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OLGU SUNUMU/CASE REPORT

Paliperidone palmitate-induced sialorrhoea

Paliperidon palmitata bağli siyalore

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Abstract

Extrapyramidal, metabolic, and cardiac side effects were reported for atypical antipsychotics; although a few resources show paliperidone-induced sialorrhea, there are no resources that show paliperidone palmitate-induced sialorrhea. In this paper, we present the paliperidone palmitate-induced sialorrhea side effects of a patient who applied on our clinic

Key words: Paliperidone palmitate, sialorrhoea, schizophrenia

Öz

Atipik antipsikotiklere ilişkin ekstrapiramidal, metabolik ve kardiyak yan etkiler bildirilmiştir. Paliperidona bağlı siyalore bildiren az sayıda kaynağa rastlanmasına karşın paliperidon palmitata bağlı siyalore bildiren kaynağa rastlanmamıştır. Bu yazımızda kliniğimize başvuran ve paliperidon palmitat başladığımız bir hastada gelişen siyalore yan etkisi sunulmuştur.

Anahtar kelimeler: Paliperidon palmitat, siyalore, şizofreni

INTRODUCTION

Clozapine, the prototype of the atypical antipsychotic drugs, is accepted as the gold standard in antipsychotic treatment and started to be used commonly in clinics 20 years after its introduction in 1959[1]. After risperidone, the first non-clozapine atypical antipsychotic drug, was introduced in 1994, other atypical antipsychotic drugs were also launched[1,2]. In 2006, the US Food and Drug Administration (FDA) certified paliperidone in schizophrenia treatment and the drug went into use[3].

Paliperidone is one of the atypical antipsychotic drugs in the market[4]. Risperidone turns into 9-hydroxyrisperidone by cytochrome P450 (CYP450) 2D6 and then the active particle paliperidone is generated[5]. Paliperidone palmitate (PP) is the long-acting and injectable form of paliperidone, which is hydrolyzed by palmitic acid[6-8]. PP is an atypical antipsychotic that is used especially in schizophrenia and its efficiency and tolerability is proven[9,10].

In treatment, many schizophrenic patients have difficulties with daily oral treatment; this is one of the most important factors that disrupt treatment compliance[11]. Therefore, long-acting antipsychotic drugs should be used for schizophrenia treatment[12,13].

As a result of sialorrhoea (also known as ptyalism, hypersalivation), patients may have physical (perioral chapping, infection, halitosis, dehydration, and aspiration pneumonia) and psychosocial (isolation, embarrassment, low self-esteem, and difficult social interaction) complications[14]. In the literature, sialorrhoea is related to clozapine; clozapine is a well-known bad example in this respect[15,16]. Rarely, other antipsychotic drugs induced sialorrhoea. In the prospectus of PP, there is a warning about increased salivation (salivary hypersecretion)[17].

In this article, a case in which sialorrhoea caused by PP is presented and probable physiopathological mechanisms and its treatment will be discussed in line with literature.

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CASE

Twenty three-year-old, single, female patient was brought to our hospital by her father because she has problems like "getting away from home, insomnia and talking to herself." Her complaints first started when she was 19 years old. She used to hear voices saying "run away from home, your family will kill you." She entered a mental hospital for 25 days after the diagnosis of paranoid schizophrenia. She was discharged from the hospital after she had been treated with haloperidol, 20 mg/day, and biperiden, 6mg/day. Later, she entered the same mental hospital 6 times (staying approximately for 20 days each time). The patient also entered the psychiatric clinic of the university hospital for two weeks. The patient had various treatments: haloperidol, zuclopenthixol, olanzapine, risperidone, paliperidone, aripiprazole, quetiapine, and risperdal consta. She did not take medicine in efficient doses or enough times during that period. In her background, she had nothing but nicotine addiction.

When the patient was examined mentally, her physical appearance was incompatible with her age and sociocultural condition. She could not have eye-contact or keep eye-contact for a long time. She could not maintain attention and go on easily. She had restricted affect and was in a euthymic state. She had audial hallucination in perception and visual hallucination in her story. The speed and themes of associations decreased. She had reference and persecution thoughts in mind. The patient also was overthinking death. Her ability of judgment, abstract thinking, and assessment of truth degraded. Psychophysiologically, her circadian rhythm was degraded, and her appetite and libido were increased. She had psychomotor retardation. She did not have insight clinically.

