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Research Article

The Color Change Observed in the Skin and Nails of COVID-19 Patients Before and After Favipiravir and Hydroxychloroquine Use

Mustafa Tanriverdi[1], Nevhiz Gündoğdu[2], Fatma Elif Yildırım[3], Demet Ari[4], Gülşen Özkan Tanriverdi[5] and Hülya Çiçek[6]*

[1]Department of Infectious Diseases, SANKO University Faculty of Medicine, Gaziantep, Turkey

[2]Department of Pulmonary Medicine, SANKO University Faculty of Medicine, Gaziantep, Turkey

[3]Department of Dermatology, SANKO University Faculty of Medicine, Gaziantep, Turkey

[4]Department of Emergency Medicine, SANKO University Faculty of Medicine, Gaziantep, Turkey

[5]Department of Anesthesia and Reanimation, Ministry of Health 25 Aralık State Hospital, Gaziantep, Turkey

[6]Department of Medical Biochemistry, Gaziantep University Faculty of Medicine, Gaziantep, Turkey

***Corresponding Author:** Hülya Çiçek, Professor, Department of Medical Biochemistry, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.

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Abstract

Background: Favipiravir, (6-fluoro-3-hydroxy-2-pyrazine carboxamide) is a broad-spectrum antiviral agent currently used in the treatment of SARS-CoV-2 infection (COVID-19).

Objectives: In this study, we aimed to evaluate the fluorescent staining of the nail surface of the patients who applied to the infectious diseases outpatient clinic of our hospital and were given favipiravir treatment with the diagnosis of COVID-19 by Wood's lamp examination.

Methods: Patients who applied to SANKO University Private Sani Konukoğlu Hospital Health Research and Application Center COVID-19 outpatient clinic were included in our study. All patients diagnosed with COVID-19 with SARS-CoV-2 PCR positivity by nasopharyngeal aspiration were given favipiravir 2*1600 mg on the first day and then 2*600 mg peroral for 4 days. Nail fluorescent staining status was evaluated again in patients with PCR (+) and healthy control group with PCR (-) at the time of admission and the end of the 1 week. Patients who were found to have staining in the first Woods lamp evaluation had an additional disease related to the nail base, were found to have the nail-related disease by the dermatology clinic, and did not want to participate in the study were excluded from the study.

Results: A total of 90 patients, 48 (53.3%) of whom were male, with a mean age of 52.9±6.5 years, were included in our study. The nail changes were evaluated with Woods light at the first admission of patients (n = 51) and the control group (n = 39). Patients (n = 51) and PCR (-) healthy control group (n = 39) were re-evaluated 1 week later. While nail base color change was detected in 45 (88.3%) of the patients who were given favipiravir, no color change was detected in the control group (n = 39, 100%) and 6 (11.7%) patients ($p < 0.001$). In our study, no difference was found between the groups with and without nail color change in terms of age, sex

distribution, frequency of HT, DM, Asthma, and COPD ($p > 0.05$). The frequency of CAH was found to be higher in the patient group with nail color change ($p < 0.001$).

Conclusion: In our study, we found that fluorescent staining under UV light increased significantly in people who used favipiravir tablets. Our current study concluded to support the presence of drug-induced fluorescent staining in hair, skin, and nails, which was detected in other previously published studies.

Keywords: Fluorescence; COVID-19; Favipiravir; Nail; Ultraviolet Light

Introduction

After the declaration of the new SARS-CoV-2 infection (COVID-19) as a pandemic by the World Health Organization (WHO) [1] and the reporting of the first COVID-19 cases in Turkey (11 March 2020), the recent period made the story of a difficult year for our country and all humanity [2]. Quinacrine hydrochloride and tetracycline are drugs that have been reported to cause fluorescence in nails [3,4]. Favipiravir, (6-fluoro-3-hydrazine carboxamideoxamide) is a broad-spectrum antiviral agent currently used in the treatment of SARS-CoV-2 infection (COVID-19) [5]. In animal studies and some limited human studies, it has been shown that there is a yellow discoloration of the paws, fur, and soles of the feet under UV light [6].

