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BOGOMOLETS NATIONAL MEDICAL UNIVERSITY
FACULTY OF PHARMACY
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THE GRADUATION QUALIFICATION WORK

CLINICAL AND PHARMACOLOGICAL FEATURES OF THE INTERACTION OF TENOFOVIR AND ENTECAVIR WITH A SUBGROUP OF BETA-LACTAM ANTIBIOTICS - CEPHALOSPORINS

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2024

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List of abbreviations

ADV	adefovir dipivoxil
ALT	alanine transaminase
AST	aspartate transaminase
AUC	concentration-time curve
CHB	chronic hepatitis B
CKD	chronic renal failure
CKD-EPI	Kidney Disease Epidemiology Collaboration
Cmax	maximum plasma concentration
DDI	Drug Interactions
eGFR	estimated glomerular filtration rate
EHR	electronic health records
ETV	entecavir
HBV	hepatitis B virus
HTN	hypertensive
LAM	lamivudine
MDRD	Modification of Diet in Renal Disease
NCA	non-compartmental analysis
PBP	penicillin-binding proteins
PCR	polymerase chain reaction
PGN	peptidoglycan
TDF	Tenofovir disoproxil fumarate
UDP	uridine diphosphate

INTRODUCTION

Relevance of the problem

Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are recommended as primary treatments for hepatitis B virus (CHB) due to their genetic resistance and ability to prevent infection. However, both TDF and ETV are associated with nephrotoxicity, although through different mechanisms such as tubular damage, apoptosis, and mitochondrial toxicity. The aim of this review is to evaluate the potential nephrotoxic effects of TDF and ETV in patients with chronic HBV infection and to make recommendations for the use of these two drugs in the treatment of CHB disease [1].

ETV and TDF arise from different processes such as renal tubular damage, apoptosis and mitochondrial toxicity [2, 3]. Previous studies have highlighted the association between chronic hepatitis B (CHB) and chronic kidney disease (CKD) with glomerular diseases such as membranous nephropathy and mesangiocapillary nephritis, defined as renal failure in CHB patients with initial onset. Factors such as medication history other than nucleoside analogs (NUC) before NUC initiation, diabetes and/or hypertension, and impaired renal function (BL) may influence the risk of ETV and/or TDF associated nephropathy.

Therefore, when choosing a suitable NUC for CHB treatment, it is important to consider renal safety, especially for patients with preexisting renal failure or a fate of permanent renal failure, an increase in the concentration of direct antiviral drugs when interacting with other groups of drugs can cause cytolytic and cholestatic syndrome, toxic liver damage [4, 5].

In addition, the main aim of this study is to investigate the interaction between tenofovir and entecavir, which are cephalosporins, a special group of betalactam antibiotics.

Objectives of the study:

To determine the clinical and pharmacological limitations of the combined use of tenofovir and entecavir with cephalosporins in patients with chronic hepatitis B and, in particular, to identify adverse effects on the liver and kidneys.

The aim of the study was to determine the adverse variants of vaso-interaction of direct antiviral drugs tenofovir and entecavir in the treatment of chronic hepatitis B and beta-lactam antibiotics from the group of cephalosporins.

The tasks of the research are:

1. Identify potentially dangerous interactions between tenafovir and antibacterial drugs from the cephalosporin group.
2. Analyze adverse variants of interactions between entecavir and cephalosporin antibiotics.
3. To determine the frequency of occurrence of cytolytic and cholestatic syndromes in patients with chronic hepatitis B who take entecavir and are simultaneously prescribed antibacterial drugs from the group of cephalosporins.
4. To analyze the frequency of hepatological complications with the simultaneous appointment of tenofovir and beta-lactam antibiotics from the cephalosporin subgroup.

Research methodology and methods.

The bibliosemantic method was used to research special literature and Internet resources on prevention, infection, treatment and elimination of the hepatitis B virus; features of the use of drugs of the first line of treatment - tenofovir and entecavir, their possible negative reactions on the patient's body.

The analytical method was based on the extraction of officially dated protocols of the interaction of tenofovir and entecavir with drugs of the cephalosporin group using the "DrugBank" (USA) and "Hep-drugs Interection" (Great Britain) databases. The analysis of the protocols took place in order to determine the safest combinations of the above drugs.

Also, 48 extracts from the medical history of patients with a diagnosis of CHB who were treated with tenofovir and entecavir and additionally used cephalosporin antibiotics were analyzed.

Scientific novelty.

In the work carried out, the potential danger of the simultaneous appointment of the direct antiviral drug entecavir in the treatment of chronic hepatitis B with the

antibiotic of the cephalosporin group - cephalexin - was established. With the simultaneous use of these drugs, there is an increase in the activity of ALT, AST in 30.8% of observed cases.

With the simultaneous appointment of entecavir with cefazolin and cetaxime, an increase in hepatocyte cytolysis was observed in only 4.5% of observations ($p<0.001$).

When using cephalosporins in patients with chronic hepatitis B who were treated with tenofovir, the appointment of antibacterial drugs from the group of cephalosporins did not have compatibility problems and did not induce hepatotoxic reactions.

Practical significance.

The obtained results can be useful when choosing an antibiotic by family doctors, therapists, infectious disease specialists in patients with chronic hepatitis B who need antibacterial therapy. In the presence of appropriate sensitivity to the microflora, the appointment of cefazolin and cetaxime are the drugs of choice at the time of admission and by the patient the direct antiviral drug entecavir. It is undesirable to use cephalexin, which in more than 30% of cases induces the development of cytolytic syndrome during the treatment of CHB with entecavir.

Tenofovir does not have dangerous interactions with cephalosporin antibiotics. If the patient has a secondary immunodeficiency condition with a high probability of bacterial infections, it is advisable to prescribe exactly tenofovir for the long-term treatment of chronic hepatitis B. This pharmacotherapeutic appointment will significantly reduce the likelihood of adverse reactions when prescribing antibiotic therapy with cephalosporins.

Approbation results research.

The results of the research were presented at the All-Ukrainian Scientific and Practical Conference with international participation "Modern Pharmacy: Present Realities and Development Prospects", which was held on April 9-12, 2024 in the city of Odesa (Ukraine), as well as at the Scientific and Practical Conference with

International with the participation of "YOUNG SCIENCE 5.0" (for young scientists), which took place on May 24, 2024.

Publications.

The results of the research were published in the collection of abstracts of reports of the All-Ukrainian Scientific and Practical Conference with international participation "Modern Pharmacy: Realities of Today and Prospects for Development", which was held on April 9-12, 2024 in the city of Odesa (Ukraine).

Hussein Burhan Hadi, Pinsky L.L., Khaitovych M.V. / Clinical and pharmaceutical analysis of the interaction of direct antiviral drugs tenofovir and entecavir with antibiotics of the beta-lactam group // Сучасна фармація: реалії сьогодення та перспективи розвитку [Електронний ресурс]: тези допов. всеукр. наук.-практич. конф. з міжнарод. участю, 9–12 квітня 2024, Одеса / під ред. к. х. н., доц. Менчука В. В., к. х. н., доц. Расколи Л. А., к. фарм. н., доц. Калько К. О., к. фарм. н., доц. Ковпак А. В., к. біол. н. Цісак А. О. – Одеса: Одес. нац. ун-т ім. І. І. Мечникова, 2024. – С. 305-306.

The structure of the work

The total number of pages of the work is 46 pages. Contains three sections: Literature review, Research materials and methods, and Results of own research. Has 2 applications. 61 literature sources were used.

CHAPTER 1. LITERATURE REVIEW

1.1 Chronic viral hepatitis B (HBV)

Hepatitis B is a global health problem, especially in regions such as subSaharan Africa and East Asia. As of 2019, approximately 257 million people worldwide suffer from this disease, and its impact on liver health cannot be ignore d. Clinical tests play an important role in the diagnosis and treatment of hepatitis B. While serological tests including HBsAg, Anti-HBc, Anti-HBs, HBeAg and Anti-HBe can provide insight into many aspects of the disease, molecular testing such as HBV can also provide insight into many aspects of the disease.

DNA PCR can help measure the spread of the virus and track the disease. Additionally, genotyping and sequencing techniques help define HBV genotypes and detect drug resistance mutations. For practical purposes, procedures such as liver excision, although rare today, are important for the assessment of liver damage and fibrosis. Noninvasive methods such as FibroScan can provide important information about the liver, while tests such as ultrasound, CT scans, and MRI can help evaluate liver morphology and detect problems.

These diagnoses are made through liver function tests, including ALT, AST, bilirubin and albumin levels, which impact liver health and function, creating a comprehensive product for the management of HBV infection and its associated complications. To describe the geographical distribution of chronic hepatitis B virus, highlighting differences in prevalence and transmission patterns in different regions. Examine factors affecting geographic distribution, including socioeconomic characteristics, medical care, and vaccination coverage [1,5].

1.1.1 Treatment of HBV:

Two nucleoside/nucleotide analogs (NA), tenofovir and entecavir, are approved for the treatment of chronic hepatitis B (CHB). Both drugs, especially tenofovir, have been shown to be effective in inhibiting HBV DNA, achieving HBeAg seroconversion, and normalizing ALT levels. Just as they have high immunity and strong

immunity, they also have low immunity and long term immunity. Tenofovir is recommended as first-line treatment in unresponsive patients and entecavir is also recommended as firstline treatment. However, current evidence does not recommend combination therapy in poor patients. Side effects of tenofovir and entecavir are generally well tolerated, but continued evaluation of these new drugs is important for long term safety and risk prevention.

