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Research Article

Hepatic Safety of 1200 Milligrams of Rifampicin in Combination With Colistin for Multidrug-Resistant Acinetobacter Baumannii in Critically Ill Patients: A Retrospective Cross-Sectional Study

Hossein Karballaei Mirzahosseini[1]*, Atabak Najafi[2], Mojtaba Mojtahedzadeh[3]

[1]Department of Clinical Pharmacy, School of Pharmacy, Semnan University of Medical Sciences, Semna,. Iran.

[2]Department of Anesthesiology and Critical Care, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[3]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background: Infection with multidrug-resistant Acinetobacter baumannii has a high mortality rate. Some studies support the use of combination therapy with rifampin and colistin in the treatment of resistant Acinetobacter baumannii, but there is concern about the liver toxicity of high doses of rifampin in critically ill patients. Critically ill patients are more susceptible to liver side effects of drugs. The present cross-sectional study seeks to investigate the hepatic safety of rifampicin at a 1200 mg daily dose in combination with colistin.

Methods: Following the acquisition of approval from the hospital's ethics committee, a cross-sectional study was conducted to assess the prevalence of hepatotoxicity associated with a daily dosage of 1200 mg of rifampicin. Patients who were treated with a rifampicin-colistin regimen and were admitted to the ICUs of Sina Hospital between April 2017 and February 2021 were identified for this study. Patients were screened for drug-related liver complications using the updated Roussel Uclaf Causality Assessment Method (RUCAM). Then the data was assessed using the SPSS software.

Results: 60 patients were included in this study with an average age of 51.76 years. 40 patients (66.66%) were male and 20 (33.33%) were female. The studied patients had a mean weight of 72.56 kg, and their average rifampicin dose (based on their body weight) was 17.03 mg/kg. Results of ANOVA and Chi-square tests indicated that the values of main hepatic parameters like baseline aspartate aminotransferase (AST) (with a mean and standard deviation (SD) of 84.27±68.30), baseline Alanine transaminase (ALT) (with a mean and SD of 86.27±75.25), and baseline total Bilirubin (TBIL) (with a mean and SD of 1.16±0.788) were significantly related to the occurrence of drug-induced hepatotoxicity ($P \leq 0.001$).

Conclusion: Critically ill patients take many drugs, some of which are categorized as hepatotoxic drugs and increase the risk of hepatic complications depending on the patient's underlying diseases. Results indicated that patients with elevated baselines of AST, ALT, and TBIL were more likely to suffer from drug-induced liver injury (DILI). It seems that a 1200 mg daily dose of rifampicin has a safe hepatic profile until meeting normal hepatic baseline requirements.

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*Corresponding author.
E-mail address: karbalayihossein1363@gmail.com

DOI:

Introduction

Treating the infection caused by antimicrobial-resistant microorganisms is among the serious problems in critically ill patients admitted to the intensive care units (ICUs). Despite huge advancements in the prevention and treatment of infectious diseases, they remain the second leading cause of mortality across the world and the third cause of death in the United States [1]. Acinetobacters are gram-negative bacteria in a coccobacilli or cocci form, which need little nutrition to grow and can survive on dry surfaces, under adverse conditions, and in aquatic environments for long times. Acinetobacters can rarely cause severe infections in people with a normal immunity level and are also less known as the natural flora in healthy people. But Acinetobacter baumannii is currently among the most prevalent causes of nosocomial infections [2]. The concern with this bacterium is more serious in patients admitted to intensive care, burn, and surgery units [3-4]. It is among the risk factors for pneumonia, septicemia, endocarditis, meningitis, and also ulcers, skin, and urinary tract infections. While colistin is usually used as the last resort to treat infections caused by resistant A. baumannii, and a number of studies have shown that combinational regimens of colistin and rifampicin can lead to desirable microbial and clinical responses [5], cases of resistance to colistin sulfate have been reported across the world; for instance, Acinetobacter's resistance was reported to increase by 35% over 2002-2007 in Spain [6]. Antimicrobial resistance is usually significantly higher in developing countries such as Iran. A 2014 study conducted on A. baumannii isolated from clinical samples of Shahid Beheshti Hospital, Kerman, revealed a 100% increase in the number of multidrug-resistant isolates [7]. Thus, the article sought to investigate the hepatic safety of high-dose rifampicin in combination with colistin in treating multidrug-resistant A. baumannii infections in critically ill patients.

