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Potential Drug-Drug Interactions with Adefovir Dipivoxil: Clinical Implications and Management Strategies

M. Shankar Ganesh, D. Asifsha and N. Venkateswaramurthy*

Department of Pharmacy Practice, JKKN College of Pharmacy, Namakkal, Tamil Nadu, India.

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This study meticulously investigates the intricate network of drug interactions, specifically focusing on adefovir dipivoxil, a nucleotide analog employed in treating chronic hepatitis B. The comprehensive analysis explores the influence of various drugs, including Nonsteroidal anti-inflammatory drugs (NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)), histamine H2 receptor antagonists, aminoglycoside antibiotics, and cytochrome P450 enzyme inducers/inhibitors, on the metabolism and elimination of adefovir dipivoxil. The pivotal role of liver enzymes and renal function in the metabolism and excretion of this drug is underscored. The discourse centers on the mechanisms, such as competitive inhibition for renal transporters, enzyme induction/inhibition, and metabolic interference, which can modify the renal elimination of adefovir dipivoxil, potentially leading to toxicity or diminished efficacy. The study highlights that alterations in liver esterase activity and renal function directly impact adefovir dipivoxil exposure. The findings conclude that drugs affecting liver enzymes or renal function significantly influence the metabolism and excretion of adefovir dipivoxil, necessitating vigilant monitoring for potential interactions to optimize the safety and efficacy of adefovir dipivoxil therapy for chronic HBV patients. This review sheds light on critical drug interactions, guiding healthcare professionals to devise safer and more effective treatment regimens for chronic hepatitis B, thereby ensuring improved patient outcomes.

Keywords: Adefovir dipivoxil; Chronic hepatitis B; Cytochrome P450 enzymes; Drug interactions; Nonsteroidal anti-inflammatory drugs (NSAIDs); Renal function.

Investigating the interplay of antiviral drugs is instrumental in empowering healthcare practitioners to devise optimal and secure therapeutic strategies for patients afflicted with viral infections. Comprehending the potential interactions between antiviral medications and other pharmaceuticals can forestall detrimental reactions, mitigate the peril of drug toxicity, and enhance the prognosis of treatment. Moreover, insights gleaned from understanding drug interactions can guide the innovation of novel antiviral treatments, thereby augmenting their efficacy and safety profiles. This knowledge is pivotal in the relentless pursuit of advancing patient care in the realm of virology.

Adefovir dipivoxil, commercially known as Hepsera, is a Nucleotide Reverse Transcriptase Inhibitor (NtRTI) utilized in the management of hepatitis B infection.[1,2,3] It operates as a nucleotide reverse transcriptase inhibitor by impeding the function of the reverse transcriptase enzyme, a crucial element in the replication mechanism of the Human Immunodeficiency Virus (HIV) and

*Corresponding author E-mail: nvmurthi@gmail.com

Hepatitis B Virus (HBV).[4] The enzyme is tasked with the conversion of viral RNA into DNA, which subsequently integrates into the host cell's genome. By inhibiting the reverse transcriptase enzyme, adefovir obstructs the replication of the virus, thereby diminishing the viral load within the body.[5] Adefovir dipivoxil is classified as a prodrug, implying that it undergoes conversion to its active form, adefovir, within the body post oral administration.[6] Prodrugs are inactive compounds that are metabolically transformed into their active state within the body via processes such as hydrolysis or oxidation. The utilization of a prodrug aims to enhance the bioavailability, stability, or ease of administration of the active drug. In the context of adefovir dipivoxil, the prodrug formulation facilitates oral administration and absorption into the bloodstream, where it is subsequently converted to adefovir, the active drug form. Adefovir dipivoxil is typically administered once daily in tablet form. It is generally well-tolerated, although common side effects may encompass nausea, diarrhea, and abdominal pain.[7]

The prescribed dosage of adefovir dipivoxil for adult patients is set at 10 mg, administered once daily. For pediatric patients, the dosage is determined based on their body weight. The guidelines are as follows:

• Patients with a body weight less than 16 kg: The recommended dosage is 3 mg, taken once daily.

• Patients with a body weight ranging between 16 kg and 23 kg: The recommended dosage is 6 mg, taken once daily.

• Patients with a body weight ranging between 24 kg and 35 kg: The recommended dosage is 9 mg, taken once daily.

