Research Article

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Potential Drug-Drug Interactions Between Oral Antiviral Agents Used for Hepatitis B Treatment and Concomitant Systemic Medications

Hepatit B Tedavisinde Kullanılan Oral Antiviral Ajanlar ve Eş Zamanlı Kullanılan İlaçlar Arasındaki Potansiyel İlaç-İlaç Etkileşimleri

Nurten Nur Aydın, Murat Aydın

University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Erzurum, Turkey

ABSTRACT

Objectives: Antiviral therapy planning for hepatitis B (HB) requires consideration of drug interactions. The aim of this study was to evaluate the potential drug-drug interactions (pDDIs) between oral antiviral drugs and concomitant medications for hepatitis.

Materials and Methods: HB patients who received oral antiviral therapy in our clinic were included. Identified pDDIs were categorized as level 1 (weak potential interaction), level 2 (potential interaction), or level 3 (contraindicated) according to the University of Liverpool Hepatitis Drug Interaction Database.

Results: Of the 205 patients included in the study, 112 (54.6%) received tenofovir disoproxil fumarate (TDF), 65 (31.7%) received entecavir (ETV), and 28 (13.7%) received tenofovir alafenamide fumarate (TAF). Patients receiving TDF, ETV, and TAF received 135, 119, and 52 concomitant systemic medications, respectively. Twenty-level 2 and two level 1 interactions were observed, but no level 3 interactions. Potential DDIs were observed in 12.6% of patients receiving TDF, 3.4% receiving ETV, and 1.9% receiving TAF. The most common pDDIs were observed with non-steroidal anti-inflammatory drugs (noted in 12 occurrens and all with TDF).

ÖZ

Amaç: Hepatit B'ye (HB) yönelik antiviral tedavi planlandığında, ilaç etkileşimlerinin dikkate alınması gerekmektedir. Bu çalışmanın amacı, HB tedavisinde kullanılan oral antiviral ilaçların, eş zamanlı kullanılan diğer ilaçlarla potansiyel ilaç-ilaç etkileşimlerini (pİİE) değerlendirmektir.

Gereç ve Yöntemler: Kliniğimizde HB tedavisi için oral antiviral ilaç kullanan hastalar çalışmaya dahil edildi. Belirlenen pİİE'ler, Liverpool Üniversitesi Hepatit İlaç Etkileşimi Veri Tabanı'na göre seviye 1 (zayıf potansiyel etkileşim), seviye 2 (potansiyel etkileşim) veya seviye 3 (kontrendike) olarak kategorize edildi.

Bulgular: Çalışmaya dahil edilen 205 hastanın 112'si (%54,6) tenofovir disoproksil fumarat (TDF), 65'i (%31,7) ETV ve 28'i (%13,7) tenofovir alafenamid fumarat (TAF) almaktaydı. TDF, ETV ve TAF alan hastalar sırasıyla 135, 119 ve 52 eşzamanlı sistemik ilaç almaktaydı. Yirmi adet seviye 2 etkileşim ve iki adet seviye 1 etkileşim gözlenmiş, ancak seviye 3 etkileşim gözlenmemiştir. TDF alan hastaların %12,6'sında, ETV alan hastaların %3,4'ünde ve TAF alan hastaların %1,9'unda pİİE gözlenmiştir. En yaygın pİİE'leri non-steroidal anti-enflamatuvar ilaçlarla gözlenmiştir (12 kez ve hepsi TDF ile).

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Address for Correspondence: Nurten Nur Aydın, MD, University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Erzurum, Turkey

E-mail: nurtennurkenc@hotmail.com **ORCID ID:** orcid.org/0000-0003-4138-2490

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Conclusion: The combination of antivirals used for chronic HB treatment with systemic drugs can lead to pDDIs, especially with TDF. All patients with HB should be screened for pDDI.
Keywords: Drug interactions, hepatitis B, tenofovir, entecavir, oral antivirals

Sonuç: HB ilaçlarının sistemik ilaçlarla kombinasyonu, özellikle TDF ile olmak üzere, pİE'lerine yol açabilir. Tüm HB hastaları pİE açısından taranmalıdır.
Anahtar Kelimeler: İlaç etkileşimleri, hepatit B, tenofovir, entekavir, oral antiviraller

