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A case of acute renal failure with COVID-19 under Molnupiravir treatment

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ABSTRACT

Objective: Diarrhea, nausea, and vomiting are the most commonly reported mild side effects of Molnupiravir. However, this case shows that it may indirectly cause acute renal failure.

Case: 67-Year-old male patient diagnosed with hypertension and chronic obstructive pulmonary disease developed severe nausea, vomiting, and diarrhea with the use of drugs. In the patient's examinations, severe deterioration in kidney functions occurred. The patient who developed acute tubular necrosis was taken to hemodialysis twice. Intravenous hydration and supportive treatments were started. In the follow-up, clinical and renal functions improved. In patients over 65 years of age and with comorbidities, the adverse effects of Molnupiravir should be considered and followed closely.

Keywords: COVID-19, SARS-COV-2, Molnupiravir, Diarrhea, Renal Failure

INTRODUCTION

Positive developments have been achieved with vaccination and anti-viral treatments against Coronavirus disease 2019 (COVID-19). Since the RNA-Dependent RNA-Polymerase (RdRp) enzyme plays an important role in the replication of the Severe acute Respiratory Syndrome Virus (SARS-COV-2), it is important for antiviral treatment targets (1, 2).

Favipravir and Remdesivir are RdRp inhibitors and have been approved for treatment. Both drugs have been shown to reduce clinical symptoms and slow down progression (3,4).

However, an alternative treatment has been sought because there are only intravenous (IV) forms of Remdesevir and its weak pharmacokinetic efficacy in Favipravir. Recently, orally available Molnupiravir has been promising due to its tolerability and positive efficacy profile. It suppressed the replication of SARS-COV-2 through inhibition of RdRp and attracted great attention by providing a rapid and effective reduction in viral load. It was developed by scientists at Emory University (USA) (5,6).

Phase-1 and 2 studies have been completed(7,8). However, Phase-3 studies are still in progress, and the efficacy, tolerability, and safety profile remain unclear(9). This case report aims to present a clinical case infected with SARS-Cov-2, who developed severe nausea, vomiting, and diarrhea with Molnupiravir treatment and progressed to severe acute renal failure (ARF) during follow-up.

CASE

A 67-year-old male patient with hypertension and chronic obstructive pulmonary disease diagnosed for 10 years, regularly uses Perindopril/Indamapid (10/2,5mg/day) tablet (TB), metoprolol (50 mg/day) tb, formoterol-budenoside 400 µg/day inhaler (inh), tiotroprium bromide (inh) drugs. The patient, who had been Synovac vaccinated 3 times before, applied to the Kırşehir Training and Research Hospital pandemic emergency on 17.02.2022 with complaints of fever, weakness, fatigue, sweating, and myalgia. There were no complaints of nausea, vomiting, or diarrhea at admission.

Due to patient's clinical status was good, laboratory examination and direct X-ray/thorax CT were not taken from the patient. Infection positivity has been checked with Polymerase Chain Reaction (PCR) test. SARS-COV-2-Omicron variant positivity has been detected. On 18.02.2022, Molnupiravir 200 mg tablet (TB) was started as 2x800 mg outpatient treatment by the healthcare teams.

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Molnupiravir was used regularly for 5 days. He continued to his own previous drugs as well. During this time, he received only paracetamol TB as an analgesic. He did not use non-steroidal anti-inflammatory. However, the patient had severe nausea, vomiting, and diarrhea 15-20 times a day with the use of Molnupiravir. Oral intake is impaired. He could not provide fluid hydration. Diarrhea disappeared after the medication was discontinued, but complaints of nausea, vomiting, and loss of appetite persisted. He applied to the emergency department on 07.03.2022 with these complaints. Fever: 36.1 (C°) Pulse: 106/minute, Blood Pressure: 90/60 mmHg, Respiratory rate: 18/minute, oxygen saturation (SpO2): % 96. His general condition was poor; he had a sluggish and tired appearance. He was re-evaluated for SARS-COV-2 infection. PCR test was negative. Pneumonia or any focus of infection was not detected. In the examinations of the patient at the time of admission to the emergency department, urea: 190mg/dl, Blood urea nitrogen (BUN):89 mg/dl Creatinine (CRE): 8,9 mg/dl, GFR: 5 ml/min, Sodium (Na): 136 mmol/l, Potassium (K): 4.8 mmol/l It came as Calcium (Ca):9 mmol/l, phosphorus(P): 5.5 mmol/l (**Table-1**).GFR levels were calculated with Chronic Kidney Disease Epidemiology Cooperation (CKD-EPI) formula (10). There was severe metabolic acidosis in venous blood gas. Ph: 7.17, PCO_2:39 mmHg, PO_2: 15.2 mmHg, HCO_3-std:13.1 meq/l, Lactate(mmol/l):0.7 detected (**Table-2**).