Critically ill patients are more susceptible to liver side effects of drugs than other patients [8]. Drug-induced liver injury (DILI) is characterized as a foreign chemical substance-induced hepatic injury in the absence of other known causes [9]. DILI can be mild, such as a simple asymptomatic elevation of transaminase, or severe and life-threatening, such as acute liver failure [10]. LiverTox has classified drugs into five categories (A, B, C, D, and E) based on the number of announced cases with DILI [11].

More than 50 cases have been published with clear association with DILI in category A, and 12–49 cases published as category B [12]. The Roussel Uclaf Causality Assessment Method (RUCAM), which was formerly named the Council for International Organizations of Medical Sciences (CIOMS), is commonly used for causal analysis in patients with suspected DILI. The RUCAM score gives the final numerical grading of causality for each suspected drug. This system evaluates clinical, biochemical, serologic, and radiologic highlights of liver injury, which reflects the likelihood of DILI due to a specific medication [12]. The RUCAM score is composed of various elements, including time-to-onset, the progression of the condition, risk factors, drugs administered concurrently, non-pharmaceutical causes of liver injury, prior instances of hepatotoxicity associated with the drug, and the response to medication rechallenge.

The total score can range from -9 to +14. A score of zero or lower suggests that the drug is "excluded" from being considered a potential cause; a score between 1 and 2 indicates that the relationship appears to be "unlikely"; a score from 3 to 5 is categorized as "possible"; a score between 6 and 8 is deemed "probable"; and a score exceeding 8 identifies the suspected drug as a "highly probable" cause of the liver damage that has occurred. [13].

Methods

The present research is a cross-sectional study. The statistical population includes the registered data from the Hospital Information System (HIS) and the medical records of patients admitted to the ICUs of Sina Hospital, an important educational treatment center of Tehran University of Medical Sciences (TUMS). These patients were admitted over 2017-2021 and treated with both rifampicin and colistin. Inclusion criteria were having the age of 18-85 years, suffering from bloodstream A. baumannii infection, a minimum of seven days of treatment with a regimen containing a 1200 mg daily dose of oral rifampicin in combination with colistin, and hepatic biochemical tests having been investigated both before the prescription of the medications and at least once again during 10 to 30 days after starting this regimen.

Registered patients' information, including demographic characteristics, laboratory data, disease process, drug history, and possible side effects of the drugs, was also documented. Patients were excluded from the study if suffering from advanced hepatic deficiencies before treatment with rifampicin, infected with COVID-19 or Mycobacterium tuberculosis, being admitted due to drug overdose, or having incomplete medical records. Patients were examined and evaluated after obtaining permission from the ethics committee of the hospital to estimate the incidence of hepatic complications induced by a 1200 mg daily dose of rifampicin and determine the factors that contributed to DILI. Besides comparing the results of changes in hepatic biochemical tests at the baseline and after receiving rifampicin and colistin, each individual was investigated

in terms of DILI diagnosis (based on the DILI expert working group) to find out if any of the following criteria were met [14]:

1. elevation of ALT or AST more than 5 times above the upper limit of normal (ULN) without liver injury symptoms
2. elevation of ALT or AST more than 5 times above their baseline values3- rise in alkaline phosphate (ALP) more than 2 times above ULN
3. rise of bilirubin more than 2 times above ULN with any rise in AST and ALT
4. rise in AST or ALT less than 5 times above ULN with liver injury symptoms

After DILI was diagnosed for the patients, the R coefficient was calculated using Equation 1 (R1), based on the recommendation of CIOMS, to determine the type of the DILI pattern, which can be either cholestatic, hepatocellular, or mixed [15].

