RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2026.26678
Mediterr J Infect Microb Antimicrob 2026;15:2026.26678
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2026.2026.26678

Drug–Drug Interactions in Patients with Brucellosis: A Retrospective Analysis

Bruselloz Hastalarında İlaç–İlaç Etkileşimleri: Retrospektif Bir Analiz

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Abstract

Introduction: The prolonged duration of drug treatment and the need for combination therapy in brucellosis increase the risk of drug-related problems. One of the most significant drug-related problems is drug–drug interactions. The aim of this study was to identify potential drug interactions that may occur during the treatment of patients with brucellosis, investigate their causes, and contribute to clinical practice.

Materials and Methods: This retrospective study included 76 patients admitted to the Infectious Diseases and Clinical Microbiology Clinic of Ege University Faculty of Medicine Hospital between January 2016 and November 2022 because of brucellosis and/or its complications. Drug interactions among the antibiotics used by the patients and between these antibiotics and other medications were investigated. Lexicomp® and Micromedex® were used as interaction databases. The severity and number of drug interactions identified in each database were assessed. Additionally, gender, age, occupation, the presence of comorbidities, and comparisons of database results across other medication groups were evaluated. Data were analyzed using SPSS version 27. Ethics committee approval was obtained, and verbal informed consent was obtained from all patients.

Results: Of the 76 patients included in the study, 49 were male, the mean age was 47.23 ± 14.16 years, and 53.95% had comorbidities. The mean number of drug interactions per patient was 4.88 ± 2.88 in LC and 2.63 ± 1.81 in MM. Significant associations were found between age, comorbidities, ciprofloxacin use, and the number of drug interactions in both databases ($p < 0.05$). When the interactions between antibiotics used for brucellosis and other medications were examined, the most common were decreased efficacy of doxycycline (97.30%), increased efficacy of gentamicin (54.17%), and decreased efficacy of rifampin (58.05%). The medications most commonly associated with decreased efficacy were statins, neurologic drugs, and antihypertensive agents ($p = 0.001$).

Conclusion: In this study, we focused on drug interactions during antibiotic treatment. Long-term treatment and polypharmacy can lead to drug interactions. This can negatively affect treatment effectiveness and prolong the duration of therapy.

Keywords: Antibiotics, drug interactions, brucellosis

Cite this article as: Çelebi B, Tüğdür Ceylan M, Yılmaz FF, Taşbakan M. Drug–drug interactions in patients with brucellosis: A retrospective analysis. Mediterr J Infect Microb Antimicrob. 2026;15:134-142

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Received/Geliş Tarihi: 20.01.2026 **Accepted/Kabul Tarihi:** 15.06.2026

Published: 11.08.2026

*This article is a revised and expanded version of a paper entitled "Bruselloz Hastalarında İlaç-İlaç Etkileşimi: Retrospektif İnceleme", which was presented at the 11th EKMUD Scientific Congress, Girne, TRNC, 3–7 May 2023.

Öz

Giriş: Bruselloz tedavisinde ilaç kullanım süresinin uzun olması ve kombine tedavi gerekliliği, ilaçla ilişkili sorunlara yol açabilmektedir. Bu sorunlardan en önemlilerinden biri ilaç etkileşimleridir. Bu çalışmanın amacı, bruselloz hastalarının tedavisi sırasında ortaya çıkabilecek ilaç etkileşimlerini belirlemek, nedenlerini araştırmak ve klinik uygulamaya katkı sağlamaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Ocak 2016 ile Kasım 2022 tarihleri arasında Ege Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'ne bruselloz ve/veya komplikasyonları nedeniyle başvuran 76 hasta dahil edildi. Hastaların kullandığı antibiyotikler arasındaki ve antibiyotiklerle diğer ilaçlar arasındaki etkileşimler incelendi. Etkileşim veritabanı olarak Lexicomp® ve Micromedex® kullanıldı. Veritabanlarında saptanan etkileşimlerin düzeyi ve sayısı değerlendirildi. Ayrıca cinsiyet, yaş, meslek, komorbidite varlığı ve veritabanı sonuçlarının diğer ilaç gruplarıyla karşılaştırılması analiz edildi. Veriler SPSS 27 ile analiz edildi. Etik kurul onayı alındı ve tüm hastalardan sözlü bilgilendirilmiş onam alındı.