Introduction

Hepatitis B (HB) continues to be a major public health problem worldwide (1). This condition can result in severe outcomes, including liver damage, cirrhosis, and liver cancer (1). Effective treatment and control of HB virus (HBV) infection are essential for preventing the spread of the disease and reducing complications (2). Oral antiviral drugs that inhibit HBV replication play a crucial role in the treatment of patients with this virus. Tenofovir disoproxil fumarate (TDF), entecavir (ETV), and tenofovir alafenamide fumarate (TAF) are used for this purpose. These drugs help patients obtain the treatment they need to stop disease progression and limit liver damage (3).

Patients with HBV often have other health problems and may need to take more than one medication. This leads to the risk of potential drug-drug interactions (pDDIs) resulting from the combination of different drugs. Drug interactions can occur through pharmacodynamic and pharmacokinetic mechanisms, each with different clinical implications. Pharmacokinetic interactions can alter the absorption, distribution, metabolism, or excretion of drugs, resulting in changes in plasma drug levels and therapeutic efficacy (4). On the other hand, pharmacodynamic interactions can influence the action of drugs at their target sites, potentially worsening side effects or worsening therapeutic outcomes. For example, concomitant use of certain medications with TDF is associated with increased renal toxicity, which is a significant problem in patients requiring multiple medications (5). Understanding these interactions is crucial for optimizing treatment strategies and minimizing side effects in patients with HB infection.

Studies examining the interaction of TDF, ETV, and TAF with other systemic drugs in patients with HB are limited. This study aimed to investigate the pDDIs between oral antiviral drugs used for the treatment of HB and other concomitant systemic drugs.

Materials and Methods

The study was conducted as a retrospective, observational study. Between 01.07.2022-01.10.2022, patients over the age of 18 who applied to the infectious diseases outpatient clinic of our hospital and were receiving antivirals (TDF, ETV, TAF) were included in the study.

The potential interactions between antivirals and other systemic drugs used concomitantly were investigated. The University of Liverpool Hepatitis Drug Interaction Database (available on www.hep-druginteractions.org) was used to identify pDDIs, which were categorized as level 1 (potential weak interaction), level 2 (potential interaction), or level 3 (contraindicated) (6).

Other concurrent medications and comorbid conditions were recorded. These data were obtained from follow-up forms of patients attending the infectious diseases outpatient clinic who were taking antivirals.

The study was approved by the Erzurum Regional Training and Research Hospital (decision no.: E-37732058-514.99, date: 06.06.2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The IBM SPSS 23.0 (IBM SPSS Statistics for Windows Version 23.0, Armonk, NY: IBM Corp., USA) statistical package program was used for data analysis. For categorical variables, descriptive statistics include numbers (n) and percentages (%); for numerical variables, descriptive statistics include means and standard deviations (SD). The chi-square test was used to analyze categorical variables in the independent groups. The Shapiro-Wilk W test and the Kolmogorov-Smirnov test were used to assess the normal distribution of continuous variables. When comparing two independent groups, the Student t-test was used for variables that followed a normal distribution, and the Mann-Whitney U test was used for variables that did not follow a normal distribution. The significance level was set at $p<0.05$.

Results

In total, 205 patients were evaluated. Among the included patients, 115 (56.1%) were male and 90 (43.9%) were female. The mean age of the patients was 50.2±13.3 years. Comorbidities were present in 109 patients (53.2%). Among them, 56 had hypertension, 29 had diabetes mellitus, 28 had peptic ulcer or gastritis, 26 had cardiovascular disease, 11 had chronic obstructive pulmonary disease, and 41 had other conditions. In addition to antivirals for HB, 124 patients (60.5%) were taking concomitant drugs. The mean number of concomitant drugs used was 1.49±1.64 per patient (Table 1).

Eighty-one (39.5%) patients were not taking any medication other than their antivirals. Thirty-seven and 37 patients were using one and two additional drugs. Twenty-five patients were using 3 additional drugs, and 14 were using four additional drugs. Data on the number of additional medication use are presented in Figure 1.

