RESEARCH ARTICLE

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Famotidine in COVID-19 Treatment

ABSTRACT

Objective: Famotidine is an H2 receptor antagonist (H2RA) and has been shown to have antiviral properties in in vitro studies. Pantoprazole is one of the proton pump inhibitors (PPI). In this study, it was aimed to compare the efficacy of famotidine with pantoprazole in the treatment of COVID-19.

Methods: Patients who were hospitalized and given famotidine and pantoprazole treatment for at least 48 hours were included in the study. Demographic, clinical and laboratory findings of the patients were analyzed retroprospectively from the patient files. The patients were divided into two groups as the famotidine group and the pantoprazole group. The groups were compared in terms of the need for intensive care and mortality rates. In addition, among the groups, the number of patients with normal oxygen saturation at discharge, number of days needed for oxygen support, number of days with fever, and length of hospital stay were evaluated.

Results: A total of 179 Covid-19 patients (85 famotidine, 94 pantoprazole) were included in the study. Demographic findings and other symptoms except dyspnea were similar in both groups. Dyspnea, chronic diseases, and the number of patients given steroids were higher in those who were given pantoprazole ($p<0.05$). Mortality and ICU need were similar in both groups (respectively; $p=0.25$, $p=0.26$). The number of days with fever, duration of hospitalization, and the number of days requiring oxygen support were less in those given famotidine (respectively; $p=0.04$, $p=0.003$, $p=0.014$).

Conclusions: Famotidine did not reduce the need for intensive care and mortality in COVID-19 patients treated in the hospital. New therapeutic agents are needed to reduce disease severity and mortality.

Keywords: COVID-19, Famotidine, Pantoprazole, Mortality.

COVID-19 Tedavisinde Famotidin Kullanımı

ÖZET

Amaç: Famotidin, bir H2 reseptör antagonistidir ve in vitro çalışmalarda antiviral özelliklere sahip olduğu gösterilmiştir. Pantoprazol, proton pompası inhibitörlerinden biridir. Bu çalışmada, COVID-19 tedavisinde Famotidinin ile Pantaprazolun etkinliğinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya en az 48 saat famotidin ve pantaprazol tedavisi verilen ve hastanede yatan hastalar dâhil edildi. Hastaların demografik, klinik ve laboratuvar bulguları hasta dosyalarından geriye dönük olarak incelendi. Hastalar famotidin grubu ve pantoprazol grubu olarak iki gruba ayrıldı. Gruplar yoğun bakım ihtiyacı ve ölüm oranları açısından karşılaştırıldı. Ayrıca gruplar arasında taburculukta oksijen saturasyonu normal olan hasta sayısı, oksijen desteğine ihtiyaç duyulan gün sayısı, ateşli gün sayısı ve hastanede kalış süresi değerlendirildi.

Bulgular: Çalışmaya toplam 179 Covid-19 hastası (85 famotidin grubu, 94 pantoprazol grubu) dâhil edildi. Demografik bulgular ve dispne dışındaki diğer semptomlar her iki grupta benzerdi. Pantoprazol verilenlerde dispne, kronik hastalıklar ve steroid verilen hasta sayısı daha yüksekti. Mortalite ve YBÜ ihtiyacı her iki grupta benzerdi (sırasıyla; $p=0.25$, $p=0.26$). Famotidin verilenlerde ateşli gün sayısı, hastanede kalış süresi ve oksijen desteği gerektiren gün sayısı daha azdı (sırasıyla; $p=0.04$, $p=0.003$, $p=0.014$).

Sonuç: Famotidin, hastanede tedavi gören COVID-19 hastalarında yoğun bakım ihtiyacını ve mortaliteyi azaltmadı. Hastalık şiddetini ve ölüm oranını azaltmak için yeni tedavilere ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Famotidin, Pantoprazol, Mortalite.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was started in Wuhan (China) in December 2019 and expanded dramatically worldwide. The virus, which caused one of the biggest epidemics of the 21st century, has had devastating effects in many countries due to its high contagiousness and high mortality rates (1). Over 110 million cases and 2.5 million deaths have been reported globally (2). The most common symptoms of COVID-19 are fever, dry cough, and tiredness. In severe cases, shortness of breath, confusion, persistent pain or pressure in the chest, and high temperature (above 38 C) are seen. Approximately 80% of symptomatic patients recover without the need for hospital treatment. While approximately 15% of them have a serious infection and need oxygen support, 5% of them become critically ill and need intensive care (3). (WHO-2020) Data from patients infected with SARS-CoV showed that severe cases characterized by cytokine storm inevitably progress to Acute Respiratory Distress Syndrome (ARDS). Tissue damage caused by the virus can induce overactivation of macrophages and granulocytes and overproduction of proinflammatory cytokines. This event results in Cytokine Storm (cytokine storm-CS) called Macrophage Activation Syndrome (MAS), and thus further tissue damage occurs (4).