Bulgular: Çalışmaya dâhil edilen 76 hastanın 49'u erkek olup, yaş ortalaması 47,23 ± 14,16 idi ve hastaların %53,95'inde komorbidite mevcuttu. Hasta başına düşen ilaç etkileşimi sayısı LC'ta 4,88 ± 2,88; MM'te 2,63 ± 1,81 olarak bulundu. Her iki veritabanında da yaş, komorbidite ve siprofloksasin kullanımı ile ilaç etkileşimi sayısı arasında anlamlı ilişki saptandı ($p < 0,05$). Bruselloz tedavisinde kullanılan antibiyotiklerin diğer ilaçlarla etkileşimleri incelendiğinde, en sık görülenler doksisiklin etkinliğinde azalma (%97,30), gentamisin etkinliğinde artış (%54,17) ve rifampisin etkinliğinde azalma (%58,05) idi. Etkinliği azalan ilaçlar arasında en sık statinler, nörolojik ilaçlar ve antihipertansifler yer aldı ($p = 0,001$).

Sonuç: Çalışmamızda antibiyotik tedavisi sırasında gelişen ilaç etkileşimleri üzerinde durulmuştur. Uzun süreli tedavi ve çoklu ilaç kullanımı ilaç etkileşimlerine neden olabilir. Bu durum tedavinin etkinliğini ve süresini olumsuz etkileyebilir.

Anahtar kelimeler: Antibiyotikler, ilaç etkileşimleri, bruselloz

Introduction

Brucellosis, also known as "undulant fever," "Mediterranean fever," or "Malta fever," is a zoonotic disease caused by *Brucella* species. The infection is almost always transmitted through direct or indirect contact with infected animals or animal products[1,2]. Brucellosis is commonly observed in Mediterranean countries and neighboring regions, including our country[3,4]. Although the highest prevalence in our country is reported in Eastern Anatolia, the exact incidence and prevalence remain unknown because of inadequate diagnosis and reporting[5]. Worldwide, more than 500,000 new cases of brucellosis occur each year, and an estimated 2.4 billion people are at risk[6,7]. This disease, which often causes prolonged fever, can affect multiple organs and organ systems, primarily involving the bones and joints, and can result in diverse clinical manifestations[8].

Brucellosis is often chronic in nature and can recur even when antimicrobial agents are administered according to the standard recommendations of the World Health Organization, thereby requiring long-term combination therapy[9,10]. The treatment duration is generally six weeks but may extend to three months in cases of complications or poor prognosis[10].

The prolonged treatment duration and the need for combination therapy also increase the risk of drug-related problems. One of the most important drug-related problems is drug–drug interactions[11]. Drug–drug interactions refer to changes in the effects of a drug that may occur because of the concomitant or closely timed use of another drug. The combined use of two drugs can lead to toxicity because of increased drug effects or to therapeutic failure because of reduced drug efficacy[12]. Inhibition or induction of cytochrome P450 drug-metabolizing isoenzymes is the most common mechanism by which clinically significant drug interactions occur[13,14]. Identifying clinically relevant drug interactions is essential for patient safety. Strategies to reduce the risk of drug interactions include minimizing the number of prescribed medications, regularly reassessing treatment, considering non-pharmacologic options, and monitoring for signs and symptoms of toxicity or therapeutic effectiveness.

In this study, we aimed to contribute to clinical practice by examining the drug interactions between antimicrobial agents (e.g., rifampin, doxycycline, ciprofloxacin, and gentamicin) used by patients diagnosed with brucellosis and other medications prescribed by physicians. We believe that this is the first study to investigate drug interactions in patients with brucellosis in our country.

Materials and Methods

Seventy-six patients admitted to the Infectious Diseases and Clinical Microbiology Clinic of Ege University Faculty of Medicine Hospital between January 2016 and November 2022 because of brucellosis and/or its complications were included in the study. Patients who met the inclusion criteria were selected from retrospective patient records (Table 1). Drug interactions between the antibiotics used by the patients and other medications were examined.