With the aim of diagnosing, hemogram, routine biochemistry, electrolytes, and thyroid panel studies were done, intended to eliminate other medical reasons for her condition. The results were normal. Ear, nose and throath (ENT) examination ruled out local pathology and allergic reaction in the pharynx. The patient did not have fever, rigidity, involuntary movements, other weakness, focal neurological deficit or signs of Parkinsonism. In her neurologic examination and in cranial MR, no pathologic symptoms were found. A psychometric test could not be done because of her inadaptability problems. Because of her story, life style, explicit impairment in her self-care, considerable regression in her social performance, and findings in the mental examination, she was diagnosed with schizophrenia.

In her treatment, PP deltoid equivalent to a 150 mg injection on the first day and PP deltoid equivalent of 100 mg injection on the eighth day were recommended. At the first follow-up examination, the patient's positive symptoms were improved and she could sleep properly. The irritation and sensitivity because of excessive napkin use, depending on the increase in saliva amount, was recognized at the first examination because the patient was explicit. Chewing gum and using two pillows to sleep was recommended to the patient with the treatment of 6mg/day biperiden. After 15 days, the patient and her father came and said that her sialorrhoea increased, there was 20 cm in diameter wetness on her pillow and it stank. The treatment with biperiden was decreased and stopped being taken. Amitriptyline was included in the treatment. The complaints of the patient lessened and ended a week later. In maintaining treatment, the patient goes on using PP equivalent to 75 mg and she comes to be checked regularly.

DISCUSSION

Mechanism of actions of atypical antipsychotic drugs were not understood exactly. These drugs' brain-function organizing clinical antipsychotic mechanisms which blocks dopamin (DA) D2-receptors (D2-R) (especially subcortical) and serotonin receptors (5-HT) (especially 5-HT2A-R) (especially cortical) are not clear[18,19].

Paliperidon has many common pharmacologic features with Risperidon[20]. Though, it is different from Risperidon because its Alpha-2 antagonism is stronger than Alpha-1(5). However, it shows antagonist effects to the adrenergic and histaminergic receptors[21]. Because it does not show antagonist effects towards cholinergic receptors, the tendency of anti-cholinergic side-effect is low[22,23]. The studies on Risperidon[17] and Paliperidon[13,24] show that they cause sialorrhoea. It was stated that paliperidon caused sialorrhoea connected to dose[13]. In the meta analysis performed by Harrington and English, 15 articles about paliperidon was searched and 3779 patients were examined and only 3 patients had sialorrhoea among very rare seen side effects[25].

Saliva is produced by major (parotis, submandibular, sublingual) and a few hundres of minor salivary glands. Salivary glands produce 750ml -1.5 lt. saliva Daily[26,27]. Sypmpathetic and parasympathetic systems act together in saliva secretion. But, saliva is actually under the control of parasympathetic muscarinic bundles[28]. Although the parasympathetic activity comes into prominence in salivary glands, it is expected to increase the secretion in sympathetic stimulation[29]. The hypothesis that is suggested on pathologic physiology of atypical antipsychotic drugs, its prototype Clozopine, drugs' causing sialorrhoea are arranged in this ways.

Firstly, the balance impairment between the M3 and M4 muscarinic receptors, α2-adrenergic antagonism, decreased larynx peristalsis, and loss of the swallowing reflex were explained[30,31]. The muscarinic hypothesis is not for PP, because it is not possible for PP to cause derangement between the M3 and M4 receptors[5]. The fact that PP causes α2-adrenergic antagonism is known[17]. In the literature, it was reported that risperidone[32-35], olanzapine[36,37], quetiapine[38], and aripiprazole[39,40] cause sialorrhoea from α2 antagonism. Possible mechanisms linked to receptor block caused by non-clozapine atypical antipsychotics on secondary sialorrhoea were summarized in Table 1.In our case, we assume that PP causes sialorrhoea using the same mechanism. In the literature, there are two case statements on the use of biperiden in sialorrhoea treatment[41,33]. We attribute the failure in our patient's treatment to the fact that PP does not affect muscarinic receptors.

Amitriptyline is used in sialorrhoea treatment triggered by atypical antipsychotic drugs[42,43]. Amitriptyline is a tricyclic antidepressant; it inhibits reuptake of noradrenaline and serotonin[44]. It may lessen the side effects of sialorrhoea with this mechanism.