• Patients with a body weight exceeding 35 kg: The recommended dosage is 10 mg, taken once daily.

Drug interaction

Adefovir dipivoxil, a nucleotide analogue antiviral drug, is predominantly employed in the treatment of chronic Hepatitis B Virus (HBV) infection. Its mechanism of action involves the inhibition of the reverse transcriptase activity of the HBV DNA polymerase, a critical enzyme for the replication of the HBV genome.

The drug is primarily excreted through the kidneys, with approximately 80% of the administered dose being eliminated unchanged in the urine. The process of secretion into the renal tubules is facilitated by organic anion transporters (OATs (Organic Anion Transporters)), which are located in the renal proximal tubules. This secretion is an active process, contingent on the expression of OATs and the concentration of the drug in the tubular fluid. OATs, a family of transmembrane proteins, play a pivotal role in the renal elimination of organic anions from the blood.9 They are primarily located in the renal proximal tubules and are instrumental in the active secretion of organic anions into the renal tubules for subsequent elimination from the body.10

Organic anions, encompassing a broad spectrum of compounds such as drugs, toxins, and metabolic waste products, are negatively charged molecules. Their secretion into the renal tubules by Organic Anion Transporters (OATs) is a crucial physiological process that prevents their reabsorption into the bloodstream, thereby facilitating their prompt elimination from the body.[11] The OAT family comprises several types, notably OAT1, OAT2, and OAT3, each characterized by distinct substrate specificities and distribution patterns.[11] The expression and activity of these transporters can be modulated by a variety of factors, including age, disease states, and drug interactions.

In the context of pharmacokinetics, OATs (Organic Anion Transporters) play a significant role in mediating drug-drug interactions (DDIs), specifically between adefovir dipivoxil and other drugs. A wide range of drug classes interact with human OAT1-3, including but not limited to NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), ACE inhibitors, angiotensin II receptor antagonists, diuretics, HMG CoA reductase inhibitors, â-lactam antibiotics, antineoplastic and antiviral drugs, and uricosuric drugs.10,11

Renal impairement

Nonsteroidal Anti-Inflammatory Drugs Interact with Adefovir Dipivoxil

Non-steroidal anti-inflammatory drugs (NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)) constitute a class of medications widely utilized for their analgesic and anti-inflammatory properties. They exert their therapeutic effects by inhibiting the production of prostaglandins, biochemical mediators implicated in pain and

inflammation.12 Notable examples of NSAIDs include Aspirin, Ibuprofen, Naproxen, Diclofenac, Celecoxib, and Indomethacin.

The mechanism of action of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) involves the reduction of renal blood flow due to vasoconstriction of renal arteries, which in turn decreases renal perfusion. This is compounded by the inhibition of prostaglandin synthesis, a group of signaling molecules synthesized from arachidonic acid and produced ubiquitously across the body. Prostaglandins play a pivotal role in maintaining normal renal blood flow and function. The inhibition of cyclooxygenase (COX), the enzyme responsible for prostaglandin production, by NSAIDs leads to vasoconstriction and reduced renal blood flow, potentially inflicting renal damage over time.

Adefovir, an antiviral drug, is primarily excreted via renal elimination, a process wherein the drug is filtered from the bloodstream by the kidneys and subsequently excreted in the urine. The organic anion transporter (OAT) system, responsible for the elimination of numerous drugs, primarily mediates the elimination of Adefovir.

The interaction of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) can impair normal renal function and potentially diminish the efficiency of Adefovir's renal elimination.13 This interaction can result in an elevated concentration of Adefovir in the bloodstream, thereby increasing the risk of drug toxicity. Understanding these interactions is crucial for optimizing therapeutic strategies and mitigating potential adverse effects.14,15

Severity

The extent of the reduction in the elimination of Adefovir dipivoxil, when co-administered with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), can potentially escalate the risk of toxicity. This severity is subject to variation and is influenced by several factors. These include the specific type of NSAID administered, the dosage and duration of treatment with both Adefovir dipivoxil and the NSAID, and patient-specific characteristics.[15]

Management

To enhance the therapeutic efficacy of Adefovir when co-administered with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), patients should consider the following strategies:

• Avoid High-Dose NSAIDs (Non-Steroidal Anti-Inflammatory Drugs): Patients concurrently receiving Adefovir and an NSAID should refrain from using high doses of NSAIDs, as this could potentially escalate the risk of toxicity.