Lexicomp® (LC) and Micromedex® (MM) were used as the interaction databases (Table 2). The severity and number of drug interactions identified in the databases were evaluated. In addition, comparisons were made between the database

results and patients' gender, age, occupation, presence of comorbidities, and other medication groups used.

Verbal informed consent was obtained from all patients.

Statistical Analysis

The data obtained in this study were analyzed using the licensed SPSS version 27 statistical software package. Initially, frequency analyses were conducted for demographic characteristics, and frequencies (n) and percentages (%) were calculated for each group. Subsequently, descriptive statistics for continuous variables were calculated, including the mean, standard deviation, minimum and maximum values.

The normality of the variables was assessed using skewness and kurtosis coefficients, and a normal distribution was assumed when the skewness and kurtosis values fell between –1.50 and +1.50. Accordingly, the variables were determined to be normally distributed. The assumption of homogeneity of variances was evaluated using Levene's test.

Because the variables were normally distributed, differences between groups were analyzed using the independent samples t-test for comparisons between two independent groups and analysis of variance (ANOVA) for comparisons among three or more independent groups. When the assumption of homogeneity of variances was violated in the parametric tests, the results of Welch's test were considered. For multiple comparisons following a significant ANOVA result, Tukey's or Tamhane's post-hoc tests were applied depending on the homogeneity of variances.

Relationships between continuous variables were examined using Pearson's correlation analysis, whereas associations between categorical variables were evaluated using the chi-square test. For the interpretation of the results, the significance level was set at 0.05, and results with $p < 0.05$ were considered statistically significant.

Ethical Approval

The study was approved by the Ege University Medical Research Ethics Committee (approval date: December 15, 2022; approval number: 22-12.1T/3).

Results

Among the 76 patients included in the study, 49 were male, the mean age was 47.23 ± 14.16 years, and 30.26% were involved in animal husbandry. While 30.26% of the patients had a history of suspected food consumption, the most common symptom was fever (75%). A total of 53.95% of the patients included in the study had comorbidities, the most common of which were cardiovascular diseases (Table 3).

When the distribution of antibiotics used for brucellosis was examined, rifampin (98.68%) and doxycycline (97.37%) were the most frequently prescribed antibiotics, as expected. According to the interaction databases, the mean number of drug interactions per patient was 4.88 ± 2.88 in LC and 2.63 ± 1.81 in MM (Table 4).

The antibiotics used by the patients and the other medications prescribed for their illnesses were grouped according to their pharmacological properties and/or effects. The distribution of drug interaction counts for all medications in both drug interaction databases was analyzed. Rifampin was the antibiotic with the highest number of drug interactions, whereas non-steroidal anti-inflammatory drugs antihypertensive agents, and antiemetics were the most common medications in the other drug groups. The similarity of drug interactions between the two databases and the distribution of potential adverse effect profiles associated with antibiotics were also examined (Table 5).

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
18 years and older (adults)	Patients under 18 years of age
Use of two or more medications	Patients with incomplete data in the Electronic Patient Record
Complete patient information in electronic and/or manual patient records	Those with pregnancy or suspected pregnancy

Table 2. Drug–drug interactions according to the Lexicomp® and Micromedex® databases.

Lexicomp®		Micromedex®	
X	Avoid concomitant use	Contraindicated	Concurrent use of medications is contraindicated
D	Consideration of treatment modification	Major	Serious interaction level, intervention required
C	Treatment monitoring should be ensured	Moderate	Treatment may need to be modified
B	No intervention required	Minor	No change in treatment is required
A	No known drug interactions		

Table 3. Frequency distribution of demographic characteristics, disease symptoms, and comorbidities.