In many case reports, findings have been published showing fluorescence of nails due to favipiravir use in COVID-19 patients [7-9] as well. Favipiravir contains polyvinylpyrrolidone (PVP) as excipients in tablets. PVP is a substance with strong fluorescent features [10]. It is assumed that PVP is responsible for the bright white fluorescence observed in patients taking favipiravir. Several new nanotechnology-based antiviral drugs have been reported to contain PVP ring(s) [10,11].

In this study, we aimed to evaluate the fluorescent staining of the nail surface of the patients who applied to the COVID-19 outpatient clinic of our hospital and were given favipiravir treatment with the diagnosis of COVID-19 by Wood's lamp examination.

Material and Methods

Patients

Patients with COVID-19 infection confirmed by PCR and 50 healthy volunteers aged 18 years or older and never diagnosed with COVID-19 were included in this study. Demographic data and the favipiravir use status of the patients were recorded. Covid-19-related clinical outcomes were recorded. Patients under the age of 18, who did not give consent to participate in our study, underwent nail-related surgery, and patients with nail-related fungus and other infections were excluded from the study. In addition, patients who used topical or oral tetracycline in the last two weeks were not included in the study.

Patients admitted to the SANKO University Private Sani Konukoğlu Hospital Health Research and Application Center COVID-19 outpatient clinic were included in our study. Nail fluorescent staining status was evaluated again in patients with PCR (+) and healthy control group with PCR (-) at the time of admission and at the end of the 1 week. Patients who were found to have staining in the first Woods lamp evaluation, had an additional disease related to the nail base, were found to have the nail-related disease by the dermatology clinic and did not want to participate in the study were excluded from the study.

COVID-19 treatment

Favipiravir is currently used in the treatment of Covid-19 in Türkiye. All patients diagnosed with COVID-19 with SARS-CoV-2 PCR positivity by nasopharyngeal aspiration were given favipiravir 2*1600 mg on the first day and then 2*600 mg peroral for 4 days.

Ethical approval

Patients admitted to the Sanko Center COVID-19 outpatient clinic were included in our study. All patients with suspected COVID-19 and who were diagnosed with COVID-19 with SARS-CoV-2 PCR positivity and COVID-19 with nasopharyngeal aspiration were given favipiravir 2*1600 mg on the first day and then 2*600 mg peroral for 4 days. Nail fluorescent staining status was evaluated again in patients with PCR (+) and healthy control group with PCR (-) at the time of admission and at the end of the 1-week period.

Wood's lamp

Wood's light is a simple and effective method for diagnosing specific dermatoses, including cutaneous fungal, bacterial infections and pigment disorders [12]. The test is performed in the clinic under the direct supervision of the treatment provider. In our study, evaluation with Wood's lamp was made according to the instructions determined by Archer® brand Wood's Lamp. Wood's lamp can detect fluorescence in addition to areas of pigmented or depigmented skin. Wood's lamp was kept on for at least 60 seconds before the procedure, and all examinations were made in the dark room. The lamp was usually kept at a distance of 10-30 cm from the skin. No additional special protective protocol was required for patients who underwent Wood's lamp. It was noted that the hands of the patients evaluated in our study had not been washed recently in detail and they had worn makeup, used deodorant, moisturizing cream, or any other topical lotion. These topical fluids can cause a false positive test. The Yellow-White fluorescent sign was considered "positive" (Figure 1).

Figure 1: An example of painted nails under the Woods lamp.

Patients who were found to have staining in the first Woods lamp evaluation, had an additional disease related to the nail base, were found to have a nail-related disease by the dermatology clinic and did not want to participate in the study were excluded from the study.

Statistical analysis

In the analysis of the variables, SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used. The cause and effect relationship between the Post-Treatment Color Change dependent variable and other explanatory variables was evaluated using the logistic regression test, Enter method. The variables were analyzed at a 95% confidence level, and a p-value less than 0.05 was considered significant.

Results

A total of 90 patients, 48 (53.3%) of whom were male, with a mean age of 52.9±6.5 years, were included in our study. The nail changes were evaluated with Woods light at the first admission of patients (n = 51) and the control group (n = 39). Patients (n = 51) and PCR (-) healthy control group (n = 39) were re-evaluated 1 week later.

