The Journal of Emergency Medicine, Vol. 28, No. 3, pp. 311–313, 2005
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0736-4679/05 $–see front matter

ELSEVIER

doi:10.1016/j.jemermed.2004.09.013

Selected Topics: Toxicology

OVERDOSE OF ARIPIPRAZOLE, A NEW TYPE OF ANTIPSYCHOTIC

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□ **Abstract—Aripiprazole is the first member of a new class of antipsychotic medications. Unlike other antipsychotics, it acts as a partial agonist at dopamine D_2 and 5-HT_{1A} receptors, thereby mitigating most of the adverse reactions such as extrapyramidal side effects and hyperprolactinemia. Additionally, most research to date has suggested a low incidence of QTc prolongation and orthostatic hypotension at therapeutic doses. Experience in the setting of intentional overdose, however, is limited. We present a case of a 27-year-old woman who intentionally ingested 330 mg of aripiprazole in a suicide attempt. Clinical effects were limited to mild sedation. Serum levels performed by the drug's manufacturer confirmed a total level (parent drug and active metabolite) of 716 ng/mL, nearly six times the upper limit of accepted therapeutic levels. This suggests that aripiprazole's therapeutic index is quite high and reinforces the drug's known safety profile.** © 2005 Elsevier Inc.

□ **Keywords—aripiprazole; antipsychotic; overdose; poisoning**

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INTRODUCTION

Aripiprazole (Abilify™, Bristol-Myers Squibb Company, Princeton, NJ/Otsuka America Pharmaceutical, Inc., Rockville, MD), 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1*H*)-quinolinone, was approved by the U.S. Food and Drug Administration on November 15, 2002 as the first in a new class of "next-generation" antipsychotics. First-generation (e.g., haloperidol, chlorpromazine, fluphenazine) and second-generation (e.g., clozapine, risperidone, olanzapine) antipsychotics exert much of their effect through antagonism of dopamine D_2 receptors. In contrast, aripiprazole acts as a partial agonist at D_2 and serotonin 5-HT_{1A} receptors, and as an antagonist at 5-HT_{2A} receptors (1–3). Its partial agonism results in effectiveness against both positive and negative symptoms of schizophrenia. Research to date has shown that aripiprazole produces no QTc prolongation or elevation in serum prolactin levels, and has a low likelihood for producing extrapyramidal side effects (4,5).

Experience with overdose is quite limited. In premarketing clinical studies, there were seven patients who suffered either intentional or accidental overdose of aripiprazole, the largest identified amount of ingestion being 180 mg. The only symptoms reported were somnolence and vomiting (6).

We report here the largest known intentional overdose

RECEIVED: 18 February 2004;
ACCEPTED: 28 September 2004

of aripiprazole, which resulted in only minimal clinical effects.

CASE REPORT

Paramedics were contacted to assess a 27-year-old suicidal woman who stated she had ingested 22 15-mg tablets of her aripiprazole, one 10-mg cyclobenzaprine tablet, and one 25-mg of her quetiapine. The paramedics administered 50 grams of activated charcoal and transported her to an emergency department (ED). Vital signs on her arrival in the ED were measured as a temperature of 36.9°C (98.4°F) orally, pulse of 115 beats per minute, blood pressure 124/83 mm Hg, respirations of 18 breaths per minute, and a pulse oximeter reading of 100% on room air. The time of her arrival at the hospital was approximately 50 minutes after the intentional ingestion, according to the history the patient provided. The past medical history included a history of paranoid schizophrenia. She recently had been started on aripiprazole and was also currently taking quetiapine and cimetidine. On physical examination, the patient appeared slightly drowsy but was easily arousable. Her physical examination was normal with no antimuscarinic findings, and the remainder of the neurologic examination was normal. The electrocardiogram performed approximately 3 hours after ingestion revealed a normal sinus rhythm at 69 beats per minute with a normal axis, QRS interval of 82 milliseconds, QT interval of 366 milliseconds, and QTc interval of 392 milliseconds.