In the case of hepatocellular liver complications, the amount of the ALT enzyme increases significantly compared to its ULN. This happens while the increase in ALP enzyme serum level is insignificant, and thus, the value of R will be equal to or over 5 in such cases. In contrast, the level of ALP enzyme increases significantly compared to ULN in the case of cholestatic DILI, so that the value of R will be equal to or smaller than 2. In case both cholestatic and hepatocellular complications occur at the same time, the value of R will be in the range of 2 to 5. Mean ALT and ALP were used instead of ULN for calculating R in case the patient had increased hepatic enzymes before receiving rifampicin (Equation 2 = *R*2).

$$R_1 = \frac{ALT/_{ULN}}{ALP/_{ULN}} \quad (1)$$

$$R_1 = \frac{ALT/_{\text{Baseline average ALT}}}{ALP/_{\text{Baseline average ALP}}} \quad (2)$$

After the determination of the DILI type in patients based on their hepatotoxicity pattern, RUCAM was used to examine the relationship between biochemical hepatic disorders and the consumption of drugs as well as determine the drug responsibility for DILI [15]. Thus, the RUCAM score of medications suspected for DILI was calculated based on the hepatotoxicity pattern for all class-A and class-B drugs according to the LiverTox classification [16]. and drugs with a score of 6 or higher were considered as probable causes of DILI. Then, the DILIN criteria [17] were used to rank the severity of the drug-induced liver damage, including the following measures:

- Mild: when ALT or ALP enzymes or both have increased, but TBL is less than 2.5 mg/dL and INR is less than 1.5
- Moderate: when ALT or ALP enzymes or both have increased and TBL is greater than or equal to 2.5 mg/dL or INR is greater than or equal to 1.5
- Moderate to severe: when either ALT, ALP, TBL, or INR has increased, leading to longer hospitalization due to DILI
- Severe: when ALT or ALP enzymes or both have increased, TBL is greater than or equal to 2.5 mg/dL, resulting in ascites, encephalopathy, or any DILI-induced tissue failure alongside liver failure.
- Fatal: mortality or liver transplantation needed due to DILI

At the final stage of the study, SPSS v.24 software was used to analyze the data. In addition to descriptive statistical methods indicating frequency, frequency percentage, mean, variance, and SD, independent t-tests and chi-square tests were also used in the study.

Results

From the 338 patients who had received rifampicin between April 2017 and February 2021, 83 had received a daily dose of 300-600 mg and suffered from tuberculosis and were thus excluded from the study. Out of the 255 remaining patients who had received a daily rifampicin dose of 1200 mg, five patients suffered from covid-19 and were excluded.

From the 250 remaining patients, 153 patients were excluded since they had been treated with a rifampicin and colistin regimen for less than 7 consecutive days, and from the remaining 97 patients who suffered from Acinetobacter baumannii, only 60 had undergone laboratory examinations regarding liver performance before and after taking rifampicin. So, these 60 patients entered the study and were examined for demographic characteristics, laboratory findings, and drug complications. The patients who entered the study had an average age of 56.71 years. 40 patients (66.66%) were male and 20 (33.33%) were female. The studied patients had a mean weight of 72.56 kg, and their average rifampicin dose based on their body weight was 17.03 mg/kg. Patients' mean glomerular filtration rate (GFR) was 71.72 ml/min. At the baseline (before starting the rifampicin and colistin regimen), 30 patients had an AST higher than the normal threshold (ULN), while 21 had ALT and 16 had higher ALP.

The values of ULN for ALT, AST, and ALP were defined to be 41, 37, and 258 units per liter in the hospital laboratory, respectively. Everyone took an average of 17.7 medications, and an average of 4.5 items fell into class-A and class-B drugs based on the LiverTox classification.

