Dermatology Practical & Conceptual

Follow-up of Favipiravir-Induced Nail Fluorescence: Implications for Nail and Drugs

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ABSTRACT

Introduction: Favipiravir creates fluorescence on nails, which can be seen with Wood's light.

Objectives: The objectives of this study are to examine the properties of fluorescence in the nail due to favipiravir and to observe whether other drugs also produce fluorescence in the nail.

Methods: The research is descriptive, prospective, and quantitative. This study recruited 30 healthcare workers who received favipiravir treatment and 30 volunteers who took or did not take any medication except favipiravir from March 2021 to December 2021. Fingernails of the patients and control groups were examined under Wood's light in the darkroom. If fluorescence was observed in the fingernails, we followed up once a month until the fluorescence disappeared. We calculated the nail growth rate by dividing the distance of nail fluorescence from the proximal nail fold by the number of days since favipiravir was started.

Results: We found nail fluorescence in all patients receiving a loading dose of favipiravir. The fluorescence in the nail decreased and disappeared in the 3rd month. The average nail growth rate at the first visit was 0.14 mm/day. The nail growth rate at the second visit was 0.10 mm/day. A statistically significant difference was found between the first and second visit nail growth rates (z: -2.576; $p=0.010<0.05$). We found that other drugs did not produce any fluorescence in the nail.

Conclusions: Nail fluorescence induced by favipiravir is dose-dependent and decreases in intensity over time. Nail fluorescence due to favipiravir is likely due to the active ingredient of the drug.

Introduction

The human eye can only process visible light (400–720 nm), which is a narrow segment of the electromagnetic spectrum (EMS). Our retina is not capable of sensing light in the UV spectrum (10-400 nm) but can detect longer wavelength fluorescence caused by the interaction of UV light with skin chromophores. Wood's light is frequently used in dermatology to detect fluorescence produced by exogenous or endogenous chromophores [1].

Favipiravir, a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazine carboxamide), is a broad-spectrum antiviral drug with inhibitory effects on a variety of RNA viruses [2]. Favipiravir is widely used in Turkey to treat coronavirus disease 2019 (Covid-19) based on the Covid-19 treatment guide of the Ministry of Health, Republic of Turkey. A loading dose of 2x1600 mg (first day) of favipiravir followed by 2x600 mg/day (4 days) for a total of 4 days is recommended.

Wood's lamp is a high-pressure mercury arc lamp filtered with barium silicate and nickel oxide, emitting ultraviolet in the 320-400 nm spectrum with a peak at 365 nm. When examining a Wood's lamp in a dark room, fluorescence is seen if there are fluorophores[3]. So far, the following fluorescence has been reported in the nail due to drug use: yellow for tetracycline, yellow/green for quinacrine, and yellow/green/blue fluorescence for favipiravir [4-9].

We wanted to follow up on whether nail fluorescence in all patients using favipiravir persisted or not and how long nail fluorescence persists. Data on the fluorescence of drugs in nails are limited to a few drugs. We wanted to collect information about whether other drugs create fluorescence in the nails by including people who use drugs as a control group in our study. We thought that the data we obtained could provide information about drug transfer to the nail and the relation between drugs and nails.

Material and Methods

Patients who received favipiravir treatment due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) positivity diagnosis among healthcare workers at our hospital were included in the study as the study group. Only an observational study was planned, without any interference with patients' drug doses or treatment duration. The reason for choosing healthcare professionals is to facilitate follow-up and eliminate the risks that may occur due to patients coming to the hospital. In the control group, individuals who did not receive favipiravir treatment and were or were not using another systemic drug were included in the study. The research is descriptive, prospective, and quantitative.

Volunteer adults between the ages of 18-65 were included in the study. An informed consent form was obtained from all participants. Those who were pregnant or breastfeeding were not included in the study. We recorded the age, gender, drug use, vitamin and supplement use of the study and control groups. The drugs taken as a criterion for systemic drug use were taken at least 15 days before and drugs taken for more than 5 days were recorded.

