Low-Dose Amisulpride and Elevation in Serum Prolactin

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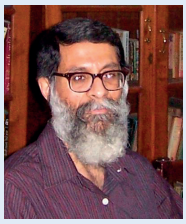

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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Clinical Question

At low doses, substituted benzamides such as sulpiride, levosulpiride, and amisulpride preferentially block the higher affinity dopamine autoreceptors that are located on the presynaptic neuron[1,2]; this results in increased release of dopamine,[1,2] an effect that is useful for the treatment of depression,[3] somatoform disorders,[4] and negative symptoms of schizophrenia.[3] At high doses, these drugs also block the lower affinity dopamine postsynaptic receptors,[1,2] effectively ameliorating positive symptoms of schizophrenia.[5] Given that dopamine inhibits the release of prolactin, would low doses of these drugs lower serum prolactin and high doses lead to hyperprolactinemia?

High and Low Doses of These Drugs Both Increase Serum Prolactin

Curiously, even though low and high doses of these substituted benzamides have opposite dopaminergic effects in the brain, both low and high doses increase serum prolactin. For example, high doses of these drugs are used for the treatment of psychosis, and the resultant hyperprolactinemia and its consequences are well-recognized adverse effects.[1,4] And, when low doses of these drugs are used for depression, negative symptoms of schizophrenia, or other indications, hyperprolactinemia is again observed.[6–11]

In a recent study, for example, Lee et al[11] found that the mean serum prolactin level was clinically elevated at 76.1 ng/mL in (mostly) young men (n = 12) and women (n = 8) who were receiving low-dose amisulpride for different indications. The dose of amisulpride was 300 mg/d in 2 patients and 100–200 mg/d in the remaining patients. The duration of treatment ranged from 1 week to more than 2 years. No patient was receiving any other medication that could explain the prolactin elevation. Even within this low dose range, higher doses of amisulpride were associated with significantly higher serum prolactin levels. The hyperprolactinemia was more marked in women (mean level = 110.7 ng/mL) than in men (mean level = 53.1 ng/mL) despite comparable amisulpride dosing (mean doses, 200 mg/d vs 188 mg/d, respectively).

These findings are in conformity with the scientific literature. For example, other authors[8,10] have reported prolactin elevation with low-dose amisulpride. Prolactin elevation has also been reported with low doses of sulpiride[9,12] and levosulpiride.[7] Finally, dose-dependent prolactin elevation and greater prolactin elevation in women than in men has been described with other antipsychotic drugs, such as paliperidone, as well.[13]

Reason Why Even Low Doses of These Drugs Increase Serum Prolactin

These drugs penetrate the blood-brain barrier poorly and therefore achieve lower concentrations inside the brain than outside it.[14] The pituitary is located outside the blood-brain barrier; so, what constitutes low-dose amisulpride in the brain might effectively be high-dose amisulpride outside the brain, as in the pituitary. Such an uncoupling or dissociation in the magnitude of amisulpride activity between the striatum

- At low doses, substituted benzamides such as sulpiride, levosulpiride, and amisulpride *increase* dopaminergic neurotransmission in the brain by preferentially blocking the higher affinity presynaptic dopamine autoreceptors. At high doses, these drugs *decrease* dopaminergic neurotransmission in the brain by also blocking the lower affinity dopamine postsynaptic receptors.
- Both low and high doses raise serum prolactin levels.
- This article discusses the reason for the absence of a biphasic effect on prolactin. Strategies are suggested for managing hyperprolactinemia associated with low-dose substituted benzamides.

and the pituitary has been demonstrated in animals[14] as well as humans.[15]

Expressed otherwise, a 100-mg dose of amisulpride may achieve concentrations in the brain that are too low to do anything more than block the high-affinity dopamine autoreceptors, thereby increasing dopaminergic neurotransmission. However, the same dose may achieve sufficient concentrations outside the blood-brain barrier, such as in the pituitary, to efficiently block the dopamine receptors there, thus raising serum prolactin.

Clinical Consequences of Hyperprolactinemia

The hyperprolactinemia induced by dopamine receptor antagonists may be therapeutically exploited, such as to induce lactation in nonlactating women after childbirth; for example, low doses of sulpiride have been used for this indication.[12,16] Hyperprolactinemia, however, more usually causes adverse effects such as decreased libido (and its consequences), amenorrhea and infertility, breast engorgement and lactation, and gynecomastia. Hyperprolactinemia may also be associated with reduced bone mineral density, especially in women. Finally, hyperprolactinemia may rarely be associated with breast cancer and pituitary tumors.[17–20]

Management

Regardless of dose, sulpiride, levosulpiride, and amisulpride should be used with caution or not at all in patients who are at risk of or already have conditions that might be aggravated by prolactin elevation. Examples of such patients are women with preexisting menstrual irregularities, women who are trying to conceive, and persons with prolactin-dependent tumors. Other patients at risk of prolactin-related adverse effects are women who are postmenopausal and at risk of osteoporosis and those who already have osteoporosis.

In such patients, if a substituted benzamide drug is considered necessary, a baseline prolactin level may be desirable to guide the interpretation of levels obtained after the initiation of therapy. In other patients, it may suffice to assess prolactin levels only if problems that are possibly prolactin-related emerge, because patients with hyperprolactinemia do not necessarily experience adverse effects related to the condition, as clinical trial data show.[13]

There are few ways to address clinically significant hyperprolactinemia that arises from the use of low-dose substituted benzamide drugs. Switching to prolactin-sparing antipsychotics such as aripiprazole[21,22] will not help, because other antipsychotics, even those that are prolactin-sparing, are not prescribed for the same indications as low doses of substituted benzamides. For the same reason, aripiprazole augmentation[23,24] is unlikely to be a viable strategy. Using dopamine agonists such as bromocriptine[25] would probably be only a temporary expedient and not a long-term solution because it could worsen psychosis.[26]

Decreasing the dose of medication is a possibility, given that Lee et al[11] found that lower doses of amisulpride occasioned less hyperprolactinemia; the risk, of course, is that lowering already low doses of a drug may compromise the efficacy of the drug. Hormone replacement[26] may be attempted if the drug responsible for prolactin elevation clearly benefits the patient and if suitable alternatives are unavailable. In the worst-case scenario, in which the adverse consequences of unresolved hyperprolactinemia outweigh the observed benefits of treatment, the drug is best discontinued.

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