Abuse of High-Dose Long-Acting Risperidone: A Case Report

Yüksek Doz Uzun Etkili Risperidon Kötüye Kullanımı: Olgu Sunumu

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Abstract
In this article, a case of simultaneous abuse with an overdose of long-acting risperidone and buprenorphine/naloxone combination in a newly diagnosed patient with bipolar disorder without a history of substance is presented. A 34-year-old male, with no past history of any psychiatric disorder or alcohol-substance abuse, abused the combination of long-acting risperidone and buprenorphine/naloxone alternately for 2-3 days (sometimes every day) for 6 months. During clinical follow-up, affective symptoms regressed. EPS side effects continued for approximately 8 weeks and decreased gradually after this period. Although quetiapine is the most commonly abused atypical antipsychotic, risperidone can also be abused among non-substance abusers. Risperidone is abused as an oral formulation, but the long-acting formulation can be abused with overdose as in this case. The level of active risperidone metabolite in serum is lower using the long-acting formulation than in the oral form. This can be advantageous in terms of side effects, especially with overdose. Cardiac side effects are common with overdose and the symptoms related to EPS. The potential for abuse of buprenorphine-naloxone which is used for opioid addiction treatment is low. The buprenorphine-naloxone combination could be abused by people without opioid experience, and other atypical antipsychotics such as risperidone can be abused simultaneously as in this case.

Keywords: Long-acting risperidone, buprenorphine/naloxone, abuse, bipolar disorder

Özet
Bu makalede, daha önce madde kullanım öyküsü olmayan yeni tanı almış bipolar bozukluğu olan bir hastada yüksek dozda uzun etkili risperidon ve buprenorfin/nalokson kombinasyonunun eş zamanlı kötüye kullanım vakası sunulmuştur. 34 yaşında erkek hasta, 6 ay boyunca ortalama 2-3 günde bir (bazen her gün) dönüşümlü olarak uzun etkili parenteral risperidon ve buprenorfin/nalokson kombinasyonunu kötüye kullanmıştı. Tedavi sonrasında afektif semptomlar geriledi. EPS yan etkileri yaklaşık 8 hafta boyunca devam etti ve bu süreden sonra giderek azaldı. En sık kötüye kullanılan atipik antipsikotik ketiapin olmasına rağmen, risperidon madde bağımlısı olmayan kişiler arasında da kötüye kullanılabilmektedir. Risperidonun genellikle oral formu olarak kötüye kullanılmaktadır, ancak bu vakada olduğu gibi uzun etkili formülasyon da yüksek dozda kötüye kullanılabilir. Serumdaki aktif risperidon metaboliti seviyesi, oral forma göre uzun etkili formülasyon kullanıldığında daha düşüktür. Bu, özellikle aşırı dozda yan etkiler açısından avantajlı olabilir. Kardiyak yan etkiler yüksek dozda ve EPS ile ilgili semptomlarda yaygındır. Opioid bağımlılığı tedavisinde kullanılan buprenorfin-naloksonun kötüye kullanım potansiyeli düşüktür. Buprenorfin-nalokson kombinasyonu opioid deneyimi olmayan kişiler tarafından kötüye kullanılabilir ve bu vakada olduğu gibi risperidon gibi diğer atipik antipsikotikler ile eş zamanlı olarak kötüye kullanılabilir.

Anahtar Kelimeler: Uzun etkili risperidon, buprenorfin/nalokson, kötüye kullanım, bipolar bozukluk

Introduction

Risperidone is an atypical antipsychotic mainly used in the treatment of schizophrenia and bipolar disorder as well as different psychiatric disorders such as behavioral disorders, anxiety disorders, and alcohol-substance use disorders (1). The drug shows high affinity for D_2, $5HT_{2A}$, $5\text{-}HT_{2C}$, α_1 and α_2 receptors; and low affinity for D_1, $5HT_{1A}$, and H_1 receptors (2). Risperidone facilitates dopamine release in the prefrontal cortex and hippocampus (3). The drug converted to its active metabolite 9-OH risperidone that with the cytochrome P450 2D6 system in the liver. The recommended optimal dose is 2-6 mg/day (4).

The long-acting formulation of risperidone has been developed to improve drug compliance in patients with schizophrenia. The recommended dose for the long-acting form is 25-50 mg / every 14 days (5). Its antipsychotic efficacy is similar to the oral formulation of risperidone (4). Atypical antipsychotics are also used in the treatment of alcohol-substance use disorders. Atypical antipsychotics are thought to have low abuse potential (6-8). However, atypical antipsychotics-most common with quetiapine-could be abused by people with alcohol and substance use disorders (9,10).

