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Can Tremor Be a Rare Side Effect Related to Molnupiravir?

Tremor, Molnupiravir İlişkili Nadir Bir Yan Etki Olabilir mi?

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Abstract

While the Coronavirus disease-2019 (COVID-19) pandemic has been going on for more than two years, the drug studies required for treatment still continue. As a result of these studies, molnupiravir, which has been approved for use in many countries in the treatment of COVID-19, has been put into use in our country with the guide published on February 12, 2022. One of the most important parameters required for a drug to be used at the appropriate dose and duration is its low side-effect profile. Molnupiravir is a generally well tolerated antiviral, and the most common side effects associated with its use are diarrhea, nausea, vomiting, headache, dizziness, and rash. In this report, it was aimed to present the details of the tremor symptom that developed during molnupiravir treatment in three patients we followed up.
Keywords: Molnupiravir, tremor, side effect, COVID-19, treatment

Öz

Koronavirüs hastalığı-2019 (COVID-19) pandemisi iki yılı aşkın süredir devam ederken tedavi için gerekli olan ilaç çalışmaları ise sürmektedir. Bu çalışmalar sonucunda, COVID-19 tedavisinde pek çok ülkede kullanım onayı alan molnupiravir ülkemizde de 12 Şubat 2022'de yayınlanan rehber ile birlikte kullanıma girmiştir. Bir ilacın uygun dozda ve sürede kullanılabilmesi için gerekli en önemli parametrelerden biri yan etki profilinin düşük olmasıdır. Molnupiravir genel olarak iyi tolere edilen bir antiviral olup kullanımına bağlı görülen en sık yan etkiler ishal, bulantı, kusma, baş ağrısı, baş dönmesi ve döküntü olarak bildirilmektedir. Bu bildiride takip ettiğimiz üç olguda molnupiravir tedavisi esnasında gelişen tremor semptomu ile ilgili detayların sunulması amaçlanmıştır.
Anahtar Kelimeler: Molnupiravir, tremor, yan etki, COVID-19, tedavi

Introduction

Molnupiravir has been put into use in our country with the Ministry of Health Coronavirus disease-2019 (COVID-19) guide published on February 12, 2022. Accordingly, it is recommended to be used in adult (≥18 years old) patients with COVID-19 who have a definite diagnosis by polymerase chain reaction (PCR), have a mild to moderate course, have symptoms in the first five days, and are at high risk for progression to severe COVID-19, regardless of vaccination status. Defined high risk groups are as follows: patients with advanced (>65) age, primary immunodeficiencies, cancer treated with chemotherapy in the last one year, solid organ transplantation, bone marrow transplantation, AIDS (CD4<200), patients who received radiotherapy in the last six months and who received Rituximab in the last year[1].

Molnupiravir is used at a dose of 2x800 mg/day for a total of five days. It can be used in outpatient setting. No special follow-up is required during the treatment process. Diarrhea, vomiting, dizziness, headache are common side effects[2,3]. A similar tremor developed during molnupiravir treatment in three patients we followed up, and the details were presented below[1].

Case Reports

Case 1

A 62-year-old male patient, who was admitted to our emergency department with complaints of weakness and

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shortness of breath that started two days ago, was transferred to the isolation service after the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) PCR test resulted positive. The patient had diagnoses of mestatic nasopharyngeal carcinoma, hypothyroidism and hypertension. In his physical examination, his general condition was good, he was conscious, cooperative, he had diffuse rales in the bilateral middle and lower zones of the lung and SaO_2 was 90% in room air. No pathology was detected in other system examinations. In laboratory tests, leukocyte count was 6300/mm^3, hemoglobin level 10.1 g/dl, platelet count 106.000/mm^3, lymphocyte count 7.5%, C-reactive protein (CRP) level 6 mg/dl, liver and kidney function tests were normal, D-Dimer level was 0.43 mg/L, IL-6 level was 4.07 pg/ml, and mild bilateral ground glass areas were observed on thorax computed tomography (CT) of the patient. On the third day of the patient's treatment, molnupiravir (1600 mg/day, in two doses) was initiated, and bilateral upper extremity tremor developed. In the physical examination, it was observed that the tremor was especially in the wrist, hand and fingers, both at rest and during motor movements. The patient's thyroid function tests were as follows: thyroid stimulating hormone (TSH): 3.72 µIU/L (reference range: 0.4-4.0 µIU/L), fT3: 3.6 pg/ml (reference range: 2.5-5.0 pg/ml), fT4: 0.7 ng/dl (reference range: 0.6-1.0 ng/dl). No additional pathology was found to explain the tremor from a neurological point of view. Molnupiravir treatment was completed for five days and discontinued, and the tremor completely regressed in a one-week follow-up.

