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Effects of rifampin coadministration on the pharmacokinetics of digoxin: a real-world data approach

JungJin Oh (iD), **Byungwook Kim** (iD), **and SeungHwan Lee** (iD) *

Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul 03080, Korea

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*Correspondence to
SeungHwan Lee
Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: leejh413@snu.ac.kr

ORCID iDs
JungJin Oh (iD)
https://orcid.org/0000-0002-2660-4617
Byungwook Kim (iD)
https://orcid.org/0000-0003-4032-6112
SeungHwan Lee (iD)
https://orcid.org/0000-0002-1713-9194

ABSTRACT

Digoxin, a cardiac glycoside, is commonly prescribed to treat heart failure and atrial fibrillation. Because digoxin acts as a substrate of P-glycoprotein (P-gp), its blood concentration may be reduced by P-gp inducers such as rifampin. To assess the real-world implications of this drug-drug interaction, a retrospective analysis was carried out on the Clinical Data Warehouse at Seoul National University Hospital between 2012 and 2017. Eleven patients who received both digoxin and rifampin with satisfying the inclusion/exclusion criteria were identified. The C_{trough} values of digoxin monotherapy were compared to those of the combination therapy with rifampin. Results demonstrated that the systemic exposure of orally administered digoxin decreased by 40% with the concurrent use of rifampin. Clinicians should be aware of potential drug interactions between digoxin and rifampin, as adjustments to digoxin dosage might be necessary for patients receiving rifampin or other P-gp inducer drugs.

Keywords: P-glycoprotein; Drug Interactions; Digoxin; Rifampin; Enterocytes

INTRODUCTION

Digoxin is a cardiac glycoside that is widely used for various circulatory diseases such as atrial fibrillation, atrial flutter, and heart failure [1]. It is known to effectively control the heart rate and increases the cardiac output. However, digoxin has a large pharmacokinetic (PK) inter-individual variability and a narrow therapeutic window [2]. Hence, the accurate therapeutic drug monitoring (TDM) is required when taking digoxin.

In clinical practice, the patients with endocarditis or mycobacterium tuberculosis infection are often treated with digoxin in combination with rifampin. However, a series of previous studies showed that the concomitant use of rifampin would have the effect of reducing the systemic exposure of the orally administered digoxin [3,4]. In contrast, the required dose of digoxin tends to decrease in patients after discontinuation of rifampin [3]. Therefore, to achieve an optimal balance between therapeutic and adverse responses, it is necessary to adjust the digoxin dose when rifampin is coadministered or discontinued.

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Author Contributions
Conceptualization: Oh J, Kim B, Lee
S; Data curation: Oh J, Kim B; Formal
analysis: Oh J, Kim B; Investigation: Kim B,
Lee S; Methodology: Oh J, Kim B; Project
administration: Lee S; Supervision: Lee S;
Visualization: Oh J; Writing - original draft: Oh
J; Writing - review & editing: Kim B, Lee S.

P-glycoprotein (P-gp) is an efflux drug transporter found in various organs, including the apical membrane of enterocytes [4]. Digoxin is primarily excreted unchanged by the kidneys through P-gp, with minimal hepatic metabolism [5]. Although *in vitro* data suggest that P-gp in renal tubular cells mediates digoxin renal secretion [6], P-gp knockout mice show increased intestinal excretion without changes in renal excretion [7]. Additionally, rifampin coadministration induces enterocyte P-gp expression, leading to reduced blood concentration of digoxin despite unchanged renal clearance [4]. A physiologically-based PK (PBPK) modeling study supports this finding, showing that rifampicin coadministration can increase intestinal P-gp abundances, leading to a decrease in digoxin concentration [8].

Real-world evidence (RWE) is a cost-effective and convenient approach for generating diverse evidence sources in real clinical settings [9]. The present study aimed to investigate the impact of rifampin coadministration on the PK of orally administered digoxin using real-world data extracted from the Clinical Data Warehouse (CDW). The Seoul National University Hospital Patient Research Environment (SUPREME) is a CDW established in 2018 at Seoul National University Hospital (SNUH). It archives and continually updates all patient data dating back to 2004.

METHODS

Study design and data source
This retrospective study utilized the CDW system at SNUH. The database contains comprehensive medical records, demographics, symptoms, clinical diagnoses, and laboratory test results, for individuals who visited SNUH for medical care. Data from this database were collected and analyzed for the purpose of this study.

Study population
Clinical data of the patients who were concomitantly administered digoxin and rifampin between 2012 and 2017 were included in the study. Among them, following inclusion/exclusion criteria were applied to determine the eligible data: (1) at least two digoxin concentrations were measured at steady-state (5 half-lives), (2) at least one concentration was measured during a rifampin-free period of more than 14 days, (3) at least one concentration was measured within 14 days of any rifampin dose, (4) digoxin was administered orally, and (5) the digoxin was administered in identical dosage, formulation, and interval for the applicable concentrations. All drug concentrations were assessed through direct blood tests. Moreover, the study did not exclude patients with decreased renal function. The patients were excluded in the analysis if drug administration history of digoxin and/or rifampin is unclear or unknown (**Fig. 1**).