Various combinations of buprenorphine, a partial opiate agonist and naloxone, an opiate receptor antagonist were approved by the FDA in 2002. This combination is a safe and effective treatment option for the treatment of opioid dependence. Therefore, it is assumed that the combination has a lower abuse potential than buprenorphine alone (11,12). The buprenorphine/naloxone ratio in the preparation that used in our country is 4/1 (2 / 0.5 and 8/2 mg sublingual tablets) (13).

In this report, we present a newly diagnosed case of bipolar disorder with no history of substance abuse who abused high-dose long-acting risperidone and buprenorphine/naloxone combination preparations alternately and sometimes simultaneously.

Case Presentation

A 34-year-old, married, male was hospitalized with court decision for demanding money and beating his mother, and recently wandering the streets. He had been working as a sergeant in the terrorist zone for the last 8 years. He had no history of previous psychiatric treatment or alcohol and substance use in himself or his family. One and a half years ago, while on duty, he witnessed the death of soldiers under his command and an investigation was initiated against him. After this event, he questioned himself about deaths and experienced anxiety and insomnia from time to time. However, he had not applied for psychiatric treatment. He obtained buprenorphine 8 mg/naloxone 2 mg by illegally procuring and started to abuse it intermittently. He had also illegally obtained long-acting risperidone, simultaneously. He was using long-acting risperidone by intramuscular injection at 2-3 day intervals when he felt anxious. He started to have conflicts with his wife and his interest in his family decreased. He was spending his entire salary to buy drugs. He decided to leave his job immediately and did not renew his contract. He used his compensation to buy parenteral risperidone and buprenorphine/naloxone combinations. He continued drug abuse for 6 months, then stopped for 4-5 months and started again. According to his own testimony, he abused 12 doses to 25 mg and 38 doses to 37.5 mg long-acting risperidone at intervals of 2-3 days, sometimes every day depending on his mood. Both injections were administered gluteally. He stated that he felt "relaxed" after the injections. Recently he had not been home for days at a time and had slept on streets. When he did not have money to buy drugs, he asked her mother for money, and when she

refused, he beat her. For this reason, he was forensically hospitalized by his family. Three days before his admission he had injected the last long-acting risperidone.

When he admitted to the clinic, pulse was 112 / min, TA: 130/70 mmHg, and temperature was 36.7 ºC. Psychiatric examination revealed euphoric, mildly sedated, increased psychomotor activity, increased speech rate, irritability, mild grandiosity and insomnia.

He scored 19 points from the Young Mania Rating Scale. Considering his past traumatic experiences, the current symptoms did not meet the diagnostic criteria for Posttraumatic Stress Disorder according to DSM-5. The patient was diagnosed as Bipolar Disorder and Other Specified Anxiety Disorder according to DSM-5. Laboratory tests including hemogram, serum electrolytes, thyroid function test and liver function tests were within normal limits. Serum CK 284 U/L (25-130), prolactin: 25.8 ng/mL (2.1-17.7) and vitamin B12: 109.5 pg/mL (160-700). QTc was calculated as 402 msec (within normal limits) on ECG.

The patient had significant rigidity, the sign of gear wheel, and tremor. He scored 18 points from the Extrapyramidal Symptoms Rating Scale. His treatment was ordered as vitamin B_{12} supplementation and with biperiden 6 mg/day, propranolol 80 mg/day, valproic acid 1000 mg/day, aripiprazole 15 mg/day, and quetiapine 400 mg/day. During follow-up, blood pressure was within normal limits; the pulse watched tachycardic from time to time.

During clinical follow-up, affective symptoms regressed, EPS side effects continued for about 8 weeks and gradually decreased after this period. At the follow-up examination 2 months after discharge, affect was euthymic and EPS symptoms completely disappeared.

Discussion and Conclusions

Alcohol and substance use is common with bipolar disorder and anxiety disorders. According to Khantzian's "self-medication hypothesis," a person starts to take substances to relieve anxiety symptoms, and then develops dependence (14).

Atypical antipsychotics may reduce the development of addiction by reducing anxiety symptoms. However, as in this case, these drugs may have caused abuse due to the sedative and anxiolytic effects of risperidone and the partial opioid effect of buprenorphine/naloxone.

The buprenorphine/naloxone combination has been developed to reduce the potential for abuse intravenously. Studies have shown that the buprenorphine/naloxone combination has a lower potential for abuse than buprenorphine alone. The combination reduces but does not eliminate the potential for abuse (12,15,16). When the combination is injected intravenously, naloxone accelerates withdrawal effects in opioid dependents, attenuates the feeling of drug satisfaction, and often leads to an unpleasant experience (17).