Approval from the Ministry of Health of the Republic of Turkey with the number 2021-01-13T13_41_11 and permission from the ethics committee of Maltepe University with the number 2021/900/19 were obtained.

We conducted this study among 30 healthcare workers who received favipiravir treatment and 30 volunteers who took or did not take any medication between 04/03/2021 and 25/12/2021. The fingernails of the patients and control groups were examined under Wood's light (Lumio®UV, 3Gen DermLite™, 40 UV LEDs, 75 mm 2x lens, U.S.A.) in the darkroom. If fluorescence was observed in the fingernails, we followed up once a month until the fluorescence disappeared. The length of the third fingernails of the left hand of all patients was measured. The left hand was chosen as it is usually the non-dominant hand and the middle finger because it is easy to position. The cuticle (eponychium) was not included when measuring nail length or fluorescence. We measured the size of the fluorescence in the nail. In addition, the distance of the fluorescence from the distal tip of the nail and the proximal nail fold was also measured. Measurements were made from the midpoint of the nail using a digital caliper (Figure 1). It was not possible to see all of the patients in the 1st month and the 2nd month. 1st month was accepted as 31±3 days, 2nd month was 61±3 days.

The first visit nail growth rate was calculated as mm/day by dividing the distance between the proximal nail fold and the first distal fluorescence by the measurement day. The 2nd visit nail growth rate was obtained by subtracting the distance of the distal fluorescent from the proximal nail fold measured at the 2nd visit from the first measured at the 1st visit and dividing by the number of days in between (Figure 2).

Statistics

Power analysis in the research was carried out with the G Power 3.1.9.7 program. Assuming that the difference between 2 observations will be examined, the t-test family was taken as reference, and the effect size was accepted as 0.8 using the wide Cohen reference since there was no similar prior study. In addition, it was concluded that it would be sufficient to have 15 people in the analysis of the main hypothesis at 80% power and 5% significance levels. Since there were 20 people who could be followed up in the study, the sample size obtained was considered sufficient.

The SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program analyzed the variables. We used the

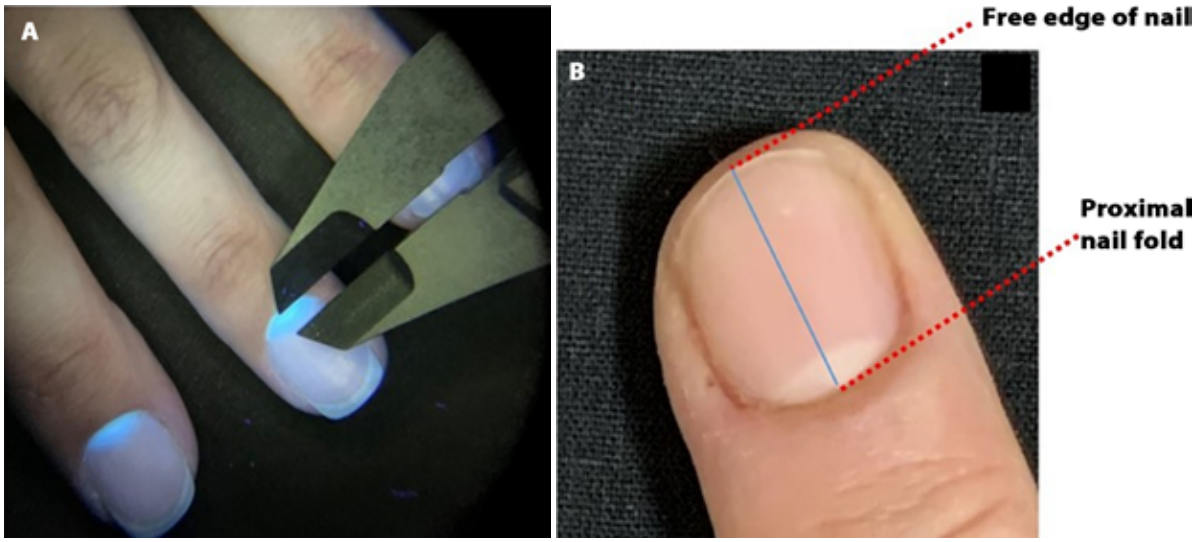

Figure 1. Measurement methods (A: Measurement method for the midpoint of the nail fluorescence B: The measurement of the third fingernails of the left hand).

