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COVİD-19'un Favipiravir ile Tedavisi Sonrası Tırnaklarda Floresan Yansıma

Fluorescence Reflection on Nails after the Treatment of COVID-19 with Favipiravir

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ÖZ

Amaç: Favipiravir, COVID-19 Türkiye Ulusal Tedavi Klavuzunda, COVİD-19 tedavisi için önerilmektedir. Türkiye'de COVID-19 ile enfekte hastalarda yaygın olarak kullanılmaktadır. Belli topikal ve sistemik ilaçlar ilaçlarla tırnaklarda Wood lambası ile floresan yansıma bildirilmiştir. Bu çalışma, COVID-19 hastalarının tırnaklarında favipiravirin floresan etkisini belirlemek için tasarlanmıştır.

Materyal ve Metot: Favipiravir ve/veya hidroksiklorokin ile tedavi edilen COVİD-19 enfeksiyonlu 85 hasta ve 50 sağlıklı gönüllünün tırnakları Wood lambası ile incelendi. Floresan yansıma ve ilaç öyküleri kaydedildi. Veriler karşılaştırıldı.

Bulgular: Hasta grubunda, 71 hastada (%83,5) UV radyasyon altında tırnaklarda floresan yansıma mevcuttu. Sağlıklı kontrol grubunda floresans gözlenmedi.

Sonuç: Favipiravir ile tedavi edilen COVİD-19 tespit edilmiş hastaların tırnaklarında floresan yansıma yaygın bir bulgudur.

Anahtar Kelimeler: COVID-19, favipiravir, floresan

ABSTRACT

Objective: Favipiravir is recommended for treatment of COVID-19 by the Turkey National Treatment Guideline for COVID-19. It has been widely used for COVID-19 infected patients in Turkey. Fluorescence of the nails with certain topical and systemic drugs with Wood's lamp was and reported in the English literature. This study is designed to determine the fluorescence effect of favipiravir in the nails of COVID-19 patients.

Materials and Methods: Eighty five patients with COVİD-19 infection who were treated with favipiravir and/or hydroxychloroquine and 50 healthy volunteers' nails were examined by Wood's lamp. Fluorescence and therapeutic interest were recorded. Data were compared.

Results: Seventy one of the patients (83.5%) had fluorescent nails under UV radiation in the patient group, where no fluorescence was observed in the healthy control group.

Conclusion: Fluorescence of the nails in the patients with confirmed COVID-19 infection who were treated with favipiravir is a common finding.

Keywords: COVID-19, favipiravir, fluorescence

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INTRODUCTION

The new coronavirus infection, which had emerged in 2019, turned out to be a worldwide pandemic. Although many treatment options have been put to use, a definitive treatment modality has not be established yet. Hydroxychloroquine, favipiravir, remdesivir are the current drugs that are being used for the treatment of COVID-19 infection. Low molecular weight heparin, H2 receptor blockers, aspirin are also prescribed frequently depending on the severity of the disease and patients are exposed to polypharmacy. Many side effects are encountered due to these drugs that enter our lives by means of COVID-19.[1]

We have observed fluorescence of nails of the COVID-19 patients under UV light in November, 2020; then it was recognized that the fluorescence does not exist in all of the patients. A detailed examination revealed that the fluorescence occurs due to medication. Quinacrine hydrochloride, tetracycline are the drugs reported to be causing fluorescence of the nails in the English literature.[1-3] A recent case series were reported from Turkey demonstrating the fluorescence of the nails with favipiravir in COVID-19 patients.[1]

This study is designed to review the fluorescein effect on the proximal parts of the nails of some particular COVID-19 patients during 2020 pandemic.

MATERIALS AND METHODS

This study was performed after it was approved by the Sakarya University Training Research Ethics Committee (Date: 28.12.2020, decision no: 654). Patients with PCR confirmed COVID-19 infection and 50 healthy volunteers who had never been diagnosed with COVID-19 aging 18 and over were included in this study. Patient who used topical or oral tetracycline within two weeks were excluded from the study. Demographic data and the information regarding actual or previous favipiravir and/or hydroxychloroquine use; and the ones who had never used any medication for COVID-19 were listed. The nails of the patients and healthy volunteers were inspected - fingernails in all, finger and toenails in the available ones- under Wood's lamp. Wood's lamp is a device radiating ultraviolet (UV) light. Inspection with Wood's lamp revealed Yellow-white fluorescence of the proximal part of the nail in each participant, patient and healthy volunteer. Favipiravir tablet fragments were examined under UV light. Spontaneous fluorescence was observed. In this study, simple descriptive statistics were applied.

RESULTS

Eighty five patients; 38 female, 47 male and age and gender matched 50 healthy volunteers participated. The average age of the patients was 49 years (18-95) and average age of the control patients was 41 (19-78). Four of the patients did not receive any medication. Seventy one of the patients (71/85) had fluorescent nails under UV radiation in the patient group, where no fluorescence was observed in the healthy control group (Table 1,2). One patient who wasn't given medication since she was breast-feeding, and

Table1. Demographic data and treatment history of the participants.

	PATIENTS	HEALTHY VOLUNTEERS
Number (n)	85	50
Female	36	17
Male	47	33
Mean age	49	41
Favipiravir	76	0
Hydroxychloroquine	5	0
No drug	1	50
Fluorescence	71 (71/76)	0

Table 2. Fluorescence rates and treatment data.