Laboratory analysis, drawn approximately 3 hours and 15 minutes after ingestion, revealed an acetaminophen level of no measurable amount and a salicylate level of no measurable amount. The plasma alcohol level was also no measurable amount. A urine immunoassay was negative for amphetamines as a class, barbiturates as a class, phencyclidine, benzoylecgonine, benzodiazepines as a class, opiates as a class, methadone, propoxyphene, and tetrahydrocannabinoids. A comprehensive toxicology screen was performed using thin layer chromatography and was reported as negative except for the presence of histamine$_2$ blocker.

The patient was observed in a monitored setting for a period of 8 hours, during which no further adverse effects were noted. She had complete resolution of the drowsiness and did not develop any symptoms to suggest orthostatic hypotension. The patient was transferred to a psychiatric inpatient unit and she suffered no further sequelae from the ingestion.

Serum obtained at the time of presentation was sent to the drug's manufacturer for determination of concentrations of aripiprazole and dehydro-aripiprazole (DA), the drug's major active metabolite. Three hours and 15 minutes after ingestion, the level of aripiprazole was 596 ng/mL and the level of DA was 120 ng/mL, for a total level of 716 ng/mL.

DISCUSSION

Aripiprazole has a different pharmacodynamic profile compared to previous antipsychotic agents. It acts as a partial agonist at dopamine D_2 receptors and serotonin $5HT_{1A}$ receptors (1–2). As a partial agonist, aripiprazole can act as either an agonist or an antagonist, depending upon the concentration of the specific neurotransmitter (so-called "functional selectivity") (3). Current theories suggest that the positive symptoms of schizophrenia are caused by excess dopaminergic activity in the mesolimbic tract, and the negative symptoms by insufficient dopaminergic activity in the mesocortical tract. Thus, aripiprazole acts as an antagonist in the mesolimbic area and as an agonist in the mesocortical tract thereby benefiting both the positive and negative symptoms of schizophrenia. Additionally, its partial agonist effects in the nigrostriatal and tuberoinfundibular regions reduce the incidence of extrapyramidal side effects and hyperprolactinemia, respectively (7).

Aripiprazole is extensively metabolized in the liver by CYP3A4 and CYP2D6. Its mean elimination half-life is 75 hours in normal patients and 146 hours in slow-CYP2D6 metabolizers (approximately 8% of Caucasians). The maximum daily dose is 30 mg (0.43 mg/kg in a 70-kg adult), which results in a peak concentration of ~120 ng/mL. At steady-state, dehydro-aripiprazole (DA), the major active metabolite, represents approximately 40% of aripiprazole area under the curve (AUC) in plasma (6). Aripiprazole has moderate affinity for the alpha$_1$ adrenergic receptors and histamine$_1$ receptors. Alpha$_1$ blockade is thought to account for the potential orthostatic hypotension that may occur. There is little affinity for cholinergic muscarinic receptors.

Our patient had a large single acute ingestion of aripiprazole (330 mg), nearly twice the previously known largest ingestion of 180 mg. The patient experienced no adverse effects other than mild sedation. Serum measurements performed by the drug's manufacturer confirmed levels of aripiprazole plus DA at 716 ng/mL, nearly six times higher than the peak level associated with a therapeutic dose of 30 mg. There is one other reported case of massive ingestion of aripiprazole, in a 2-year-old girl who ingested 17.1 mg/kg and presented with central nervous system depression but no cardiovascular instability, respiratory compromise, or electrocardiographic effects. Serum testing revealed a level of aripiprazole plus DA at 1873 ng/mL (8).

Our report suggests that the therapeutic index of aripi-

prazole in intentional overdose is wide. The drug's partial agonist effects should, theoretically, prevent many of the adverse effects associated with many other antipsychotic medications.

CONCLUSION

Ingestion of an excessively large dose of aripiprazole seems to be associated with relatively minimal adverse effects.

Acknowledgment—We acknowledge the support of the drug's distributor, Bristol-Myers Squibb, which performed the serum drug level testing.

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