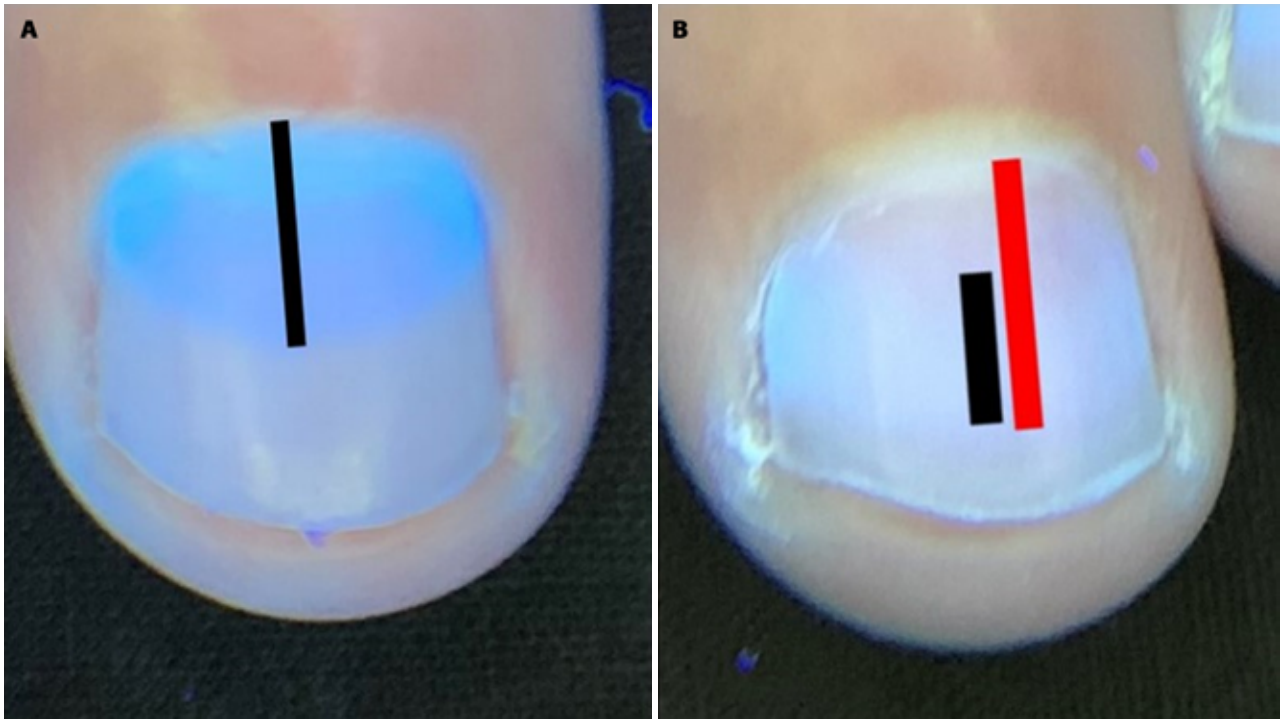

Figure 2. The first (A) and second (B) visit measurement of the nail fluorescence size (Black lines indicate the size of the fluorescence. The red line shows the distance between the distal end of the fluorescence and the proximal nail fold).

Pearson chi-square test to examine whether there was a gender difference between the control group and the study group. We examined the distribution of age by skewness and kurtosis (-1 - +1). Accordingly, we examined the ages of the study/control groups with the t-test.

When comparing the elongation rates of the nail fluorescence, the Gaussian distribution was examined and it was found that it was not normal. Accordingly, the Wilcoxon Signed-Rank test was used. Hypothesis tests were performed with the help of the SPSS 22.0 program at a 95% confidence level.

Quantitative variables were expressed as mean (± standard deviation), and median (minimum-maximum), while categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level, and a p-value less than 0.05 was considered significant.

