A Case of Risperidone-Induced Priapism in a Patient with Glucose-6-Phosphate Dehydrogenase Deficiency

To The Editor:

Priapism is a state of penile tumescence which persists for four hours or beyond and is unrelated to sexual stimulation (1-3). Antipsychotic medications—both typical and atypical—have been associated with this medical condition (4, 5), the proposed mechanism being venous stasis due to blockade of α1 adrenoceptors in the corpora cavernosa (4, 6). Here we present a case of risperidone-induced priapism in a man with glucose-6-phosphate dehydrogenase (G6PD) deficiency. To date, there are only two case reports of priapism associated with G6PD deficiency (7, 8), whereas there are no case reports on priapism associated with antipsychotic use in people with G6PD deficiency.

Case Report

Mr. H is a 20-year-old African-American man with history of schizophrenia and G6PD deficiency who was referred to our inpatient facility for increasing agitation, psychotic symptoms, disorganized behavior and medication noncompliance. He was restarted on oral risperidone 1 mg BID and benztropine 1 mg/day. He was also placed on clonazepam 2 mg/day to help control his agitation. On day 2, his risperidone was increased to 2 mg BID and on the same day he received a single dose of haloperidol 5 mg orally for increased agitation.

The next morning, Mr. H awoke with an erection. Later that day his erection was noticed by staff, but it was considered part of his sexually inappropriate behavior. However, the erection persisted and by 6:50 p.m. it had become painful. Priapism was diagnosed and Mr. H was immediately sent to the medical emergency room where urology was consulted. He received intracavernosal phenylephrine injection along with aspiration and irrigation of the corpora cavernosa. Mr. H returned to the unit the following day and was continued on risperidone 2 mg BID, benztropine 1 mg/day, and clonazepam 2 mg/day. Over the course of nine days, the patient's condition improved and no further recurrences of priapism were noted. Mr. H had no known history of sickle cell disease, which is one of the most common ischemic causes of priapism in young African-American men, or any other documented cause of priapism.

Discussion

Priapism is a medical emergency that can lead to erectile dysfunction in 30–90% of cases. Fifteen to 41% of priapism cases are caused by medications, of which 15 to 26% are caused by antipsychotics (9). The propensity of an individual antipsychotic to induce priapism seems to be related to its degree of α1-adrenergic blockade which leads to sympathetic-parasympathetic imbalance favoring parasympathetic-mediated vasodilation and erection (4, 6). Risperidone alpha-adrenergic antagonist properties are relatively higher than those of other antipsychotics due to risperidone's increased affinity for α1 and α2 receptors (10). Alpha-1 blockade leads to direct arteriolar dilatation that enhances blood flow into the corpora cavernosa and ultimately promotes erections (11). The role of alpha-2 receptors in priapism remains to be fully elucidated but it has been proposed that alpha-2 antagonism releases nitric oxide (11, 12). Nitric oxide is a smooth muscle relaxant that could potentiate vasodilation and, therefore, promote erections (11-13). G6PD deficiency results in decreased phosphodiesterdase-5 activity and disruption of nitric oxide signaling. Nitric oxide signal pathways are involved in the molecular basis of priapism (13). Consequently, patients with G6PD deficiency have an increased risk of priapism (7, 8). Haloperidol, a high potency typical antipsychotic, has some α-adrenergic antagonism and—along with its metabolite—inhibits CYP2D6 (4, 14). Risperidone is a substrate of CYP2D6 and 3A4 (15). It is plausible that the isolated dose of haloperidol that our patient received increased risperidone levels. It is likely, therefore, that the patient's priapism resulted from interplay of his genetic deficiency coupled with increased α-adrenergic blockade from concomitant use of risperidone and haloperidol.

Our case proposes a potential interaction between G6PD deficiency, risperidone and haloperidol that could lead to priapism. It is important for physicians to be aware of this plausible interaction but there is not enough evidence yet to warrant a change in clinical practice.

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Aripiprazole-Induced Hypoprolactinemia in an Adult Male with First-Episode Psychosis

To the Editor:

Propst et al., in their recent paper entitled "Aripiprazole-Induced Hypoprolactinemia in an Adult Male with First-Episode Psychosis" (1), stated that no documented cases of hypoprolactinemia associated with aripiprazole use in adults exist to date. Regarding this statement, we would like to point out that Lozano et al., in two previous papers, described cases of prolactin deficiency associated with aripiprazole, with a mean dose of 17 mg.

The first paper—"Can Aripiprazole Normalize Iatrogenic Hyperprolactinemia?"—was presented at the 14th Virtual Congress of Psychiatry (Interpsiquis 2013) (2). We aimed to study prolactin decreases induced by aripiprazole when taken as part of various therapeutic regimens, alone or in combination with other antipsychotics (prolactin- and nonprolactin-raising antipsychotics), in order to minimize the risk of hyperprolactinemia without affecting efficacy of treatment. In a sample of 306 outpatients treated with different combinations of antipsychotics, after excluding 128 patients with less than one year of treatment and/or without follow-up of prolactin levels, a case control study was conducted. The study group consisted of all patients treated with aripiprazole (n=22), and the control group consisted of patients in treatment with prolactin-raising or nonprolactin-raising antipsychotics, other than aripiprazole (n=156). All patients had been referred to the Mental Health Unit of the Hospital Real de Nuestra Señora de Gracia in Zaragoza (Spain). Aripiprazole treatment was defined as the exposure variable and a case was defined by a prolactin level <3 ng/mL (90 mIU/L).