There is no direct evidence or specific recommendations given in studies for the use of NAs with the β-lactam antibiotic subgroup (especially cephalosporins) in the context of HBV eradication. The research results mainly focus on the efficacy, effectiveness and safety of tenofovir and entecavir in the treatment of hepatitis B, as well as the role of antiviral drugs in pain in patients with hepatic-liver failure due to hepatitis B. risk of infection.

Therefore, based on available in formation, it is important to consult a doctor for specific instructions on the use of this antibiotic in combination with pesticides to eliminate HBV infection; including the potential for drug interactions and patient factors. In summary, tenofovir and entecavir are recommended as first-line treatment for chronic hepatitis B; Its effectiveness is good and there is no drug resistance.

However, research results did not provide specific information regarding the use of NAs in combination with β-lactam antibiotics for the elimination of HBV infection [6]. Tenofovir and entecavir are widely used in the treatment of hepatitis B (CHB) with good efficacy and tolerability, but they can cause hematological complications such as anemia. This review explores treatment strategies for anemia in hepatitis B patients receiving hepatitis B virus (HBV) eradication therapy.

Antibiotic monitoring and treatment, consideration of erythropoiesis stimulating agents (ESAs), red blood cell transfusions, iron supplements, bone marrow transplantations, and addressing the consequences of diabetes disease, striking a balance between effective treatment and reducing hematological effect s are discussed [7].

1.1.2.Tenofovir and Entecavir

Tenofovir is a nucleotide analog that behaves differently than nucleoside analog

s. When used orally as dipyroproxil, it undergoes deesterification and has a bioavailability of more than 20%; There is a slight increase in bioavailability when taken with fatty foods [8].

Its small size and low protein content helps support the overall tissue and is excreted by the kidneys as an unchanged glomerular filtration and active tubular secretion drug, dosage adjustment required in renal failure. The intracellular half-life of tenofovir exceeds the blood halflife by more than 10 fold, resulting in fewer drug interactions due to its pharmacokinetic properties [9].

The bioavailability of didanosine from antiretroviral drugs may be increased when used together with tenofovir, therefore a dose reduction is recommended. Tenofovir can be used without modification with other nucleoside and nonnucleoside reverse transcriptase inhibitors. Although protease inhibitors may slightly increase the bioavailability of tenofovir, this effect does not appear to be clinically significant. On the other hand, minor interactions with nonantibiotic drugs have also been reported [10].

Increased hepatitis B virus (HBV) DNA levels increase the risk of fibrosis and hepatocellular carcinoma (HCC) development in individuals with hepatitis B (C HB) [9, 10]. Therefore, the main goal in the treatment of CHB is to completely eliminate HBV DNA through antibiotic treatment [11, 12].

Before the advent of high pathogenicity nucleoside analogs (NAs) such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), long-term use of low-pathogenicity NAs such as Adefovirdipivoxil (LAM), adefovir-disoproxil fumarate (TDF) and dipivoxil (ADV) and telbivudine (LdT) frequently cause drug resistance in CHB patients [13, 14].

For individuals resistant to these drugs, the treatment regimen should be to add ADV to LAM or LdT. However, the effectiveness of combination treatments, particularly those involving LAM or LdT and ADV, has been shown to be superior [15, 16].

This increases the risk of drug resistance and progression to advanced liver disease and cancer [16, 17]. Current clinical guidelines essentially consider keeping

serum HBV DNA levels below the limit of detection as an important clinical goal [18, 19, 20].

Previous studies focused on investigating the effectiveness of ETVbased therapy in patients unresponsive to primary treatment [21, 22]. Since the introduction of TDF, which has the potential to be effective in the treatment of chronic hepatitis B (CHB), efforts have been directed towards the use of TDF monotherapy or in combination with other nucleoside(t)ide analogs (NA) checking patients with different reactions [23, 24].

Berg and colleagues [25] conducted a randomized controlled trial to compare the antiinflammatory effects of TDF monotherapy with TDF combined with emtricitabine (FTC) in patients with poor response to adefovir dipivoxil (ADV). Their study showed a comparable complete virological response (CVR) rate at 48 weeks between the TDF monotherapy group and the TDF + FTC combination group.

Similarly, a retrospective study by Cho et al. [26] showed that in lamivudine (L AM)-resistant CHB patients with poor response to ADV, the CVR of the TDF monotherapy group and TDF with other NA groups was not significant different. In a small, randomized controlled study, Lee et al. [27] compared the anticancer effects of switching to TDF + NA therapy and continuing ADV + NA therapy in patients resistant to ADV based therapy and found that TDF + NA therapy had a higher CVR [28].

Furthermore, TDF compared to adefovir dipivoxil (ADV) has been shown to be effective in patients with multiresistant CHB, including resistance to lamivudine (LAM) and many vaccines. Lim et al. [29].

Compared the effectiveness of TDF monotherapy and TDF combined with ETV in patients with ETV refractory CHB and multidrug failure and showed that there was no significant difference in CVR between the two groups [30]. In addition, several studies have shown no difference in CVR between TDF monotherapy and TDF + ETV combination (best NA combination) in CHB-resistant patients. It may be more than [31].

In a study comparing TDF monotherapy with the combination of TDF and ETV

in patients with ADV refractory CHB and multiple treatment failure, CVR at 48 weeks was 62 and 63. 5% in the TDF or TDF/ETV groups, respectively. There was no difference between the two groups (P = 0.88)[7, 32].

Wu et al. a randomized controlled trial was conducted to evaluate TDF + ETV therapy compared to LAM/LdT + ADV therapy in LAM-resistant patients who responded poorly to LAM + ADV therapy. As expected from previous clinical studies, their results showed that the TDF + ETV group had a better response compared to the LAM / LdT + ADV control group at 48 weeks (93.33% vs 6.52%, P<0.001). The importance of this research is to confirm the need for previous studies through rigorous evaluation of future experiments.

However, these results should be interpreted in the context of various studies, including those conducted by Lim and colleagues [33, 34]. This study has an important limitation in that it does not directly compare the effectiveness of TDF monotherapy with TDF + ETV treatment, despite the hypothesis that TDF monotherapy alone may be effective despite patients responding poorly to LAM + ADV. In real-world situations, many poor-responding patients have been treated with TDF as TDF monotherapy or in combination with other nucleoside analogs. Therefore, the results of this study can be considered to be of little clinical significance.

Clinical results over 244 weeks were recently shown in patients participating in two studies by Lim et al. After s witching from TDF + ETV to TDF monotherapy at week 48. At week 240, virological rates increased to 84.4% and 73.5% in the ETV group and ADVresistant group, respectively, and there was no difference between groups (P = 0 .07). However, both estimated glomerular filtration rate (eGFR) and bone miner al density decreased at 240 weeks compared to baseline (P < 0.001), indicating concerns regarding the long term safety of TDF use [35,36[xxvii]].

Due to adverse effects associated with TDF, the use of tenofovir alafenamide (TAF) has recently been recommended, particularly in patients with renal or bone marrow involvement [37, 38]. Therefore, future clinical studies are needed to evaluate the effectiveness of TAF- based therapies in resistant or diseased hepatitis B (CHB) patients who respond poorly to various nucleotide analogs (NA).

1.2. β-lactam antibiotics

The most important class of antibiotics worldwide are β-lactam antibiotics. The discovery and commercialization of penicillin G, the first betalactam antibiotic, was a turning point in modern medicine. Since then, many other betalactam antibiotics have been developed, changing the way the disease is treated. However, their effectiveness is affected by the emergence of antibiotic-resistant bacteria. Among the mechanisms of drug resistance, the production of β-lactamases has been widely studied and recognized. The combination of β- lactamase inhibitors and broad-spectrum β-lactam antibiotics has proven to be a good strategy in the fight. This article focuses on the properties of various β-lactam antibiotics (including penicillins, cephalosporins, carbapenems, monocyclic lactams, and penems) and examines their stability, sensitivity to β-lactamase, mechanism of regulation of organisms, and function. Additionally, it provides an in-depth discussion of β-lactamase inhibitors related and unrelated to the β-lactamase system and their proposed inhibitory mechanisms [39].

In 1928, Alexander Fleming, while serving as director of the Department of Dis ease Control in St. Petersburg, made an observation while working in a laboratory. Mary's Hospital, Paddington, London. It turned out that some petri dishes containing staphylococci were left unattended in the laboratory at the beginning of the summer and were not identified with the bacteria called Penicillium. He also found an open area around the mold that showed bacterial lysis. Analysis of the reduced growth and lysis of Staphylococcus aureus colonies indicates the ability of this bacterium to produce bactericidal activity. In 1932, Alexander Fleming published a report on his research on new antibiotics from Penicillium metabolites. He named this new antibiotic "penicillin" from the genus Penicillium. Initially, Fleming's findings did not attract much attention and were not used to correct targets until World War I [40].

The bacterial wall is a strong covering surrounding the cytoplasmic membrane and plays an important role in the growth and development of bacteria. This wall consists of diaminopimelic acid, muramic acid, teichoic acid, amino acids, carbohydrates and lipids and forms a complex macromolecule called peptidoglycan (PGN)

or mucin. PGN, a heteropolymer component of cell walls, provides mechanical stability and stiffness through its interconnected lattice structure. It has glycan chains, which are linear bands of alternating amino sugars (N- acetylglucosamine and N-acetylmuramic acid) linked together by crosslinked peptide chains. The specific composition of crosslinked peptide chains varies between different organisms [41, 42].

