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İlk doz paliperidon palmitat enjeksiyonu sonrasında gelişen akut hepatotoksisite: bir olgu sunumu

Özet

Paliperidon palmitat (PP), şizofreninin akut ve sürdürüm tedavisinde ayda bir kez IM olarak uygulanan, uzun etkili bir antipsikotiktir. Özellikle oral ilaç uyumu iyi olmayan hastalarda başarılı olduğu bildirilmiştir. En sık görülen yan etkileri baş dönmesi, uykululuk, anksiyete, enjeksiyon bölgesi reaksiyonları ve ekstrapiramidal sistem belirtileridir. Bu yazıda ilk doz PP kullanımının hemen sonrasında yüksek ateş ve karaciğer fonksiyon testlerinde yükseklik gelişen bir olgunun tartışılması amaçlanmıştır.

Anahtar kelimeler: Paliperidone palmitat, hepatotoksisite, karaciğer enzimleri

Development of acute hepatotoxicity following the first dose of paliperidone palmitate: a case report

Abstract

Paliperidone palmitate (PP) is a long-acting antipsychotic administered intramuscular once a month in the acute and maintenance treatment of schizophrenia. It has been reported to be successful especially in patients with poor oral drug compliance. The most common side effects are dizziness, sleepiness, anxiety, injection site reactions, and extrapyramidal system symptoms. The aim of this study is to draw attention to the rare side effect of PP and contribute to the literature by presenting a case of high fever and high liver function tests after the first dose of application.

Keywords: Paliperidone palmitate, hepatotoxicity, liver enzymes

INTRODUCTION

The inability of schizophrenia patients adapting to the treatment still remains an important problem in the management of the disorder. It was shown that more than 35% of the patients had compliance problems in the first few weeks of treatment and only 25% was fully adapted after two years (1). Long-acting injectable (LAI) formulations of antipsychotic agents have been reported to provide advantages in the treatment of acute and maintenance of schizophrenia patients having difficulty in oral medication with relapse risk (2,3). Paliperidone palmitat (PP) is a benzyloxazole derivative which is hydrolyzed into the active part of the paliperidone, and absorbed into systemic circulation, among the last generation antipsychotics developed as long-term effective injection (4). Following intramuscular administration of single doses, a higher peak concentration of 28% is observed on the deltoid muscle compared to the injection in the gluteal muscle. However, after four injections, the maximum plasma concentration between the two injection sites is balanced. (4, 5) Therefore, administration of two initial doses of deltoid muscle at days 1 and 8 will ensure rapid access to therapeutic drug concentrations (6).

In addition to the benefits of atypical antipsychotic drugs to patients, serious side effects limiting the clinical use of these new agents can be seen. Especially appropriate prescription and dosing of LAIs is required because of their long half-lives, delayed release, and risk of post-injection side effects. In terms of reliability, it has been reported that atypical antipsychotic agents can cause reversible/irreversible movement disorders such as tardive dyskinesia, increase in sleep time, weight gain, and impaired glucose and lipid metabolism (7-9). Common adverse events with PP were headache, vomiting, extremity pain, and injection site pain (10). Patients with schizophrenia who developed acute persistent circulatory failure and extrapyramidal symptoms requiring vasopressors and mechanical ventilation, and resulted with death after receiving injections of paliperidone palmitate was reported in the literature (11, 12). In the literature, there are also cases with delirium and liver enzyme elevation caused by PP (13,14). In this article, it is aimed to present a case in terms of high fever and high liver function tests immediately after the first dose of PP.

Case

Male patient, at the age of 25, single, high school graduate, with diagnosis of schizophrenia-acute exacerbation was hospitalized to the psychiatry clinic for treatment. Written informed consent was obtained from patient. The patient was unable to go to work for 2 years and lived with his parents. The psychiatric examination of the patient had intense persecution and reference delusions. It was learned that he believed aliens were placed in the body of his parents. He attacked his mother with a knife because of the auditory hallucinations of these creatures and their neighbors interpreting and directing him. He had delusions associated with all his actions were followed by external cameras placed in his home. When the outpatient psychiatric clinic records were examined, it was observed that he had not adapted to oral medication treatment for the last two years. He had discontinued his medications many times, and he applied to the emergency service with acute agitation. Routine blood tests (fasting glucose, hemogram, thyroid function tests, liver function tests, urea, creatinine, hepatitis markers, lipid profile, B12, folic acid, ferritin, vitamin D) were requested on the first day of hospitalization, and results were found in the normal range. PP injection was applied once in the inpatient service at a dose of 150 mg due to treatment compliance problems. One day after the application; high fever (39.5 C^0), diarrhea, nausea, weakness, muscle pain and liver function test (LFT) values increased. In the physical examination, he was conscious and there was no increase in muscle tonus, there was'nt any sign of rigidity in the neck and four extremities. Following these developments, the patient was evaluated by specialists of the infectious and the internal diseases. Suggested tests were performed for medical differential diagnosis. Detailed viral, autoimmune and serological tests were within normal limits and the urine was found to be negative. Serology was negative for viral hepatitis (HBsAg= 0.10 UI/ml, anti-HBsIg G=6 mIU/ml, anti-HCV=0.08 S/CO), HIV (anti-HIV=,0.3 S/CO), acute infection with cytomegalovirus (Anti-CMV IgM=3 S/CO), herpes simplex (HSV-1 IgM=16 U/ml), and Epstein-Barr viruses (Anti EBV IgG=0.4 ISR). Antinuclear antibody (ANA<1/40)), liver-kidney microsomal antibody (LKM<1/40), antimitochondrial antibody (AMA<1/40), smooth muscle antibody (SMA<1/40) and perinuclear antineutrophil cytoplasmic antibody (PANCA=4 U) were also negative. Therefore, infection-induced and autoimmune causes were excluded. Upper and lower abdomen ultrasound scan