The drug is co-administered with rifampicin and colistin, and their administration percentages are as

follows:74.2% of patients received pantoprazole, 34.8% received atorvastatin, 28.1% received sodium valproate, 39.3% received acetaminophen, 34.8% received levetiracetam, 68.1% received meropenem, 83.3% received heparin, 46.9% received furosemide, 40.9% received midazolam, 57.5% received vancomycin, 7.5% received metformin, 31.8% received aspirin, 56% received norepinephrine, 46.9% received fentanyl, 22.7% received hydrocortisone, 28.7% received ampicillin-sulbactam, 40.9% received fluconazole, 34.8% received phenytoin, 6% received levofloxacin, 39.3% received vitamin C, 4.5% received baclofen, 50% received spironolactone, 18.1% received carvedilol, 3.39% received N-acetyl cysteine, 1.5% received cyclophosphamide, 46.9% received amikacin, 3.8% received clopidogrel, 33.3% received piperacillin/tazobactam, 22.7% received losartan, 11.6% received citalopram, 4.5% received aminophylline, 16% received phenobarbital, 15.1% received dexamethasone, 16.6% received methadone, 21.2% received metoprolol, 9% received midodrine, 16.6% received erythropoietin, 18.3% received folic acid, 20% received captopril, 10% received metoclopramide, 3% received nimodipine, 10% received pentoxifylline, 16.6% received amiodarone, 11.6% received metronidazole, 3% received sotalol, 25% received L-carnitine, 11.6% received amlodipine, 13.3% received amphotericin B, 20% received propofol, 8.3% received propranolol, 5% received clonidine, 8.3% received ciprofloxacin, 6.6% received trazodone, 10% received labetalol, 3.3% received filgrastim, 8% received iron sucrose, 3.3% received intravenous immunoglobulin, 3.3% received memantine, 3.3% received milrinone, and 3.3% received vasopressin. Categorical diagnoses at admission to the ICU are shown in (Table 1).

Out of the 60 studied patients, 11 were suspected of DILI based on its criteria. Thus, the RUCAM score for all the suspected patients was calculated based on the hepatotoxicity pattern for all class-A and class-B drugs according to the LiverTox classification as indicated in (Table 2), and the probability of drug-induced hepatotoxicity was also estimated for these medications.

Results of Table 2 indicate that out of the 11 patients (18.3%) suspected of drug-induced hepatic complications, 6 (11%) patients suffered from mild hepatotoxicity, 4 (6.66%) suffered from moderate hepatotoxicity, 1 (1.66%) suffered from severe hepatotoxicity along with jaundice and nausea and vomiting symptoms, and the remaining 49 (81.7%) patients showed no drug-induced hepatic complications. Among these patients, 10 (16.66%) suffered from cholestatic hepatotoxicity, and only one patient had mixed-pattern hepatotoxicity.

(Table 3) demonstrates the relationship between various risk factors and the incidence of hepatotoxicity using ANOVA and chi-square tests. The risk factors of baseline AST (mean and SD of 84.27±68.30), baseline ALT (mean and SD of 86.27±75.25), and baseline total bilirubin (mean and SD of 1.16±0.788) were revealed to have significant relationships with the incidence of hepatotoxicity ($P \leq 0.001$). An elevation in the baseline levels of AST, ALT, and total bilirubin in patients correlates with a heightened risk of hepatotoxicity. Meanwhile, it was found that hepatotoxicity does not have a significant correlation with gender, age, weight, GFR, baseline ALP, direct bilirubin, INR, ESR, CRP, lactate, the total number of co-medications, and the quantity of hepatotoxic drugs administered.

Table 1- Specific admission diagnosis among 60 studied Patients

Specific diagnosis	Frequency (n)	Percent (%)
sepsis syndrome	24	(40%)
pneumonia	16	(26.6%)
intracranial hemorrhage	7	(11.6%)
diffuse brain injury	2	(3.3%)
benign intracranial hypertension	1	(1.6%)
pneumonitis dueto food and aspiration	1	(1.6%)
traumatic subdural hemorrhage	1	(1.6%)
traumatic epidural hematoma	1	(1.6%)
myasthenia gravis	1	(1.6%)
gastritis	1	(1.6%)
ischemic stroke	1	(1.6%)
brain contusion	1	(1.6%)
unilateral inguinal hernia	1	(1.6%)
diabetic ketoacidosis	1	(1.6%)
Guillain-Barré syndrome	1	(1.6%)

Table 2- the values of RUCAM score, Drug-Induced Liver Injury Likelihood, Severity of Hepatotoxicity and hepatotoxicity patterns.