While nail base color change was detected in 45 (88.3%) of the patients who were given favipiravir, no color change was detected in the control group (n = 39, 100%) and 6 (11.7%) patients ($p < 0.001$). In our study, no difference was found between the groups with and without nail color change in terms of age, sex distribution, frequency of HT, DM, Asthma and COPD ($p > 0.05$). The frequency of CAH was found to be higher in the patient group with nail color change ($p < 0.001$) (Table 1).

	The State of Fluorescence of Nails			p
	Total (n = 90)	**No (n = 45)**	**Yes (n = 45)**	
	Mean (SD.) (min/max)	**Mean (SD.) (min/max)**	**Mean (SD.) (min/max)**	
Age (years)	52.9 (6.5) (41-66)	51.5 (6.8) (41-65)	54.2 (5.9) (41-66)	0.043 [t]
	n(%)	n(%)	n(%)	
SARS-CoV-2 PCR (+)	51 (56.7)	6 (13.3)	45 (100)	<0.001 [c]
Sex (Male)	48 (53.3)	18 (40.0)	30 (66.7)	0.020 [c]
Smoking	52 (57.8)	23 (51.1)	29 (64.4)	0.286 [c]

Comorbidity	90 (100.0)	45 (100.0)	45 (100.0)	-
Hypertension	45 (50.0)	23 (51.1)	22 (48.9)	0.999 [c]
Diabetes Mellitus	36 (40.0)	17 (37.8)	19 (42.2)	0.830 [c]
Asthma	20 (22.2)	13 (28.9)	7 (15.6)	0.204 [c]
COPD	2 (2.2)	0 (0.0)	2 (4.4)	0.494 [f]
CAH	15 (16.7)	1 (2.2)	14 (31.1)	<0.001 [c]
Use of Favipiravir	51 (56.7)	6 (13.3)	45 (100.0)	<0.001 [c]
	Median (q1/q3)	Median (q1/q3)	Median (q1/q3)	
SpO_2 (Admission)	98 (98/99)	98 (98/99)	98 (97/99)	0.659[u]
[t] The Independent Samples T-test (Bootstrap), [u] Mann Whitney U test (Monte Carlo), [c] Pearson Chi-Square Test (Monte carlo), [f] Fisher's Exact test (monte carlo), q1:1st quartile, 3rd quartile, OR: Odds Ratio				

Table 1: Fluorescence of nails under the Wood's lamp after treatment.

Discussion

In our study, we found that fluorescent staining increased significantly under UV light in people using favipiravir tablets. Our current study concluded to support the presence of drug-induced fluorescent staining in hair, skin, and nails, which was detected in other previously published studies.

Due to some drugs, fluorescence in nails has been reported [3,4]. The anti-malarial drugs; quinacrine, hydroxychloroquine, and tetracycline are the reported systemic drugs associated with fluorescence under Wood's lamp. When used topically, tetracycline also fluoresces with Wood's lamp [13]. Favipiravir is an antiviral agent primarily used mainly for the treatment of influenza as an RNA polymerase inhibitor. It has been used in Turkey since March 2020 to reduce the viral load in the treatment of coronavirus [14]. Favipiravir is considered a drug with a low side effect profile. Case reports have been published that detected fluorescent staining under Wood's light on the nails of patients treated for COVID-19 infection [7,15,16] Although this situation was primarily considered to be related to COVID-19, it was considered to be secondary to the use of favipiravir.

Drug-induced pigmentation may occur due to drugs that are excreted through the nails or accumulated in the nails [13]. Some drugs, such as tetracyclines and quinacrine, are known to accumulate in the implants, dental, and conjunctival tissues of patients using these drugs, and cast bright yellow fluorescence under Wood's lamp [17,18]. However, this staining depends on the dose and usually develops after a long treatment period.

Conclusion

This type of pigmentation disappears very slowly, or sometimes it does not disappear at all, even after the discontinuation of the drug [19,20]. Antivirals such as tenofovir, ribavirin, and zidovudine are also known to cause nail pigmentation [21]. Skin rash, muscle pain, dyspepsia, pruritus and tachycardia were some of the known side effects associated with favipiravir. Favipiravir-associated fluorescent glow in nails is a newly defined finding, as has been reported recently and can be seen in our study [7]. Our current study concluded to support the presence of drug-induced fluorescent staining in hair, skin, and nails, which was detected in other previously published studies.

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