• Stagger the Doses of Adefovir and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs): To minimize potential drug-drug interactions, it may be beneficial to stagger the administration times of Adefovir and NSAIDs.

• Monitor Symptoms Vigilantly: Patients on both Adefovir and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) should diligently monitor their symptoms and maintain regular communication with their healthcare provider. Prompt reporting of any side effects or changes in symptoms to their healthcare provider is crucial.16

Histamine-2 (H2) Receptor Antagonist Interact with Adefovir Dipivoxil

Histamine H2 receptor antagonists, a class of medications used to treat various gastrointestinal conditions such as gastroesophageal reflux disease (GERD), peptic ulcers, and acid indigestion, function by blocking the action of histamine at the H2 receptors in the stomach.[17,18] Histamine is a bodily substance that stimulates the production of gastric acid. Famotidine (Pepcid), Ranitidine (Zantac), Cimetidine (Tagamet), and Nizatidine (Axid) are examples of histamine H2 receptor antagonists, available in both prescription and over-the-counter forms. Notably, Adefovir can interact with Cimetidine and Ranitidine.[19.20]

Theoretically, the coadministration of Adefovir dipivoxil with H2 receptor antagonists that are eliminated by active tubular secretion could result in increased plasma concentrations of Adefovir. This is due to the competitive inhibition of renal excretion. Both Adefovir dipivoxil and certain H2 receptor antagonists are eliminated by active tubular secretion, a process wherein drugs are transported from the bloodstream into the urine. During this process, the drugs are absorbed by renal proximal tubular cells and secreted into the urine. This process is mediated by transporters such as the Organic Anion Transporter (OAT) and the Organic Cation Transporter (OCT).[21] When two drugs that are eliminated by active tubular secretion are taken together, they can compete for the same transporters in the renal proximal tubular cells. This competition can lead to decreased elimination of

one or both drugs, resulting in increased plasma concentrations of the coadministered drugs. Understanding these interactions is crucial for optimizing therapeutic strategies and mitigating potential adverse effects.[21,22]

Severity

The interplay between H2 receptor antagonists and adefovir dipivoxil can range from mild to moderate in severity, contingent upon the individual patient's condition and specific circumstances. Adefovir dipivoxil, albeit rarely, can induce severe side effects such as renal complications and hepatic damage. These adverse effects are typically deemed severe and necessitate immediate medical intervention.[23]

Management

To enhance the efficacy of Adefovir when co-administered with Histamine H2 receptor antagonists, patients should adhere to the following guidelines:

• Avoid High-Dose H2 Receptor Antagonists: Patients on both Adefovir and H2 receptor antagonists should refrain from using high doses of H2 receptor antagonists, as this could potentially escalate toxicity levels.

• Stagger Doses of Adefovir and H2 Receptor Antagonists: Spacing out the doses of Adefovir and H2 receptor antagonists could help minimize potential drug interactions.

• Consider Alternative Therapies: If deemed necessary, healthcare professionals may suggest alternative treatments to reduce the potential for interactions between Adefovir and H2 receptor antagonists.

• Monitor Symptoms Closely: Patients on both Adefovir and H2 receptor antagonists should vigilantly monitor their symptoms and maintain regular communication with their healthcare provider. Any side effects or changes in symptoms should be promptly reported to their healthcare professional.[24]

Aminoglycoside Antibiotic Interact with Adefovir Dipivoxil

The interaction between aminoglycoside antibiotics and adefovir dipivoxil, an antiviral medication utilized for the treatment of chronic hepatitis B infection, has been a subject of concern due to its potential nephrotoxic effects. Aminoglycoside antibiotics, specifically gentamicin, when used concomitantly with adefovir dipivoxil, have been linked to an elevated risk of kidney toxicity. This is attributed to the inherent nephrotoxic properties of both gentamicin and adefovir dipivoxil, which when combined, may exacerbate the risk of renal complications.[25,26,27] The aminoglycoside class of antibiotics encompasses gentamicin, amikacin, tobramycin, neomycin, and streptomycin. This critical interaction underscores the importance of cautious co-administration of these medications, warranting further investigation and clinical vigilance.

