like our own, with coronary artery and cerebrovascular disease, require more careful monitoring. Since QTc prolongation and ventricular arrhythmias can potentially result in fatal cardiac processes, we suggest that risperidone use should be monitored with ECG, especially with the elderly, who are more susceptible to decompensation.

References

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Withdrawing Syndrome After Delayed Tramadol Intake

To the Editor: Tramadol is a centrally active synthetic analgesic drug with opioid and nonopioid properties (norepinephrine and serotonin reuptake inhibition). Its widespread use in benign and malignant painful conditions is due to the following: 1) tramadol is a nonscheduled medication, 2) most people are unaware of its opioid nature, 3) its name does not produce “opiophobia” like morphine does, and 4) it is not considered a drug that produces severe adverse effects, dependence, or abuse. However, some studies have reported tramadol abuse, respiratory depression in patients with renal failure, cerebral depression, and even a fatal outcome in association with a benzodiazepine (1, 2).

In patients with or without a history of drug abuse who were treated with tramadol for chronic benign pain, also in therapeutic doses (up until 400 mg/day), dependence and withdrawal syndrome after abrupt discontinuation have been reported (3, 4). Tramadol is the third active principle most frequently involved in withdrawal syndromes (5). We could not locate in the literature any case of withdrawal in cancer patients taking tramadol.

Ms. A was a 51-year-old nonsmoking woman with breast cancer, lung metastases, and brachial plexopathy, with no history of chemical or alcohol dependence. She was referred to the outpatient clinic because of severe pain. She had been taking tramadol for 2 years: 50 mg t.i.d. increasing to 100 mg t.i.d., plus 50 mg intramuscularly as needed. Switching to a strong opioid was proposed, but Ms. A refused for 2 months, notwithstanding her uncontrolled pain, because she said she became very agitated when delaying or skipping the tramadol administration, and she had learned to recognize the onset and then fear this nervousness, which reversed only by taking tramadol.

One day she did not take tramadol twice in a row. After a few hours of having missed the first administration, she became very nervous. Upon missing the second dose, she began to have anxiety, anguish, a feeling of pins and needles all over her body, sweating, and palpitations. She knelt down and rolled on the floor, pressing her hands against her head so as “not to feel and not to understand what was happening” and begged her husband to take her back home immediately so she could have her tramadol dose. When we asked about her pain on that occasion, she replied, “I do not know because I felt too bad.” She described what happened very clearly and with great preoccupation because she felt like a “drug addict,” and when we suggested changing the opioid, she agreed so as not to undergo another similar experience. We stopped tramadol and prescribed oral methadone, 5 mg t.i.d., reducing it to 3 mg t.i.d. after a week, which resulted in analgesic benefit and no adverse effects.

“Physical dependence” is the term used to describe the phenomenon of withdrawal when an opioid is abruptly discontinued. The severity of withdrawal is a function of the patient’s prior opioid exposure. Here we have a case of withdrawal due to physical dependence on tramadol even if no tolerance had developed over 2 years. The patient became nervous and agitated if the tramadol intake was merely delayed. When the patient missed the dose twice in a row, her withdrawal symptoms became severe, with an overwhelming need to take the drug that could appear as psychological dependence.

We believe that 1) patients must be advised to take tramadol regularly and to stop gradually especially after long-term periods, 2) physicians should consider the potential physical dependence when they prescribe tramadol for pain, and 3) any form of “dependence” of cancer patients taking tramadol, however, needs to be further explored. In fact, we are observing some patients who continue to take tramadol in order “to achieve a feeling of well-being,” even though their pain is controlled after disease regression or switching to strong opioids. This may be related to the inhibition of serotonin reuptake of tramadol.

References