	Favipiravir	Hydroxychloroquine	No drug
Number	76	5	50
Fluorescence	68	3	0

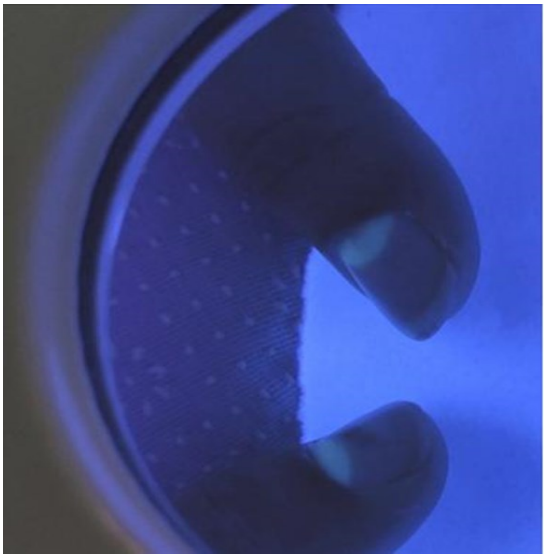

Figure 1. A patient with 4 days after favipiravir use.

Figure 2. UV light appearance when favipiravir tablet breaks.

three cases who had refused to take medication were the cases who did not show any fluorescence. Five cases were treated only with hydroxychloroquine and one case with both favipiravir and hydroxychloroquine, two of the former and the latter showed fluorescence. Two cases did not fluoresce although they had been treated with hydroxychloroquine 3 and 7 months ago. Eight patients with actual or previous favipiravir treatment did not show fluorescence, one of them was on the first day and first dose of induction, the remaining seven cases were on the 5th-17th days of or after favipiravir (Figure 1, 2).

DISCUSSION AND CONCLUSION

Fluorescent nails were assumed to be associated with COVID-19 infection at first, but no fluorescence was detected in the patients without specific treatment. Eighty nine percent (89%) of the cases treated with favipiravir showed fluorescence, demonstrating an obvious relation with favipiravir. This finding was reported on 4 patients recently for the first time.[1]

Fluorescence of the nails with some certain medications had been reported.[2,3] Antimalarial drugs quinacrine, hydroxychloroquine and tetracycline are the reported systemic drugs associated with fluorescence under Wood's lamp. Tetracycline also shows fluorescence with Wood's lamp when used topically.[4]

Pigmentation related to drugs may appear due to either drugs which are excreted via the nails or accumulated in the nails.[5] Gold salts and tetracycline may color the nail plate yellow.[5,6] Topical anthralin accumulates superficially on the nail plate and causes brown-to-black pigmentation.[5,7] This kind of pigmentation moves as the nail grows. Other pigmentation patterns may occur as the accumulation of pigment in the dermis or periungual tissue, in which the pigmentation does not move as the nail grows. Minocycline and antimalarial associated grayish blue pigmentation is an example of this pattern. This type of pigmentation fades very slowly or sometimes never, even after the withdrawal of the medication.7,8 Antivirals are also reported in association with nail pigmentation such as tenofovir, ribavirin and zidovudine.[9]

The usual long-wave UV light, known as Wood's lamp, is a useful tool in medicine. Wood's lamp's long-wave UV radiation is produced by a high-pressure mercury arc placed in a filter made of barium silicate with 9% nickel oxide, which is named ''Wood's filter". This filter is permeable for a band between 320 and 400 nm with a peak at 365 nm. Elastin (fluorophore unknown), collagen (pyridinoline crosslinks), aromatic amino acids (predominantly tryptophan and its oxidative products), nicotinamide adenine dinucleotide (NAD), and maybe pioneers or products of melanin are the estimated components of tissue fluorescence origin.[10] Fluorescein spectrum of skin may differ with chronic sun exposure, owing to alteration in dermal elastin.

Favipiravir is the treatment of choice in the Turkish Treatment Guideline for COVID-19. Favipiravir inhibits RNA dependant RNA polymerase (RdRP) selectively. It functions as a purine analogue and is

incorporated instead of guanine and adenine. Inside the cell, favipiravir is converted into its active phosphorylated form and is then recognized as a substrate by viral RdRP.[11] It is not clear whether the fluorescence effect may appear due to drug metabolites or the ingredients like titanium dioxide and/or yellow ferric oxide. It was reported that the concentration of the drug's active phosphorylated metabolite and fluorescence intensity in human plasma comply.[1,11]

We had no experience of favipiravir treatment before the pandemic, we have been prescribing favipiravir very commonly with the pandemic. That's why favipiravir has been widely used for Turkish patients.[12]

Skin eruption, pruritus, tachycardia were some of the side effects that we have experienced with favipiravir, but the fluorescence effect on the nails a new defined effect.[1] It is observed that fluorescence starts with the induction dose on the first day, continuing for several weeks after completion of the favipiravir treatment and the fluorescence moves distally.

We also wanted to see if any fluorescence did exist in the favipiravir tablets and the fluorescence also was detected under the film layer of the tablet by UV radiation.

There were eight patients who were treated by favipiravir and no fluorescence was detected, one of them was on the first dose of the first day of therapy: The reasons of showing no fluorescence despite favipiravir therapy in some patients even though very few, remains to be elucidated. It could be speculated to be due to limited distribution and or very low accumulation in tissues.

We are becoming more familiar with the side effects of this new drug and we would like to conclude that fluorescence of the nails in the patients with confirmed COVID-19 infection who are treated with favipiravir is a common finding, and requires no further investigation.

Ethics Committee Approval: This study was performed after it was approved by the Sakarya University Training Research Ethics Committee (Date: 28.12.2020, decision no: 654).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Author Contributions: Concept – OK, MY, BSD, EG; Supervision – OK; Materials –MY, BSD; Data Collection and/or Processing –MY, BSD, EG; Analysis and/ or Interpretation – BSD, EG; Writing – OK, MY, BSD, EG.

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