Results

24 (80.0%) of the participants included in the study group were women; 6 of them (20.0%) were male. Their mean age is 36.10±9.03 years. The average length of the left-hand third

Table 1. Demographic Data of Study and Control Groups.

Study group				
	n		**%**	
Female	24		80	
Male	6		20	
Total	30		100	
	Min	**Max**	**Mean**	**SD**
Age	21	51	36.1000	9.03003
Left-hand 3rd nail length	7.80	15.30	11.2833	1.88334
Control group				
	n		**%**	
Female	20		66.7	
Male	10		33.3	
Total	30		100	
	Min	**Max**	**Mean**	**SD**
Age	19	64	37.37	13.12
Left-hand 3rd nail length	8.60	15.70	11.8633	1.85370

Table 2. Comparison of Study and Control groups according to left-hand 3rd nail length.

	n	Mean	SD	t	p
Study	30	11,2833	1,88334	-1,202	0,234
Control	30	11,8633	1,85370		

t: Independent samples t-test value

fingernails is 11.28±0.188. In the control group, 20 (66.7%) of the 30 participants were female, and 10 (33.3%) were male. Their mean age is 37.37±13.12. The average length of the left-hand third fingernails is 11.86±1.85. In total, 44 of 60 participants were women; 16 of them were male. Their mean age is 36.73±11.19 years. The average length of the left-hand third fingernails is 11.57±1.88 (Table 1).

When the study and control groups were compared according to the length of the left-hand third fingernail, no statistically significant difference was found (p>0.05) (Table 2).

In the study group, fluorescence was observed in 27 of 30 patients (90%) using favipiravir. The three patients without fluorescence did not use the total dose of favipiravir. One of these patients vomited after taking eight tablets on the first day, one took only five tablets of favipiravir, and one did not take the loading dose on the first day (Figure 3). Blue fluorescence was observed in the fingernails of all patients who used 2x1600 mg (day 1) of favipiravir, followed by 2x600 mg/day for a total of 4 days.

The earliest evaluation after starting favipiravir was on the 5th day of treatment, and we did not see fluorescence in her nail. 2 patients were evaluated on day eight, and we found fluorescence of 1 mm in one patient and 3.3 mm in the proximal nail in the other (Figure 4). Furthermore, in a patient who received favipiravir twice, examined on the 62nd day of the 1st dose and the 48th day of the 2nd dose, fluorescence was observed in the entire nail (Figure 5).

In the measurements made from the 3rd nail of the left hand, the nail fluorescence of 10 patients could be measured in the 1st month. The mean nail fluorescence length was 3.95±0.67 mm (min-max 3-5) in the first month. The nail fluorescence of 20 patients could be measured in the second month and the mean nail fluorescence length was 4.3±0.77 mm (min-max 2.9-5.9).

The last visits of the patients were between 62-122 days (92.07±11.28). Nail fluorescence intensity gradually decreased in all patients with fluorescence and disappeared completely in the third month.

The first visit nail growth rate could be calculated in 25 patients, and the mean was 0.14 mm/day min-max 0.06-0.22. The second visit nail growth rate could be calculated in 20 patients whose fluorescence measurement could be made in the 2nd-month follow-up, and it was 0.10 mm/day min-max 0.07-0.19. In the analysis comparing the differences between the first and second nail growth rates, a statistical difference was found (z: -2.576; p=0.010<0.05) (Table 3).

Some patients in the study group took additional medications such as valproic acid, lithium carbonate, levothyroxine, olanzapine, mirtazapine, methylphenidate, paroxetine, vitamin D3, zinc, vitamin B1/B2/B6/B12, vitamin C, nicotinamide, biotin, folic acid, paracetamol, enoxaparin, nebivolol, N-acetyl cysteine, magnesium, colchicine, prednisolone, metformin, pantoprazole, pheniramine maleate, amoxicillin/clavulanic acid, ketoprofen, levocetirizine/montelukast, acetylsalicylic acid, omega 3 and blackberry extract. The