Peptidoglycan (PGN) biosynthesis involves approximately 30 enzymes and can be divided into three main stages. The first step occurs in the cytoplasm and requires the formation of uridine diphosphate (UDP)-acetylmuryl pentapeptide, commonly known as Park nucleotides. The final react ion in Park's nucleotide synthesis involves the addition of the D-Ala-D-Ala dipeptide.

Synthesis of this dipeptide must be preceded by L-alanine racemization and condensation catalyzed by D-alanyl-D- alanine synthetase. In the second step, interaction between UDP- acetyl cellulose pentapeptide and UDP-acetylglucosamine occurs, uridine nucleotides are released and long polymers are formed. Initiation of heteropolymer formation involves the binding of pentapeptide sugars to phospholipids in the cytoplasmic membrane via pyrophosphate b ridges. A second sugar (UDP-acetylglucosamine) is then added and five glycine residues are then combined. The first unit, pentaglycine, undergoes cross linking of antibodies across the cytoplasmic membrane and orients itself through the periplasmic space between the membrane and the cytoplasmic membrane [43].

The final step is to complete the synthesis via transpeptidase, which occurs in the periplasmic space. Transpeptidases catalyze the transpeptidation reaction in which serine residues in the active site are used to form peptide bonds. These enzymes interact with the D-Ala-D-Ala dipeptide found in the pentapeptide structure, especially the carboxyl group of the fourth moiety (D-Ala).

Next, the amino terminal subunit of the last glycine residue of the pentaglycine unit is covalently linked to the carboxyl group of the fourth residue bound to the transpeptidase, a fifth residue (D-Ala) is formed, and the enzyme is reformed. The final step of peptidoglycan bio synthesis, mediated by transpeptidases, is the target

of β-lactam antibiotics. Lack of peptidoglycan and transpeptidase in eukaryotic cells increases the toxicity of β-lactam antibiotics and therefore their use in animals and humans is safe [44].

Beta-lactam antibiotics effectively inhibit the catalytic function of bacterial transpeptidase, increasing the safety of beta-lactam antibiotics in animals and humans. Also known as penicillin binding protein (PBP). In general, most bacteria have at least four PBPs. For example, in E. coli, high molecular weight PBPs 1–3 act as transpeptidases and transglucosylases, while low molecular weight PBP s 4–6 act as d-alanine carboxypeptidase [45].

1.2.1. Cephalosporins

Cephalosporin antibiotics have played an important role in combating infections since their clinical introduction in the early 1960s. The aim of this review is to investigate new second- and third-line cephalosporin antibiotics. Second- line cephalosporins include cefamandole sodium, cefoxitin sodium, cefadroxil, and cefaclor; Third generation cephalosporins include cefotaxime sodium, mosalamide, and cefoperazone.

Cephalosporins act as antibiotics by inhibiting cell wall synthesis, leading to the accumulation of uridine-5-pyrophosphate-containing nucleotides and subsequently acetyl derivatives of muramic acid. Sensitive cells elongate into filaments and protoplasts. This antibiotic is resistant to hydrolysis by beta lactamase produced by Staphylococcus aureus. Second generation cephalospori ns show antibacterial activity and have a positive effect on many species such as Enterobacteriaceae, Proteobacteria, Bacteroidetes, Clostridium, Peptococcus an d Peptostreptococcus.

Cefazolin is a first-generation cephalosporin antibiotic widely used in the treatment of various infec tions such as cellulitis, urinary tract infections, pneumonia and endocarditis. It is also used prophylactically before surgery and against B streptococcal infection during childbirth. Cefazolin interacts with the bacterial cell wall, making it effec tive against Gram positive bacteria such as Staphylococcus aureus and Streptococcus. It is less active against gram negative bacteria and is ineffective against Staphylococcus aureus (MRSA), whi ch contains methicillin.

Cefazolin is generally safe during pregnancy and breastf eeding, but caution is advised for premature infants and newborns. Patients with kidney disease may need to modify the dosage, but cefazolin dosage is not affe cted by liver disease. Side effects are generally mild and include diarrhea, abdo minal pain, vomiting and rash. Patients with penicillin allergy may develop cefa zolin allergy. Note that cefazolin has an N-methylthiadiazole (NMTD) side chain, which can cause hypoprothrombinemia and interaction with ethanol. Its mechanism of action involves inhibition of cell wall biosynthesis by binding to penicillin-binding proteins and causing bacterial lysis.

Cefazolin metabolism is carried out mainly in the liver, the kidneys are slightly separated. The pharmacological pro perties of cefazolin include a broad spectrum of activity against Grampositive bacteria, stability against β-lactamase, and low permeability to the central nervous system [46].

1.2.2. Second Generation Cephalosporins

Sufficient blood levels of cefamandole (Mandol) are achieved through intramuscular or intravenous administration. Peak serum concentrations are reached within 30 minutes to one hour, with no detectable drug remaining in the serum after eight hours following a 500-mg dose. Intravenous administration results in no detectable drug in the serum after four hours, and the entirety of the antibiotic is rapidly excreted in the urine. Cefamandole is widely distributed in body fluids, excluding cerebrospinal fluid, and adequate concentrations are reached in pleural, bile, ascitic, and synovial fluids [47].

The rise of ampicillin resistant Haemophilus influenzae in recent years has led to increased utilization of cefamandole and chloramphenicol for treating diseases caused by such strains. Cefamandole should be administered only after excluding the possibility of meningitis. Numerous studies have explored its efficacy in treating cellulitis, pneumonia, arthritis, and epiglottitis in children. Infections previously treated with aminoglycosides or chloramphenicol, caused by various species of Enterobacteriaceae and Proteus, are now being managed with cefamandole. Broad antibacterial activity and minimal side effects make it a preferred antibiotic for treating

patients with gram-negative septicemia [48].

Regarding Cefoxitin, it exhibits lower activity against gram-positive cocci compared to other cephalosporins, yet it demonstrates strong efficacy against gram-negative organisms, making it suitable for treating severe gram-negative infections. It is also effective against anaerobic bacteria, including the majority of Bacteroides fragilis strains, and other Bacteroides species. Recent research by Santos et al. confirms the safety and effectiveness of cefoxitin in treating cellulitis in 31 children caused by H. influenzae type b, Staphylococcus aureus, and Group A β-hemolytic Streptococcus. Additionally, cefoxitin has proven effective in treating infections involving bone, endocardium, and the respiratory tract, with susceptibility observed in Proteus mirabilis, Salmonella, and Shigella.

In contrast, cefaclor demonstrates high activity against H. influenzae, including strains producing β-lactamase. It achieves peak serum concentration of 12 to 15 μg/mL after one hour, with minimal impact from concurrent ingestion of food. Unlike first-generation oral cephalosporins, cefaclor does not penetrate the meninges. It exhibits higher salivary concentration compared to other cephalosporins, and its levels in middle ear fluid are adequate for eradicating important bacterial pathogens causing otitis media [49].

Cefuroxime**,** marketed under the brand name Zinacef, is a second-generation cephalosporin antibiotic used to treat and prevent various bacterial infections such as pneumonia, meningitis, otitis media, sepsis, urinary tract infections, and Lyme disease. It can be administered orally or via injection into a vein or muscle. Common side effects include nausea, diarrhea, allergic reactions, and injection site pain, while serious side effects may include Clostridium difficile infection, anaphylaxis, and Stevens-Johnson syndrome. Cefuroxime is considered safe for use during pregnancy and breastfeeding.

It functions by interfering with bacterial cell wall synthesis, ultimately leading to bacterial death. The drug was patented in 1971 and approved for medical use in 1977, and it is included on the World Health Organization's List of Essential Medi-

cines. Cefuroxime exhibits activity against a wide range of bacteria, including susceptible strains of Staphylococci, Streptococci, and gram-negative organisms. It is less susceptible to beta-lactamase compared to first-generation cephalosporins, making it more effective against certain bacteria such as Haemophilus influenzae, Neisseria gonorrhoeae, and in the treatment of Lyme disease. Unlike other second-generation cephalosporins, cefuroxime can cross the blood-brain barrier. Side effects are typically transient, with gastrointestinal symptoms being the most common.

There is a perceived risk of cross-allergy between cephalosporins and penicillin, but recent assessments have shown no increased risk for cross-allergic reactions with cefuroxime and several other second-generation or later cephalosporins. Cefuroxime axetil is an oral prodrug of cefuroxime, which is effective when taken by mouth. Metabolism of cefuroxime primarily occurs in the liver, with approximately 50% of the drug excreted unchanged in the urine and the remainder eliminated through bile. Cefuroxime may interact with other medications, and caution should be exercised when co-administering with drugs such as probenecid.

Pharmacologically, cefuroxime exhibits broad-spectrum activity against gram-positive and gram-negative bacteria, with enhanced stability against betalactamases compared to first-generation cephalosporins [50].

Cefaclor**,** marketed under the brand name Ceclor, is a second-generation cephalosporin antibiotic used to treat and prevent a variety of bacterial infections, including respiratory tract infections, otitis media, urinary tract infections, and skin and soft tissue infections. It is available in oral and injectable formulations and is generally well-tolerated, with common side effects including gastrointestinal disturbances and allergic reactions.