From the first days of the pandemic, antivirals that could be effective on COVID-19 have been investigated and antivirals are shown to be effective in the treatment of SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) have been started to be used in in vitro and in vivo studies. However, unfortunately, since complete success cannot be achieved with these treatments, the effectiveness of drugs with antiviral and anti-inflammatory effects, which are thought to be effective against COVID-19, are being investigated (5). Famotidine is an H2 receptor antagonist (H2RA) that suppresses stomach acid production. Previous data show that H2RAs have antiviral properties that inhibit in vitro HIV replication (6). In this study, it was aimed to investigate the effectiveness of Famotidine treatment in COVID-19.

MATERIAL AND METHODS

Study Place and Design: This study was conducted in Sakarya Training and Research Hospital, which has a total of 1000 beds. The study protocol was approved by the institutional review board of the Sakarya University (IRB No: 71522473/050.01.04/465). Patients who used famotidine or pantoprazole for at least 2 days in addition to the standard COVID-19 treatment were included in the study. Patients who died before the second day of the standard treatment and those who were switched to another while using one of the compared drugs were not included in the study.

Patients and Standard Therapy: The patients were divided into two groups as the famotidine group and the pantoprazole group. The groups were compared in terms of the need for intensive care and mortality rates. In addition, among the groups, the number of patients with normal oxygen saturation at discharge, number of days needed for oxygen support, number of days with fever, and length of hospital stay were evaluated.

Statistical Analysis: We evaluated the data with SPSS v.23 statistics program. We gave the number and percentage distributions to examine the descriptive features in the analysis. We calculated the central tendency and prevalence measures (mean, median, standard deviation, 1st, and 3rd quartiles) of data with continuous variable character. We used the chi-square test (Pearson and Fisher's exact test) to compare categorical variables. We evaluated the suitability of continuous variables to a normal distribution using the Shapiro Wilk test, and numerical data that did not conform to normal distribution we compared by using Mann Whitney U test. We accepted the statistical significance value as $p < 0.05$ at 95% confidence interval.

RESULTS

179 Covid-19 patients were included in the study. Pantoprazole was given to 94 (52.5%) of the patients, while famotidine was given in 85 (47.5%) of them. When the patients were grouped according to their use of famotidine and pantoprazole, the mean age was 62.0 ± 15.8 and 65.8 ± 14.5, respectively, and there was no statistically significant difference between the groups' mean age ($p=0.65$). While 50.6% (n=43) of those using famotidine were female, 49.4% (n=42) were male; 47.9% (n=45) of those using pantoprazole were female and 52.1% (n=49) were male ($p=0.71$). The distribution of some of the characteristics of the patients during their application according to the gastric protective drug they use is given in Table 1.

Chronic diseases, immunosuppressive therapy, malignancy, hydroxychloroquine, enoxaparin, antibiotics, acetylsalicylic acid, tocilizumab/anakinra, convalescent plasma and vitamin D were similar in patients using famotidine and pantoprazole ($p>0.05$). Also, the presence of symptoms was similar in both groups ($p>0.05$).

The relationship between the gastric protective medication used by the patients and the average of the laboratory values at the time of application is given in Table 2.

Table 1. The distribution of some characteristics of the patients during their application according to the gastric protective drug they used

(n=179)	Famotidine	Pantoprazole	
	n (%*)	n (%*)	p
Presence of chronic illness			
Hypertension	28 (32.9)	42 (44.7)	0.10
Diabetes mellitus	17 (20.0)	30 (31.9)	0.07
Coronary artery disease	11 (12.9)	17 (18.1)	0.34
Chronic obstructive pulmonary disease	8 (9.4)	13 (13.8)	0.35
Chronic renal failure	8 (9.4)	5 (5.3)	0.29
Receiving immunosuppressive therapy	3 (3.5)	3 (3.2)	0.90
Presence of malignancy	2 (2.4)	3 (3.2)	0.73
Comorbidity presence	20 (23.5)	35 (37.2)	0.04
Drug use			
Favipiravir	74 (87.1)	92 (97.9)	0.005
Hydroxychloroquine	11 (12.9)	6 (6.4)	0.13
Enoxaparin	69 (81.2)	79 (84.0)	0.61
Antibiotic	46 (54.1)	52 (55.3)	0.87
Steroid	33 (38.8)	60 (63.8)	0.001
Asetylsalicylic acid	16 (18.8)	27 (28.7)	0.12
Tociluzimab/Anakinra	2 (2.4)	8 (8.5)	0.10[a]
Convalescent Plasma	8 (9.4)	9 (9.6)	0.97
Vitamin D	2 (2.4)	2 (2.1)	0.91
Presence of symptoms			
Fatigue	43 (50.6)	60 (63.8)	0.07
Cough	39 (45.9)	52 (55.3)	0.20
Dyspnea	23 (27.1)	55 (58.5)	<0.001
Muscle-joint pain	34 (40.0)	33 (35.1)	0.49
Fever	29 (34.1)	26 (27.7)	0.35
Anosmia	8 (9.4)	11 (11.7)	0.61
Diarrhea	10 (11.8)	9 (9.6)	0.63
Headache	10 (11.8)	8 (8.5)	0.47
Sore throat	7 (8.2)	6 (6.4)	0.63
Respiratory rate	85 (47.4**)	94 (52.6**)	
X̄±SD (Median)	21.4±2.2 (22.0)	21.4±2.0 (22.0)	0.78[b]

