Recommendations for the selection of nucleoside analogues as antihuman herpesvirus drugs: A real-world analysis of reported cases from the FDA adverse event reporting system

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Abstract

Objective: Based on the discovery and summary of adverse drug reactions of nucleotide analogues against herpes virus drugs, this study aims to analyze the situations of ADRs in the real world, put forward reasonable drug use recommendations, refine the rules of use, and formulate necessary alternative strategies to provide protection against herpes virus infection, and provide guidance and reference for the rational and individualized use of clinical drugs. Methods: All ADRs data of the drugs from the Q1 of 2004 to the Q4 of 2022 were obtained from the FDA Adverse Event Reporting System database. Duplicate reports, reports with uncertain information, and other reports containing abnormal information were excluded from the obtained data, and the data with more than 3 reports were selected. Apply the ROR, PRR and BCPNN in the disproportionality analysis for data mining . Results: All data from the Q1 of 2004 to the Q4 of 2022 were screened from the FAERS database. For ADEs with high frequency SOC level, we found that several important signals, including ADEs of ACV, GCV and VACV, simultaneously involved the following SOC systems: kidney and urinary system diseases, nervous system disease, skin and subcutaneous tissue diseases and mental diseases. Conclusion: Analysis of the FAERS database suggests that in addition to paying attention to efficacy, drug administration should be individualized according to the specific condition and potential risk of disease.

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Abstract

Objective: Based on the discovery and summary of adverse drug reactions (ADRs) of nucleotide analogues against herpes virus drugs, this study aims to analyze the situations of ADRs in the real world, put forward reasonable drug use recommendations, refine the rules of use, and formulate necessary alternative strategies to provide protection against herpes virus infection, and provide guidance and reference for the rational and individualized use of clinical drugs.

Methods: All ADRs data of the drugs from the first quarter of 2004 to the fourth quarter of 2022 were obtained from the FDA Adverse Event Reporting System (FAERS) database. Duplicate reports, reports with uncertain information, and other reports containing abnormal information were excluded from the obtained data, and the data with more than 3 reports were selected. Apply the Reporting odds ratio (ROR), Proportional reporting ratio (PRR), and Bayesian confidence progressive neural network method (BCPNN) in the disproportionality analysis for data mining .

Results: All data from the first quarter of 2004 to the fourth quarter of 2022 were screened from the FAERS database, and a total of 8420, 11625, 3115, and 344 ADEs related reports were obtained for Acyclovir (ACV), Valaciclovir (VACV), Ganciclovir (GCV) and Famciclovir (FCV), respectively. For ADEs with high frequency SOC level, we found that several important signals, including ADEs of ACV, GCV and VACV, simultaneously involved the following SOC systems: kidney and urinary system diseases, nervous system disease, skin and subcutaneous tissue diseases and mental diseases; ADEs of ACV, VACV and FCV are involved in nervous system disease; The only drugs that affect injuries, poisoning, surgical complications, infections and invasions, and disorders of the blood and lymphatic systems are GCV; FAV is involved in the SOC system of heart diseases; The SOC system involved in gastrointestinal diseases is VACV. For ADEs with strongly correlated SOC levels, only ACV is involved in benign, malignant, and unknown tumors (including cysts and polyps); GCV is involved in metabolic and nutritional disorders, gastrointestinal dysfunction, and pregnancy, postpartum, and perinatal conditions; FAV is involved in skin and subcutaneous tissue diseases, heart diseases; and VACV is involved in mental diseases. All detected safety signals are confirmed using disproportionate signal reporting methods.

Conclusion: The safety reports of the nucleoside analogues "Lovir" family of drugs are variable. Analysis of the FAERS database suggests that in addition to paying attention to efficacy, drug administration should be individualized according to the specific condition and potential risk of disease.

Introduction

In recent years, herpes virus infection has become a global concern due to its significant threat to public health. Herpesvirus is an infectious agent belonging to the herpesviridae family, which can cause latent

and lytic infections in humans and various animals [1]. According to its genome organization and sequence, herpes viruses are subdivided into three subfamilies, namely α Herpesvirus, β Herpesvirus and Herpesvirus C [2]. There are currently eight known types of herpes viruses that can infect humans, known as human herpesvirus HHV, including herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), EB virus, human herpesvirus 6 (variants A and B), human herpesvirus 7, Kaposi sarcoma associated herpesvirus, and human cytomegalovirus (CMV) [3, 4]. The main feature of this virus family is its opposition to replication within the host cell and is not completely eliminated, leading to latent infection [2]. During the incubation period, the expression of viral protein is restricted, which limits the detection of the host immune system [5, 6]. According to the World Health Organization, there are currently 3.7 billion people under the age of 50 infected with herpes simplex virus type 1 and 491 million people aged 15 to 49 infected with herpes simplex virus type 2 worldwide.