No pDDIs with antivirals were detected in 185 (90.2%) patients. Twenty patients had pDDIs with antivirals. A comparison of patients with and without pDDIs is presented in Table 1. No significant differences were found between the two groups in terms of age, gender, and number of comorbid diseases (Table 1). The mean number of additional medications was 2.40±1.35 for the PDDIs group and 1.39±1.64 for the non-PDDI group, and the difference was statistically significant (p=0.001).

Among the patients, 112 (54.6%) were on TDF, 65 (31.7%) were on ETV, and 28 (13.7%) were on TAF. Fifty-eight (51.8%) of the patients receiving TDF, 47 (72.3%) of the patients receiving ETV, and 19 (67.9%) of the patients receiving TAF were concurrently using other systemic medications. There were 135 additional drug

use cases in patients on TDF, 119 in patients on ETV, and 52 in patients on TAF. In patients receiving TDF, 15 (11.1%) of 135 drugs had a level 2 interaction, and two (1.5%) had a level 1 interaction. A level 2 interaction was found with four of the 119 drugs (3.4%) in patients receiving ETV and one of the 52 drugs (3.4%) in patients receiving TAF. No pDDIs were found in 87.4% of patients receiving TDF, 96.6% of patients receiving ETV, and 98.1% of patients receiving TAF (Table 2).

Drug interactions were most commonly observed with nonsteroidal anti-inflammatory drugs (NSAIDs) in patients receiving TDF (noted in 12 occurrences). Among the NSAIDs, the most common drug interaction was with dexketoprofen (noted in 6 occurrences). The drugs that interacted with antivirals are presented in Table 3.

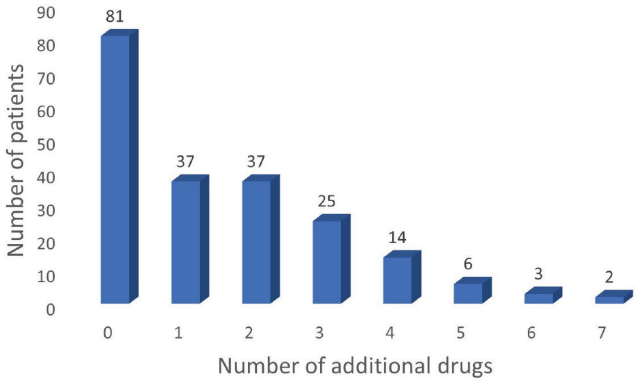

Figure 1. Patients taking drugs other than antivirals

Discussion

Our findings showed that a significant proportion of patients included in the study received additional systemic medications. This result demonstrates that patients with HB often have multiple health problems and therefore may need to take more than one medication. This polypharmacy carries the risk of pDDIs. Although this study had a limited amount of patient data on pDDIs, the significance of these interactions is worth noting. This study revealed a higher risk of pDDIs, particularly in patients receiving TDF. This result suggests that patients taking TDF should be monitored more carefully and should receive special attention for drug combinations.

Patients with HB may have various comorbidities, including liver cirrhosis, liver cancer, renal dysfunction, cardiovascular disease, and diabetes mellitus (7,8). Previous studies have shown that patients with HB can have several comorbidities, often resulting in the use of multiple drugs (9,10,11). In our study, more than half of the patients (53.2%) had comorbidities. Furthermore, most patients (60.5%) were taking additional medications other than antivirals for HB.

Table 1. Demographic data of patients and pDDIs

	Total	No pDDI	pDDIs	p-value
Male, n (%) Female, n (%)	115 (56.1%) 90 (43.9%)	103 (55.7%) 82 (44.3%)	12 (60.0%) 8 (40.0%)	0.894
Mean age ± SD	50.2±13.3	49.9±13.3	53.1±13.3	0.312
Comorbidity, n (%)				
Hypertension Diabetes mellitus Peptic ulcer/gastritis CVD COPD Others	56 (27.3%) 29 (14.1%) 28 (13.7%) 26 (12.7%) 11 (5.4%) 41 (19.7%)	49 (26.5%) 25 (13.5%) 27 (14.6%) 22 (11.9%) 10 (5.4%) 36 (19.5%)	7 (35.0%) 4 (20.0%) 1 (5.0%) 4 (20.0%) 1 (5.0%) 5 (25.0%)	0.584 0.496 0.322 0.293 1.000 0.560
Number of Comorbidities, mean ± SD	0.94±1.08	0.92±1.08	1.10±1.07	0.371
Number of additional drugs, mean ± SD*	1.49±1.64	1.39±1.64	2.40±1.35	0.001