It was found that the percentage of cases of hypoprolactinemia among the study group was 45.4% versus 1.3% among the control group. The odds for prolactin deficiency in the aripiprazole group was 0.83 (10/12) and in the group not exposed to aripiprazole, 0.013 (2/154). Thus, we found an increased frequency of prolactin deficiency among aripiprazole-treated patients, with an odds ratio (OR) of 64.1667 (95% confidence interval [CI] 12.5987–326.8096; z=5.010; p<0.0001) (see Table 1, Research No. 1).

In the second paper—"Prolactin Deficiency by Aripiprazole" (3)—we carried out a post hoc case control study based on data from our first study. After excluding all patients on prolactin-raising antipsychotics, a total of 126 outpatients were included in the study. The control group (n=106) consisted of all patients with therapeutic regimens that consisted of nonprolactin-raising antipsychotics, and the study group (n=20) consisted of all patients with treatment regimens that included aripiprazole, at a mean (SD) dose of 17.3 (7.7) mg. We determined that the odds of prolactin deficiency among the study group was 0.81 (9/11) and among the control group it was 0.029 (3/103). Based on these findings, aripiprazole-treated patients had a higher risk of prolactin deficiency (OR 27.8182, 95% CI 7.3688–105.0168; z=4.918; p<0.0001), as well as to display associated symptoms (see Table 1, Research No. 2).

Hyperprolactinemia can lead to both short-term (e.g., disturbances in gonadal function, gynecomastia, galactorrhea, menstrual irregularities, infertility, sexual dysfunction, acne, hirsutism and parkinsonism) and long-term (e.g., osteopenia, osteoporosis, metabolic syndrome and thromboembolic events) (4, 5) adverse events. Hypoprolactinemia or serum prolactin deficiency, however, is also associated with significant adverse events, including ovarian dysfunction in women, and metabolic syndrome, arteriogenic erectile dysfunction, premature ejaculation, oligozoospermia, asthenospermia, hypofunction of seminal vesicles and hypoandrogenism in men, as well as psychiatric symptoms, such as anxiety, insomnia and/or depressed mood (6-9). Therefore, when using aripiprazole, alone or in combination with other atypical antipsychotics, for alleviating drug-induced hyperprolactinemia, it should be administered at a low dose to prevent prolactin deficiency and to avoid symptoms related to hypoprolactinemia.

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Table 1 Patient Characteristics of Control and Study Groups

	Research No. 1		Research No. 2	
Initial sample	N=306		N=306	
Excluded	N=128		N=180	
Final sample	Control Group N=156	Study Group N=22	Control Group N=106	Study Group N=20
	Diagnosis (DSM-IV*) # patients (%)		**Diagnosis (DSM-IV*) # patients (%)**	
Schizophrenic	62 (40)	9 (41)	32 (30)	8 (40)
Bipolar Disorder	39 (25)	4 (18)	36 (34)	2 (10)
Schizoaffective	25 (16)	7 (32)	20 (19)	6 (30)
Other	30 (19)	2 (9)	18 (17)	4 (20)
	Demographics		**Demographics**	
Female, # (%)	89 (57)	11 (50)	61 (58)	11 (55)
Age, years	46±14	47±12	47±14	47±13
Weight, Kg	83±19	78±13	80±18	79±10
BMI, kg/m^2	30±6	29±6	29±5	30±5
	Biochemical Values		**Biochemical Values**	
Cortisol, ug/dL	19±7	20±6	20±7	21±5
Prolactin, mIU/L	596±751	196±158	427±723	185±137
Tiroxyn, ng/dL	1.0±0.3	1.3±1.4	1.0±0.3	1.4±1.7
	Statistical		**Statistical**	
Odds	0.013 (2/154)	0.83 (10/12)	0.029 (3/103)	0.81 (9/11)
Odds Ratio	64.1667 (IC:12.5987–326.8096) z=5.010; p<0.0001		27.8182 (IC: 7.3688–105.0168) z=4.918; p<0.0001	

Plus-minus values are means ± standard deviation.
**DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

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Dr. Propst and Colleagues Reply

To the Editor:

In our Case Report entitled "Aripiprazole-Induced Hypoprolactinemia in an Adult Male with First-Episode Psychosis" we stated that, to our knowledge, no documented cases of abnormally low prolactin levels in aripiprazole-treated adults have been published (1). The above letter from Dr. Roberto Lozano and colleagues indicates otherwise. They report that they found an increased rate of hypoprolactinemia in aripiprazole-treated patients compared to patients taking other antipsychotics in a 2013 case control study, with an odds ratio of 64.1667. In their 2014 post hoc analysis, they found an increased rate of hypoprolactinemia in aripiprazole-treated patients compared to patients taking specifically nonprolactin-raising antipsychotics, with an odds ratio of 27.8182. We would like to thank Dr. Lozano and colleagues for bringing these studies to our attention.

The first study did not appear in our literature search as

it was published in Spanish and we only searched English-language papers; the second study was published after our search was conducted. These studies support the finding described in our Case Report and highlight the potential side effect of abnormally low prolactin levels in patients taking aripiprazole.

As previously discussed in our paper, hypoprolactinemia has medical consequences including decreased sperm motility (2), decreased sperm count and abnormal sperm morphology (3), and failure to lactate after delivery when used during pregnancy (4). Low prolactin levels are also associated with immune dysfunction in rodents (5), although the effects of hypoprolactinemia on human immune function remain unknown. We hope that as data emerge that support the link between aripiprazole and abnormally low prolactin levels, these often unnoticed side effects will be investigated, monitored, and treated in the appropriate fashion.

Conflicts of Interest

Alanna J. Propst—no conflicts; G. Eric Jarvis—no conflicts; Howard C. Margolese—Dr. Margolese is a consultant/paid speaker for and/or grant recipient from Amgen, BMS, Janssen, Lundbeck, Novartis, Otsuka, Roche, Sunovion.

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