Variable	Category	n	%
Gender	Female	27	35.53
	Male	49	64.47
Occupation	Farmer	8	10.53
	Livestock	23	30.26
	Other	45	59.21
Suspicious food consumption		23	30.26
Variable		Mean ± SD	Min–max
Age		47.23 ± 14.16	18–71
Symptoms		n	%
Fever		57	75
Joint pain		46	60.53
Muscle pain		51	67.11
Variable		n	%
Comorbidities		41	53.95
Cardiovascular disease		26	34.21
COPD		4	5.26
Psychiatric and neurological disorders		12	15.79
Diabetes		11	14.47
Other		28	36.84

SD, standard deviation; Min, minimum; Max, maximum; COPD, chronic obstructive pulmonary disease.

Table 4. Distribution of antibiotics used and number of drug interactions.

Variable		n	%
Doxycycline		74	97.37
Rifampin		75	98.68
Gentamicin		39	51.32
Ciprofloxacin		24	31.58
Variable	Mean ± SD	Min–max	
LC drug interaction count	4.88 ± 2.88	1–12	
MM drug interaction count	2.63 ± 1.81	1–9	

SD, standard deviation; Min, minimum; Max, maximum; LC, Lexicomp®; MM, Micromedex®.

To make the interaction descriptions in the databases easier to understand with respect to antibiotics, they were classified into five groups according to the antibiotic's susceptibility to interactions. These groups were "Antibiotic Effect Decreases," "Antibiotic Effect Increases," "Antibiotic Not Affected, Side Effect May Occur," "Antibiotic Not Affected, Other Drug Effect Decreases," and "Antibiotic Not Affected, Other Drug Effect Increases." Regarding the distribution of database categories, category C was the most common in LC, whereas the moderate category was the most common in MM. In terms of interaction status, the group characterized by a decrease in antibiotic effect was the most frequently observed (Table 6).

When the levels of drug interactions in the drug interaction databases were compared with the study variables, a significant association was found in LC, and in both databases, between the number of drug interactions and age, the presence of comorbidities, and ciprofloxacin use (Tables 7 and 8).

Only seven patients in our study experienced recurrence. When the number of drug interactions was compared between patients who experienced recurrence and those who did not, no statistically significant difference was found (Table 9).

When the drugs, database categories, and frequency distributions of interaction statuses in the drug interaction databases were examined, the most common interaction

category was "decreased antibiotic effect." When the interactions between antibiotics used for brucellosis and other medications were evaluated, the most common findings were decreased efficacy of doxycycline (97.30%), increased efficacy of gentamicin (54.17%), and decreased efficacy of other drugs associated with rifampin (58.05%). The medications most frequently associated with decreased efficacy were statins, neurologic drugs, and antihypertensive agents ($p = 0.001$). Statistically significant differences were found between the antibiotic adverse effect profiles that could result from drug interactions and the similarity of drug interactions between the databases (Table 10).

Table 5. Distribution of drugs involved in drug interactions.

Variable	Category	n	%
Antibiotics used for brucellosis	Rifampin	213	56.95
	Doxycycline	75	20.05
	Gentamicin	24	6.42
	Ciprofloxacin	38	10.16
	Other	24	6.42
Medications used for other reasons	Antihypertensives	53	14.17
	Antidiabetics	10	2.67
	NSAIDs and other analgesics	78	20.86
	Antiemetics	54	14.44
	PPIs	43	11.50
	Statins	5	1.34
	NPM	12	3.21
	Other medications	20	5.35
	Other antibiotics	99	26.47
	QT prolongation	9	2.41
	Nephrotoxicity	9	2.41
Antibiotic side effects	Ototoxicity	2	0.53
	Hypoglycemia	1	0.27
	None	353	94.39
LC-MM same situation	Different	255	68.18
	Same	119	31.82

NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; NPM, neurological and psychiatric medications; LC, Lexicomp®; MM, Micromedex®.

Table 6. Frequency distribution of drug interactions.

Variable	Category	n	%
LC interaction level	B	21	5.61
	C	307	82.09
	D	24	6.42
	X	22	5.88
MM interaction category	Major	65	17.38
	Moderate	137	36.63
	None	172	45.99
Interaction status	Antibiotic effect decreasing	165	44.12
	Antibiotic effect increasing	40	10.70
	Antibiotic effect not affected side effects may occur	21	5.61
	Antibiotic not affected, effect of other medications reduced	131	35.03
	Antibiotic unaffected, other drug effects increasing	17	4.55

LC, Lexicomp®; MM, Micromedex®.