Rare but serious adverse effects such as Clostridium difficile infection, anaphylaxis, and Stevens-Johnson syndrome may occur. Cefaclor is considered safe for use during pregnancy and breastfeeding. It works by inhibiting bacterial cell wall synthesis, leading to bacterial death, and is effective against both gram-positive and gram-negative organisms. While it is susceptible to beta-lactamase, cefaclor demonstrates enhanced effectiveness against certain bacteria compared to first- generation

cephalosporins. Although cross-allergic reactions with penicillin have been noted, recent assessments suggest a low risk of such reactions with cefaclor and other second-generation or later cephalosporins. Cefaclor is primarily metabolized in the liver and excreted unchanged in the urine, with potential interactions with drugs like probenecid [51].

1.2.3. Third Generation Cephalosporins

In the last five years, significant research has been conducted on a group of drug s with a broader spectrum of action than second-generation cephalosporins. Among these drugs, cefotaxime, moxalactam, and ce foperazone have been extensively studied in animal and human studies. Unlike first- and second-generation cephalosporins, these compounds can penetrate blood vessels in the brain, making them useful in treating intracranial and meningeal diseases.

Cefotaxime, trade name Claforan, is a semisynthetic drug. Cephalosporins are used parenterally. Its structure includes an a minothiazolyl acetyl side chain replaced by a methoxyamino group, characterist ic of beta-lactam antibiotics. Its antibacterial effect is due to competitive inhibition of enz ymes important for cell wall synthesis and is potent in the action of various beta -lactamases. In addition to covering all Gram-positive and Gramnegative bacteria targeted by first and second generation cephalosporins, cefota xime also shows significant activity against many Citrobacter species and especi ally Pseudomonas aeruginosa. Inhibits 90% of Citrobacter freundii, Escherichia coli, Klebsiella, Proteus, Salmonella and Shigella species at a concentration of 0 .5 gg/mL or less. It also shows activity against some gentamicin-resistant Escherichia coli, Klebsiella pneumoniae and Serratia marcescens speci es. Cefotaxime rapidly reaches therapeutic levels in blood and other body fluids after intramuscular or intravenous administration. In normal adult volunteers, a 500 mg or 1 gm dose of cefotaxime achieved peak results of 11.7 and 20.5 gg/m L at 30 minutes. Approximately 25% of the IV dose is excreted unchanged in th e urine. Note that in patients with renal impairment, no increase in blood glucos e levels of cefotaxime is observed even with creatinine clearance as low as 20 m L/min/1.73 m^2, although its renal half-life is longer in severe cases [52].

Ceftriaxone is a third-generation cephalosporin antibiotic with broadspectrum activity against Gram-positive and Gram negative bacteria. Metabolism occurs mainly in the liver via phase II conjugation reactions, resulting in the formation of inactive metabolites that are excreted in the urine. This medicine is used to treat many diseases such as pneumonia, me ningitis and stomach infections.

Ceftriaxone is classified as a prodrug that requir es metabolic activation for its active form and is usually administered intraveno usly or intramuscularly. While gastrointestinal symptoms such as nausea, vomiti ng, and diarrhea are common side effects, more serious side effects such as anap hylaxis, seizures, and pseudomembranous colitis are rare but can occur. It is im portant to remember that ceftriaxone may interact with medications that affect li ver function (such as warfarin) and possibly increase the risk of bleeding. There fore, drug interactions should be carefully evaluated and adverse drug reactions monitored during ceftriaxone treatment [53].

Cefotaxime is a third type of cephalosporin antibiotic with many activities again st ceftriaxone. Its metabolic process is carried out mainly by phase II synthesis i n the liver, producing inactive metabolites, which are subsequently eliminated through urine. Cefotaxime is widely used to treat many diseases, including pneu monia, pneumonia, and stomach infections. These medications are usually given by intravenous injection or intramuscular injection and, like similar medication s, can cause gastrointestinal symptoms leading to side effects such as nausea, vo miting, and diarrhea. Although allergic reactions, seizures, and pseudomembran ous colitis are rare, they do have side effects, so caution is important. Additional ly, cefotaxime has a tendency to interact with drugs that affect liver function, su ch as warfarin, highlighting the importance of careful management to reduce the risk of bleeding. Therefore, it is important to carefully evaluate potential drug i nteractions and carefully monitor side effects during cefotaxime treatment [54].

Cefixime is a third-class cephalosporin antibiotic with similar activity to ceftriaxone and cefotaxime. Hepatic metabolism occurs mainly through II conjugation reactions and prod uces inactive metabolites that are excreted in the urine. Cefixime is widely used in the treatment of many diseases, especially respiratory diseases such

as otitis media and sinusitis. These medications, usually taken orally, can cause gastroint estinal symptoms such as nausea, vomiting, and diarrhea, as well as rare but seri ous side effects such as allergic reactions, epilepsy, and pseudomembranous coli tis. Note that cefixime may interact with medications that affect liver function, s uch as warfarin; This demonstrates the importance of careful monitoring to redu ce the risk of bleeding. Therefore, it is important to have a good understanding o f potential drug interactions and to be alert for adverse reactions in cefixime trea tment [55].

Ceftazidime is a third class cephalosporin antibiotic along with ceftriaxone, cefo taxime and cefixime. Metabolism occurs primarily in the liver via phase II conjugation reactions, resulting in inactive metabolites that are excreted in the urine. Ceftazidime is widely used in the treatment of many diseases such as pneumoni a, meningitis and stomach infections. These medications, usually given by inject ion or intramuscular injection, can cause gastrointestinal symptoms such as naus ea, vomiting, and diarrhea, as well as rare but serious side effects such as allergic reactions, seizures, and pseudomembranous colitis. It is worth noting that ceft azidime may interact with drugs that affect liver function, such as warfarin, incr easing the risk of bleeding. Therefore, during ceftazidime treatment, attention should be paid to possible drug interactions and adverse reactions should be carefully monitored [56].

1.3. Drug Interactions (DDI)

Pharmacovigilance, also known as post marketing surveillance, aims to identify and assess risks associated with drug use. Its main goal is to improve our understanding of adverse drug reactions (ADRs) and their underlying mechanisms. ADRs are medical complications that may result in more frequent or longer hospitalizations. Among the many causes, drug-drug interactions (DDIs) are particularly common in the elderly, especially thos e receiving combination therapy. These combination therapies increase the com plexity of patient management, thereby increasing the potential for clinically sig nificant drug interactions, which may lead to adverse effects from reducing or s upplementing treatment. Additionally, combination therapy may lead to an unde sirable “prescription cascade” where new medications are

prescribed to manage unwanted side effects, leaving patients with additional side effects [57].

DDIs are generally divided into two groups [58]:

· Pharmacokinetic interactions: These interactions include changes in the absorption, distribution, metabolism and excretion of the drug and

· Pharmacodynamic interactions: These can be divided into three groups: (1) those that directly affect receptor activity, (2) those that interact with biological or physical regulatory mechanisms, and (3) complement/anti-drugs.

Pharmacokinetic interactions are usually measured based on the individual characteristics of each drug and are determined by monitoring the patient's response and changes in the blood to the drug. These interactions affect the entire process from drug absorption to excretion.

1.4. Cephalosporins as a side effect in the use of tenofovir and entecavir

Interactions between cephalosporin antibiotics and antiviral drugs such as tenofovir and entecavir are problematic due to adverse reactions and drug interactions. Tenofovir and entecavir are potent nucleoside analogs used to treat hepatitis B virus (HBV) infection. For example, cephalosporins are broad spectrum antibiotics commonly used to treat bacterial infections. Both tenofovir and cephalosporin antibiotics carry a risk of nephrotoxicity, especially in patien ts with renal impairment. Using these drugs together may increase the risk and potential for kidney damage.

Moreover, although tenofovir and entecavir are generally well tolerated, hepatotoxicity is a serious side effect. However, cephalosporin antibiotics can also cause liver damage. The combination of these drugs may cause hepatotoxicity and requires careful monitoring of liver function. It is important to closely monitor kidney function, liver enzymes, and electrolyte levels when tenofovir or entecavir is used in combination with cephalosporin antibiotics.

Depending on the patient's renal function and overall treatment, the antibiotic or antibiotic dose should be adjusted to reduce the risk of side effects. Physici ans should carefully consider the benefits and risks of side effects when using these

drugs together, especially in patients with comorbidities or kidney or liver problems. If the risk of nephrotoxicity or hepatotoxicity outweighs the benefits of cephalosporin therapy, other antibiotics with less risk of kidney or liver disease may be considered.

Collaboration between medical professionals, hepatologists, and nephrologists is essential in treating patients who require antiretroviral therapy for hepatitis B and antibiotic therapy for infections. Patients should be informed of the risks associated with use of tenofovir or entecavir with a cephalosporin antibiotic and instructed to report any new or adverse symptoms. Adherence to medication regimens and regular monitoring are important aspects of patient management [59].

Ceftriaxone is a third-class cephalosporin antibiotic widely used in the treatment of various infections such as respiratory, urinary, skin and soft tissue infections. Bacterial infections and meningitis. Side effects may include gastrointestinal disturbances, allergic reactions, and local irritation at the injection site. Less common but serious side effects may include liver damage, kidney damage, and hematological abnormalities.

Ceftriaxone has been associated with biliary pseudolithiasis, particularly in pediatric patients and those receiving chronic treatment. Although there is no information about a direct interaction between ceftriaxone and tenofovir/entecavir, caution is advised when combining medications that may cause liver or kidney damage. Tenofovir and entecavir are antibiotics commonly used to treat hepatitis B and may cause rare side effects such as hepatotoxicity and nephrotoxicity. As a rule, taking Ceftriaxone with these antiinflammatory drugs may increase the risk of liver or kidney problems, especially in patients with liver or kidney problems.