Mechanism

Adefovir, a weak base, is excreted from the bloodstream into the urine via a mechanism known as cationic secretion, a process facilitated by Organic Anion Transporters (OATs). Concurrently, certain aminoglycoside antibiotics, including gentamicin, undergo a similar excretion process. This parallel pathway can result in a competitive scenario where adefovir and aminoglycosides vie for secretion through the OATs. The co-administration of adefovir and aminoglycoside antibiotics can exacerbate this competition, leading to an increased renal accumulation of both drugs. This heightened concentration can potentially escalate the risk of renal damage. This interplay underscores the importance of careful drug administration and monitoring when these two classes of drugs are used concomitantly.[28,29]

Management

• The importance of vigilant renal function monitoring cannot be overstated, particularly when administering medications such as adefovir and aminoglycosides, known for their potential to exacerbate renal damage. This surveillance may encompass the assessment of creatinine levels, a reliable indicator of renal function, and the computation of the creatinine clearance rate, which offers a more precise evaluation of renal performance.

• In instances where renal function is compromised, it may be necessary to modify the dosing of adefovir and/or aminoglycosides to mitigate the risk of additional renal damage. This adjustment could entail a reduction in the dosage of one or both medications, or a transition to an alternative antibiotic.

• Furthermore, the recommendation of alternative medications may be warranted in certain cases to decrease the risk of renal damage. For instance, if

aminoglycosides are implicated in nephrotoxicity, a shift to a different class of antibiotics, such as beta-lactams, may be advised.

Hepatic impairement

Cytochrome P450 (Cyp450) Enzyme

The Cytochrome P450 (CYP450) enzyme system, a collection of enzymes predominantly found in the liver and other tissues, plays a pivotal role in drug metabolism.[30,31] This system comprises numerous subtypes, including but not limited to CYP1A2, CYP2D6, CYP2C19, CYP3A4, and CYP2E1. Each subtype is characterized by a distinct set of substrates that it can metabolize.

The activity of these enzymes is subject to variation due to a multitude of genetic and environmental factors. This variability in the functionality of the CYP (Cytochrome P450)450 enzyme system can significantly influence the efficacy and safety profile of drugs. Consequently, understanding the dynamics of this system is crucial for optimizing pharmacological interventions and mitigating adverse drug reactions.31,32

Enzyme Inhibition

The strategic inhibition of enzymatic activity serves as a potent therapeutic approach in mitigating the progression of various diseases. This is exemplified by numerous oncology drugs that specifically target enzymes integral to DNA synthesis or cellular division, thereby decelerating the proliferation of cancerous cells. In a parallel vein, statins, a class of drugs designed to lower cholesterol levels, function by inhibiting an enzyme crucial to cholesterol biosynthesis, consequently leading to a decrease in blood cholesterol concentrations. This underscores the potential of enzyme inhibitors as a viable strategy in disease management and treatment.[33]

Enzyme Induction

Induction of enzymes involved in drug metabolism can increase the rate at which a drug is cleared from the body, leading to a decrease in its efficacy.[34,35] This can be a problem for drugs that require a constant level in the body to maintain their therapeutic effect. An example of a drug that interacts with enzyme induction is Phenobarbital. Phenobarbital is a barbiturate drug that is used as an anticonvulsant and sedative.[36,37]

Phenobarbitone Interact with Adefovir Dipivoxil

Phenobarbital, a barbiturate medication, is primarily employed for its anticonvulsant and sedative properties. It undergoes metabolism in the liver, facilitated by the cytochrome P450 (CYP (Cytochrome P450)) enzyme system. Studies have demonstrated that Phenobarbital can induce the expression of specific CYP enzymes, thereby augmenting their activity. This escalation in enzymatic activity subsequently enhances the metabolism of other drugs that are substrates of the CYP system. Consequently, this can result in a reduction in the therapeutic efficacy of these co-administered drugs. This intricate interaction underscores the importance of considering potential drug-drug interactions in clinical practice to ensure optimal therapeutic outcomes.40,41,42

A key characteristic of Phenobarbital is its role as an enzyme inducer, specifically enhancing the activity of the cytochrome P450 (CYP (Cytochrome P450)) enzyme system. This induction has been demonstrated to stimulate the expression of several CYP enzymes, including CYP2B6, CYP2C9, CYP2C19, and CYP3A4. The heightened activity of the CYP enzyme system can lead to an accelerated metabolism of certain drugs, such as Adefovir. This increased metabolic

Table 1. Example for enzyme inhibition and enzyme induction.[38,39]