Statistical analysis
SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) and the R statistical package version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

The PK parameters of digoxin monotherapy were compared to those of the combination therapy of digoxin and rifampin, and the Wilcoxon signed-rank test was performed on the logarithm of the C_{trough} values, measured 30 within minutes prior to the digoxin administration. In addition, the geometric mean ratio of combination therapy to monotherapy was calculated, along with its corresponding 90% confidence intervals.
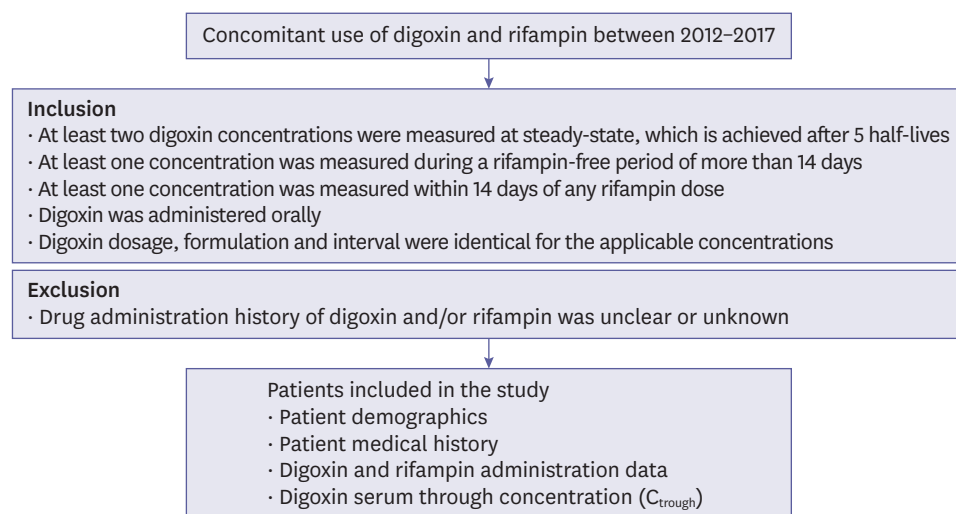
Figure 1. Study diagram.

RESULTS

Study population

A total of 81 patients who received the concomitant administration of rifampin and digoxin were identified. Among them, 11 patients who met the inclusion/exclusion criteria were selected for analysis. The median (range) values of age, height, weight, and body mass index were 47 (19.4–78.1) years, 160.8 (150–176) cm, 56.8 (36.6–86) kg, 22.9 (15.4–27.8) kg/m^2 respectively. The indications for taking digoxin were atrial fibrillation (27.2%), heart failure (36.3%), and others (36.4%) (**Table 1**). Most patients received a dose of 0.125 mg/day of digoxin, while only one or two patients received 0.1875 or 0.25 mg/day, respectively (**Table 2**). Additionally, five patients received 900 mg/day of rifampin, three patients received 450 mg/day, and three patients received 600 mg/day. The average duration of rifampin administration was 7 days.

Effect of rifampin on the PKs of digoxin

The systemic exposure of digoxin, as measured through direct blood test, decreased by 40% when administered with concomitant rifampin ($p < 0.05$) (**Table 2, Fig. 2**).

Table 1. Baseline demographic characteristics and digoxin dosage

Variables	Total (n = 11)
Sex	
Male	6 (54.5)
Female	5 (45.5)
Age (yr)	47 (19.4–78.1)
Height (cm)	160.8 (150–176)
Weight (kg)	56.8 (36.6–86)
Body mass index (kg/m^2)	22.9 (15.4–27.8)
Indications for digoxin administration	
Atrial fibrillation	3 (27.2)
Heart failure	4 (36.4)
Others	4 (36.4)
Digoxin dosages	
0.125 mg/day	8 (72.7)
0.1875 mg/day	1 (9.1)
0.25 mg/day	2 (18.2)