Table 7. Comparison of Lexicomp drug interaction levels with variables.

Variable	Level	LC-DI		Statistics		
		Mean	SD	Test value	p	d
Occupation	Farmer(1)	7.13	3.52	2.902[A]	0.041*	1>3
	Livestock farmer(2)	4.78	2.15			
	Other(3)	4.53	2.97			
Additional medical condition	None	3.14	1.57	−6.088[t]	0.001*	-
	Present	6.37	2.93			
Doxycycline	None	4.50	4.95	−0.188[t]	0.851	-
	Yes	4.89	2.86			
Rifampin	None	8.00	1.00	1.091[t]	0.279	-
	Yes	4.84	2.88			
Gentamicin	None	4.57	2.81	−0.924[t]	0.359	-
	Yes	5.18	2.95			
Ciprofloxacin	None	4.23	2.48	−3.052[t]	0.003*	-
	Yes	6.29	3.24			
Age				0.281[r]	0.014*	-

*p < 0.05; F: ANOVA test; t: independent samples t-test; r: correlation test; d: post hoc Tukey comparison; (1) Farmer, (2) Livestock farmer, (3) Other.

Table 8. Comparison of Micromedex drug interaction levels with variables.

Variable	Level	MM-DI		Statistics		
		Mean	SD	Test value	p	d
Occupation	Farmer(1)	3.63	2.50	1.409	0.251	-
	Livestock(2)	2.61	1.67			
	Other(3)	2.47	1.73			
Additional medical condition	None	1.49	0.74	−6.645	0.001*	-
	Present	3.61	1.88			
Doxycycline	None	1.50	0.71	−0.895	0.374	-
	Yes	2.66	1.82			
Rifampin	None	2.00	1.00	−0.349	0.728	-
	Yes	2.64	1.82			
Gentamicin	None	2.81	1.84	0.839	0.404	-
	Yes	2.46	1.79			
Ciprofloxacin	None	2.31	1.46	−2.022	0.021*	-
	Yes	3.33	2.28			
Age				0.312	0.006*	-

*p < 0.05; F, ANOVA test, difference; Tukey test, t, independent samples t-test; r,: correlation test; d, difference; MM-DI, Micromedex drug interaction count; SD, standard deviation.

Table 9. Relationship between recurrence and the number of drug interactions.

Variable	Category	Disease relapse status			p
		Mean	SD	Median	
Lexicomp drug interaction count	Yes	5.29	3.64	5.00	0.763
	No	4.84	2.83	4.00	
Micromedex drug interaction count	Yes	2.71	1.70	2.00	0.897
	No	2.62	1.83	2.00	

*p <0.05; independent samples t-test; SD: standart deviation.

Table 10. Chi-square test results regarding the relationship between medications used and interaction status.