Urinary catheter inserted. Residual urine output of 10-20 cc was observed. Proteinuria, 1 (+) erythrocyte, and leukocytes were detected in spot urine (**Table-3**). According to clinical and laboratory findings, an emergency hemodialysis (HD) indication was made in the patient. He was placed on hemodialysis for 2 hours with a temporary HD catheter. Ultrafiltration (UF) was not performed because there were no signs of hypervolemia such as pretibial edema and pulmonary edema. Low molecular weight heparin was used as anti-coagulation. 80 cc/hour saline (0.9%) IV was started.

Nephrotoxic agents avoided. After the first dialysis, he was taken to HD for a second time for another 4 hours, as uremia and acidosis continued at a serious rate in his control examinations (**Tables-1 and 2**). UF is not done again. In terms of aetiology, urinary system USG was performed. The parenchymal echogenicity of both kidneys was observed as grade-1 increased (**Table-3**).

In the follow-ups, the patient's clinic tended to improve. Urine output was about 70-80 cc per hour. He was followed up without dialysis. Anti-hypertensive drugs were not used during the hospitalization. Blood pressures remained stable. Renal functions (Table-1) and proteinuria returned to normal (**Table-3**). Haemodialysis and urinary catheters were removed. He was discharged with recommendations.

Table-1. Changes in the patient's kidney function tests and complete blood count

Variables	History						
	First day	Second day	Third day	Fourth day	Fifth day	Sixth day	Seventh day
Urea (mg/dL)	190	153	123	103	75	59	32
BUN (mg/dL)	89	71	57	48	35	28	15
CRE (mg/dL)	8,9	7	3,13	1,78	1,42	1,31	1,04
GFR (mL/min)	5	7	20	39	51	56	74
Na (mmol/L)	136	137	137	139	142	141	140
K (mmol/L)	5	4,3	4,2	4,1	3,8	4,3	4
Ca (mmol/L)	9	8,4	8,4	8,3	8,1	7,8	7,9
P (mmol/L)	5,5	5,3	4	3,5	3	3	3,2
WBC (10^3/µL)	10,01	8,89	9,58	10,81	13,05	10,57	8,55
Hgb (g/dL)	14,9	13	11,6	11,6	11,3	11,2	11,1
Hct %	47	39,9	34,7	35,1	34	34,4	32,9
MCV (fL)	92,9	90,7	89	88	89,9	89,4	88,4
MCH	29,4	29,5	29,7	29,1	29,9	29,1	29,8
PLT (10^3 /µL)	281	236	185	190	193	204	222

BUN:Blood Urea Nitrogen;Cre:Creatinin;GFR:Glomerular Filtration Rate; Na:Sodium,K:potassium, Ca:calsium ;P: phosphorus,;WBC:White Blood Cell; Hgb:Hemoglobin;Hct: hematocrit;Plt: Platelet; MCV: Main Corpuscular Volume;MCH: Mean Corpuscular Hemoglobin