Case 2

A seventy-five-year-old male patient, who was admitted to our emergency department with the complaint of weakness that started a few days ago, was hospitalized in the isolation service after positive SARS-CoV-2 PCR result. The patient had known coronary artery disease, hyperlipidemia and hypertension. No pathology was found in his physical examination and SaO_2 in room air was 96%. In laboratory examinations; leukocyte count was 5700/mm^3, hemoglobin level 14 g/dl, platelet count 231000/mm^3, lymphocyte count 27.6%, CRP level 0.52 mg/dl, liver and kidney function tests normal, D-Dimer level 0.47 mg/L, IL-6 level 4.31 pg/ml, and no infective pathology was observed in the thorax CT of the patient. On the third day of the patient's treatment, molnupiravir (1600 mg/day, in two doses) was initiated, and bilateral upper extremity tremor developed. In the physical examination, it was observed that the tremor was especially in the wrist, hand and fingers, both at rest and during motor movements. No neurological pathology was found to explain the tremor, and molnupiravir treatment was completed for five days and stopped. The tremor disappeared in the one-week follow-up after the end of the treatment.

Case 3

A 45-year-old female patient with known diagnosis of metastatic breast carcinoma, epilepsy, tachycardia and hypothyroidism was admitted to the isolation service after the positive SARS-CoV-2 PCR test, which was requested before hospitalization due to platelet replacement. No pathology was found in her physical examination, except for bibasilar rales, and her SaO_2 in room air was 94%. In laboratory examinations; leukocyte count was 11000/mm^3, hemoglobin level 7.8 g/dl, platelet count 16000/mm^3, lymphocyte count 4.6%, CRP level 21.3 mg/dl, liver and kidney function tests normal, D-Dimer level 4.53 mg/L, and bilateral basal consolidations were detected in thoracic CT of the patient. On the third day of the patient's treatment, molnupiravir (1600 mg/day, in two doses) was initiated, and bilateral upper extremity tremor developed. In the physical examination, it was observed that the tremor was only in the wrist and distal both at rest and during motor movements. Patient's thyroid function tests were as follows: TSH: 2.56 mIU/L (reference range: 0.4-4.0 mIU/L), fT3: 4.1 pg/ml (reference range: 2.5-5.0 pg/ml), fT4: 0.82 ng/dl (reference range: 0.6-1.0 ng/dl). No additional neurological pathology was found to explain the tremor, and molnupiravir treatment was completed in five days. In the one-week follow-up after the treatment, it was observed that the tremor complaint completely regressed.

Discussion

More than 460 million patients and more than six million deaths have been reported so far in the COVID-19 pandemic[4]. Although the hospitalization and death rates due to the disease have decreased with the vaccines developed, the need for antivirals for the treatment of the disease still continues[5].

Molnupiravir, which has been shown to be effective *in vitro* against SARS and Middle East Respiratory Syndrome coronaviruses and seasonal/pandemic influenza viruses, has started to be produced for use in the treatment of SARS-CoV-2 infection. It acts by preventing RNA replication through multiple mutations in the RNA polymerase of SARS-CoV-2[6].

According to studies, molnupiravir was well tolerated in patients with COVID-19, no dose-limiting side effects were observed in 800 mg twice daily use, and the frequency of side effects was found to be similar to placebo groups. Diarrhea (3%), nausea (2%), dizziness (1%), headache (1%) were the most frequently reported adverse events[5-8].

As far as we know, tremor is not among the side effects of molnupiravir in the literature[5-8]. It was thought that the tremor that occurred in our patients might be due to the metabolism of molnupiravir or a possible reaction between other drugs used by the patients and molnupiravir.

When the drugs taken by the patients were examined (Table 1), it was seen that there were no other drugs used in common except molnupiravir in three patients.

Commonly used calcium channel blockers (amlodipine and nifedipine, respectively) were used by Case 1 and Case 2, and when the interaction between molnupiravir and calcium channel blockers was investigated, no interaction was found.