*Number of drugs other than antivirals
COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease, pDDI: Potential drug-drug interaction, SD: Standard deviation

Table 2. pDDIs of antivirals with other drugs

HB drugs	Patients using additional drugs, n (%)	Number of additional drugs	No interaction, n (%)	Level 1 pDDIS, n (%)	Level 2 pDDIs, n (%)	Level 3 pDDIs, n	Total number of pDDIs, n (%)
TDF, n=112	58 (51.8%)	135	118 (87.4%)	2 (1.5%)	15 (11.1%)	0	17 (12.6%)
ETV, n=65	47 (72.3%)	119	115 (96.6%)	0	4 (3.4%)	0	4 (3.4%)
TAF, n=28	19 (67.9%)	52	51 (98.1%)	0	1 (1.9%)	0	1 (1.9%)

HB: Hepatitis B, ETV: Entecavir, pDDIs: Potential drug-drug interactions, TAF: Tenofovir alafenamide fumarate, TDF: Tenofovir disoproxil fumarate

Table 3. Drugs with pDDIs with antivirals

Drugs with pDDIs	Number of patients	Level of pDDIs	Possible outcome
TDF			
NSAIDS*	12	Level 2	Increased renal toxicity
Valsartan	2	Level 2	Increase in the concentration of both drugs
Furosemide	1	Level 1	Decreased renal absorption of TDF
Amiodarone	1	Level 2	Increased absorption of TDF
Tacrolimus	1	Level 1	Increased renal toxicity
ETV			
Furosemide	2	Level 2	Increase in ETV concentration
Methotrexate	1	Level 2	Change in the concentration of both drugs
Captopril	1	Level 2	Increase in ETV concentration
TAF			
Amiodarone	1	Level 2	Increase in TAF concentration

*Acetylsalicyclic acid was used by one patient, dexketoprofen by six patients, diclofenac by two patients, ibuprofen by one patient, indometacin by one patient
pDDIs: Potential drug-drug interactions, TDF: Tenofovir disoproxil fumarate, NSAIDS: Nonsteroidal anti-inflammatory drugs, ETV: Entecavir, TAF: Tenofovir alafenamide fumarate

ETV, TDF, and TAF are important antiviral agents used to treat chronic HB. These drugs effectively suppress viral replication (12). In our study, we analyzed the pDDIs of these medications and other systemic drugs used concomitantly by patients. Drug interactions may occur with antiviral agents used for HB treatment due to various mechanisms. For example, tenofovir is a substrate of the P-glycoprotein (P-gp) transporter and increases its interaction potential with other drugs that are excreted via renal P-gp pathways, whereas ETV interacts with renal transporters such as hOAT1 and hCNT2, which can inhibit the uptake of other drugs (13,14). Neither tenofovir nor ETV interact significantly with the cytochrome P450 system, which is advantageous because it minimizes the risk of metabolic interactions with other systemic drugs (15). Such mechanistic insights help us understand the potential pharmacokinetic and pharmacodynamic interactions that may occur with these agents. Potential DDIs with antivirals were identified in 9.8% of patients in our study. This was significantly associated with the number of other drugs used (p=0.001). This suggests that the use of additional medications for HB treatment should be carefully considered. A study of drug interactions in patients with viral hepatitis found that 44% of 69 patients with HB had DDIs (16). The higher incidence of pDDIs in comparison with our study can be explained by the fact that the study was conducted on patients who were hospitalized, and all drugs used by these patients were assessed for pDDIs. However, our study only included outpatients, and we only assessed antivirals and other systemic drugs for interactions.