Acyclovir (ACV) is an antiviral drug of guanine nucleoside analogues and is highly selective α Herpesvirus inhibitors [7] [8], due to their high selectivity and low cytotoxicity, are considered the beginning of a new era of antiviral therapy [9, 10]. Discovered in the early 1970s, it entered clinical research in 1977 and was first approved as an antiviral drug in 1982[7, 11, 12]. Subsequently, many potential anti herpesvirus compounds were synthesized, and currently, many have been approved and marketed [13-15]. They include GCV and derivatives (prodrugs) of these drugs, VACV and FCV [11, 16, 17]. These are nucleoside analogues, which are highly selective inhibitors of virus encoded DNA polymerase (DNA pol). Its antiviral effect is due to the inhibition of viral DNA synthesis in the mechanism of competitive incorporation of deoxyguanosine triphosphate (dGTP) into the DNA chain [18], thereby reducing symptoms, virus excretion and outbreak frequency, which can be used as inhibitory treatment, prophylactic treatment and risk adaptive prevention. These studies provide more novel structures for the development of ACV like antiviral drugs, which can more effectively address the shortcomings of ACV and improve antiviral ability, bringing a more open perspective for disease treatment [10] [19].

So far, there has been no targeting of people β Specific, efficient, and safe antiviral drugs for herpes virus and human herpesvirus C [17]. Currently, registered anti herpesvirus drugs can only control infections caused by HSV, VZV, and CMV [17] [20]. ACV is a first-line treatment drug for HSV-1, HSV-2, and VZV. ACV and VACV can be used as inhibitory treatments to prevent oral and genital recurrence of diseases caused by HSV-1 and HSV-2 [15, 16]. GCV inhibits replication of herpes A virus, CMV, EB virus, HHV6, 7, and 8, as well as hepatitis B virus (HBV). In clinical practice, it is the preferred drug for treating cytomegalovirus infections [21-23]. With the widespread use of the "lovir" family of drugs, drug related ADEs have also received attention. Unfortunately, little is known about the differences in the real world of the "lovir" family of drugs, and there are still many doubts about their medication choices, apart from focusing on therapeutic effects.

FAERS is a spontaneous reporting system for post market drug adverse events in the United States. It has a large amount of data, diverse data information, and is open to the public for free, including adverse events and medication errors submitted to the FDA [24]. The information reported in this database is aimed at supporting the FDA's post market safety monitoring program for drugs and therapeutic biological products. Therefore, it can be used to identify new drug related adverse events that were not previously observed in clinical trials. Currently, both domestically and internationally, adverse event signal mining methods based on FAERS big data are widely used, which can fully utilize a large amount of real-world ADEs data, monitor drug safety information after marketing, and timely discover new and serious ADEs.

To rationalize the selection of anti-herpes virus drugs in the real world, this article is based on the FAERS database and conducts signal mining on the ADEs of DNA polymerase inhibitor class anti herpetic drugs. Based on the discovery and summary of DNA polymerase inhibitor class anti herpetic drugs ADEs, it aims to analyze their causes in the real world, propose reasonable medication recommendations, refine their usage rules, and develop necessary alternative strategies, To provide protection against herpes virus infection and provide guidance and reference for the rational and individualized use of clinical drugs.

Methods

Data sources

Obtain ASCII data packages from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) for case reports from the first quarter of 2004 to the fourth quarter of 2022, which are divided into seven tables, including patient demographic information (DEMO), drug information (DRUG), reported indications for drug use (INDI), treatment start and end dates (HER), and adverse events (REAC), Adverse event outcome (OUTC) and reporting source (RPSR). Import data cleaning and signal mining into SAS9.4 software. Using the common names of acyclovir, valacyclovir, ganciclovir and famciclovir to retrieve the obtained data, and obtain the ADR report records of the first suspected drugs.