When the interactions of four drugs (dexamethasone, levothyroxine sodium, budesonide, ipratropium bromide monohydrate/salbutamol sulfate) and molnupiravir were investigated in Case 1 and Case 3, no interaction was found.

When the interaction of all drugs taken by the subjects with molnupiravir was investigated separately for each drug, no interaction was found to explain the tremor.

In all three patients, tremor was observed in the bilateral hands and occurred on the third day of molnupiravir treatment. It was observed that the tremor continued both at rest and during motor movement. Since the patients were in the population at risk for progression of COVID-19, molnupiravir continued to be used and five days of treatment was completed. The tremor was completely regressed in all 3 patients during the one-week follow-up after the completion of molnupiravir treatment.

The time to reach high plasma concentration of molnupiravirin is 1.5 hours and its half-life is 3.3 hours[9]. Excretion of the drug is via the urinary tract (3%)[9]. The rapid and complete regression of tremor in our patients after molnupiravir was discontinued might be related to the drug's metabolism and elimination from the body. Again, in the comparisons made in terms of possible drug interaction, the absence of any reaction between molnupiravir and the drugs taken by the subjects suggests that tremor may be a side effect due to molnupiravir.

There are many causes of drug/substance-related tremor, primarily caffeine, beta-adrenergic agonists, selective serotonin reuptake inhibitors, and tricyclic antidepressants (Table 2)[10,11].

Some of the drugs in the table above that can cause tremor are among the drugs used by our patients. While cases 1 and 3 received molnupiravir, they also received levothyroxine and dexamethasone. Of these drugs, levothyroxine was used both before and after molnupiravir treatment in both patients, and

Table 1. Drugs that the cases were taking during molnupiravir treatment

Case 1	Case 2	Case 3
- Dexamethasone	- Paracetamol	- Dexamethasone
- Diltiazem	- Nifedipine	- Enoxaparin
- Calcium and zinc	- Atorvastatin	- Metoprolol
- Rivaroxaban	- Acetylsalicylic acid	- Budesonide
- Esomeprazole		- Ipratropium bromide monohydrate/salbutamol sulfate
- Amlodipine/perindopril		- Magnesium
- Sertraline		- Levothyroxine sodium
- Budesonide		- Pantoprazole
- Ipratropium bromide monohydrate/salbutamol sulfate		- Levetiracetam
- Levothyroxine sodium		- Acetylcysteine
- Levofloxacin		
- Acetylcysteine		

Table 2. Drugs and substances that can cause tremor[11]

Antiarrhythmic drugs	Amiodarone
Antidepressant drugs	SSRI, SNRI, tricyclic
Antiepileptic drugs	Carbamazepine, phenytoin, valproic acid, lamotrigine
Beta agonists	Albuterol, terbutaline
Glucocorticoids	Dexamethasone, prednisone
Mood stabilizers	Lithium
Other drugs	Cyclosporine, tacrolimus, theophylline
Substances	Caffeine, nicotine, cocaine
Sympathomimetics	Amphetamine, methylphenidate, epinephrine
Thyroid hormones	Levothyroxine
Toxins	Arsenic, DDT, naphthalene, cyanide

SNRI: Serotonin-norepinephrine reuptake inhibitor, SSRI: Selective serotonin reuptake inhibitor, DDT: Dichlorodiphenyltrichloroethane

the thyroid function tests of the patients were within normal limits, so levothyroxine was not considered as the cause of tremor. Dexamethasone was started together with molnupiravir treatment (6 mg/day) in Case 1, then it was tapered off. In Case 3, molnupiravir was started on the fourth day of treatment, but tremor occurred one day before dexamethasone was started. In addition, although dexamethasone was continued after molnupiravir treatment was completed in Case 3, the tremor disappeared, so it was not considered as dexamethasone-related tremor.

Conclusion

In conclusion, since there were similarities in the time of onset and disappearance of tremor, its reversibility, and the mode of occurrence (at rest and in motion) in all three of our patients, it was thought that this symptom might be related to molnupiravir. There is a need for detailed studies that can also explain the physiopathogenesis in order to use clearer expressions.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.M., İ.K., Concept: İ.K., Design: İ.K., Data Collection or Processing: S.M., Analysis or Interpretation: S.M., İ.K., Literature Search: S.M., İ.K., Writing: S.M.

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