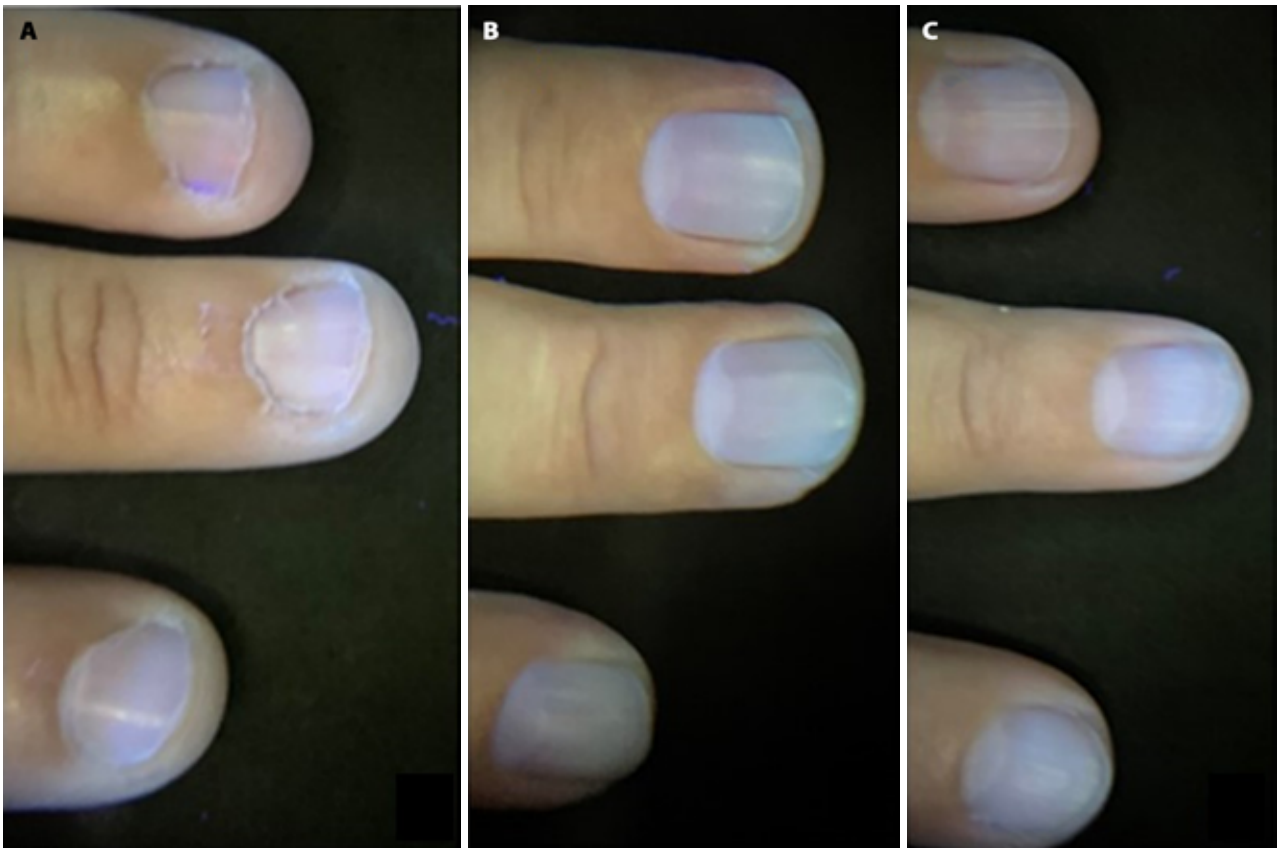

Figure 3. Patients without nail fluorescence. (A: The patient vomited after taking eight tablets, B: The patient took only five tablets, C: The patient did not take the loading dose of favipiravir.