In our study, pDDIs were observed to be more frequent, particularly in patients receiving TDF. The interaction between tenofovir and other systemic drugs has not been well investigated. In a case report, virological reactivation occurred in a patient with chronic HB during TDF treatment, and it was thought that this may be related to drug interactions. After discontinuation of antidepressant drugs (venlafaxine, paroxetine and zolpidem), a good response to TDF treatment was observed during follow-up (17). In a study evaluating the coadministration of TDF with etravirine and lamivudine, no significant drug-drug interaction was observed (18). In another study, the drug interaction between TDF and didanosine was investigated, and it was emphasized that the dose of didanosine should be reduced due to drug interaction in concomitant use (19).

The most common pDDI was caused by concomitant use of TDF and NSAIDs. In a retrospective analysis of HIV-positive patients receiving antiretroviral therapy with and without TDF, it was found that 14.6% of patients receiving TDF developed acute kidney injury after the initiation of NSAIDs (diclofenac), but no acute kidney injury occurred in patients receiving a drug regimen without TDF (5). A case report describes the development of biopsy-proven acute tubular necrosis occurring 5 days after the initiation of NSAIDs (diclofenac) in an HIV-positive patient receiving TDF treatment (20). In another case report, proximal tubular dysfunction was documented in an HIV-positive patient receiving TDF treatment, occurring 2 weeks after the initiation of ibuprofen therapy (21). Complete recovery of renal function occurred within a week of stopping ibuprofen and continuing TDF. In our study, pDDIs with TDF were commonly associated with impaired renal function. The concomitant use of TDF-NSAIDs should be avoided because of the risk of acute renal failure. If both drugs are used concomitantly, it is important to monitor patients closely for renal dysfunction.

The rate of PDDIs in patients receiving ETV was 3.4% in this study. A previous study investigating the potential of ETV to interact with renal solute carriers (SLC) *in vitro* showed that ETV interacts with these transporters, but these interactions occur with low affinity (14). This study showed that the potential of ETV to cause nephrotoxicity and DDIs were significantly lower than that of adefovir, tenofovir, and cidofovir. It was also stated in the package insert that ETV does not affect the CYP enzyme system and is not likely to interact with drugs affected by the CYP system (22). In a study examining the pharmacology/pharmacokinetics and therapeutic efficacy of ETV in patients with chronic HBV infection, pDDIs associated with the use of ETV were also reviewed, and it was stated that the potential for drug interaction with ETV was minimal (23). The study stated that drugs that inhibit tubular secretion of drugs (e.g., probenecid) may increase the serum concentration of ETV. In our study, serum concentrations of ETV-

associated pDDIs may increase or serum concentrations of both drugs may be altered.

The only pDDI observed in patients receiving TAF was associated with concomitant amiodarone use in our study. The concomitant use of both drugs was not investigated. As a P-gp substrate, TAF is expected to exhibit increased absorption when used in combination with P-gp inhibitors, such as amiodarone, leading to a higher systemic concentration (6).

Study Limitations

This study has some limitations. The drug interactions observed in this study are potential interactions; therefore, there are no data on actual interactions. For the assessment of pDDIs, only the University of Liverpool Hepatitis Drug Interaction Database was used. Further research can be conducted by combining different databases. Larger sample sizes and longer follow-up periods are needed to comprehensively study drug interactions.

Conclusion

In conclusion, this study highlighted the significance of pDDIs during the treatment of HB. This study provides important information for clinicians to guide treatment regimens for patients with HB and select appropriate drug combinations. It is important that treatment plans for patients with HB take into account interactions with other medicines and that patients are monitored regularly. This approach can potentially optimize treatment responses and contribute to the management of HB infection. Further research is needed to improve the treatment of HB infection and reduce the risk of developing pDDIs.

Ethics

Ethics Committee Approval: The study was approved by the Erzurum Regional Training and Research Hospital (decision no.: E-37732058-514.99, date: 06.06.2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: The study was conducted as a retrospective, observational study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.N.A., M.A., Concept: N.N.A., Design: M.A., Data Collection or Processing: N.N.A., M.A., Analysis or Interpretation: M.A., Literature Search: N.N.A., M.A., Writing: N.N.A.

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

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