*Percentages are column percentages. **Percentages are percent of rows. [a]Fisher's exact test was used. [b]Mann Whitney U test was performed due to skewed distribution.

Table 2. The relationship between the gastric protectant used by the patients and the mean laboratory values at the time of application. Laboratory values Stomach protection used in the treatment

Laboratory values	Famotidine (n=85)	Pantoprazole (n=94)	Total	p value*
WBC				<0.001
X̄±SD(Median)	5.9±2.9 (5.4)	7.6±3.7 (6.8)	6.8±3.5 (5.8)	
1st quarter-3rd quarter	4.3-6.3	5.1-9.2	4.6-8.3	
Lymphocyte				0.15
X̄±SD (Median)	1370.8±767.8 (1270.0)	1231.0±711.4 (1065.0)	1297.4±739.9 (1169.0)	
1.st quarter- 3rd quarter	841.0-1800.0	759.0-1518.0	785.0-1640.0	
Hemoglobin				0.007
X̄±SD (Median)	13.1±1.8 (13.3)	12.4±1.8 (12.5)	12.7±1.8 (13.0)	
1st quarter-3rd quarter	12.2-14.1	11.3-13.7	11.7-13.9	
Hematocrit				0.02
X̄±SD (Median)	40±5.6 (40.5)	38±6.1 (38.5)	38.9-5.9 (39.3)	
1st quarter -3rd quarter	36.7-43.4	33.9-42.3	35.6-43.1	
Ferritin				0.11
X̄±SD (Median)	470.1±579.2 (266)	573.8±682 (378)	524.6±635.6 (316)	
1st quarter-3rd quarter	132-478	157-736	146-618	
LDH				0.009
X̄±SD (Median)	304.8±130.5 (277)	384.3±297.2 (319)	346.5±236.2 (313)	
1st quarter-3rd quarter	214-351	258-419	240-395	
D dimer				0.02
X̄±SD (Median)	1058.5±1793.4 (500)	1316.4±1639.7 (639.5)	1193.9±1714.4 (568)	
1st quarter -3rd quarter	218.0±1120	403-1570	312-1220	
C-Reactive Protein				0.001
X̄±SD (Median)	52.8±56.3 (40)	83.3±68.8 (73.5)	68.8±64.8 (53.2)	
1st quarter-3rd quarter	12.7-62.4	26-122	15.2-107	
CK				0.46
X̄±SD (Median)	287±1148 (90.0)	175.1±232.3 (78)	228.2±808.2 (82)	
1st quarter-3rd quarter	60-197	46-192	52-197	

* Mann Whitney U test was used because of the skewed distribution.

The relationship between the gastric protective treatment they used in the treatment and the number of days of hospitalization, the number of days when oxygen saturation improved and fever

subsided is given in Table 3. Oxygen saturation was low in 21 (24.7%) of the patients using famotidine at the first admission, while it was low in 52 (55.3%) of those using pantoprazole (p<0.001). Oxygen saturation decreased in the first days of follow-up in four of the patients who were given both famotidine and pantoprazole during their hospitalization. Oxygen saturation improved in 76 (78.4%) of 97 patients with low oxygen saturation (mean: 6.32±4.1 days). The mean hospitalization period of patients using famotidine for treatment was 7.7±4.6 days, and the mean hospitalization period of patients using pantoprazole was 9.4±5.4 days (p=0.003). While the fever of the patients using famotidine for treatment decreased in an average of 2.4±1.4 days, the fever of the patients using pantoprazole decreased in an average of 3.0±1.4 days (p=0.04).

Table 3. Relationship between gastric protective treatment used by the patients in treatment and the number of days of hospitalization, days when saturation improved and fever subsided.