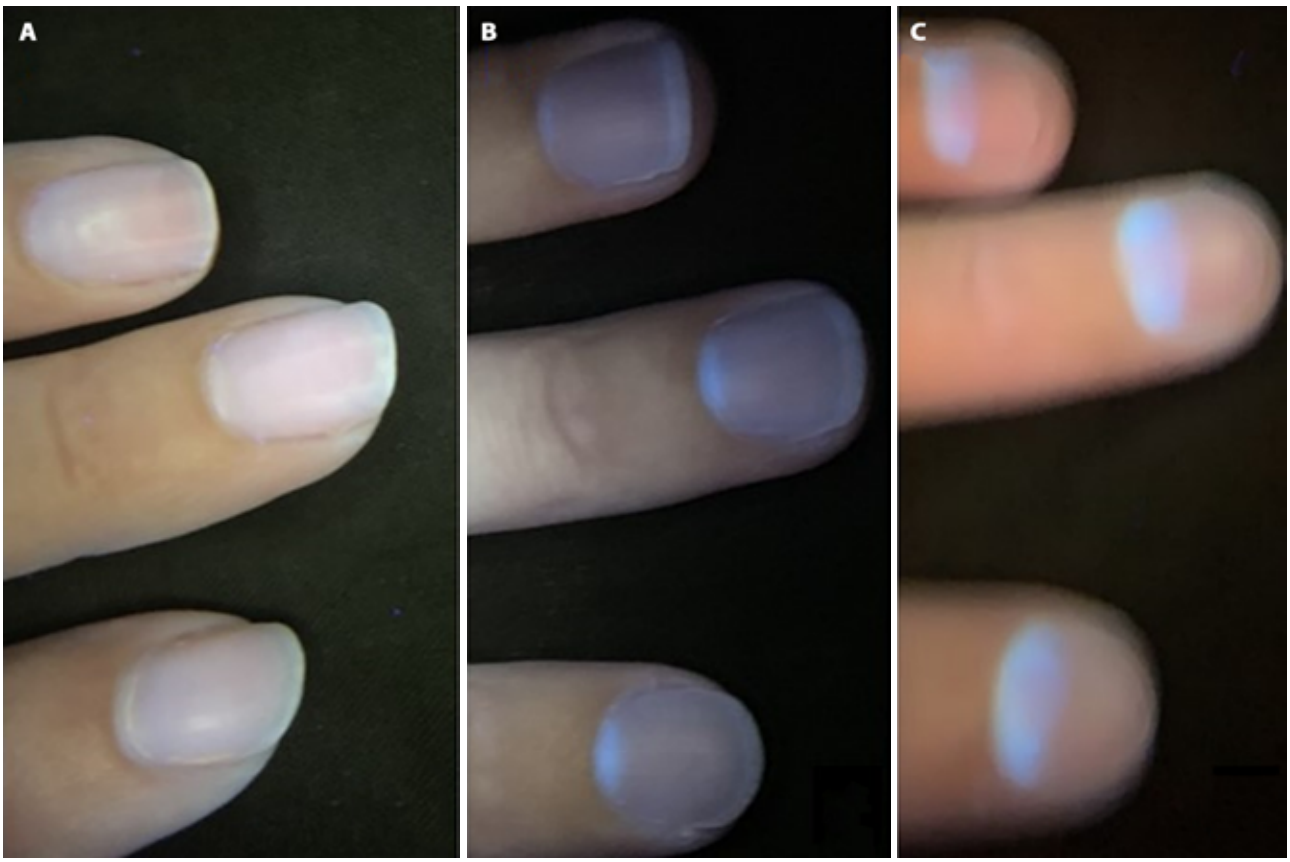

Figure 4. The earliest evaluation of the nail fluorescence for three patients after starting favipiravir. A: 5th day of treatment, and no fluorescence is visible. B: 8th day of treatment, and 1 mm fluorescence is seen. C: 8th day of treatment and 3.3 mm of fluorescence is observed).