Additionally, ceftriaxone-induced biliary pseudolithiasis can be problematic in patients with chronic hepatitis B, as they are more likely to affect the gallbladder. In clinical management, it is important to carefully monitor for liver or kidney problems and gallbladder problems when prescribing ceftriaxone to hepatitis B patients taking tenofovir and entecavir. Patients should be educated about possible side effects and advised to report new or worsening symptoms. Collaboration between

healthcare professionals, including specialists and hepatologists, is recommended to ensure appropriate patient management and care [60].

SECTION 2: MATERIALS AND RESEARCH METHODS

2.1. Justification of the expediency of choosing objects and methods of research:

Our decision to focus our research on Hepatitis B (CHB) stems from our recognition of its enormous impact on global health. Chronic hepatitis B is a serious health problem that affects millions of people worldwide and places a heavy burden on healthcare services. The high risk of CHB and its complications, including cirrhosis and hepatocellular carcinoma, underscores the urgent need for effective treatment strategies.

However, the frequent occurrence of comorbidities makes the clinical picture of CHB even more complex. These additional medical conditions, such as heart disease and lipid disorders, often coexist with chronic hepatitis B and can affect the disease and treatment. Despite advances in antiviral therapy, the diverse interactions between hepatitis B virus and infectious diseases present a complex clinical picture that requires further investigation.

Additionally, despite extensive research in recent years, there are still significant gaps in our understanding of hepatitis B and its comorbidities. These gaps hinder our ability to improve healthcare and improve patient outcomes. It is therefore important to delve deeper into areas of uncertainty and discover new ways of medical intervention.

We aim to solve this experience by directing our research to solve the chronic problem of hepatitis B and its comorbidities. Our goal is not only to improve our understanding of disease processes, but also to find new avenues for self healing strategies. Through rigorous research and analysis, we want to contribute to the development of better treatments and ultimately improve the quality of life of patients with hepatitis B and infectious diseases.

In summary, our research focuses on the interaction between hepatitis B and

comorbidities, providing insights that have the potential to change practice and patient care. By understanding the complexity and comorbidities of chronic hepatitis B, we aim to improve the future of those affected by this complex disease. A retrospective review of the medical records of patients diagnosed with chronic hepatitis B will be conducted to identify and analyze the literature.

The analysis will involve extracting relevant information such as the name of the drug, dosage, frequency of the drug, and duration of treatment. After this, frequency analysis will be done to determine the drug patterns present in doctors. Analytical analysis, including descriptive and statistical analysis, will then be used to document frequency and identify key trends or relationships.

Joint measures will be taken to improve security measures. This will begin with a thorough review of available data on the hepatotoxicity of drugs commonly used to treat chronic hepatitis B to determine risks and contraindications. There will also be consultations with hepatologists, pharmacists and other experts to evaluate the safety of various drug combinations. Based on these findings, guidelines for the combination of potentially hepatotoxic drugs with cardiotonic and hypolipidemic drugs will be developed. Finally, the developed protocol will be validated by consensus of a panel of hepatology and pharmacotherapy experts.

2.2. Justification of Research Methods:

Participant selection included hepatitis B patients treated in the hepatology department of the hospital. Inclusion criteria included age, diagnosis of hepatitis B, a current tenofovir or entecavir treatment. Their exclusion may be related to conflict of interest or individual intolerance.

Statistical analysis will use methods such as logistic regression or Cox proportional hazards models to examine the relationship between tenofovir/entecavir use and beta-lactam antibiotic-lactam interactions.

Reliability and validity will be checked through regular audits, reliability testing of candidates and data entry procedures, and any such discrepancies will be resolved by agreement or professional consultation.

ALGORITHM FOR CONDUCTING A MASTER'S STUDY

Research stages	The content of research areas
1. Study of potentially dangerous combinations of Tenofovir and entecavir with subgroup of beta-lactam	Creation of interaction protocols in "Drug Bank" and "Hep Drug Interactions"
2. Analysis of the frequency of prescriptions by doctors of dangerous or potentially dangerous combinations of subgroup drugs in the treatment of HBV	Analysis extracts from the case histories of HBV patients who underwent virus elimination with antibiotic drugs.
3. Development of safe combinations	Analysis and selection of relatively safe combinations of Entecavir or Tenofovir with subgroup of beta lactam

The research was carried out using techniques such as data semantics, statistics and graphics.

Semantic data from the Internet and research data used to study the current method to eliminate the virus in chronic hepatitis B patients. Treatment is direct antibiotics and their combination with subgroup of beta lactam drugs.

Statistical methods were used to evaluate the consequences of doctors prescribing potentially dangerous drugs in conjunction with prescribing cardiotonic drugs in the treatment of hepatitis B.

SECTION 3. RESULTS OF OUR RESEARCH

3.1. Potentially dangerous combinations of direct antivirals with other drugs

People with hepatitis B (CHB) have chronic infection from the hepatitis B virus (HBV) that can last for a long time, even decades. Long-term exposure to this disease can lead to various liver diseases, such as mild elevations of liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), or more serious symptoms such as jaundice, which indicate that the liver is not healthy. Working properly. Additionally, chronic hepatitis B may remain symptom-free for long periods of time or cause nonspecific symptoms such as fatigue, abdominal discomfort, or sometimes jaundice, making diagnosis and treatment difficult. Besides

its direct impact on treatment, chronic hepatitis B also has a significant impact on complications, leading to disease-related morbidity and mortality. Chronic hepatitis B infection increases the risk of liver disease, ultimately leading to diseases such as cirrhosis and hepatocellular carcinoma (HCC). Liver fibrosis continues to progress due to chronic inflammation and hepatocellular damage; This indicates an urgent need for preventive strategies to reduce the slow progression of the disease and prevent adverse outcomes.

From an epidemiological perspective, transmission of hepatitis B virus (HBV) indicates its activity as a blood borne virus and is usually transmitted through percutaneous or mucosal contact with body fluids. High-risk behaviors such as unprotected sexual intercourse, needle sharing among drug users, and maternal transmission of infection are important mechanisms of hepatitis B infection. Additionally, there are significant regional differences in hepatitis B (CHB) prevalence; Sub-Saharan Africa, East Asia and Oceania regions have come under a heavy burden due to various cultural, social and health problems.

In this clinical and epidemiological situation, the use of cardiotonic drugs in the treatment of chronic hepatitis B involves many issues that must be carefully evaluated by physicians. Given the important role of the liver in drug metabolism and elimination, pharmacokinetics may be altered in patients with hepatitis B, which may affect the effectiveness and safety of the drug. Also, having chronic hepatitis B along with other diseases such as hypertension, heart disease or cardiac arrhythmias should have a good approach to the selection of drugs and drugs used in medicines that may affect or negatively affect the disease.

In conclusion, the interaction between hepatitis B virus (CHB) and cardiotonic drug use demonstrates the interaction between treatment, disease and pharmacy that directs patients affected by this disease in many ways. By integrating clinical expertise, evidence based practice, and patient care, physicians can work to improve outcomes and improve quality of life for patients with hepatitis B and heart disease. Additionally, the combination of entecavir with other drugs that are eliminated by the activity of tubular secretion may increase the plasma concentration of one or

both drugs. This increase is due to competitive inhibition of transport in the renal tubules. Drugs suspected of causing systemic disease include acyclovir, allopurinol, aminosalicylic acid, cidofovir, cimetidine, creatine, dipillin, famciclovir, famotidine and flecainide, ganciclovir, levetiracetam, metformin, methodrinexate, mydrexatec, procainamide, quinide, triamterene, ranitidine, tenofovir, triamterene. trimethoprim, valacyclovir, valganciclovir, zalcitabine, zidovudine and many beta-lactam and quinolone antibiotics.

3.2. Potential metabolism of interactions between the drugs

Types of cephalosporins:

a. First-generation cephalosporins:

Cefazolin

Cephalexin

Cefadroxil

b. Second-generation cephalosporins:

Cefuroxime

Cefaclor

Cefoxitin

Cefprozil

c. Third generation cephalosporins:

Ceftriaxone

Cefotaxime

Ceftazidime

Cefixime

Cefdinir

Cefpodoxime

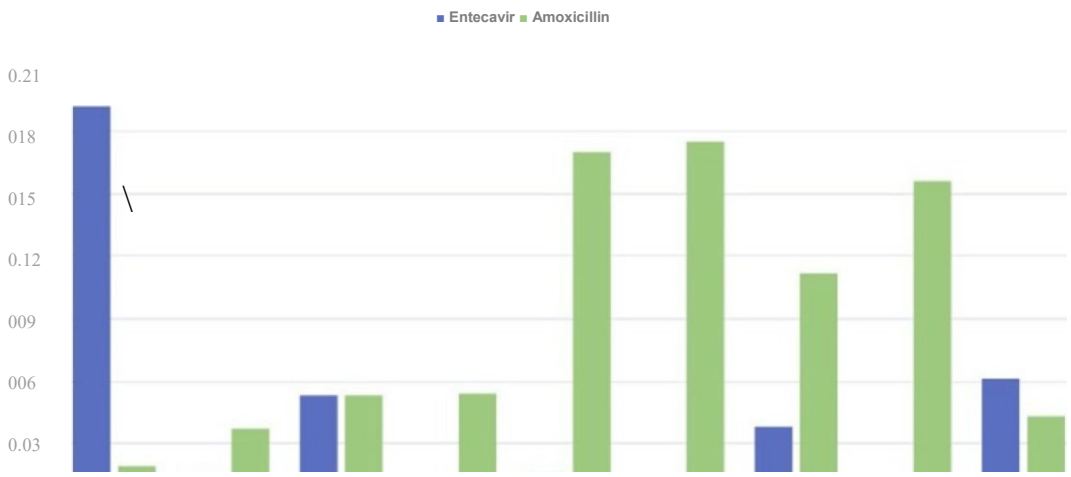
d. Fourth generation cephalosporins:

Cefepime

e. Fifth generation cephalosporins:

Ceftaroline

Figure1: Potential Metabolism Interactions are illustrated in the below figure.