Table 2. Changes in the patient's venous blood gas

Venous Blood Gas Variables	History			
	First day	Second day	Third day	Seventh day
pH	7,17	7,19	7,40	7,46
PO_2 (mmHg)	15,2	16,3	43,4	24,6
PCO_2(mmHg)	39,7	40,9	29,2	37,2
HCO_3-std(meq/L)	13,1	13,3	19,9	25,9
Lactate(mmol/L)	0,7	0,5	0,5	0,8
SpO_2(%)	26	38	62	68

pH: potential hydrogen; PO_2: partial oxygen; PCO_2: partial carbon dioxide; HCO_3-std: standard bicarbonate; SpO_2: Oxygen saturation

Table 3. Urinary system USG and spot urine examinations

Urinary system USG	Both kidney sizes and localization are normal. Parenchymal echogenicity is compatible with grade-1 nephropathy. Bilateral PVE was not observed. The bladder is not full enough, there is a slight increase in trabeculation in the wall.	
Spot urine variables	**History**	
	07.03.2022	**14.03.2022**
Spot urine protein	2(+)	Negative
Spot urine Density	1024	1012
Spot urine erythrocyte	1(+)	Negative
Spot urinary leukocytes	1(+)	1(+)
Hyaline eraser	Negative	Negative
Granular roller	Negative	Negative
Bacterium	Negative	Negative
Spot urine prote/CRE(mg/dl)	497	148

USG: Ultrasonography; PVE: Pelvicalyceal Ectasia

DISCUSSION

Nausea, vomiting, and diarrhea developed as side effects of Molnupiravir in the patient. As a result, dehydration occurred. This may be due to the SARS-COV-2 infection itself. However, the patient did not have these symptoms when he was diagnosed with COVID-19. It started with the use of medication, and the patient's diarrhea regressed after the treatment was completed. In a randomized study by Bernal et al. on outpatients using Molnupiravir, the most frequently reported side effects were diarrhea, nausea, and dizziness. Painter et al. also reported that the most common side effect of Molnupiravir is diarrhea in a placebo-controlled study (11,7).

Continuation of anti-hypertensive drugs together with these side effects, caused hypotension and hypovolemia, which leading to severe renal perfusion failure.

The patient applied to the emergency department approximately 10 days later, although the use of the medication ended and his complaints continued. Because of this delay in admission to the hospital, the initial prerenal azotemia progressed further, causing severe reductions in renal perfusion. As a result of these, it is possible that acute renal failure due to ischemic acute tubular necrosis has developed.

Because the causes leading to prerenal azotemia (nausea, vomiting, bleeding, burns, dehydration, fluid sequestration into the third spaces) can lead to ischemic acute tubular necrosis. Both have the same spectrum (12). BUN/CRE: 89/8.9=10 at the time of first presentation of the case. This is a finding in favour of acute tubular necrosis. Because this rate is <20, it shows that it is of renal origin (13). A small amount of residual urine after urinary catheterization indicated that there was no post-renal ARF. Nausea and vomiting during emergency admission are due to uremia. He was taken to haemodialysis only 2 times, on 07-08.03.2022. With adequate hydration and hemodynamic stabilization, his clinic tended to improve. Normal urine output was achieved. In this case, diagnostic renal biopsy was not performed due to rapid improvement with emergency haemodialysis and hydration treatments. In fact, this situation also removed the diagnosis of interstitial nephritis. There was no need for steroid treatment. In the last examination of the patient who was hospitalized for 7 days and treated, Urea: 32 mg/dl, BUN: 15 mg/dl, CRE: 1.04, GFR: 74 ml/min.

CONCLUSION

The decrease in haemoglobin values may have resulted from blood loss during venous catheter insertion, repeated tests, and haemodialysis sessions (**Table-1**). Complaints such as nausea, vomiting, and diarrhea due to the use of Molnipiravir in patients over 65 years of age and those with chronic diseases should be seriously considered. It should be included in the category of significant side effects in phase-3 studies. This situation may cause severe dehydration and ARF in patients. The patient should definitely be informed and communicated. When necessary, the nearest health institution should be consulted. Otherwise, it may lead to increased mortality and morbidity. It may bring an additional financial burden. It should be followed closely in terms of chronic nephrotoxicity.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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