Disproportionality analysis

Exclude duplicate reports, information uncertainty reports, and other reports containing abnormal information from the standardized data, and filter out data with a number of reports [?] 3. According to the four grid table (Table 1), calculate the corresponding ROR, PRR, IC, and the corresponding 95% confidence interval (CI) lower limit, and count the number of signals to exclude reports that do not meet the threshold requirements. The larger the lower 95% CI limit of the ROR value, the stronger the signal, indicating a stronger connection between the target drug and the target ADR. In this study, in order to overcome the high false positive rate caused by estimation errors in traditional frequency methods to some extent, we chose signals that meet the standards of the three algorithms mentioned above for research. The criteria for determining the signal strength of the BCPNN method are: no signal (-): IC [?] 0; Signal weak (+): 0 ¡ IC [?] 1.5; In the signal (++): 1.5 ¡ IC [?] 3; Signal strength (+++): IC>3.

Results

Descriptive Analysis

A total of 15,942,925 reports from the first quarter of 2004 to the fourth quarter of 2022 were screened from the FAERS database, and a total of 8,420, 11,625, 3,115 and 344 reports related to ACV, VACV, GCV, and FCVADEs were obtained, respectively. In addition to GCV, the gender of patients in the report is mainly female, with ACV accounting for 47.16%, VACV accounting for 57.99%, and FCV accounting for 60.17%. The patient's age is mainly outside the range of 15-60 years old (ACV 77.61%, VACV 82.35%, GCV 77.98%, FCV 88.08%). The reporting personnel are mainly medical personnel and consumers themselves. The main route of administration, excluding unknown and lost routes, is oral administration (ACV 29.19%, VACV 74.87%, GCV 22.57%, FCV 63.37%). The reporting countries are mainly developed countries (Table 2).

Table 3 lists the high-frequency PT related to the use of ACV, VACV, GCV, and FCV in the ADEs report (top 10). Among the top 10 indications for ACV, VACV, and FCV, herpes zoster, herpes simplex, oral herpes, herpes virus infection prevention, antiviral prevention, genital herpes, and other confirmed indications were all present. Encephalitis (2.11%) is a separate indication in ACV. Facial nerve paralysis (1.16%) and necrotizing retinitis (0.87%) were the two indications of FCV. High frequency indications in GCV include cytomegalovirus infection (24.11%), cytomegalovirus viremia (4.33%), cytomegalovirus chorioretinitis (3.88%), congenital cytomegalovirus infection (3.05%), and cytomegalovirus colitis (2.09%).

Disproportionality analysis

The ADEs signals of ACV, VACV, GCV and FCV were screened, and the total number of PT reports with signals was finally divided into 18,901, 6,299, 371 and 24,606 cases by ROR, PPR and BCPNN. On this basis, taking ROR method as an example (ROR and PPR methods have

good consistency in specificity and signal detection ability, and the sensitivity of ROR method is higher), PT sorting and SOC classification are performed according to the top 10 reports (a value) of this ADEs, and the results are shown in Table 4. The high-frequency PT of ACV (Drug ineffective N=917,ROR=1.28; Pyrexia N=318,ROR=1.64; Condition aggravated N=252,ROR=1.69; Drug resistance N=213,ROR=16.15)、VACV(Drug ineffective N=1505,ROR=1.88)、GCV (Drug resistance N=317,ROR=84.25)、FCV(Drug ineffective N=40,ROR=1.76;Feeling abnormal N=11,ROR=2.41;Malaise N=15,ROR1.85) affects general diseases in the SOC system and occurs simultaneously in the four lovir drugs mentioned above, indicating that the SOC system has the highest cumulative number of reported ADEs. High frequency PT in ACV (N=957, ROR=8.88), FCV (N=16, ROR=4.55) and VACV (N=857, ROR=6.95) simultaneously involved kidney and urinary system diseases, and the PT was acute kidney injury.The high-frequency PT in ACV (N=324 ROR=3.51), FCV (N=11, ROR=3.72), and VACV (N=451, ROR=4.31) simultaneously affects mental disorders, and these PTs are all in a Confusional state. Nervous system disease (ACV: Neurotoxicity N=394,ROR=47.47 FCV: Headache N=23,ROR=2.05;Altered state of consciousness N=18,ROR=50.40; Dizziness N=18,ROR=2.01 VACV: Dizziness N=608,ROR=1.92; Altered state of consciousness N=569,ROR=46.43; Headache N=563,ROR=1.41; Dysarthria N=427,ROR=17.54), Skin and subculture tissue disorders (ACV: Rash N=330 ,ROR=1.33; Pruritus N=244,ROR1.21; Erythema N=213 ROR=1.79 FCV: Pruritus N=13,ROR=2.03 VACV: Rash N=473,ROR=1.68) are simultaneously involved in high-frequency PT of ACV, FCV and VACV. The SOC of high-frequency PT alone affecting GCV is: injury, poisoning, and surgical complications (Off label use N=394, ROR=3.59; Product use issue N=107, ROR=3.76), infection and invasion (Cytomegalovirus infection N=392, ROR=157.11; Cytomegalovirus viremia N=146, ROR=262.86; Pathogen resistance N=134, ROR=100.87) Disorders of the blood and lymphatic system (Neutropenia N=255, ROR=12.76; Leukopenia N=166, ROR=20.82; Thrombocytopenia N=129, ROR=7.26; Pancytopenia N=124, ROR=14.04 (11.76-16.77); The SOC that individually affects FCV is: heart disease (Palpitations N=10 ROR=4.75); The SOC that affects VACV alone is gastrointestinal disease (Nausea N=690, ROR=1.39; Vomiting N=466, ROR=1.59).