Table 1: Secondary sialorrhoea to receptor block caused by non-clozapine atypical antipsychotics

Publication	Patients and Diagnosis	Drugs used	Dose and Time	Comment
Mendhekar DN et al (2010)	18-year-old, Male, Schizophrenia	Paliperidone+ Divalproex sodium	Paliperidone: 6 mg/day,Divalproex sodium: 500 mg/day, Within 12 hours	Dystonic dysphagia
Brahm NC et al (2007)	46-year-old, White female, Mental retardation (IQ:20)	Risperidone	2 mg/day, Within a day	Associated with parkinsonian symptoms
Varghese ST et al (2006)	38-year-old, Male, Schizophrenia	Risperidone	4 mg/day, After 6 months	Drug-induced pseudoparkinsonism
Stewart JT et al (2003)	76-year-old, Male, Dementia of Alzheimer type	Risperidone	1 mg/day, After 3 months	Dystonic reaction
Nair S et al (2001)	35-year-old Caribbean male, Schizophrenia	Risperidone	4 mg/day, After 8 hours	EPS-related dysphagia
Kılınç S et al (2015)	14-year-old, Male, Moderate intellectual disability+Cerebral Palsy	Aripiprazole	5 mg/day, After 4 weeks	Pseudoparkinsonian bradykinesia
Lin TW et al (2012)	54-year-old, Male, Schizophrenia	Aripiprazole	30 mg/day, In 3 weeks	Neuroleptic-induced parkinsonism
Kohen I et al (2009)	66-year-old, Female, Bipolar disorder+Cerebellar dysfunction	Quetiapine+ Lorazepam+ Citalopram	Quetiapine: 200 mg/day, Lorazepam: 1.5 mg/day, Citalopram: 20 mg/day, After several months	EPS-related dysphagia
Sagar R et al (2005)	24-year-old, Male, Bipolar affective disorder	Olanzapine+ Sodium valproate	Olanzapine:20 mg/day Sodium valproate: 1000 mg/day, After 5 days	A rare side effect of olanzapine.

Table 2: Secondary sialorrhoea associated with dysphagia caused by non-clozapine atypical antipsychotics

Publication	Patients and Diagnosis	Drugs used	Dose and Time	Comment
Usta MG et al (2012)	14-year-old, Male, Mental Retardation +Cerebral Palsy	Risperidone	1 mg/day, After a week	Alpha-2 adrenergic receptor block
Liang CS et al (2010)	63-year-old, Chinese, female, Schizophrenia	Risperidone	4 mg/day, After 2 months	Alpha-2 adrenoceptor block
Panagiotidis PT et al (2007)	18-year-old, Female, Paranoid Schizophrenia	Risperidone	6 mg/day, On the fourth day	Central adrenergic antagonism
Gajwani P et al (2001)	22-year-old, African –American male, Paranoid Schizophrenia	Risperidone	10 mg/day, No data	Alpha-2 adrenergic receptor block
Praharaj SK et al (2009)	27-year-old, Indian male, Bipolar affective disorder	Aripiprazole+Sodium Valproate	Aripiprazole: 10 mg/day Sodium valproate: 1000 mg/day, After 3 months	Alfa-2 adrenergic antagonism
Allen S et al (2007)	36-year-Old, Korean female Schizoaffective disorder	Quetiapine	25 mg/day, Within a day	Alpha-2 adrenergic receptor block
Hori T et al (2006)	34-year-old, Japanese male, Delusional disorder	Olanzapine+Fluvoxamine	Olanzapine: 7.5 mg/day Fluvoxamine: 200 mg/day Within a day	Cholinergic (as an agonist M4) receptors activity
Perkins DO et al (1998)	20-year-old, Caucasian female Schizophrenia	Olanzapine	15 mg/day, Within a day	Cholinergic (as an agonist M4) receptors activity

Lastly, schizophrenia and atypical antipsychotic drugs impair the swallowing reflex and cause dysphagia[45-48]. In dysphagia, sialorrhoea is seen, depending on saliva accumulation[28]. Dysphagia in schizophrenics is mostly ignored[48]. In the literature, there are study cases and search texts which state that atypical antipsychotic drugs cause dysphagia related to the drug; these are clozapine[45,49], risperidone[45-47,50,51], paliperidone[45,48], olanzapine[45,52], quetiapine[53,54], and aripiprazole[55] (Table 2). Our patient did not complain about dysphagia with solid or liquid food, and the patient and her family did not give any information about such a complaint. We did not expect that our patient had dysphagia because of the drug. After all, it may be the dysphagia that goes with subthreshold symptoms and is not described by the schizophrenic. We assume that this study case we made on PP-induced sialorrhoea will make an important contribution to the literature. In order to clarify this case, case declarations and studies with extensive samples are needed.

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