3.3. **Analysis of potentially dangerous interactions between tenofvir and entecavir and cephalosporin antibiotics**

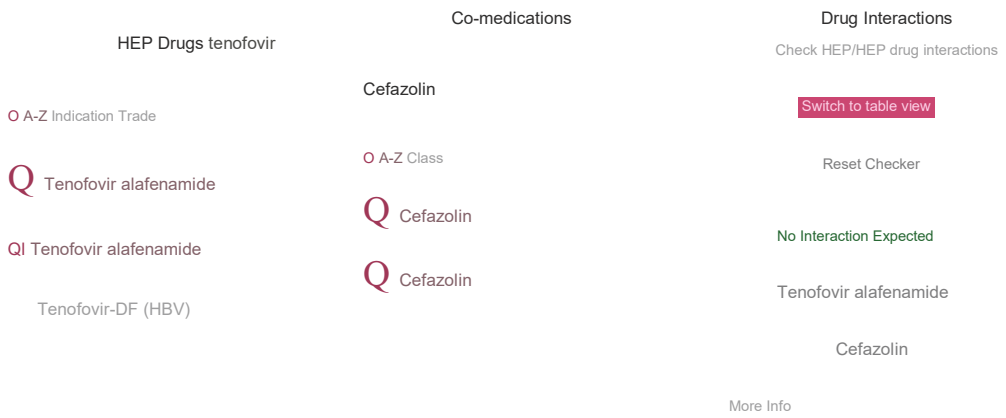
1. Interaction report retrieved from www.hepatology-druginteractions.org Page 1 of 1 www.hepatology-druginteractions.org

Report ID: Production date: Second Month 11, 2024

Combination Medicine Co., Ltd. - Drug Tenofovir Alafenamide Cefazolin

This table lists the drug interactions in the above table (e.g. "Red", "Amber" and "Yellow" groups) in points. Interventions with “green” or “gray” classification (i.e., no clinically meaningful intervention or clear data) are reviewed and listed at the end of this report, but no details are available. Please note that some herbal combinations may require dosage adjustments due to poor liver function. For a complete summary of all interactions, visit www.hepatology-druginteractions.org. Interaction Reporting Not expected to be clinically significant (green). Tenofovir Alafenamid + Sefazolin

Figure 2: Interaction of Tenofovir alafenamide with Cefazolin

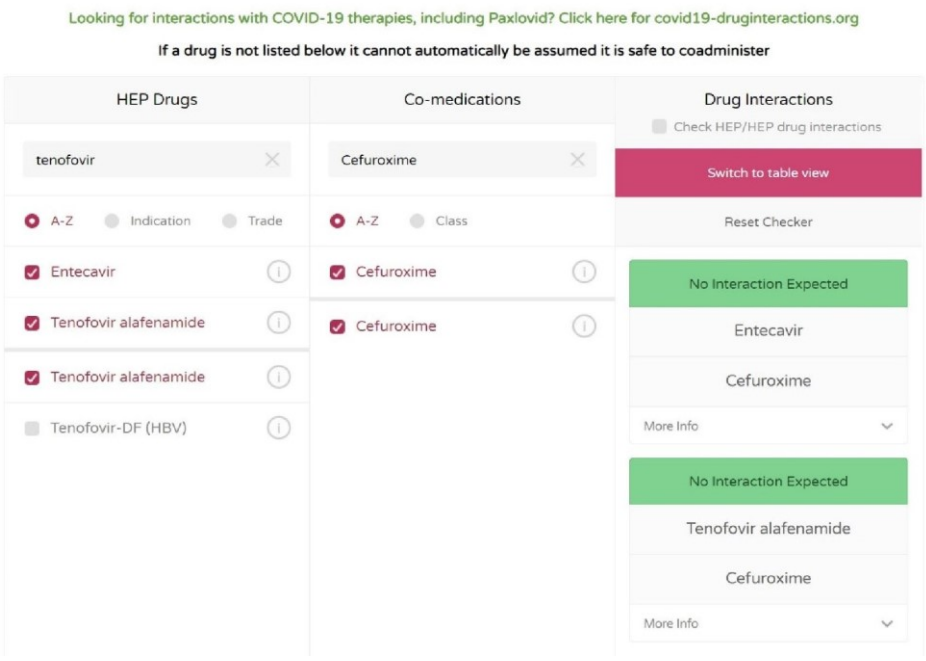


Report ID: Created Date: February 11, 2024

Interactive Report Liver Disease Treatment Liver Disease Treatment Concomitant Drugs Concurrent Drugs Entecavir Tenofovir Alafenamide Cefuroxime

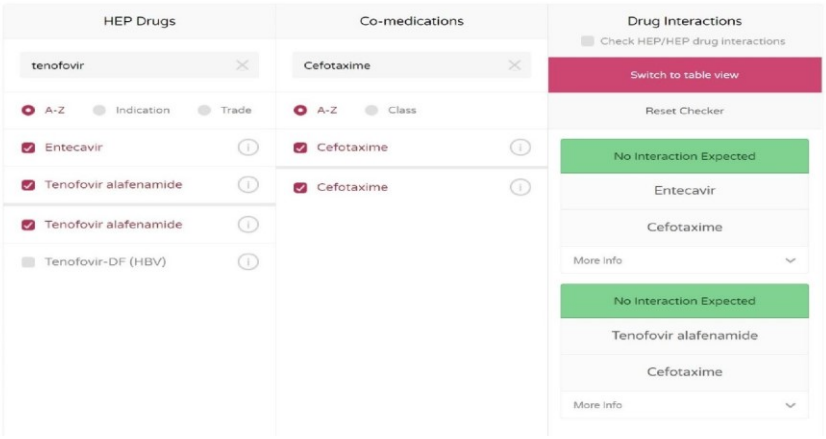
This report lists the content of the interactions., In the table above "and "Yellow" classification) were used for drugs included. Interaction with "green" or "gray" classification (i.e. no clinical effect or no clear data) was analyzed and presented at the end of the report not here, but details are not shown. Please note that some herbal combinations. Note that dosage adjustments may be required due to poor liver function. For complete details of each treatment interaction, visit www.hepatology-druginteractions.org. Interaction Guide No clinically significant interaction (green). Entecavir + Cefuroxime Tenofovir Alafenamide + Cefuroxime

Figure 3: Interaction of Entecavir + Cefuroxime Tenofovir alafenamide + Cefuroxime



2. Report ID: Publication date: February 11, 2024 Interaction Discussion Report for the Treatment of Liver Disease Concomitant Drugs Entecavir Tenofovir Alafenamide Cefotaxime This leaflet provides details of interactions. ," "Amber" and the "yellow" classification for the drug in the table above. It was reviewed and eventually listed with a "green" or "gray" classification (e.g., no interaction or clear information in the clinic). Details of this report were not disclosed. Please note that some herbal combinations may require dosage adjustments due to poor liver function. For a complete summary of all interactions, visit www.hepatology-druginteractions.org. Interaction Reporting Not expected to be clinically significant (green). Entecavir + cefotaxime Tenofovir alafenamide + cefotaxime

Figure 4: Interaction of Entecavir + Cefotaxime Tenofovir alafenamide + Cefotaxime



3. Report ID: Date: February 11, 2024 Interaction Report Liver Disease Treatment Liver Treatment Concomitant Drugs Entecavir Tenofovir Alafenamide Ceftaroline. This leaflet provides information about interactions. "Red", "Amber" and "yellow" classification for chemicals in the table above. Interactions with "green" or "gray" classification (i.e., no interaction in hospital or no clear data) were analyzed and listed. Please note that some herbal combinations may require dosage adjustments due to poor liver function. For a complete summary of all interactions, visit www.hepatology-druginteractions.org. Interaction Reporting Not expected to be clinically significant (green). Entekavir + Seftarolin Tenofovir Alafenamid + Seftarolin

Figure 5: Interaction of Entecavir + Cefotaxime Tenofovir alafenamide + Cefotaxime