Variable	Category	Interaction					Chi-square Test
		AED	AEI	AA-SE	AEU-ODE	AEU-ODI	
		n	n	n	n	n	z
Antibiotics used for *Brucellosis*	Rifampin	78 (38.05%)	5 (2.44%)	0 (0.00%)	119 (58.05%)	3 (1.46%)	345.777 (p = 0.001*)
	Doxycycline	72 (97.30)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.70%)	
	Gentamicin	4 (16.67%)	13 (54.17%)	6 (25.00%)	1 (4.17%)	0 (0.00%)	
	Ciprofloxacin	6 (21.43%)	11 (39.29%)	1 (3.57%)	5 (17.86%)	5 (17.86%)	
	Other	2 (9.09%)	9 (40.91%)	7 (31.82%)	0 (0.00%)	4 (18.18%)	
Antibiotics and medications used for other reasons	AHT	10 (21.28%)	5 (10.64%)	5 (10.64%)	23 (48.94%)	4 (8.51%)	277.053 (p = 0.001*)
	Antidiabetics	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (50.00%)	5 (50.00%)	
	NSAID	7 (9.09%)	22 (28.57%)	1 (1.30%)	47 (61.04%)	0 (0.00%)	
	Antiemetics	31 (67.39%)	0 (0.00%)	2 (4.35%)	12 (26.09%)	1 (2.17%)	
	PPI	28 (68.29%)	2 (4.88%)	0 (0.00%)	11 (26.83%)	0 (0.00%)	
	Statins	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (80.00%)	1 (20.00%)	
	NPM	0 (0.00%)	0 (0.00%)	0 (0.00%)	10 (83.33%)	2 (16.67%)	
	OM	2 (11.11%)	1 (5.56%)	1 (5.56%)	13 (72.22%)	1 (5.56%)	
	OA	84 (86.60%)	8 (8.25%)	5 (5.15%)	0 (0.00%)	0 (0.00%)	
Antibiotic side effect	QT-p	0 (0.00%)	0 (0.00%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	117.805 (p 0.001*)
	Nephrotoxicity	0 (0.00%)	0 (0.00%)	9 (100.00%)	0 (0.00%)	0 (0.00%)	
	Ototoxicity	0 (0.00%)	0 (0.00%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	
	Hypoglycemia	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	
	None	162 (47.79%)	38 (11.21%)	0 (0.00%)	125 (36.87%)	14 (4.13%)	
LC-MM	Different	85 (34.84%)	38 (15.57%)	14 (5.74%)	97 (39.75%)	10 (4.10%)	48.522 (p 0.001*)
	Same	77 (70.64%)	0 (0.00%)	0 (0.00%)	28 (25.69%)	4 (3.67%)	

*p < 0.05; chi-square test AED, antibiotic effect decreasing; AEI, antibiotic effect increasing; AA-SE, antibiotic not affected, side effects may occur; AEU-ODE, antibiotic effect remains unchanged, other drug effect decreases; AEU-ODI, antibiotic effect not affected, other drug effect increasing; AHT, antihypertensives; NPM, neurological and psychiatric medications; OM, other medications; OA, other antibiotics; LC-MM: Lexicomp-Micromedex

Discussion

Lexicomp® and Micromedex® databases were used in our study to identify drug interactions. Statistical analyses revealed that the number of drug interactions identified in both databases was significantly associated with age, the presence of comorbidities, and ciprofloxacin use, whereas occupation was significantly associated only in the Lexicomp database. A review of the literature indicates that, although studies investigating drug interactions in patients with brucellosis are limited, numerous studies have examined drug interactions involving currently available antibiotics.

In a study published in 2021, drug interactions, particularly those involving HIV medications and antimicrobial agents, were examined using three different databases (Micromedex, Drugs.com, and the Liverpool HIV Interactions Programme). The Liverpool database reported 10% contraindications, Micromedex reported 14% contraindications and 59% major interactions, and Drugs.com reported 21% major interactions[15]. These findings demonstrate that the frequency and severity of drug interactions may vary considerably depending on the database used.

A study conducted at Augusta University's Georgia Medical School examined interactions between antimicrobial agents and anticoagulants. It found that certain antimicrobial agents inhibit warfarin metabolism, particularly in patients receiving warfarin. The antimicrobials most likely to cause these interactions include trimethoprim/sulfamethoxazole, metronidazole, and fluconazole. Other antimicrobials, such as ciprofloxacin, levofloxacin, azithromycin, and clarithromycin, have also been shown to have similar effects[16]. In a multicenter study conducted in our country, the Micromedex database was used to evaluate drug interactions. Potential antimicrobial-related drug interactions accounted for 26.4% of all interactions[17].

Unlike previous studies, our study evaluated the number of drug interactions in relation to several patient-related parameters. The increase in the number of comorbidities and medications used with advancing age was found to affect the number of drug interactions, which was considered an expected finding.

Our results showed that drug interactions were significantly more frequent in both databases among patients treated with ciprofloxacin. This finding is consistent with the pharmacological properties of ciprofloxacin reported in the literature. Tamma et al.[18] emphasized that ciprofloxacin inhibits the CYP1A2 enzyme, thereby increasing the risk of metabolic interactions with drugs such as theophylline, clozapine, tizanidine, and warfarin, potentially leading to toxicity. Owens and Ambrose[19] also reported that fluoroquinolones may cause clinically significant pharmacokinetic and pharmacodynamic interactions, particularly in patients receiving multiple medications, and highlighted the need for careful monitoring of cardiovascular, neurologic, and gastrointestinal adverse effects. Similarly, in our study, interactions associated with an increased risk of QT prolongation related to ciprofloxacin were identified in both databases.

