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Aripiprazole and Haloperidol: Beneficial Combination Antipsychotic Therapy for a Schizophrenic Patient

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Abstract

Objective:
Schizophrenia is a chronic disease that is treated with dopamine antagonists. These drugs can produce intolerable side effects through their blockade of central nervous system dopamine receptors unrelated to schizophrenia. The atypical antipsychotic aripiprazole, a dopamine receptor partial agonist, has mixed agonist-antagonist effects. Its partial agonism is said to protect the patient from the side effects caused by full antagonists at the same time that its antagonism treats the schizophrenia effectively.

Case:
We report a case in which a low dose of the full antagonist haloperidol, added to aripiprazole, improved antipsychotic efficacy in a 41-year-old man diagnosed with undifferentiated schizophrenia.

Result:
A 15-mg/d aripiprazole/7.5-mg/d haloperidol regime in this patient improved all previous psychotic symptoms and caused no adverse side effects. The patient's final prolactin concentration using this combination was normal.

Conclusion:
Further studies are warranted to confirm this observation and to determine the mechanism through which a carefully titrated combination of a full antagonist with a partial agonist can cause such improvement.

Key Words: aripiprazole, partial agonist, haloperidol, schizophrenia

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Aripiprazole is a new antipsychotic with efficacy comparable to that of typical antipsychotics.[1–6] However, it does not produce the side effects caused by conventional antipsychotic agents such as haloperidol, which are full dopamine D2 antagonists.[3] Aripiprazole is a partial agonist, and its mixed agonist/antagonist effect is thought to be responsible for its favorable efficacy/side effect profile.[7,8]

It is not known at this time whether combinations of aripiprazole and conventional antipsychotics (that is, a combination of a partial agonist and a pure antagonist) will be beneficial or detrimental to therapy. Consensus guidelines for aripiprazole treatment advise that aripiprazole not be used in long-term treatment with other antipsychotics,[6] but this advice is based on theoretical considerations and also probably because there is little or no data on the subject. The following is a case report of a beneficial effect of an aripiprazole/haloperidol combination.

CASE

A 41-year-old married, male teacher, diagnosed with schizophreniform disorder by *Diagnostic and Statistical manual of Mental Disorders, Fourth Edition* criteria, first visited our outpatient clinic on November 15, 2005. The patient had a previous history, beginning in October, of poorly controlled psychotic symptoms, including the following: auditory hallucinations every minute (the voice of Buddha instructing him to identify humans and ghosts, with midnight sessions devoted to decoding), delusions of control (his actions and thoughts were being controlled), delusions of pursuit (a consistent belief in an implanted microchip that mediated and tracked his thoughts and activities), delusions of persecution (belief that death would occur if he did not execute the auditory commands), and eccentric behavior (childish voice and activities). These symptoms had caused him to be unable to perform his job. The patient had previously taken 5 mg/d olanzapine for less than 1 week at another institution but had discontinued this drug due to experiencing the side effects of sedation and rigidity. With the reassurance that the proposed drug would produce a noticeable improvement in his symptoms, but had a low

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incidence of side effects, an initial prescription of 10 mg/d aripiprazole was given. Fifteen days later, the dose was increased to 15 mg/d because his symptoms had not improved. At the higher dose, by December 7, the "implanted microchip" delusion had ceased, and by the 21st, his auditory hallucinations were only heard when he was reading or writing. By January 25, 2006, the patient had developed insight into his psychosis. However, on February 8, the patient complained of a fragmented long-term memory and a consistent continuation of his auditory hallucinations. The patient also expressed anxiety over reapplication to his previous occupation. A simultaneous prescription of 2.5 mg/d of haloperidol was then added because 9 weeks of aripiprazole alone (15 mg/d) had not achieved complete remission. The haloperidol dose was then increased to 5 mg/d on February 22 because the auditory hallucinations had become louder and more frequent. With this dose, by March 1, the frequency of the auditory hallucinations had decreased, and the patient's ability to concentrate had improved. By March 15, the patient's long-term memory had become more organized, and auditory hallucinations only occurred when reading for more than 10 minutes. On May 3, haloperidol was increased to 7.5 mg/d because no further decrease in auditory hallucinations had occurred, and the patient expressed anxiety and fear about the impending deadline for reapplication to his occupation. By May 10, and 17, the auditory hallucinations were completely gone, no side effects from the drug combination were observed, and the patient's fragmented long-term memory had completely recovered. A prolactin level obtained on August 1 was within normal range (8.86 ng/mL), and the patient successfully resumed his former employment. By May 2, 2007, after 1 year of continuous remission of psychotic symptoms, the patient's occupational functioning, memory, and insight into his psychosis were completely restored, and his spouse remarked that a complete recovery of the patient's functioning had occurred.