Enzyme	Inhibitors	Inducers
CYP1A2	Ciprofloxacin, fluvoxamine	Phenytoin, Rifampin
CYP2C9	Fluconazole	Carbamazepine, Rifampin
CYP2D6	Bupropion, fluoxetine, paroxetine	-
CYP3A4	Macrolides (Erythromycin, Clarithromycin), Azole Antifungals (Itraconazole, Ketoconazole, Fluconazole), Protease Inhibitors (Ritonavir, Indinavir), Grape fruit Juice, Ciprofloxacin	Carbamazepine, Modafinil, Phenytoin, Phenobarbitone, Rifabutin, Rifampicin.

rate results in a more rapid clearance of drugs from the body that are metabolized by the CYP system. Consequently, this can lead to a reduction in their efficacy, posing a significant challenge for drugs that necessitate a stable concentration within the body to maintain their therapeutic effect. This intricate interplay between Phenobarbital and the CYP enzyme system underscores the importance of considering drug interactions in clinical pharmacology.43,44

Management

Phenobarbital can increase Adefovir metabolism via the CYP (Cytochrome P450) enzyme system, potentially requiring a dosage adjustment under medical supervision. In some cases, switching to a non-CYP metabolized antiviral may be considered. This decision depends on various factors like the patient's medical history and HBV infection severity. Phenobarbital may also speed up the metabolism of other drugs, possibly leading to liver toxicity, necessitating regular liver function monitoring. Avoiding other CYP inducers like carbamazepine, rifampicin, and alcohol can help prevent further CYP system induction and reduce potential drug interactions and side effects.45

Azole Antifungals Interact with Adefovir Dipivoxil

Azole antifungals represent a distinct category of therapeutic agents, specifically designed to combat fungal infections. Their mechanism of action is primarily centered around the suppression of fungal proliferation and growth. This is achieved by obstructing the biosynthesis of ergosterol, an integral constituent of the fungal cellular membrane. The disruption of ergosterol synthesis consequently compromises the structural and functional integrity of the fungal cell membrane, thereby exerting the antifungal effect. This succinct elucidation of the pharmacological action of azole antifungals underscores their significance in the clinical management of fungal infections.[46,47,48]

Azole antifungals, a class of compounds known for their inhibitory action on the cytochrome P450 enzyme family, specifically target the isoforms CYP (Cytochrome P450)3A4 and CYP2C19. This inhibition can significantly impact the metabolic processes of drugs such as Adefovir dipivoxil, which are metabolized by these enzymes.

Notably, certain azole antifungals, including ketoconazole and itraconazole, are recognized as potent inhibitors of CYP (Cytochrome P450)3A4. This isoform plays a crucial role in the metabolism of a wide range of drugs, encompassing various antibiotics, antivirals, and immunosuppressants. The inhibition of cytochrome P450 enzymes by azoles can lead to an elevation in the plasma levels of Adefovir dipivoxil. This increase could potentially heighten the toxicity of the drug, underscoring the need for careful monitoring and dosage adjustments when co-administering these medications.49,50,51

Management

To mitigate potential interactions with Adefovir and Ketoconazole, it is advisable to avoid or exercise caution when using other drugs metabolized by the Cytochrome P450 enzyme system. If necessary, the dosage of Adefovir can be adjusted to minimize toxicity risk, considering the patient's renal function and overall health status.

CONCLUSION

In the context of drug interactions, it is crucial to consider the metabolic and excretory pathways of adefovir dipivoxil. This pharmaceutical agent is predominantly metabolized in the liver via hydrolysis and subsequently excreted through the kidneys. Consequently, any medications that interact with liver enzymes or influence renal function have the potential to modify the metabolism and excretion of adefovir dipivoxil, thereby altering the patient's exposure to the drug. Given these considerations, vigilant monitoring for potential drug interactions is paramount to ensure the optimal efficacy and safety of adefovir dipivoxil therapy in patients with chronic Hepatitis B Virus (HBV) infection. This underscores the importance of personalized medicine and careful pharmacological management in the treatment of chronic HBV infection.

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Author Contribution

Shankar Ganesh M and Asifsha D conducted the research and data analysis for the study on potential drug-drug interactions with adefovir dipivoxil, while Dr. Venkateswaramurthy N provided critical oversight and guidance throughout the project. All authors contributed to the drafting and revision of the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Conflict of Interest

There are no Conflicts of Interest.

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