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Worsening Psychosis in an Adolescent Female Chronically Abusing Dextromethorphan when Benztropine was added to the Treatment Regimen

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Abstract

Recently, there has been an increase in the use of over-the-counter (OTC) medications as recreational drugs of abuse in adolescents. It is important to recognize that some of these medications, such as Dextromethorphan (DXM) at doses beyond recommended, have detrimental effects to mental health. The symptoms DXM precipitates appear as a mental illness in acute exacerbation rather than intoxication and/or overdose. Having sufficient knowledge on how to treat adequately those patients who abuse OTCs such as DXM is of utmost importance in determining an assertive treatment intended to subside and recuperate successfully. Using the example of DXM, which is a substrate of CYP2D6 and metabolized by the enzyme, we must have awareness that many other medications are affected by this route as well. This case illustrates how Benztropine precipitated symptoms of psychosis and euphoric mood on a 14 year old Hispanic female, which was assumed to be effectively responding with Risperidone treatment. We theorize that chronic DXM abuse evoked an induction of the CYP2D6, which ultimately hindered the antipsychotic treatment efficacy. Risperidone dose was increased whereas Benztropine discontinued on the subsequent day which corresponded to the rapid subside of her psychosis. We recommend caution when adding Benztropine to antipsychotic treatment for a patient having psychotic symptoms precipitated by chronic DXM abuse, as well as considering the use of neuroleptics that are minimally or not metabolized by the CYP2D6 P450 metabolic pathway.

Keywords: Dextromethorphan abuse; Psychosis; CYP2D6; NMDA

Introduction

Dextromethorphan has recently become a drug of abuse by the adolescent population seeking for a euphoric, dissociative, and anti-anxiety with a care free state [1]. Metabolized by the hepatic cytochrome P450 isoenzyme 2D6 (CYP2D6), Dextromethorphan is converted into the active metabolite Dextrorphan, which has phencyclidine-like behavioral effects in animal models [2]. Dextrorphan (DOP) is a metabolite with strong non-competitive N-methyl-D-aspartate (NMDA) receptor antagonistic activity just like phencyclidine, contributing to the psychoactive effects of dextromethorphan. NMDA receptor blockade can produce euphoria, hyperactivity, and psychosis [1,3]. It is worth noting that 84.3% of the USA population has a rapid metabolizer CYP2D6 phenotype, which can be responsible for dissociative psychosis induced by Dextrophan's non-competitive NMDA receptor antagonism. Pharmacological induction of CYP2D6 can also result in rapid metabolism of dextromethorphan into the active and 10 fold more potent form DOP, and a patient subjected into becoming more prone to having neuropsychiatric manifestations with significant drug interaction [4]. The specific psychiatric effects experienced by Dextromethorphan abusers include paranoia, various types of delusions, depersonalization, having severe changes in body image, euphoria, occasional aggressive behavior, mood state alterations, impulsivity, hallucinations, and loss of ego boundaries. The present case illustrates how Benztropine precipitated a patient's psychosis, which was presumably being treated effectively with Risperidone. Benztropine's mechanism of action leads to augmentation in dopamine levels, but we believe that a theoretical induction of CYP2D6 by chronic DXM abuse could have also caused Risperidone to become a culprit in the exacerbation of psychotic symptoms [5].

Case Presentation

A 14 year old Hispanic female presented to ER due to bizarre behavior with symptoms of psychosis and euphoric mood. During the ED course, the patient became stuporous and admitted to the Intensive Care Unit. On the second day after admission, the patient remained in a partially stuporous state in what appeared to be delirium by history of waxing and waning level of consciousness provided from the medical team. Psychiatry was consulted, but she was unresponsive to any type of stimuli, and an evaluation was not possible. During her third day of admission the patient was awake, but in a dissociative state, with childlike behavior, acting with a

primitive drive, totally disinhibited, with multiple bizarre and paranoid delusions, and having auditory and visual hallucinations. After brain CT scan and MRI, laboratory results, and a thorough neurology evaluation ruled out organic causes for her symptoms, the patient was admitted into the inpatient psychiatric unit.