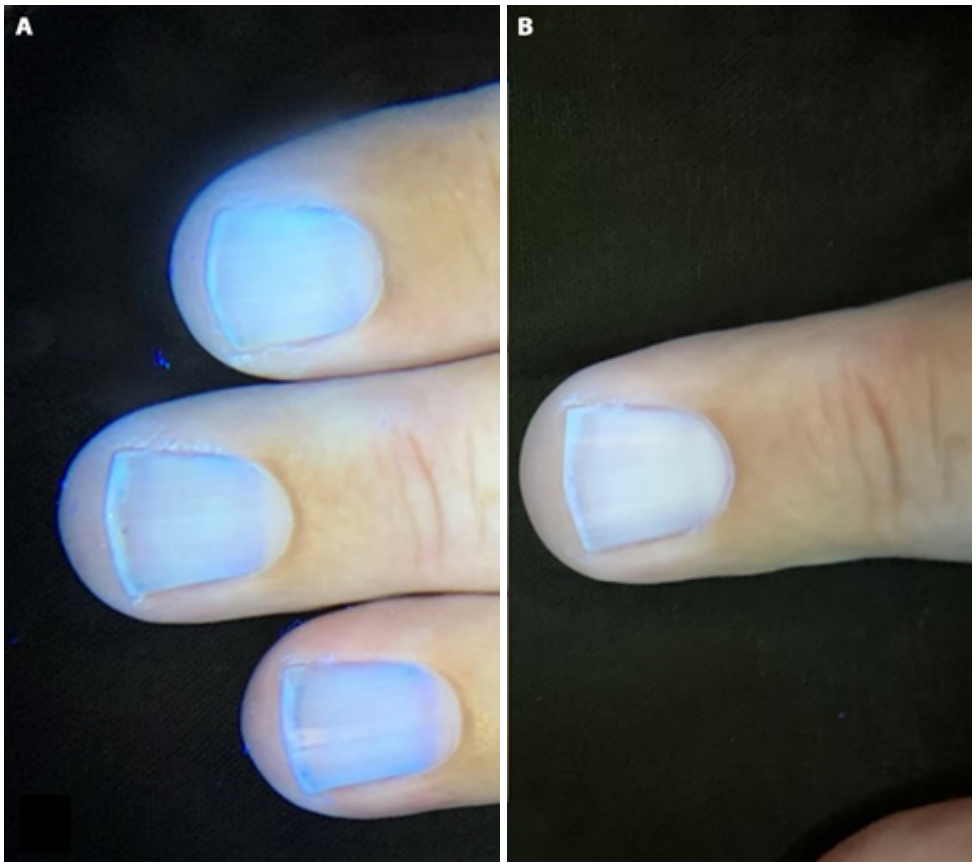

Figure 5. The patient received favipiravir twice. (A: Upon examination on the 62nd day of the 1st dose and the 48th day of the 2nd dose, nail fluorescence was observed in the entire nail. B: Upon examination on the 103rd day of the 1st dose and the 89th day of the 2nd dose, nail fluorescence disappeared.

Table 3. Comparison of 1st visit and 2nd visit nail growth rate (N=20).

	Mean±SD	Median (Q_1-Q_3)	z	p
1st visit nail growth rate	0.14±0.044	0.14 (0.10-0.19)	-2.576	0.010*
2nd visit nail growth rate	0.10±0.034	0.09 (0.08-0.11)		

z: Wilcoxon signed-rank test statistics value; Q_1: 25. percentile; Q_3: 75. percentile; *: $p<0.05$

fluorescence seen in the nail was consistent with the intake of favipiravir, we did not observe that the above-mentioned drugs affected this fluorescence.

In the control group, the drugs taken by the patients include metformin, nebivolol, sertraline, levothyroxine, drospirenone/ethinylestradiol, desloratadine/montelukast, fluoxetine, budesonide/formoterol, isotretinoin, ibuprofen, ramipril/hydrochlorothiazide, iron/folic acid, terbinafine, perindopril/indapamide, alfuzosin, diltiazem, pregabalin, duloxetine, carvedilol, escitalopram, telmisartan, amlodipine, candesartan, enalapril, ofloxacin, zinc, biotin, and melatonin. Nail fluorescence was not observed in any of the control group patients.

