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CASE REPORT



Significant improvement of risperidone-induced retrograde ejaculation on drug holidays: a case report

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ABSTRACT

Risperidone, which is one of the most commonly prescribed second-generation antipsychotics can cause several sexual adverse effects. To date, research on the sexual side effects of risperidone has been mostly restricted to symptoms of decreased libido, erectile dysfunction and delayed ejaculation and far too little attention has been paid to risperidone associated retrograde ejaculation. What is not clear is that whether this side effect appears in a dose-dependent manner and whether structured treatment interruptions/drug holidays can diminish sexual adverse effects without a reduction in treatment efficacy. Another question is whether concurrent use of opiates and risperidone can increase the risk of retrograde ejaculation due to their anticholinergic and adrenergic blocking properties. Here we describe a case of a 30-year-old male with schizophrenia and opium dependence who developed risperidone-induced retrograde ejaculation; however, the ejaculatory dysfunction improved significantly on drug holidays. This is the first report on the use of structured treatment interruptions in the management of risperidone-induced retrograde ejaculation.

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Risperidone; ejaculation;
structured treatment
interruption; opiate

Introduction

Risperidone is one of the most widely used second-generation antipsychotics in clinical practice. It is approved for the treatment of schizophrenia, bipolar disorder and behavioural disturbances in children and adolescents with autistic spectrum disorders. It is also effectively used to treat other psychotic disorders, including schizoaffective and delusional disorder, psychotic disorder due to another medical condition, substance-induced psychotic disorder, depressive disorder with psychotic features and behavioural symptoms in neurocognitive disorder [1]. Risperidone inhibits dopaminergic D2 receptors, serotonergic 5-HT_{2A} receptors and alpha-adrenergic receptors, while it is considered to have minimal anticholinergic effects [2]. Despite its efficacy, risperidone has several adverse effects including extrapyramidal effects, dizziness and metabolic disturbances as well as sexual side effects [3].

To date, research on the sexual side effects of risperidone has been mostly restricted to symptoms of decreased libido, erectile dysfunction and delayed ejaculation and far too little attention has been paid to risperidone associated retrograde ejaculation. Recently, few studies have reported the occurrence of retrograde ejaculation associated with risperidone use resulting in a negative effect on treatment compliance [4–6]. What is not clear is that whether this side effect appears in a dose-dependent manner and

whether structured treatment interruptions/drug holidays can diminish sexual adverse effects without a reduction in treatment efficacy.

In addition, a number of studies have reported ejaculatory disturbances noted in chronic opiate users [7,8]. The question is whether concurrent use of opiates and risperidone can increase the risk of retrograde ejaculation due to their anticholinergic and antiadrenergic effects.

Here we describe a case of a 30-year-old male with schizophrenia and opium dependence who developed risperidone-induced retrograde ejaculation; however, the ejaculatory dysfunction improved significantly on drug holidays.

Case presentation

The patient was a 30-year-old male referred to the hospital with a 1-year history of psychotic symptoms such as running commentary auditory hallucinations, transient visual hallucinations and persecutory delusions. He also suffered from insomnia, dysphoric mood and impaired social function; however, he did not experience suicidal or homicidal thoughts. He had no previous history of active psychiatric treatment or admission to a psychiatric ward or hospital. He did not report any history of medical illness including genitourinary surgery, diabetes mellitus or neurological injuries. There was no previous history of ejaculatory

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dysfunction. The patient had not taken any medication for at least six months before his first visit. He reported an active period of problematic methamphetamine and cannabis use for about five years, followed by a period of partial abstinence over the past five years. He smoked about two grams of opium every day, since 4 years ago. He had some pathologic personality traits such as impulsivity, risky behaviours and intolerance but he did not meet criteria for any specific personality disorder. His physical examination including a thorough neurological assessment was unremarkable.

Considering the course of psychotic symptoms, a diagnosis of schizophrenia was made according to DSM-5¹ criteria [9]. The oral form of risperidone was initiated and the dose was titrated gradually to 6 mg/day over 2 weeks. As mentioned above, the patient smoked about two grams of opium every day, since 4 years ago and he did not change the amount or route of opium use during treatment with risperidone. Although psychotic symptoms responded well to risperidone, the patient developed the manifestations of retrograde ejaculation including dry orgasm and cloudy urine when the dose of 6 mg/day was reached. The patient received a comprehensive medical workup including a thorough urologic examination. The diagnosis of retrograde ejaculation was confirmed by the urologist and possible structural causes for ejaculatory dysfunction were ruled out. In spite of retrograde ejaculation, he had normal sexual desire and adequate erectile function. On the laboratory work up; serum prolactin level was in normal range and the patient didn't show any manifestations of hyperprolactinemia. The side effect of retrograde ejaculation was suspected to be associated with the use of risperidone, however decreasing the dose of risperidone was not helpful and a switch to perphenazine (24 mg/day) resolved the sexual dysfunction, but nevertheless, psychotic symptoms returned after 2 weeks.