	Famotidine	**Pantoprazole**	**Total**	**p value***
Hospitalization time (days)				0.003
n	85	94	179	
X̄±SD (Median)	7.7±4.6 (6)	9.4±5.4 (8)	8.6±5.1 (7)	
1st quarter-3rd quarter	5-9	6-12	5-10	
Time to recovery saturation (days)				0.014
n	21	55	76	
X̄±SD (Median)	5.0±3.5 (4)	6.9±4.2 (6)	6.3±4.1 (6)	
1st quarter-3rd quarter	3-6	4-8	3.5-8	
Duration of fever (days)				0.04
n	29	26	55	
X̄±SD (Median)	2.4±1.4 (2)	3.0±1.4 (3)	2.7±1.4 (2)	
1st quarter-3rd quarter	1-3	2-3	2-3	
Oxygen saturation				
Improved / Not improved n (%)	21 (75)/7 (25)	55 (80)/14 (20)		0.61

* Mann-Whitney U test was used due to the skewed distribution.

In our study, mortality and the need for follow-up in the intensive care unit, were similar in both groups (Table 4). Gastrointestinal bleeding was detected in a patient using famotidine.

Table 4. Survival and need for intensive care according to the gastric protective drug used by the patients.

	Famotidine	**Pantoprazole**	
	n (%*)	**n (%*)**	**p**
Survival status			0.25
Deceased	5 (5.9)	10 (10.6)	
Discharged with healing	80 (94.1)	84 (89.4)	
Intensive care need			0.26
No	77(90.6)	80 (85.1)	
Yes	8 (9.4)	14 (14.9)	
Total	85 (45.7)	94 (52.5)	

* Percentages are column percentages.

DISCUSSION

This study investigates the real-life effectiveness and safety of famotidine in moderate and severe COVID-19 patients in a tertiary care hospital. Mortality and intensive care need in patients given famotidine were found to be statistically similar to those given pantoprazole (p>0.05).

Histamine is a natural body precursor synthesized from L-histidine. Histamine acts through 4 types of receptors (H1R, H2R, H3R, H4R). It causes immune system activities such as mast cell degranulation, antibody synthesis, Th1 cytokine production through H2R (7). It can cause tissue damage in the lungs by stimulating inflammation and cytokine release (8). Both H1 and H2 receptor antagonists have been demonstrated to inhibit both histamine and cytokine secretion. Also, the immunomodulatory activity H2 receptor antagonists has been shown in multiple studies (9).

The antiviral effect of famotidine has not been studied in detail in patients. Bourinbaiar et al. reported that H2R antagonists, including famotidine, inhibited human immunodeficiency virus replication without affecting lymphocyte viability in vitro (6). Likewise, it was thought to directly inhibit the SARS-CoV-2 virus, but recent studies using two different cell lines, including a human cell line originating from lungs have failed to demonstrate any direct inhibitory effect of famotidine on SARS-CoV-2 infection (10).

Freedberg et al. reported that in patients hospitalized with COVID-19 who were not initially

intubated, the use of famotidine resulted in a 2-fold reduction in clinical worsening leading to intubation or death, and this effect was not seen in patients using PPI (11). In our study, mortality and ICU requirement were similar in patients who received famotidine and those who received PPI. In patients given famotidine, the duration of hospitalization, recovery time of oxygen saturation and the number of days when fever decreased to normal values were found to be significantly less than those given PPI. However, we think that this effect is related to the fact that patients who were given famotidine had a milder clinical picture and had fewer risk factors than those given PPI. The number of patients presenting with dyspnea and comorbidities such as hypertension and diabetes mellitus, whose relationship with mortality was shown in previous studies, were higher in patients who were given PPI. In addition, LDH, D-dimer and C-reactive protein levels were higher in patients with PPI. It has been shown in previous studies that these laboratory parameters increase in direct proportion to the severity of the disease (12). Our study has some limitations. Since drugs such as enoxaparin and acetylsalicylic acid, which can cause gastrointestinal system side effects, were given to all patients in the center where the study was conducted, gastric medications such as famotidine or pantoprazole are started for all patients followed in the hospital. For this reason, patients who were given famotidine could not be compared with patients who did not use any gastric medication. Another limitation of our study is that patients given pantoprazole had more severe COVID-19 patients compared to patients who were given famotidine. This is due to the retrospective design of the study. If the baseline values of the patients in the two groups were found to be similar, we could have made a more precise judgment.

As a result, famotidine was not reduce the need for ICUs and mortality in COVID-19 patients treated in hospital. Since there is no antiviral whose efficacy has been shown with certainty, randomized controlled studies are needed to clearly demonstrate the effectiveness of famotidine, which is used for alternative treatment searches, in COVID-19 disease.

Ethical Statement: The study was approved by the Ethics Committee of Sakarya University,

Declaration of Competing Interest: The authors have no conflicts of interest to declare.

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