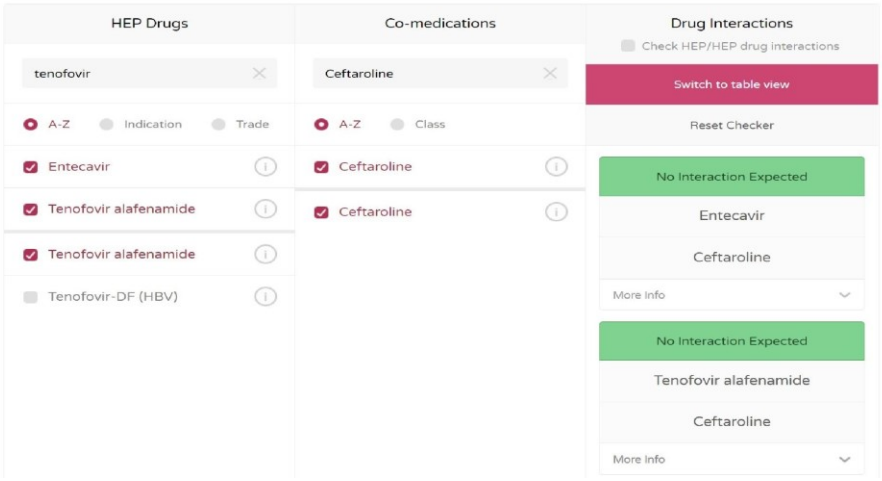
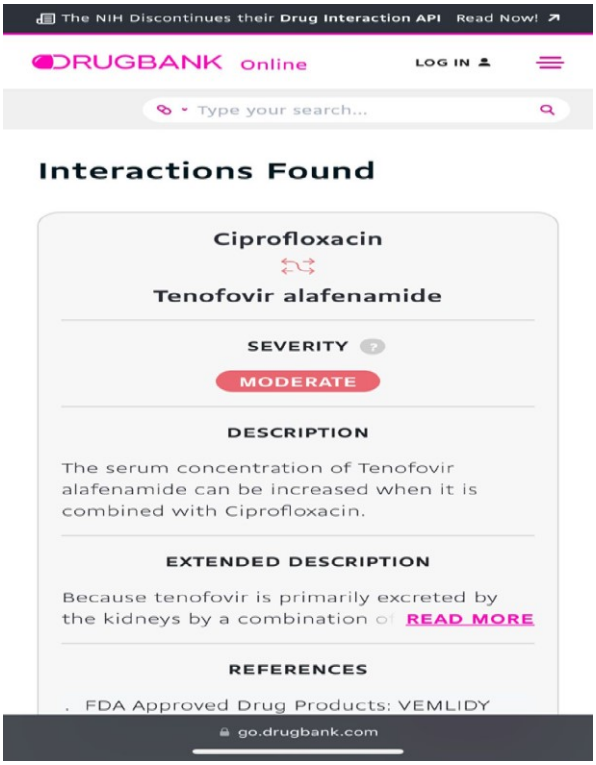


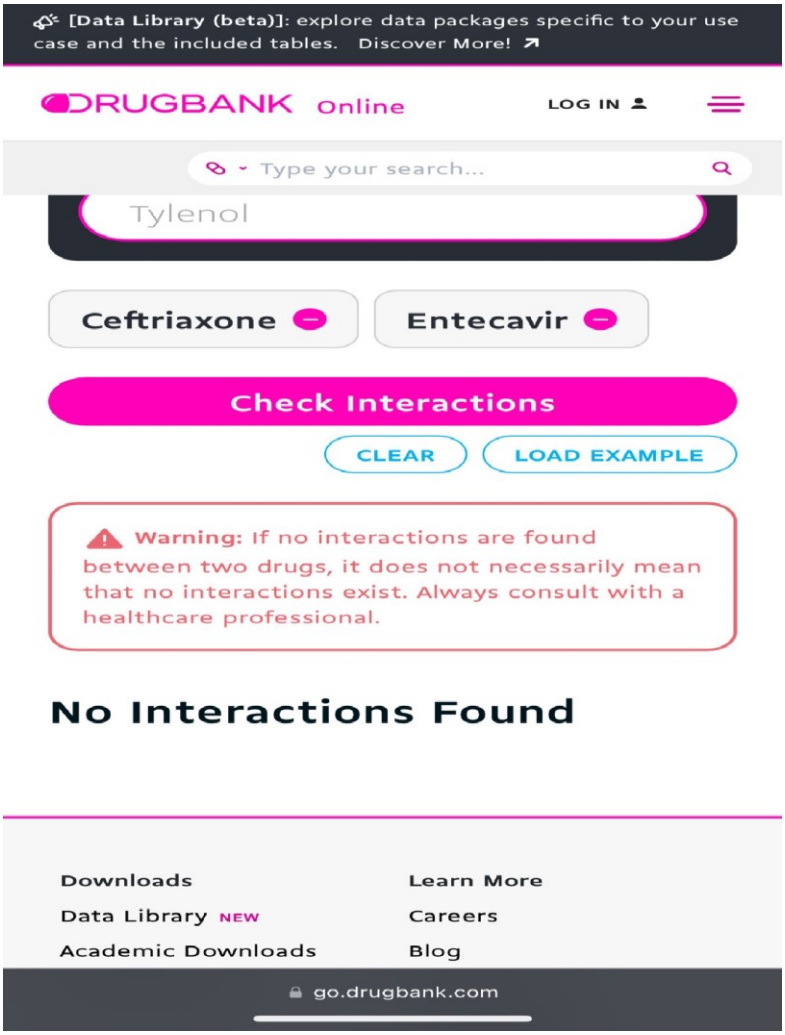
Figure 6: Interaction between Ciprofloxacin and Tenofovir



Because tenofovir is primarily excreted by the kidneys via a combination of glomerular filtration and active tubular secretion, coadministration of VEMLIDY with drugs that reduce renal function or compete with active tubular secretion may result in the risk of tenofovir and other renal elimination drug concentrations; can increase.

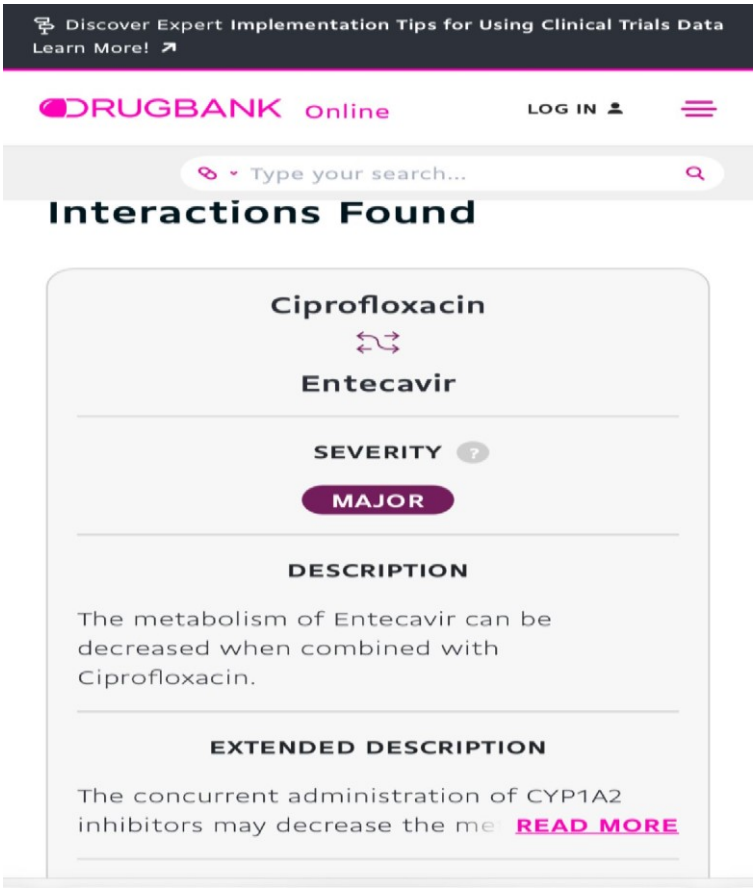
Risk of adverse events: The combination has not been studied, but based on metabolism and elimination, a significant treatment interaction is unlikely. Ciprofloxacin is eliminated un changed by the kidneys mainly by glomerular filtration and tubular secret ion via OAT3. It is also partially metabolized and eliminated through the bile and intestines.

Figure 7: Interaction between Ciprofloxacin and Tenofovir



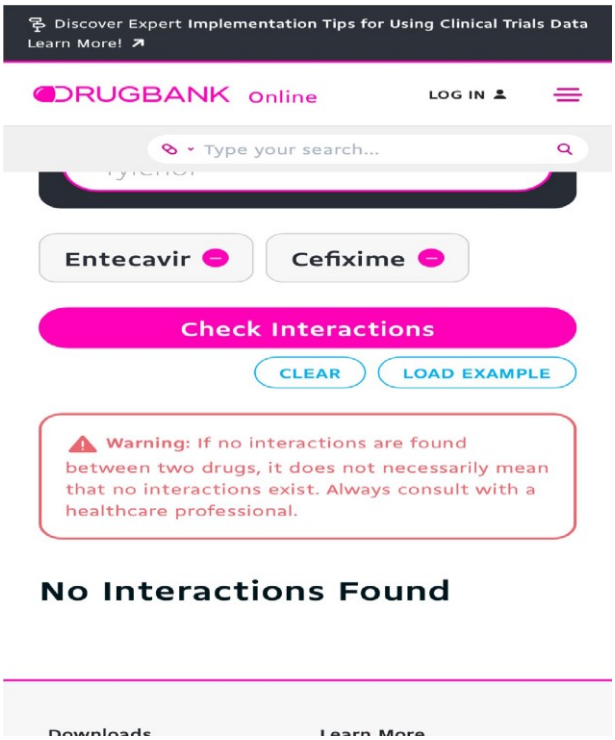
It is not possible to cancel important appointments at the hospital. Ceftriaxone is excreted mainly by glomerular filtration, with little active tubular secretion. Entecavir is eliminated in the urine primarily by glomerular filtration and tubular secretion of OAT1. The potential for interaction with entecavir is very low due to competition with renal transport.

