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Acute Kidney Injury and Neuropsychiatric Reactions with Anti-Herpesvirus Drugs: Analysis of Spontaneously Reported Adverse Events

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Abstract

Objectives: Acute kidney injury and neuropsychiatric reactions have been reported with intravenous (IV) acyclovir, oral acyclovir, valacyclovir and famciclovir. The aims of this study were to explore acute kidney injury and neuropsychiatric reactions signals with these anti-herpesvirus drugs by using the public release version of the U.S. FDA adverse event reporting system (AERS) database from 2004 to second quarter 2012. Methods: Medical Dictionary for Regulatory Activities (MedDRA) terms were mapped to predefined categories of acute kidney injury and neuropsychiatric reactions. Disproportionality analysis was used to calculate the reporting odd ratio (ROR) and corresponding 95% confidence intervals (CI) for adverse event categories, and stratified by indication. Results: IV acyclovir, oral acyclovir, valacyclovir and famciclovir were identified as the suspect medications in 8,037 reports in the FDA AERS database. Neuropsychiatric reactions were the most frequently reported ADRs. We identified a signal for acute kidney injury with IV acyclovir, oral acyclovir, valacyclovir and famciclovir (ROR 17.68, ROR 3.09, ROR 3.97, ROR 2.93, respectively), and a signal for neuropsychiatric reactions with famciclovir (ROR 2.93). Acute kidney injury and neuropsychiatric reactions were more frequently reported in patients with varicella zoster virus (VZV) infection than in those with herpes simplex virus (HSV) infection. Conclusion: The results of the present paper confirmed the higher frequency of acute kidney injury and neuropsychiatric reactions with IV acyclovir, oral acyclovir, valacyclovir and famciclovir, although more data were needed. Clinicians should stress this risk in the shared decision-making process.

Keywords

Acute Kidney Injury, Neuropsychiatric Reactions, Acyclovir, Valacyclovir, Famciclovir, Postmarketing Safety Surveillance

1. Introduction

Acyclovir (ACV), valacyclovir (VACV, the L-valyl ester of ACV, metabolized in vivo to acyclovir), and famciclovir (FCV) are prescribed to treat infections caused by herpes simplex virus (HSV) and varicella zoster virus (VZV). Clinical trials have shown that these drugs are effective in reducing pain, shortening the healing time, and limiting the spread of virus and the formation of new lesions [1-3]. Accordingly, these antivirals have been used worldwide. The current standard of therapy is oral medication. Acyclovir is the only antiviral medication available for intravenous administration.

All of the medications are generally safe in most circumstances but may occasionally have mild side effects such as nausea, vomiting, diarrhea or headache. Other side effects such as increasing creatinine and acute kidney injury (AKI) have been reported in dehydrated patients or in cases where acyclovir has been given too fast intravenously (IV). However, there are several case reports and observational studies that describe AKI events with oral preparations of acyclovir, valacyclovir or famciclovir [4-6], and in rare cases neuropsychiatric reactions such as dizziness, hallucinations, confusion and neurotoxicity induced by these medications have developed [7, 8].

The availability of real-world data from FDA's Adverse

Event Reporting System (AERS) provides a rich opportunity to detect novel and rare post-marketed adverse drug reactions. Despite limitations of the AERS, it may provide timely information with fewer costs [9, 10]. In this study, we compared reporting odds ratios (ROR) as a signal of risk for AKI and neuropsychiatric reactions associated with acyclovir (oral and IV route), valacyclovir and famcyclovir, using data from FDA AERS database from January 2004 to June 2012.

2. Methods

The AERS contains reports of adverse drug events spontaneously submitted by physicians, pharmacists, other health care professionals, manufacturers, and consumers from the US and other countries. From the first quarter (Q1) of 2004 through the second quarter (Q2) of 2012, tables including demographic information—DEMO file; drug information—DRUG file; adverse events coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology—REAC file; and indications for use (diagnoses)—INDI file for the reported drugs were considered. A unique ISR number allows linking all information from different tables and a unique DRUG_SEQ number identifies a drug for an ISR. As the AERS database has some duplicate reports [11], we removed the older ones from duplicate reports by sorting case identification numbers.

Definition of acute kidney injury (AKI) and neuropsychiatric reactions were as follows:

Definition of AKI events: The Standard MedDRA Queries (SMQs) are groupings of PT terms, which relate to defined medical conditions or areas of interest [12]. In this study, version Beta 3.1 of MedDRA was used. The AKI SMQ [20000003] consists of 43 PT terms; 17 AKI PT terms (e.g., renal failure acute, anuria) and 26 AKI laboratory PT terms (e.g., blood creatinine increased, blood urea increased). 43 PT terms found in the AKI SMQ were defined as AKI complications. (Table 5)

Definition of Neuropsychiatric reactions: Before the analysis, we searched the publications of neuropsychiatric reactions associated with acyclovir, valacyclovir and famciclovir in MEDLINE, and mapped adverse event terms from MedDRA coded as 10029205 (Nervous system disorders) and 10037175 (psychiatric disorders) that we thought represented previously reported their neuropsychiatric reactions. (Table 5)

The association between anti-herpesvirus drugs and AKI or neuropsychiatric reactions was analyzed using the reporting odds ratio (ROR) and corresponding 95% CI data mining algorithm. ROR values for an interested drug denote the ratio of the observed to expected number of reported interested events compared with all other drugs in the dataset during the analysis period [13]. The ROR was calculated as (a:c)/(b:d) (Table 1).