Then, PT ranking was performed based on the top 10 bits of signal strength ROR (95% CI) for the three algorithms that simultaneously satisfy the ROR, PPR, and BCPNN methods, in order to identify PT with high correlation (i.e. strong signal) (Table 5).Among them, only ACV is affected by PT, which affects Neoplams benignant, malignant, and unspecified (including cycles and polymers) (Cerebellar haemangioma N=3,ROR=246.03); GCV refers to metabolic and nutritional disorders(Cell-mediated cytotoxicity N=255,ROR=740.01), gastrointestinal dysfunction (Oesophagopleural fistula N=146,ROR=568.21, pregnancy, postpartum, and perinatal conditions(Leukopenia neonatal N=129,ROR=357.40); FCV refers to skin and subcutaneous tissue diseases(Cutaneous vasculitis N=8,ROR=104.81), as well as heart diseases(Bundle branch block left N=3,ROR=35.83); The condition that affects psychiatric disorders (Cotard's syndrome N=16,ROR=344.43;Imperception N=4, ROR=196.26) is VACV. The corresponding PT names and ROR are shown in Tables 4 and 5. Cytomegalo viremia (N=146, ROR=262.86) is present in both high-frequency ADEs of GCV and its strongly correlated ADEs. Changes in consciousness state (N=18, ROR=50.40) occur both in high-frequency ADEs of FCV and in its strongly correlated ADEs.

SOC system distribution

According to MedDRA's SOC classification and sorting of all signal PTs, there are 11, 9, 6, and 11 SOC systems with signals for ACV, GCV, FCV, and VACV, covering a total of 14 SOC systems. ADEs of the four "lovir" families can be involved in two SOC systems: congenital, familial and hereditary diseases, kidney and urinary system diseases; The cumulative number of ADEs involved in the SOC system of nervous system disease is the largest, but GCV drug ADEs do not involve this system; The only drugs that affect the SOC system (N=1049, ROR=1.08) for injuries, poisoning, and surgical complications are GCV; The only drugs that affect the SOC system (N=218, ROR=1.26) during pregnancy, postpartum, and perinatal periods are VACV (Table 6, Figure 1).

Discussion

According to Grand View Research, the global antiviral drug market size in 2018 was approximately $56.4 billion, with a domestic market value of approximately $20 billion. The main type of anti-herpesvirus drugs is "lovir" nucleoside analogues. In recent years, the overall market size of hospital anti herpesvirus drugs has remained stable, with a corresponding market size of approximately 2 billion yuan for drugs on sale. The widespread use of antiviral drugs such as "lovir" DNA polymerase suggests that it is necessary to refine their usage rules and develop necessary alternative strategies to provide protection against herpes virus infection or remove latent viruses from infected host cells.