DISCUSSION

The patient described here did not achieve full recovery from his psychosis with aripiprazole alone, but the combination of the partial dopamine receptor agonist aripiprazole and the full antagonist haloperidol did achieve this goal. Low-dose haloperidol was added to aripiprazole when 15 mg/d of the latter drug failed to control the patient's symptoms sufficiently. The reason this course was chosen instead of increasing the dose of aripiprazole was because our Department of Health regulations require further documentation and protocols for aripiprazole prescriptions exceeding 15 mg/d. The knowledge that the patient had suffered intolerable side effects when 5 mg/d olanzapine was given as monotherapy kept us from discontinuing the aripiprazole and shifting the patient to haloperidol alone.

A benefit of a partial agonist is thought to be that, whereas it controls the positive symptoms of schizophrenia through its antagonism of mesolimbic dopamine receptors, its partial agonism allows it to retain enough dopaminergic function in the striatum and the pituitary to avoid the extrapyramidal symptoms and hyperprolactinemia seen when pure antagonists are used. Combining a partial agonist and a pure antagonist might either improve therapy or block the therapeutic effects of the antagonist or the beneficial side effect profile of the partial agonist.

The outcome of such a combination will depend greatly on the doses used and the intrinsic activity of the partial agonist. Partial agonists with high intrinsic activity have not been efficacious in treating schizophrenia,[9,10] but aripiprazole, which has a relatively low intrinsic activity, has good efficacy in treating this disease. The simultaneous short-term use of other antipsychotics while switching from them to aripiprazole has caused no problem.[1] However, simultaneous doses of aripiprazole (30 mg/d) and haloperidol (20 mg/d), and aripiprazole (15 and 30 mg/d) added to quetiapine (800 mg/d) were reported in 2 previous case histories to cause a worsening of positive schizophrenic symptoms.[11,12] In combining haloperidol and aripiprazole, we started by adding a very low dose (2.5 mg/d) of haloperidol to a fixed 15-mg/d dose of aripiprazole and then increased the haloperidol dose in small increments to 7.5 mg/d. We achieved success through this approach.

In summary, this report describes a case where a low dose of a D_2 dopamine receptor antagonist (haloperidol) carefully titrated against a fixed dose of the partial agonist aripiprazole achieved good therapeutic

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results. More research needs to be done to ascertain whether partial agonist/antagonist combinations offer an advantage in the treatment of schizophrenia and, if so, what type of dosage titration is necessary to exploit the advantages and avoid the disadvantages of such treatment.

REFERENCES

1. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology (Berl)* 2003;166:391–399.
2. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs* 2004;18:251–267.
3. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther* 2004;26: 649–666.
4. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002;63:763–771.
5. Potkin SG, Saha AR, Kukawa MJ, et al. Aripiprazole, an anti-psychotic with a novel mechanism of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 2003;60:681–690.
6. Travis MJ, Burns T, Dursun S, et al. Aripiprazole in schizophrenia: consensus guidelines. *Int J Clin Pract* 2005;59:485–495.
7. Burris KD, Molski TF, Ryan E, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 2002;302:381–389.
8. Grunder G, Carlsson A, Wong DF. Mechanism of new antipsychotic medications. *Arch Gen Psychiatry* 2003;60:974–977.
9. Benkert O, Grunder G, Wetzel H. Dopamine autoreceptor agonists in the treatment of schizophrenia and major depression. *Pharmacopsychiatry* 1992;25:254–260.
10. Tamminga CA. Partial dopamine agonists in the treatment of psychosis. *J Neural Transm* 2002;109: 411–420.
11. Burke MJ, Lincoln J. Aripiprazole and haloperidol: a clinically relevant interaction with a dopamine antagonist and partial agonist. *Ann Clin Psychiatry* 2006;18:129–130.
12. Reeves RR, Mack JE. Worsening schizoaffective disorder with aripiprazole. *Am J Psychiatry* 2004; 161:1308.