ROR values <1 indicate no exposure-event associations; estimates>1 depict exposure-event safety signals. From the regulatory science perspective, safety signals are considered significant when the ROR estimates and the lower limit of the corresponding 95% CI are ≥ 2 [14].

Table 1. *Two by two table used for the calculation of the reporting odds ratios.*

Exposure	Interested events	Other events
Anti-herpesvirus drugs	a	b
Other drugs	c	d

We included all adverse events for which the reporter identified acyclovir (coded as 'oral 'or 'intravenous'), valacyclovir and famciclovir as suspect (coded as 'PS' or 'SS'). Because these anti-herpesvirus drugs have a number of indications—VZV (e.g., herpes zoster, herpes zoster oticus); HSV (e.g., herpes simplex, oral herpes, genital herpes) and antiviral prophylaxis et al. As the condition being treated could be related to reported events, we stratified our analysis by condition. We evaluated reports for VZV group and HSV group separately.

Statistical analysis was performed using R version 2.15.2 software.

3. Results

After removing the duplicate report, we selected 8,037 reports related to the use of IV acyclovir, oral acyclovir, valacyclovir and famciclovir as suspect medications. The number of patients stratified for indications are shown in Table 2. Of overall reports, 1,174 (14.6%) involved AKI, and 2,790 (34.7%) involved neuropsychiatric reactions. Neuropsychiatric reactions were the most frequently reported ADRs and AKI ranked the second.

Table 2. *Distribution of FDA AERS reports associated with IV acyclovir, oral acyclovir, valacyclovir and famciclovir stratified by indications.*

indications	IV acyclovir	Oral acyclovir	Valacyclovir	Famciclovir
	[n=960]	[n=979]	[n=5957]	[n=349]
VZV	248 (25.8%)	227 (23.2%)	1574 (26.4%)	176 (50.4%)
HSV	153 (15.9%)	220 (22.5%)	1152 (19.3%)	61 (17.5%)
other indications	559 (58.4%)	532 (54.3%)	3231 (54.2%)	112 (32.1%)

Abbreviations: IV, intravenous; VZV, varicella zoster virus; HSV, herpes simplex virus

The unmapped MedDRA terms in relation to AKI with relatively high frequency were renal failure acute, blood creatinine increased and blood urea increased. IV acyclovir showed strongest safety signals for the three preferred terms. It also revealed that the signals were stronger with valacyclovir than with oral acyclovir use. (Table 3)

For the mapped events of AKI, disproportionality analysis found significant ROR signals for IV acyclovir (ROR 17.68, 95%CI 15.52–20.13), oral acyclovir (ROR 3.09, 95%CI 2.51–3.81), valacyclovir (ROR 3.97, 95%CI 3.68–4.30) and famciclovir (ROR 2.93, 95%CI 2.05–4.20) (Figure 1). IV acyclovir showed a strongest safety signal in relation to AKI

events.