Patient No.	R (*ratio*)	Pattern of Hepatotoxicity	Severity of Hepatotoxicity	Hepatotoxic drugs	RUCAM Score	Likelihood of DILI
1	$R_2 = 0.281$	Cholestatic	Severe	atorvastatin	+6	Probable
				sodium valproate	+4	Possible
				rifampin	+3	Possible
				phenytoin	+5	Possible
				heparin	+2	Unlikely
2	$R_2 = 0.234$	Cholestatic	Mild	atorvastatin	-1	Excluded
				sodium valproate	+3	Possible
				rifampin	0	Excluded
				phenytoin	+3	Possible
				heparin	-1	Excluded
				metformin	0	Excluded
3	$R_2 = 0.134$	Cholestatic	Moderate	atorvastatin	+5	Possible
				sodium valproate	+3	Possible
				rifampin	+2	Unlikely
				fluconazole	+1	Unlikely
				heparin	-1	Excluded
4	$R_2 = 1.57$	Cholestatic	Moderate	phenobarbital	+3	Possible
				rifampin	+1	Unlikely
				phenytoin	+6	Probable
				heparin	-1	Excluded
5	$R_2 = 1.044$	Cholestatic	Mild	clindamycin	0	Excluded
				phenobarbital	+3	Possible
				rifampin	+2	Unlikely
				fluconazole	-1	Excluded
				heparin	0	Excluded
				captopril	-1	Excluded
6	$R_2 = 0.205$	Cholestatic	Mild	rifampin	0	Excluded
				fluconazole	+2	Unlikely
				heparin	-2	Excluded
7	$R_2 = 0.109$	Cholestatic	Moderate	amiodarone	+6	Probable
				rifampin	+1	Unlikely
				phenytoin	+3	Possible
				heparin	-1	Excluded
8	$R_1 = 0.046$	Cholestatic	Mild	atorvastatin	+2	Unlikely
				rifampin	+2	Unlikely
				heparin	+1	Unlikely
				captopril	+1	Unlikely
9	$R_2 = 2.627$	Mixed pattern	Moderate	phenobarbital	+5	Possible
				sodium valproate	+8	Probable
				rifampin	+3	Possible
				phenytoin	+3	Possible
10	$R_2 = 0.691$	Cholestatic	Mild	sodium valproate	+3	Possible
				rifampin	+1	Unlikely
				phenytoin	+4	Possible
				fluconazole	+2	Unlikely
				heparin	+1	Unlikely
11	$R_2 = 0.388$	Cholestatic	Mild	clindamycin	0	Excluded
				atorvastatin	+2	Unlikely
				rifampin	+5	Possible
				phenytoin	+4	Possible
				heparin	+1	Unlikely

RUCAM; Roussel Uclaf Causality Assessment Method, DILI; drug-induced liver injury

Table 3- relationship between the risk factors of hepatotoxicity incidence

Hepatotoxicity	Yes	No	P value

Risk factors		Mean ± standard deviation	Mean ± standard deviation	
Gender	Male	10 (16.66%)	30 (50%)	0.56
	Female	1 (1.66%)	19 (31.16%)	
Age		48.36±14.59	58.59±16.20	0.059
Weight (kg)		76.54±8.86	71.67±9.29	0.119
GFR (ml/min)		85.81±42.50	69.77±28.48	0.131
baseline AST (units/L)		84.27±68.30	43.57±32.65	0.004
baseline ALT ((units/L)		86.27±75.25	32.35±2327	0.000
baseline ALP (units/L)		249.0±121.15	215.20±96.37	0.320
Baseline TBL (mg/dL)		1.16±0.788	0.757±0.351	0.011
baseline DBL (mg/dL)		0.612±0.477	0.478±0.338	0.276
baseline INR		1.120±0.137	1.263±0.369	0.215
baseline ESR (millimetres /hour)		77.90±41.551	69.55±36.245	0.504
baseline CRP (mg/dL)		77.267±52.463	103.01±62.593	0.161
baseline Lactate		28.454±10.443	26.734±17.968	0.762
number of co-medications		16.27±3.901	17.02±3.461	0.529
number of hepatotoxic drugs taken		4.90±0.943	4.16±1.624	0.149