In a recent review by Zhou et al.[20], clinically significant drug–drug interactions between quinolones and statins were highlighted, and close monitoring of creatine kinase levels and muscle-related symptoms was recommended, particularly in patients receiving high-dose atorvastatin or simvastatin in combination with ciprofloxacin.

In this study, rifampin, a potent inducer of cytochrome P450 enzymes, was shown to significantly reduce the efficacy of other medications, particularly antihypertensive agents, statins, and neurologic drugs. Conversely, doxycycline was found to be associated with reduced antibiotic efficacy through drug–drug interactions. A significant association was observed in the drug interaction data, as concomitantly administered medications, especially proton pump inhibitors, reduced the bioavailability of doxycycline. Furthermore, in our study, statins and neurologic drugs were the other medication classes whose efficacy was reduced as a result of antibiotic-related drug interactions, in descending order of frequency.

In a case report by Han et al.[21], a patient diagnosed with HIV/AIDS was reported to have concurrent pulmonary tuberculosis, chronic hepatitis C, and systemic brucellosis. A standard antituberculosis regimen containing rifampin was initiated for tuberculosis treatment, whereas doxycycline-based antibiotic therapy was used for brucellosis. In the management of chronic hepatitis C infection, the selection and timing of antiviral therapy were carefully adjusted because of the potential risk of hepatotoxicity. Antiretroviral therapy was continued for HIV/AIDS; however, clinical modifications were made in consideration of the potential reduction in antiretroviral drug levels caused by the cytochrome P450 enzyme-inducing effect of rifampin. Throughout the course of treatment, close clinical and laboratory monitoring was emphasized as essential because of both drug–drug interactions and the risk of hepatotoxicity[21]. Considering the prolonged duration of brucellosis treatment, close monitoring of medications used for concomitant diseases is of great importance throughout the treatment period, and clinically significant potential drug–drug interactions should not be overlooked.

Study Limitations

Because of the retrospective study design based on medical record review, patients with incomplete data were excluded, which may have limited the sample size. As a result of the

retrospective design, the clinical outcomes of the identified potential drug–drug interactions, such as adverse effects or their impact on treatment effectiveness, could not be directly observed. In addition, changes in patients' medication regimens after hospital discharge and the potential drug–drug interactions arising from these changes could not be evaluated. Furthermore, the single-center design and the relatively small sample size limit the generalizability of the findings. Therefore, prospective, multicenter studies incorporating post-discharge follow-up and clinical outcome assessment are warranted to provide more comprehensive evidence.

Conclusion

Long-term antibiotic regimens used to treat brucellosis pose a substantial risk of clinically significant drug–drug interactions. These interactions may not only compromise treatment efficacy but also prolong treatment duration and create considerable challenges in the management of comorbid conditions. Our findings demonstrate that the identification of drug interactions varies significantly depending on the drug interaction database used, indicating that potential interactions should be evaluated not only according to their frequency but also in terms of their clinical significance. In particular, treatment regimens containing ciprofloxacin or rifampin warrant careful review of concomitant medications, with a patient-specific assessment of potential interactions. In this context, the active involvement of clinical pharmacists as part of the multidisciplinary health care team is essential for the early identification, prevention, and effective management of clinically meaningful drug–drug interactions, thereby ensuring safe and optimized treatment strategies for patients with brucellosis.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Medical Research Ethics Committee (approval date: December 15, 2022; approval number: 22-12.1T/3).

Informed Consent: The verbal informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T.C., M.T., Concept: B.Ç., F.F.Y., Design: B.Ç., M.T., Data Collection or Processing: F.F.Y., Analysis or Interpretation: M.T.C., Literature Search: B.Ç., M.T.C., Writing: B.Ç., M.T.C., M.T.

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

Financial Disclosure: The authors declared that this study received no financial support.

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