Prolactin Elevation With Ziprasidone

TO THE EDITOR: With the exception of risperidone, atypical antipsychotics have been thought to elevate prolactin only transiently (1–3). We report on a 41-year-old woman who developed clinically significant hyperprolactinemia while taking both risperidone and ziprasidone, which resolved with the introduction of quetiapine.

Ms. A had a history of bipolar disorder and developed postpartum psychosis after her first child was born. She responded to lithium and risperidone. After the delivery of a second child while taking lithium, she again required risperidone (1.5 mg/day) for mood instability and obsessive ruminations about harming her baby. She had trace cogwheeling but no other extrapyramidal symptoms. She did not breast-feed, but she was amenorrheic for several months. Her prolactin level was 164.5 ng/ml. Brain magnetic resonance imaging showed no evidence of a pituitary microadenoma. Two weeks after she stopped taking risperidone, her prolactin level returned to normal, and she menstruated 1 week later. Because her ruminations returned, she was given oral ziprasidone, starting at 20 mg b.i.d., increased over 2 weeks to 60 mg b.i.d. for 3 weeks, then lowered to 100 mg at bedtime for 2 weeks because of sedation. Her ruminations disappeared, but she developed 1+ cogwheeling, tremor, and masked facies and did not menstruate; her prolactin level rose to 124 ng/ml.

Ms. A was switched to quetiapine (400 mg/day) with resolution of extrapyramidal symptoms and a decrease in her prolactin level to 8.2 ng/ml. Her menses resumed within 3 weeks of stopping ziprasidone and remained regular for at least a year. Her prolactin level remained normal.

To our knowledge, this is the second case documenting clinically significant hyperprolactinemia with ziprasidone (4). Our patient concurrently had extrapyramidal symptoms, implying dopamine D_2 receptor antagonism in the nigrostriatal and tuberoinfundibular tracts (1). Quetiapine did not produce either side effect, consistent with its relatively weak and transient binding at D_2 receptors compared to risperidone and ziprasidone and its tolerance in patients with Parkinson's disease (1, 5).

Although a case report showed reversal of risperidone-induced hyperprolactinemia upon switching to ziprasidone, our findings illustrate the potential of ziprasidone at average doses to cause clinically significant hyperprolactinemia (6). Of note, the only symptom of hyperprolactinemia in men may be sexual dysfunction (1).

References

1. Maguire GA: Prolactin elevation with antipsychotic medications: mechanisms of action and clinical consequences. J Clin Psychiatry 2002; 63(suppl 4):56–62
2. Bench CJ, Lammertsma AA, Grasby PM, Dolan RJ, Warrington SJ, Boyce M, Gunn KP, Brannick LY, Frackowiak RS: The time course of binding to striatal dopamine D2 receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by positron emission tomography. Psychopharmacology (Berl) 1996; 124:141–147
3. Miceli JJ, Wilner KD, Hansen RA, Johnson AC, Apseloff G, Gerber N: Single and multiple-dose pharmacokinetics of ziprasidone under non-fasting conditions in healthy male volunteers. Br J Clin Pharmacol 2000; 49(suppl 1):5S–13S
4. Jordan MP: Ziprasidone-associated galactorrhea in a female teenager. J Am Acad Child Adolesc Psychiatry 2003; 42:4–5
5. Friedman JH, Fernandez HH: Atypical antipsychotics in Parkinson-sensitive populations. J Geriatr Psychiatry Neurol 2002; 15: 156–170
6. Kunwar AR, Megna JL, Gorman JM: Ziprasidone substitution in a patient with risperidone-induced hyperprolactinemia. J Psychiatr Pract 2003; 9:245–247

SHARI I. LUSSKIN, M.D.
ROBERT CANCRO, M.D.
LINDA CHUANG, M.D.
JESSICA JACOBSON
New York, N.Y.

Clozapine and Typical Antipsychotics

TO THE EDITOR: Margaret G. Woerner, Ph.D., and colleagues reported the interesting observation that clozapine, in comparison with fluphenazine, was similarly efficacious for new-onset patients with schizophrenia or schizoaffective disorder (1). These results were similar to a recent study by Lieberman et al., which they referenced. They also pointed out that these results stand in contrast to the comparisons between clozapine and typical antipsychotics in treatment-resistant patients, which have found that clozapine results in dramatically higher response rates.

Although the lack of an advantage for clozapine in new-onset patients may be disappointing, these studies raise an interesting question: why is clozapine, compared with typical antipsychotics, dramatically more efficacious for treatment-resistant psychosis but merely similarly efficacious for new-onset schizophrenia? We would like to propose an answer to this question.

It long has been thought that patients taking long-term neuroleptic medication experience upregulation of dopamine D_2 receptors in their brains. For example, dopaminergic upregulation in the nigrostriatal tracts is thought to underlie the pathophysiology of tardive dyskinesia, and there now is long-awaited human data to support this idea (2). Typical antipsychotics may cause the upregulation because they dissociate slowly from the D_2 receptor (3), and the neurons respond by trying to overcome the chronic blockade. In contrast, clozapine, which is a fast dissociator (3), may allow endogenous dopamine to activate the receptor enough to avoid the problem of upregulation.

In addition to dopaminergic upregulation in the nigrostriatal tracts, many investigators have suggested that dopaminergic upregulation may occur in mesolimbic or mesocortical tracts, leading to a worsening of psychosis beyond the original level. This phenomenon has been called "tardive psychosis" or "supersensitivity psychosis" (4). Because increasing the dose of the neuroleptic eventually will make the problem worse, tardive psychosis may be a major form of treatment-resistant psychosis. Although not proven, the concept of tardive psychosis may provide heuristic value for understanding the effects of antipsychotic medication.

Clozapine, in comparison with typical antipsychotics, may be more efficacious for treatment-resistant psychosis because it allows the reversal of the dopaminergic upregulation