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Letter to the Editor

Aripiprazole and Haloperidol: A Clinically Relevant Interaction with a Dopamine Antagonist and Partial Agonist

MICHAEL J. BURKE, MD, PHD, and JANA LINCOLN, MD

Dr. Burke and Dr. Lincoln are in the Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine

To the Editor:

Aripiprazole (ARI) is a relatively recent addition to the antipsychotic drug armamentarium, approved by the U.S. Food and Drug Administration (FDA) in November 2002. It is uniquely characterized among currently marketed typical and atypical antipsychotic drugs as a partial dopamine-2 (D2) receptor agonist (1,2). The mechanism of action of ARI as an antipsychotic agent is not yet known. D2 receptor binding is believed to contribute to its effectiveness in treating Schizophrenia (SCHZ) (1,2).

Although mono-drug antipsychotic therapy may be a desirable goal in the treatment of SCHZ, in practice co-therapy with more than one antipsychotic agent is not uncommon particularly for treatment resistant illness. There has been little systematic investigation of the simultaneous use of multiple antipsychotic agents. The following case suggests a clinically relevant pharmacodynamic interaction between ARI and haloperidol (HAL), which affected the efficacy and tolerability of HAL in a patient with SCHZ. This interaction is proposed to be due to the D2 partial agonist property of ARI and potentially generalizes to other co-prescribed antipsychotics with full D2 antagonist activity.

Mr. Z, a 30-year-old, Caucasian male diagnosed with Schizophrenia (Undifferentiated Type), was hospitalized with poorly controlled psychotic symptoms characterized by auditory hallucinations, mental disorganization, and paranoia associated with aggressive outbursts. He had done well on olanzapine for several years but approximately six months prior he had developed a bowel obstruction requiring change of the antipsychotic medication. Subsequently, the patient underwent several outpatient antipsychotic drug trials with only marginal benefit.

At the time of this admission the patient had been taking ARI 10 mg/day and haloperidol (HAL) 5 mg twice a day (BID) for approximately three weeks. The initial plan for hospitalization was to advance the ARI dose to achieve the desired therapeutic effect and then taper the HAL. The ARI dose was advanced to 30 mg/day, but the patient became more paranoid and aggressive. The HAL was increased to 10 mg BID for four days with only marginal improvement in psychotic symptoms and a notable absence of extrapyramidal symptoms (EPS).

A potential pharmacodynamic interaction was considered as the cause for the patient's lack of clinical response to HAL, whereby the partial D2 agonist properties of the ARI might be interfering with the D2 antagonism of the HAL. A prolactin level obtained to assess D2 receptor antagonism was in the normal range (12.6 ng/ml). The ARI was discontinued and over the next four days the patient's psychotic symptoms and agitation improved to the level that he could be discharged to his mother's home. The discharge plan included HAL 10 mg BID and daily attendance in a partial hospital program. He was noted to exhibit mild cogwheel rigidity at discharge and a repeat prolactin level at that time was elevated at 19.7 ng/ml. Two weeks after discharge a repeat prolactin level was 54.2 ng/ml. Although Mr. Z had continued to do well on HAL 10 mg BID with psychotic symptoms largely in remission, he was

Address correspondence to Michael J. Burke, MD, PhD, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine, 1010 N. Kansas, Wichita, KS 67214. E-mail: mjburke@kumc.edu

Table 1 Effect of Aripiprazole (ARI) and Haloperidol (HAL) on Serum Prolactin Levels

	After 6 Days on Steady Doses	3 Days After ARI Discontinued	2 Weeks After ARI Discontinued
ARI Dose	30 mg/d	–	–
HAL Dose	10 mg BID*	10 mg BID*	10 mg BID*
Serum Prolactin Level**	12.6 ng/ml	19.7 ng/ml	54.2 ng/ml

*BID refers to twice a day dosing.
**Normal male serum prolactin level (2.5–17.0 ng/ml).

experiencing increased EPS since hospital discharge and was now taking benztropine 1mg BID, diphenhydramine 25–75 mg at bedtime and propranolol 10 mg/day.

ARI is a D2 receptor partial agonist that has been shown in vitro to potently activate human D2 receptors as evidenced by inhibition of D2 receptor-mediated accumulation of cyclic adenosine monophosphate (cAMP) (3). ARI (K_i = 0.34 nM) and HAL (K_i = 1.0 nM), a full D2 antagonist, have similar binding affinities for the D2 receptor with some suggestion that ARI may actually have a higher binding affinity than HAL (2,4). In the presence of both drugs, considerable competition for D2 binding sites would be anticipated. Clinically, competitive binding of a partial agonist like ARI in the presence of a full antagonist like HAL would be expected to result in some degree of functional D2 agonist activity and the appearance of decreased functional D2 antagonist activity (1). These findings suggest a possible pharmacodynamic mechanism for drug interaction whereby ARI, competing with HAL for D2 binding sites and activating those receptor sites, could decrease the functional D2 antagonism seen with HAL alone. The case of Mr. Z supports this hypothesized interaction in that the antipsychotic efficacy, EPS and prolactin elevation associated with HAL appear to have been decreased in the presence of ARI. The expected effects of HAL became more prominent as ARI was eliminated from the patient's system consistent with the mean half-life of ARI of approximately 75 hours (2). This hypothesis is further supported by earlier work demonstrating an antagonistic action of terguride, a D2 receptor partial agonist, on HAL induced prolactin elevation and behavioral change in rats (5).

ARI is a novel antipsychotic agent by virtue of its partial agonist properties at D2 receptors. When used as mono-drug therapy, clinical trial data supports its antipsychotic efficacy for many patients with SCHZ (1,2). However the novel biological activity of ARI may limit its utility in combination with other commonly prescribed antipsychotic agents. The case of Mr. Z illustrates the need to alert practitioners to make careful consideration when using ARI in conjunction with other antipsychotic agents. Systematic investigation is necessary to further clarify the potential for pharmacodynamic interactions between ARI and other conventional and atypical antipsychotic agents. The primary concern in the case of Mr. Z was decreased antipsychotic efficacy. However, with further study, this interaction may be found to have an advantageous use in minimizing adverse effects associated with conventional antipsychotic therapy.

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