Data are presented as median (range) or number (%).
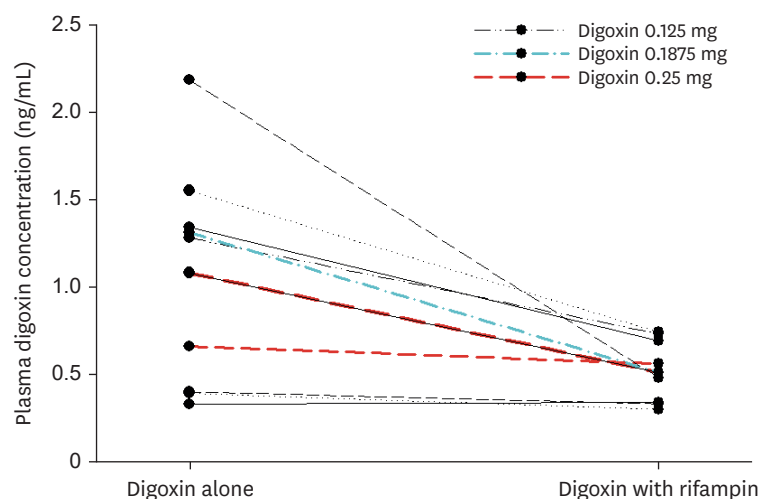
Figure 2. Individual plasma through concentration of digoxin measured after oral administration of digoxin alone and coadministered with rifampin.

Table 2. Plasma trough concentration of digoxin during monotherapy and coadministration with rifampin

Parameter	Digoxin alone (ng/mL)	Digoxin with rifampin (ng/mL)	Geometric mean ratio (90% CI)*	*p*-value
C_{trough}	1.00 ± 0.59	0.53 ± 0.16	0.60882 (0.4617–0.8028)	0.0164

Data are presented as mean ± standard deviation.
CI, confidence interval.
*Geometic mean ratio of 'digoxin with rifampin' to 'digoxin alone.'

DISCUSSION

The present study investigated the effect of rifampin on the PKs of digoxin. The results showed a significant decrease in the systemic exposure of orally administered digoxin when administered in combination with rifampin. Given the narrow therapeutic window of digoxin, ranging between 0.15–1.5 ng/mL for atrial fibrillation and 0.5–0.9 ng/mL for heart failure, the observed 40% reduction in drug concentration signifies a clinically significant drug-drug interaction (DDI). Therefore, this interaction must be considered when determining digoxin's therapeutic dosage.

In this study, rifampin was administered to subjects for an average of 7 days. Additionally, the study included patients with impaired renal function. No significant confounding factors, such as noteworthy changes in renal function or alterations in concomitant medication, were observed when comparing digoxin monotherapy to its combination therapy with rifampin.

P-gp is an efflux pump located on the luminal side of enterocytes in the intestine [4]. Because most P-gp substrates are lipophilic, they can passively diffuse across the membranes [8]. As digoxin diffuse passively through the enterocyte, P-gp can extrude the substrate back into the intestinal lumen, leading to a decrease in systemic exposure. Rifampin is a well-known P-gp inducer that causes 3.5-fold increase in enterocyte P-gp expression [4]. Although digoxin is mainly eliminated through kidney via P-gp, the effect of rifampin coadministration on digoxin PKs is attributed to the induction of intestinal P-gp, not renal P-gp. This is evident from the lack of change in digoxin clearance, while the systemic exposure of orally administered digoxin is affected within the first 3 hours after administration with a shift in T_{max} [4]. Conversely, no potential DDI between the two drugs is observed during intravenous

administration [4]. Nonetheless, further investigation is necessary to examine the induction of intestinal P-gp by rifampin.

The findings of the present study are consistent with those of the previous PBPK modeling study, in which the induction of intestinal P-gp by rifampin was also implicated [8]. The final PBPK model of this work demonstrated a 3–4 fold increase in the abundance of intestinal P-gp by rifampin [8], assuming that P-gp mediated efflux activity in the intestine is proportional to increasing P-gp abundances. This result is also consistent with the results of another study we referenced [4].

However, it should be noted that the induction of P-gp by rifampin may also decrease the concentration of digoxin in cardiomyocytes in which P-gp is also present [10]. A study showed that mdrlb P-gp (-/-) mice had significantly increased accumulation of doxorubicin, a P-gp substrate, in heart, brain and liver compared to wild type mice [11]. Therefore, further study is needed to investigate the effect of P-gp induction on the drug concentration in myocytes.

The present study acknowledges certain limitations, particularly in relation to the sample size, which may restrict the generalizability of our findings to a wider demographic. Therefore, it is required that future investigations incorporate a larger and more diverse sample to enhance the robustness, validity, and generalizability of our results to the broader population. While RWE may hold a lower degree of evidence than randomized controlled trials, its substantial benefits, including cost-effectiveness, time efficiency, and reduced patient risk due to its observational nature, are significant. Consequently, the use of RWE in DDI studies is becoming increasingly prevalent, as demonstrated in recent research involving potential DDIs with newly approved direct-acting antiviral agents or patients receiving chronic warfarin therapy [12,13].

In conclusion, this study confirms that rifampin induces intestinal P-gp, leading to reduce the systemic exposure of orally administered digoxin. Additionally, given the narrow therapeutic window of digoxin, it is crucial to determine an appropriate dosing regimen for digoxin when coadministered with rifampin.

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