was found to be normal. Acute hepatotoxicity in the patient was attributed to PP. In order to provide hydration, 3000 cc/day balanced electrolyte solution was administered intravenously for 2 days. Peripheral cold application was performed. Body temperature returned to normal at day 4. When the blood tests were examined retrospectively, it was determined that LFT values increased after injection by the first day of hospitalization. (AST: 155, ALT: 200, GGT: 260). (Table 1). CPK levels were also within the normal range. PP 8th day dose was not administered. It was found that there was no previous medical history of any general medical illness and no liver dysfunction in family history. At the end of the third week, LFT values gradually decreased. After LFT values returned to normal, the patient was followed up for 1 week without psychotropic medication. Then, oral haloperidol 10 mg/day was followed by lorazepam 1.25 mg/day treatment in order to maintain sleep continuity. He was discharged with partial improvement in his psychotic symptoms and lack of elevation in his LFT values.

Table 1 Here

Discussion

In this case report, a young adult schizophrenia patient who developed acute hepatotoxicity after PP was presented. The LAI antipsychotics provides a consistent distribution of drugs, regardless of the ability or willingness to take orally on a regular basis. This reduces the risk of taking too much or too little medication intentionally or accidentally and minimizes dosage deviations. The frequency of being preferred in the treatment of schizophrenia in the last 10 years has increased due to these advantages (15, 16). According to double-blind, placebo-controlled, acute treatment studies, the most common adverse events associated with PP were EPS (0-5%), injection site reactions (0-10%), dizziness (2-6%), and drowsiness/sedation (5-7%). In four fixed-dose, double-blind, placebo-controlled trials, the frequency of PP therapy was reported to be 5.8% due to adverse events (10, 17-19). When the literature has been reviewed, it is observed that there are few case reports about the elevation of LFT related to PP. It was seen in a female patient who had deterioration of LFT after the first dose of PP that the enzyme levels returned to normal at the 6th day. After the 2nd dose PP administration, it increased again, and the drug was discontinued (14). Moreover, acute onset delirium was seen after the second PP dose in an adolescent with schizophrenia (13). In our case, the use of LAI form of haloperidol was not considered

due to traminitis reported in the literature (20-22). Risperidone-induced hepatotoxicity has also been reported in another patient using synthetic cannabinoid (23). When the patient is evaluated in terms of differential diagnosis, he did not show any evidence of autonomic system imbalance and there was no rigidity or other features indicative of neuroleptic malignant syndrome. In our case, LFT returned to normal level in the third week and in the long term, the patient was followed with a typical long-acting antipsychotic treatment (zuclopenthixol decanoate 200mg/2 weeks dose). The role of liver metabolism in cytochrome P450 2D6 and 3A4 was limited because 60% of paliperidone was excreted unchanged in the urine. It has been reported that in the case of renal insufficiency, dosage adjustment is recommended for creatinine clearance, whereas in mild and moderate liver failure no dose adjustment is required (24). Although there is a suggested psychotropic effect in liver failure (25), if individual sensitivities are present as in this case, it is appropriate to monitor LFT and other clinical parameters when fever is observed by initiating PP. Our report raising awareness of clinicians about this rare side effect contributes to the literature. Controlled and longitudinal studies are required to assess the short- and long-term hepatotoxic effects of PP.

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Table 1. Evaluation of laboratory test results of the patient

	First Day	Third Day	First week	Third week	Normal Range
Hemoglobin (g/l)	14.8	14.3	13.6	13.2	13.4-19.6
White blood cell count (mm ³)	4.280	6.800	5900	4800	2.74–6.15

Platelet count (mikrolitres)	284.450	220.603	260.300	302.100	150.000- 400.000
Alanine aminotransferase (U/l)	24.6	200	146.7	38.9	17.5-34.5
Aspartate aminotransferase (U/L)	29.5	155	80.6	33.2	15-41
Alkaline phosphatase (U/L)	78.5	160.4	80.5	68.4	0-120
γ glutamyltransferase (U/L)	44.2	260	150.4	60.5	0-55
Creatinine phosphokinase (U/L)	35.4	98.7	46.6	34.2	30-200
Lactic acid dehydrogenase (U/L)	132.2	440.8	290.5	160.6	120-220