This patient who had no previous opioid experience, experienced the pleasant effect of buprenorphine a little after the use of the buprenorphine/naloxone combination and therefore may continue to use it repeatedly. Studies on the pharmacokinetic properties of risperidone have shown that there are some differences between oral dose and plasma levels of risperidone, and may vary according to age, body weight, and genetic factors. Drug metabolism may be altered in persons with complete deficiency or ultra-rapid metabolisers with respect to related to CYP2D6 activity. Serum risperidone and active metabolite concentrations are lower in treated with long-acting risperidone than using the oral form of risperidone (4).

No clinically significant pharmacokinetic interaction has been reported with the concomitant use of risperidone and buprenorphine. However, as a result of pharmacodynamic interactions increased sedation or cognitive dysfunction might occur (18).

Risperidone-related side effects are dose-dependent (3). Risperidone may cause sedation with reflex tachycardia and orthostatic hypotension due to potent α1-adrenergic receptor blockade. Risperidone should produce a clinically insignificant prolongation of the QT interval. Some patients may develop some acute serious side effects such as akathisia, dystonia and parkinsonism (19). Prolactin level may increase, epileptic seizures may develop.

At high doses, imbalance in serum electrolytes may be observed (20,21). There are also some cases of respiratory arrest, possibly related to dystonia (22,23). In cases of overdose, no adverse effects have been reported with the use of up to 6 times the recommended daily oral dose of risperidone (24). In a study analysing overdose cases, risperidone doses were between 8-248 mg (25). No serious side effects were observed in risperidone overdose cases, which were mostly asymptomatic, and mostly (in 10% of cases) minimal side effects such as tachycardia, sedation and dystonic reactions were reported (24,25). Supportive treatment is usually recommended for overdose (1).

Cases of atypical antipsychotic abuse are often based on reports from studies focussing on side effects. In a study analyzing data from the FDA Adverse Event Reporting System, there were cases of abuse of risperidone as well as quetiapine, aripiprazole, and olanzapine among the second-generation antipsychotics (8). Risperidone is the drug with the highest abuse potential after quetiapine according to the National Poison Advisory System data in the USA (10).

The cases of risperidone overdose or abuse reported to date are related to the oral form of risperidone. Only one case of long-acting risperidone overdose was found in the literature. In this case, a patient diagnosed with schizoaffective disorder was found unconscious at home after unintentional injecting 37.5 mg of long-acting risperidone on consecutive days to manage psychotic symptoms. This patient was taking clozapine and doxepin in addition to long-acting risperidone and was partially compliant with the treatment. The loss of consciousness was thought to be due to epileptic seizures. This case was discharged after three weeks of follow-up for possible antipsychotic side effects due to the high dose (26). Unlike the previous case, the dose of long-acting risperidone was much higher in this case; 12 doses of the 25 mg form and 38 doses of the 37.5 mg form were given intramuscularly at 2-3 day intervals, sometimes every day.

In addition, a case of overdose with paliperidone has also been reported. The patient injected a second dose of 234 mg of long-acting paliperidone five days after the first injection at the same dosage. Due to name similarity, a third dose was administered six days after the second dose. No side effects were reported in this case (27).

In this case, following cases in the literature, no serious side effects were observed, except for mild tachycardia and EPS-related side effects despite multiple intermittent and repeated injections. These symptoms resolved completely after 12 weeks. A small portion of long-acting risperidone is released initially, with the main release starting after 2 weeks and continuing for up to 4-6 weeks. Perhaps for these reasons, serious side effects may not be observed. Although the genetic analysis was not performed, the patient may be a

fast metabolizer, but it is a weak possibility.

Some cases of abuse have been reported with the oral form of risperidone. Cases of abuse related to the long-acting form of risperidone have not been found in the literature. This case is the second case of an overdose of long-acting risperidone and the first case of abuse of long-acting risperidone, as far as accessible. It should be kept in mind that the long-acting formulation of risperidone can be abused as much as the oral form of risperidone. Serum risperidone metabolite levels are lower in patients using extended-release risperidone than in those using the oral form (18). However, it is a disadvantage that risperidone blood levels were not studied in this case. Since the main release of the drug starts after a few weeks, possible side effects may occur in the late period.

This case suggests that the buprenorphine/naltrexone combination may be abused in cases without opioid dependence and that the long-acting form of risperidone may be as abused as the oral form. Although various side effects have been observed even at standard doses of risperidone and it is assumed that possible side effects can be adversely controlled when long-acting formulations are used, this case shows that long-acting risperidone may be safe even at high doses.

Abbreviations

EPS: Extrapyramidal syndrome
FDA: Food and Drug Administration

Declarations
Ethics approval and consent to participate

Written informed consent was obtained from the patient.

Consent for publication

Consent for publication was obtained from the patient.

Availability of data and materials

The documents of this case report are available from the corresponding author Dr. Neriman ARAS on reasonable request.

Competing interests

The author declares no conflict of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

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