Finally, perphenazine was discontinued and risperidone was started again and weekend drug holidays were planned in order to reduce the symptom of ejaculatory dysfunction. The omission of risperidone on weekends (i.e. withdrawal of the medication each Thursday and Friday) led to improved ejaculatory function during weekends without a clinically significant reduction in treatment efficacy, although ejaculatory problems were still bothering during the rest of the week. Overall the treatment plan was effective and tolerable for the patient during the 6-month follow-up period.

Discussion

This is the first report on the use of structured treatment interruptions for the management of risperidone-induced retrograde ejaculation. We reported a patient with schizophrenia and opioid dependence who

experienced retrograde ejaculation during risperidone treatment. Retrograde ejaculation refers to the failure of the semen to be ejected out through the urethra. The semen is refluxed into the urine bladder as a result of inadequate bladder neck closure. Throughout normal ejaculation, sympathetic system maintains closure of the bladder neck to prevent retrograde flow of semen. Partial or complete loss of sympathetic input to the smooth muscles of the bladder neck can lead to retrograde ejaculation [10]. This condition can occur as a result of neurogenic or anatomic abnormalities or may be associated with the use of various medications [11]. Several studies thus far have revealed that postsynaptic antagonism of the alpha1 adrenergic receptor is implicated in developing retrograde ejaculation by altering the sympathetic tonus of the bladder or urethral sphincter [12]. Therefore, it has been suggested that risperidone which has potent alpha1 adrenergic blocking effects may cause retrograde ejaculation by a similar mechanism [13]. Till now a few number of cases of risperidone-induced retrograde ejaculation have been reported [4–6]. In contrast to previously reported cases, in which retrograde ejaculation was related to a rapid dose increase, our patient developed ejaculatory dysfunction with gradual dose titration of risperidone. Therefore, it seems likely that this sexual adverse effect is not related to the rate of increase in the dose of risperidone. Moreover, in our case, contrary to those previously published, the ejaculatory problem did not resolve with the reduction of the risperidone dose and thus the ejaculatory dysfunction may not be a dose-dependent phenomenon. Interestingly, the omission of risperidone on weekends resulted in a remarkable reduction of sexual side effects and the patient had an adequate ejaculatory function on drug holidays without a clinically significant reduction in efficacy of antipsychotic therapy. This finding has an important clinical implication with regard to medication adherence in patients; however, further investigations are required to specifically address the effectiveness of drug holidays during risperidone treatment.

It is also important to note that our patient's serum prolactin level was within the normal range and he did not experience any clinical manifestations of hyperprolactinemia during treatment with risperidone. It can thus be suggested that the development of retrograde ejaculation was most probably due to alpha1 adrenergic blockade and was not related to elevated prolactin level.

As was pointed out in the introduction to this paper, a number of researchers have reported ejaculatory disturbances noted in chronic opiate users [7,8]. Opiates can lead to ejaculatory dysfunction through hypogonadal and androgen-inhibiting effects as well as blockade of alpha-adrenergic, cholinergic and opioid receptors in the ejaculatory circuit [14]. It is noteworthy that the patient described here did not change his pattern and amount of opium use during treatment,

therefore, it seems unlikely that the ejaculatory dysfunction was merely due to opium use. However, it can be assumed that in our patient, concurrent use of opium and risperidone severely interrupted normal ejaculatory function and possibly exacerbated retrograde ejaculation.

Taken together, this case report aims to convey two clinical messages. First, risperidone-induced retrograde ejaculation is possibly unrelated to dose. Secondly, performing structured treatment interruptions can result in a remarkable reduction of sexual side effects without a clinically significant reduction in treatment efficacy. This report provides new insights into the management of retrograde ejaculation associated with risperidone and perhaps other antipsychotics. We also considered the greater likelihood of risperidone-induced retrograde ejaculation when opiates are used concurrently.

Note

1. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Disclosure statement

No potential conflict of interest was reported by the authors.

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