The initial psychiatric evaluation was conducted with the patient's mother present, who provided most of the information at the time, pertinent for the examination. Patient had no previous psychiatric or medical history, developmental milestones were adequately met, was a fair student; lived with mother, stepfather, and two younger siblings, had no legal issues, and as per mother "has been hanging around the wrong crowd after we moved to a new neighborhood." There is a positive psychiatric family history from the patient's father, who has a diagnosis of Bipolar Disorder type I. A patient history of substance abuse was disclosed as per mother, obtained through gathering information from the younger siblings, the patient's close friends, and by her own observations. The patient had been chronically abusing dextromethorphan, by using different forms of OTC medications for the past 6 months. The frequency was "almost daily" and 2-3 times per day at dosages, as high as, 10 times the recommended for cough. On the first day of admission in the inpatient psychiatric unit, the patient was started with a treatment regimen consisting of Risperidone 1 mg PO QHS. This was then increased to Risperdal 1 mg PO BID during the second day of treatment in the unit. Minimal positive improvements in her mental state were noticed after the medication adjustments, but signs of Extra Pyramidal Symptoms (consisting of slight rigidity) developed. With fear that her EPS could have worsened, Benztropine 2 mg PO daily was added to the treatment plan. During the following late afternoon, the patient began to deteriorate and continued with childlike behavior stating "I am three years old", with a tone of voice particular for a child around that age range. Later in the evening, her auditory and visual hallucinations worsened, responding to internal stimuli, euphoria was precipitated again, disorganized thoughts and speech, irrational thoughts and behavior, having a primitive drive with loss of ego boundaries (patient went into the shower for more than two hours masturbating and painting herself with blood from her period), self-mutilating behavior, aggression, and growling like a wild animal was also observed. Hence, the Risperidone dose was increased to 2 mg PO BID and the Benztropine was discontinued on the next day.

The aforementioned symptoms and behavior rapidly subsided in a matter of fewer than 14 hours, with a substantial 9-10 hours of sleep within that period of time. Within two hours after the patient awakened, her behavior significantly improved. She was calm, cooperative, communicating appropriately, without psychosis, having a euthymic mood, pleasant, without disinhibition, acting as a normal age appropriate adolescent and revealing her true age when asked. Without any further changes to her medication regimen, the patient continued to improve until discharge three days later.

Discussion

Benztropine partially blocks cholinergic activity in the basal ganglia and has been shown to also increase the availability of dopamine by blocking its reuptake and storage sites, and hence prolonging dopaminergic activity [6]. In addition, Benztropine is very useful in patients using antipsychotic medications who present with extrapyramidal symptoms due to the atypical dopamine reuptake inhibitor properties, which increases the extracellular concentration of dopamine and ultimately enhancing transmission [7]. Interestingly, prior reports have linked Benztropine, along with other anticholinergics, to psychosis [8].

We speculate that Benztropine increased the availability of dopamine by means of the mechanisms explained above (blocking its reuptake and storage sites), potentiating its release and effects accordingly. These well documented pharmacologic mechanisms, is what we believe the patient experienced, and led to her spontaneous deterioration. Hence, clinicians should make a concerted analysis when choosing the most appropriate acute treatment for a patient with a history of Dextromethorphan abuse.

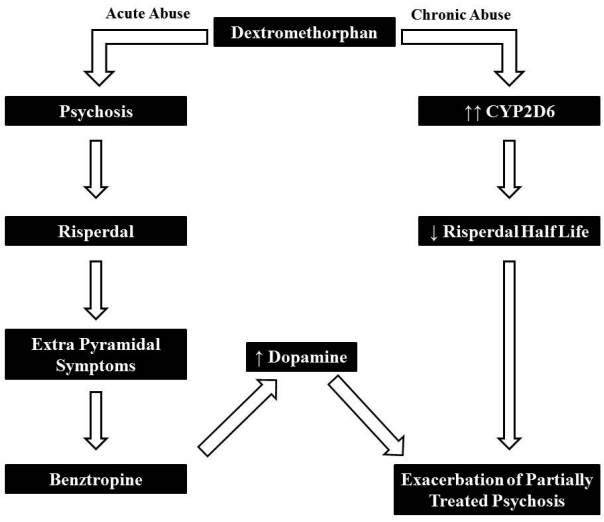

Figure 1: Proposed mechanism of worsening psychotic symptoms when treating dextrometorphan induced psychosis, using Benztropine and Risperidone

It should also be noted that both Dextromethorphan and Risperidone and are extensively metabolized by CYP2D6 into active the metabolites Dextrorphan and 9-hydroxyrisperidone, respectively. The chronic and extensive use of Dextromethorphan in this patient might have caused an induction of CYP2D6 levels and function. Therefore, theoretically by way of rapid metabolism, Risperidone half-life was reduced, leaving insignificant amounts of 9-hydroxyrisperidone (active metabolite) in plasma during the initiation of treatment. The balance of Risperdal to 9-hydroxyrisperidone ratio was also disrupted in this process,

adding to the diminished antipsychotic effects (**Figure 1**). With this in mind, it should be considered using an antipsychotic medication not metabolized through CYP2D6 or aggressively titrating higher doses of Risperidone during treatment initiation. Moreover, the possibility of EPS increases with higher dose titrations when using Risperidone and other antipsychotics in general [5]. Furthermore, a psychotic reaction could be triggered with Benztropine when attempting to treat the EPS. Due to their mechanism of action and/or interactions, Risperidone and Benztropine should be used with caution in a patient with Dextromethorphan induced psychosis who has been abusing it chronically.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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