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What does antipsychotic-associated hypoprolactinemia mean in patients with chronic schizophrenia?

Takahiko Nagamine, M.D., Ph.D.

Division of Psychiatric Internal Medicine, Seiwakai-Kitsunan Hospital, Yamaguchi, Japan

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Hyperprolactinemia is a common side effect in patients receiving antipsychotics, but little is known about hypoprolactinemia associated with antipsychotic treatments. During the six-year period from July 2005 to Jun 2011, 304 patients underwent prolactin (PRL) measurements at our facility for some reason during oral antipsychotic therapy. The serum PRL levels were PRL > 30 ng/mL in 203 cases, 3 ng/mL < PRL ≤ 30 ng/mL in 77 cases and PRL ≤ 3 ng/mL in 24 cases. Some patients on antipsychotics exhibited severe hypoprolactinemia.

In the 24 patients with PRL ≤ 3 ng/mL, we retrospectively analyzed their gender, age, duration of illness, types and doses of antipsychotics and reasons for undergoing PRL measurement. These 24 patients consisted of 15 males and 9 females, all of whom were patients with schizophrenia. Their ages ranged from 24 to 78 years (mean ± SD: 49.2 ± 16.5 years), and their durations of illness ranged from 4 to 51 years (27.3 ± 18.9 years). Their serum PRL levels ranged from 0.1 to 3.0 ng/mL (1.7 ± 1.6 ng/mL). The antipsychotic used in all 24 patients was aripiprazole (alone), at dosages ranging from 12 to 30 mg/day (21.1 ± 10.1 mg/day). Twenty-one of the patients had been receiving one or more antipsychotics before switching to aripiprazole (number of antipsychotic drugs used: 2.1 ± 1.3), at total doses ranging from 750 to 2200 mg/day chlorpromazine equivalents (1380 ± 731 mg/day). The types of previous antipsychotic medications before switching to aripiprazole were: conventional antipsychotic monotherapy (4 patients); atypical antipsychotic monotherapy (3 patients); combinations of conventional antipsychotics (6 patients); atypical antipsychotics (3 patients); and conventional plus atypical antipsychotics (5 patients). The period required to completely switch to aripiprazole ranged from 2 to 12 weeks (5.1 ± 4.5 weeks), and the duration of aripiprazole administration at the time of PRL measurement ranged from 6 to 24 weeks (13.2 ± 8.7 weeks).

The reasons for measuring PRL were: in 22 patients, aggravated psychotic symptoms, such as agitation, suspiciousness, delusions, and hallucinations; in 10 patients, akathisia; in 6 patients, hypersexuality; and, in 4 patients, self-mutilating behavior. These results indicate that switching to aripiprazole is a major risk factor for hypoprolactinemia, and the risk is higher when accompanied by the long-term use of multiple antipsychotics.

There are no reports that link hypoprolactinemia directly to aggravated psychotic symptoms or akathisia. According to one previous report about the correlation between the serum PRL level and psychopathology, the serum PRL level does not correlate to the severity or psychopathology of schizophrenia [1]. It is not uncommon for decreased serum PRL levels to be observed in well-controlled patients in the clinical setting, especially those receiving aripiprazole monotherapy.

First, hypoprolactinemia has to be acknowledged as a direct effect of aripiprazole, a dopamine agonist, on the tuberoinfundibular system, irrespective of its therapeutic effects for schizophrenia. In such situations, gradually switching from a dopamine antagonist to a partial agonist is advisable, because long-term exposure to dopamine antagonists may

Corresponding Author: Takahiko Nagamine, M.D., Ph.D., Division of Psychiatric Internal Medicine, Seiwakai-Kitsunan Hospital, 3381 Suzenji, Yamaguchi-shi, Yamaguchi-ken, 747-1221, Japan
e-mail: anagamine@ybb.ne.jp

have already resulted in denervation supersensitivity in dopamine receptors. However, the average period over which patients switched drugs in this study was rather short, so the deterioration in psychotic symptoms might have at least partly resulted from problems with the switching process.

In this study, however, some patients exhibited aggravated psychotic symptoms and hypoprolactinemia even after sufficiently long switching periods. Furthermore, these psychotic symptoms in patients with hypoprolactinemia are similar to those of supersensitivity psychosis, because an association between the sudden worsening of psychotic symptoms and akathisia was observed [2][3]. Second, both aggravated psychotic symptoms and hypoprolactinemia may have often resulted from hypersensitivity to a dopamine agonist under up-regulated dopamine receptors, followed by long-term dopamine receptor antagonism.

Most individuals with schizophrenia or ARMS (at risk mental state for psychosis) are sensitive to dopamine [4]. The dopamine receptor has high- and low-affinity states [5]. The D2High state is functional for dopamine or dopamine-like agonists. Although antipsychotics alleviate psychosis and reverse the elevation of D2High receptors, long-term use of antipsychotics can further enhance dopamine supersensitivity [5][6]. Experimentally, dopamine supersensitivity occurs after the long-term use of antipsychotics [7]. Animal models of psychosis show that a variety of genetic and non-genetic risk factors are associated with behavioral supersensitivity to dopamine, reflecting elevated levels of dopamine D2High receptors [7]. Aripiprazole is a partial agonist that exerts intrinsic activity on dopamine D2 receptors. Therefore, switching from antagonistic antipsychotics to agonist antipsychotics can result in the emergence of both psychotic symptoms and hypoprolactinemia.

Aripiprazole-induced severe hypoprolactinemia may be a sign of supersensitivity to dopamine in some patients with chronic schizophrenia. To prove this hypothesis, however, an association between serum PRL levels and clinical response in a larger number of patients switched to aripiprazole from long-term dopamine antagonists will be objectively investigated.

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