Discussion

The nail plate is composed of layers of keratinized cells produced by the nail matrix and extends distally over the nail bed. The elongation of fingernails is about 0.1 mm/day and differs between individuals [10]. While aging, acute infections, systemic illness, and malnutrition slow down nail growth, nail growth is faster in those with pregnancy, warmer temperatures, and minor trauma [11]. In the study group, the 1st visit nail growth rate, which represents approximately the 1st month, was found to be significantly higher than the 2nd visit nail growth rate, which approximately represents the 2nd month. The increase in nail growth rate may be related to Covid-19 infection, use of favipiravir, taking vitamins due to illness, or trying to eat better. Since we could not evaluate the nail growth rate in the control group, we cannot comment. Since we could only make the nail growth rate comparison in 20 patients, it is impossible to say this with certainty. In addition, since what we are measuring is fluorescent, the intensity of the light decreases over time, which may have caused inaccuracies in the measurements.

The incidence of fluorescence in nails due to the use of favipiravir was previously reported as 81.9% and 84% [9, 12]. Similar to the findings in these studies, we observed fluorescence in the nail in 90% of our patients using favipiravir, and we observed that there was fluorescence in the nail in 100% of the patients who received the full loading dose.

Nail manifestations associated with COVID-19 included a red half-moon sign, transverse orange nail lesions, Mees' lines, and Beau's lines [13]. No nail disorder was observed in any of our patients who had Covid-19.

Nail fluorescence due to favipiravir was seen in all patients who received the total dose of favipiravir. It was observed that the density decreased in the 2nd month and disappeared in all patients in the 3rd month. Nail fluorescence was not observed in patients who did not receive the loading dose. The fluorescence produced by favipiravir in the nails is dose-dependent and decreases over time. These findings showed that the drug dose is important in drug transfer to the nail.

Drug delivery to the nail is most important in the treatment of onychomycosis. Continuous therapy and intermittent pulse regimens for terbinafine and itraconazole can be used to treat onychomycosis. Similar efficacy and side-effect rates have been reported in a meta-analysis [14]. We evaluated the fluorescence in the nails due to the use of high-dose favipiravir for 5 days in our patients as an opportunity to monitor the transfer of the drug to the nails and how long it took to disappear. And the decrease of this fluorescence over time showed that the drug concentration in the nail did not remain the same, and we did not see any fluorescence in the distal 1/3 of the nail, except in one patient who took favipiravir twice. In onychomycosis, the distal lateral subungual type, in which the distal and lateral parts of the nail are affected, is the most common [15]. We think that insufficient access of antifungal drugs to the micelles located in the distal nail may be an important factor in treatment failure in onychomycosis.

The maximum plasma concentration of favipiravir occurs 2 hours after oral administration and then decreases rapidly with a short half-life of 2-5.5 hours [2]. Itraconazole has plasma half-lives of 42 hours and terbinafine of up to 100 hours [16]. It can be thought that it can affect a much larger area of the nail than favipiravir.

It is not known in what way the use of favipiravir creates fluorescence in the nails. In one study, it was claimed that it could be caused by excipients such as titanium dioxide and yellow ferric oxide added to the favipiravir tablet for photo stabilization due to the "fluoro" in the favipiravir formulation [17, 18]. Pure favipiravir has been shown to exhibit blue fluorescence in microscopic fluorescence examination [19]. In addition, titanium dioxide and yellow ferric oxide were among the additives of the drugs taken by some patients in the patient and control groups, and fluorescence was not observed in the nails due to these drugs in these patients. Based on this information, we think that favipiravir-induced nail fluorescence is mainly caused by the drug rather than the favipiravir tablet additives. However, since these drugs were one-per-day tablets, it would not be correct to compare the dose with 16 tablets a day, as in favipiravir.

Since the nail is in a structure that can indicate long-term exposure to a substance, it is used to evaluate environmental exposure, in the detection of abused drugs and poisoning [20]. It should be taken into account that the substance accumulated in the nail may decrease over time when drug measurement is made in the samples obtained by nail clipping. And although the time the nail is cut varies from person to person, it gives information about 3-4 months prior in the average fingernail.

Conclusion

Favipiravir-induced nail fluorescence is dose-dependent, and its intensity decreases over time. We think that the concentration of the drugs in the nails decreases over time. Nail fluorescence due to favipiravir is probably due to the active ingredient in the drug. We think that the information we have obtained may be useful in the treatment of conditions such as onychomycosis where drug transfer to the nail is important and in determining the concentration of nail exposure substances.

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