Tables 4 and 5 respectively reflect the cross or parallel SOC involvement in ADEs of ACV, GCV, FCV, and VACV in terms of high incidence and strong correlation. The SOC system, which involves damage, poisoning and surgical complications, infection and invasion, as well as blood and lymphatic system disorders, only occurs in the top 10 ADEs with an incidence rate after taking GCV. Its toxicity can cause bone marrow suppression, namely neutropenia, thrombocytopenia, and leukopenia, which can lead to dose changes or cessation of treatment [25-28]. CMV is a major complication of immunocompromised patients, especially in hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT) patients [29]. GCV is the main treatment method for preventing and treating CMV in SOT recipients [30]. However, cytomegalovirus infection and cytomegalovirus emia exhibit high incidence in the real world after taking GCV, indicating that GCV may also bring more serious results during the treatment process. But we cannot elucidate the causal relationship between them, and can only prompt doctors to continuously monitor the patient's condition during the medication process. Existing data show that the oral treatment of valganciclovir is not inferior to the intravenous treatment of GCV, and its bioavailability is about 60%, almost 10 times that of oral GCV [29]. However, this article does not evaluate the safety of Valganciclovir in the prevention and treatment of CMV in SOT recipients. ADEs exhibit a high incidence of cardiovascular system involvement in the real world, only after taking FCV, and there are currently no reports on their adverse reactions to the cardiovascular system. It is strongly suggested that patients with or at risk of cardiovascular disease should carefully choose FCV and switch to reasonable alternative drugs. ADEs involving gastrointestinal diseases are most common in VACV, which is consistent with current reports of side effects of this drug [31].

Among the top 10 ADEs with strong correlation, ACV was the only one involved in the SOC system of benign, malignant and unknown tumors (including cysts and polyps). The one associated with PT was Cerebellar haemangioma, although it has not been reported definitively with ACV. However, current studies suggest that ACV may be a potential therapeutic supplement for glioblastoma and the mechanism of ACV administration on NCI-H1975 non-small cell lung cancer: mitochondria may be the initial target and/or site of ACV cytotoxicity in cancer cells [32, 33]. Meanwhile, we found one case of ACV associated with glioma and one case of ACV associated with non-small cell carcinoma reported in FAERS. GCV involves metabolic and nutritional disorders, gastrointestinal dysfunction [34] and pregnancy, puerperium and perinatal conditions; FCV involved skin and subcutaneous tissue diseases and heart diseases. VACV is involved in mental disorders [35].The top 10 PT in ACV, GCV and VACV are also involved in the following SOC systems: kidney and urinary system diseases, nervous system diseases, skin and subcutaneous tissue diseases, and psychiatric diseases. At this time, FCV can be used as an alternative drug for HHV-infected patients with these primary diseases.

SOC system general diseases and administration site conditions after taking ACV; Infection and disturbance after taking GCV; General diseases and administration site conditions, nervous system disease, heart diseases, skin and subcutaneous tissue diseases after taking FCV; After taking VACV, mental disease, nervous system disease, general disease and administration site conditions not only express a high incidence rate, but also express a strong correlation. These signals strongly suggest that herpes virus infected patients with corresponding primary diseases should carefully choose corresponding drugs and use other alternative drugs.

Of course, this study also has limitations. Firstly, due to the spontaneity of FAERS reporting, there are some inherent limitations that result in poor data quality, including missing information, incorrect and misclassified information, over reporting, underreporting, and selective reporting. Secondly, FAERS is limited

by its nature and cannot draw precise conclusions about the prevalence, incidence, and causal relationship of adverse drug reactions, and there may be significant deviations in reporting based on national concerns or regional awareness [36]. Third, the lack of denominators for drug users limits our ability to estimate the true incidence rate of specific ADEs [24]. However, despite these limitations, data mining in FAERS database can still be regarded as Exploratory research to detect signals of unknown or unexpected ADEs, rather than verification or hypothesis testing of any causal relationship. The safety signals identified from FAERS data should be further investigated in clinical practice [37, 38].

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Conception or design of the work: CXG, XMD and XQ; Acquisition,analysis,or interpretation of data: CXG,XMD and ZZ; Management and checking of all data: CXG, XMD, XQ, JZ, LJM and ZZ; Drafting the article: CXG. All authors critically reviewed the manuscript and interpreted the results. The final manuscript was read, checked and approved by all authors.

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Data availability statement

The data underlying this article are available in the FDA adverse events reporting system (FAERS). The datasets were derived from sources in the public domain: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Ethics statement

The Medical Research Ethics Review Committee of the First Affiliated Hospital of Chongqing Medical University decided to waive the original ethic application procedure, based on the reason that the open public database used in this project.

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