Kg; kilogram, GFR; Glomerular filtration rate, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, TBL; total bilirubin level, DBL ;direct bilirubin level, INR; international normalized ratio, ESR ,erythrocyte sedimentation rate, CRP; C-reactive protein

Discussion

Rifampin has been utilized in the treatment of meningitis and tuberculosis since 1968. However, the typical dosages, which range from 150 mg to 300 mg daily, prove ineffective against resistant Acinetobacter baumannii infections. Consequently, higher dosages are required, and the safety of rifampin in patients within intensive care units needs further investigation [18.] Results from the demographic characteristics examined in the previous section indicate that patients had an average age of 51.76 years and around 67% of them were male. Besides, the rifampicin dose prescribed for the patients was calculated to be 17.03 mg/kg. Other results indicated that out of the 11 patients suspected of drug-induced hepatic complications, six patients suffered from mild hepatotoxicity, four suffered from moderate hepatotoxicity, and one suffered from severe hepatotoxicity along with jaundice, nausea, and vomiting symptoms. The remaining 49 patients showed no drug-induced hepatic complications. Factors such as age, male gender, and underlying disease were revealed to increase the probability of hepatotoxicity and increased hepatic enzymes significantly in patients taking rifampicin over long periods [14]. In the case of the impact of demographic features on hepatotoxicity of colistin, the results of Park et al. indicated that age had a positive and significant impact on hepatotoxicity due to long periods of taking colistin, while factors such as body mass index (BMI) and gender yielded no statistically significant results [19]. Another study conducted in 2021 revealed that hepatic and renal toxicity caused by colistin in treating pneumonia due to A. baumannii were 42.4% and 51.5%, respectively [19]. Results of examining the incidence of hepatotoxicity with cholestatic and mixed patterns indicated that 16.66% of the patients suffered from cholestatic hepatotoxicity and only one patient had mixed-pattern hepatotoxicity. In a study aimed at determining the efficiency and safety of colistin for extremely drug-resistant (XDR) A. baumannii, researchers examined 55 patients hospitalized in the ICU who were treated with colistin. Results indicated that prolonged colistin administration increased total bilirubin and hepatic enzymes significantly [20]. Results of a study investigating the hepatotoxicity resulting from a 600 mg daily dose of rifampicin over four months indicated that the increase in hepatic enzymes and overall hepatotoxicity associated with rifampicin administration was not significant in patients suffering from pulmonary tuberculosis [21]. Results seeking to determine the relationship between various hepatotoxicity risk factors indicated that the risk factors of baseline AST, ALT, and total bilirubin had a significant relationship with the incidence of hepatotoxicity. This means that an increase in patients' baseline AST, ALT, and total bilirubin increases the likelihood of hepatotoxicity. Various studies have suggested that rifampicin administration results in a significant increase in ALT, AST, ALP, and total serum bilirubin levels and a significant decline in serum albumin and total protein in studied patients [22]. A similar study focused on the resistance, toxicity, and pharmacodynamics of colistin antibiotics indicated that the incidence of hepatic, renal, and neural toxicity was rare due to prolonged colistin administration [23]. Finally, Falagas et al. reported no serious hepatic or renal toxicity as a result of intravenous colistin administration in treating gram-negative multi-drug-resistant bacterial infections in a study seeking to examine hepatic or renal toxicity as a result of prolonged intravenous colistin administration [24].

Conclusion

Since the administration of various medications such as antimicrobials is very common in critically ill patients, the risk of drug-induced liver complications is higher in these patients compared to the general population. This is mostly due to their underlying diseases. The investigation in the present study and other relevant studies indicated a significant relationship between the mentioned risk factors and baseline values of AST, ALT, and total bilirubin in patients, which increases the probability of hepatotoxicity. This retrospective study observed no case of probable hepatotoxicity associated with a 1200 mg daily dose of rifampicin. A regimen of 1200 mg daily rifampicin alongside colistin appears to be hepatic-safe in treating A. baumann.

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