Figure 8: Interaction between Entercavir and Ciprofloxacin



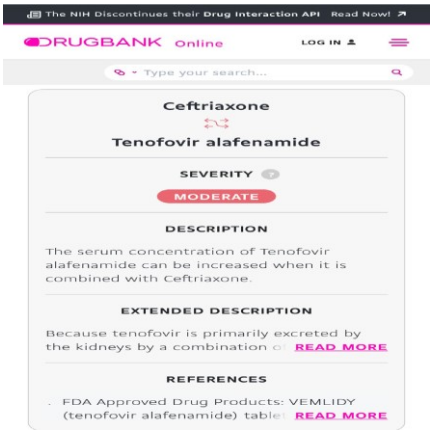
Coadministration with CYP1A2 inhibitors may decrease the metabolism of CYP1A2 substrates, increasing their exposure and risk of toxicity. Ceftriaxone is excreted mainly by glomerular secretion, with a very small amount of active tubular secretion. Entecavir is eliminated in the urine primarily by glomerular filtration and tubular secretion of OAT1. The potential for interaction with entecavir is very low due to competition with renal transport.

Figure 9: interaction between entecavir and cefixime



Coadministration has not been studied, but clinically significant interactions are unlikely due to metabolism and elimination. Cefixime is excreted primarily by the kidneys by glomerular filtration, with no apparent active tubular secretion. Entecavir is eliminated in the urine primarily by glomerular filtration and tubular secretion of OAT1. The potential for interaction with entecavir is low by competing for renal elimination transport.

Figure 10: interaction between Tenofovir and ceftriaxone



Because tenofovir is primarily excreted by the kidney through a combination of glomerular filtration and active tubular secretion, coadministration of VEMLIDY with drugs that reduce renal function or compete with tubular secretion may compromise tenofovir and other renal clearance of drug concentrations, this may increase the risk.

From this we conclude that tenofovir and entecavir have interactions with most cephalosporins that have not been studied, but since renal function is similar to abolishing the use of these drugs, coadministration may cause renal damage.

In our analysis of potentially harmful combinations of beta-lactam antibiotics (BL) with tenofovir and entecavir using Liverpool HEP Interactions, we found that tenofovir does not have adverse interactions with BL.

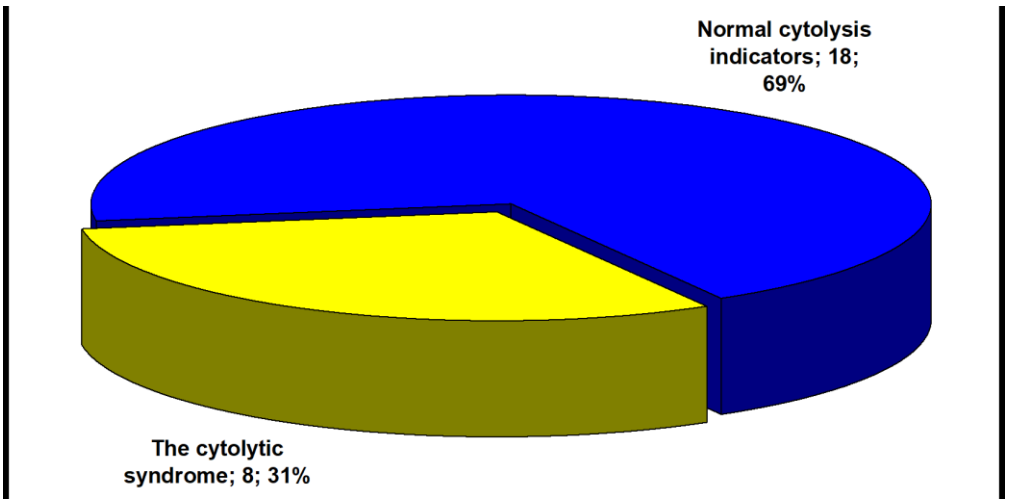
However, entecavir in combination with cephalexin during tubular secretion may compete for the renal transporters OAT1 and MATE1, which can lead to a significant increase in the concentration of both drugs.

3.4. Analysis of the clinical effects of simultaneous administration of direct antiviral drugs and cephalosporins

We analyzed 26 extracts from medical histories and outpatient records of patients with CHB who took entecavir and, according to indications (acute and chronic bronchitis, community-acquired pneumonia, sinusitis, skin infections, etc.) the cephalosporins for 7 - 14 days.

After the prescription of antibacterial therapy, 8 patients (30.8%) developed laboratory indicators of moderate cytolytic syndrome - increased activity of ALT, AST without signs of hyperbilirubinemia. After completion of antibiotic therapy, spontaneous normalization of serum enzyme activity occurred in patients within 2-3 weeks.

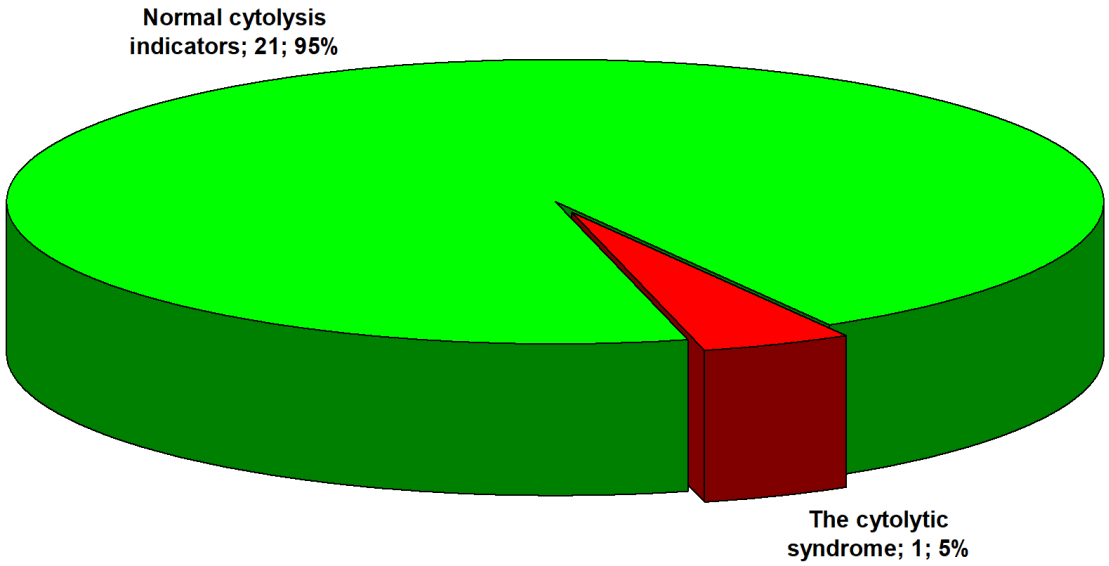
Figure 11: Frequency of cytolytic syndrome when prescribing entecavir and cephalosporins (cephalexin) in patients with chronic hepatitis B



In a group of 22 patients with CHB who also took entecavir, when clinical signs of bacterial infections appeared, beta-lactam antibiotics were prescribed - cefazolin, cefotaxime in medium therapeutic doses for 7-14 days.

A transient increase in transaminases in patients with CHB was verified in only 1 patient (4.5%). Thus, the problems of compatibility of the direct antiviral drug entecavir with beta-lactam antibiotics in patients with CHB can be solved by excluding ampicillin, benzylpenicillin, cephalexin from antibacterial treatment and prescribing amoxicillin, cefazolin or cefotaxime instead.

Figure 12: Frequency of cytolytic syndrome when prescribing entecavir and cephalosporins (cefazolin, cefotaxime) in patients with chronic hepatitis B



In the case of frequently recurring relapses of bacterial infection and the need to prescribe beta-lactam antibiotics, if chronic viral hepatitis B is detected in this group of patients, it is advisable to start treatment not with entecavir, but with tenofovir. Tenofovir has no adverse interactions with this group of antibiotics.

Findings

1. Treatment of tenofovir and entecavir with a group of betalactam antibiotics, particularly cephalosporins, and pharmaceutical findings have revealed some important information. Tenofovir and entecavir are antiviral medications commonly used to treat hepatitis B virus (HBV) infection and can effectively suppress viral infections while reducing the risk of drug reactions. However, the interaction of these antibiotics with other drugs, especially antibiotics, is important in the treatment.
2. Cephalosporins are a type of beta-lactam antibiotics commonly used to treat various infections and may interact with tenofovir and tenofovir. Entecavir due to common metabolic pathways or renal elimination mechanisms. Understanding the nature and extent of this interaction is important to improve clinical outcomes and prevent adverse reactions in patients receiving immunosuppressants, combinations, and antibiotics.
3. Research results showing pharmacokinetic and pharmacodynamic interactions between tenofovir/entecavir and cephalosporins. Pharmacokinetic studies provide insight into how these drugs are absorbed, distributed, metabolized, and excreted from the body, including changes in these processes when taken together. Pharmacodynamic studies are investigating the combination of these drugs for immunity, disease clearance, and overall clinical benefit.
4. Major findings may include changes in drug concentrations due to changes in absorption or metabolism when tenofovir/entecavir is combined with cephalosporins. These changes may affect the effectiveness and safety of anti-inflammatory and

antiinflammatory drugs, requiring changes in dosage or careful monitoring of patients, dangerous or ineffective treatment.

5. In addition, this study may reveal potential mechanisms for the interaction between tenofovir/entecavir and cephalosporins, such as competition for the renal pathway or inhibition or induction of enzymes in the metabolic pathway. Understanding these mechanisms is important for effectively predicting and managing drug interactions in clinical practice.

6. Overall, the research results provide a better understanding of the clinical and pharmacological interactions between tenofovir/entecavir and cephalosporin antibiotics, providing physicians with certification information to improve treatment and guidelines for patient safety and quality management. With HBV infection and viral infections requiring antibiotics.

Bilbiography

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