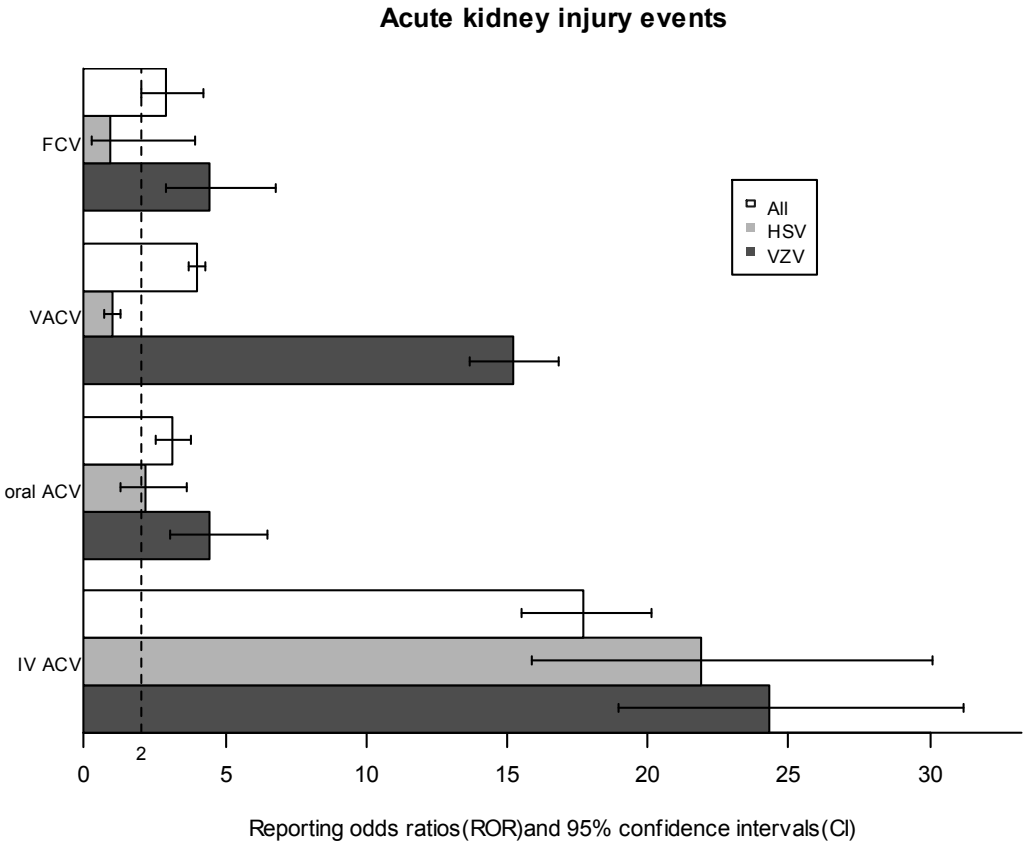

Figure 1. *ROR and 95% CI for AKI events with anti-herpesvirus drugs stratified by indications.*

Abbreviations: IV, intravenous; ACV, acyclovir; VACV, valacyclovir; FAC, famciclovir; VZV, varicella zoster virus; HSV, herpes simplex virus ;AKI, acute kidney injury.

Table 3. *ROR of specific acute kidney injury terms frequently reported with anti-herpesvirus drugs.*

Specific AKI terms	N	ROR	95% two-sided CI
Renal failure acute			
IV acyclovir	225	30.34	26.12-35.24
Oral acyclovir	40	4.20	3.06-5.76
Valacyclovir	392	7.01	6.32-7.77
Famciclovir	8	2.31	1.15-4.65
Blood creatinine increased			
IV acyclovir	106	21.6	17.64-26.44
Oral acyclovir	18	3.24	2.03-5.17
Valacyclovir	257	7.90	6.97-8.96
Famciclovir	9	4.58	2.36-8.88
Blood urea increased			
IV acyclovir	46	20.83	15.48-28.04
Oral acyclovir	12	5.11	2.89-9.04
Valacyclovir	191	13.97	12.07-16.16
Famciclovir	9	10.90	5.62-21.14

Abbreviations: ROR, reporting odds ratios; CI, confidence intervals; IV, intravenous; AKI, acute kidney injury

The signal for AKI was not consistent for VZV and HSV groups. For valacyclovir, AKI events appeared to have significantly stronger signals in the VZV group (ROR 15.21, 95% CI 13.71–16.87) compared with the HSV group (ROR 0.96, 95% CI 0.69–1.32). The data mining algorithm did not show a statistically significant result for the HSV group.

Similar to valacyclovir, exposure to oral acyclovir and famciclovir was associated with higher than expected reporting of AKI events for VZV group (ROR 4.44, 95% CI 3.04–6.49; ROR 4.44, 95% CI 2.88–6.82, respectively), while the data mining algorithm did not show a statistically significant result for the HSV group (ROR 2.20, 95% CI 1.32–3.67; ROR 0.95, 95% CI 0.23–3.90, respectively).

The patients in VZV group with AKI events were 72.1±16.7 years old (mean±S.D.) and females accounted for 63.6%. On the other hand, the patients in HSV group with AKI events were 54.9±23.4 years old and females were 53.4%. It revealed that compared with HSV group, the association between AKI and the anti-herpesvirus drugs in VZV group was more frequently reported in old female patients.

The most common neuropsychiatric reactions with the anti-herpesvirus drugs were dizziness, headache, depressed level of consciousness, confusional state. Some neuropsychiatric terms (e.g. dizziness, headache) appeared to have weak signals (not shown in Table 4). Several unmapped neuropsychiatric terms with relative strong safety signals are shown in Table 4. The signals for neurotoxicity were significantly stronger with IV cyclovir (ROR 59.78) or oral cyclovir (ROR 31.74) than with valacyclovir (ROR 6.42) or famciclovir use (no reports existed in the database). The

signals for ataxia were significantly stronger with oral cyclovir (ROR 23.88) than with valacyclovir (ROR 3.07), famciclovir (ROR 9.87) or IV cyclovir use (only one reports existed in the database). Depressed level of consciousness, altered state of consciousness, encephalopathy and dysarthria were more frequently reported with valacyclovir or IV acyclovir and less with oral acyclovir or famciclovir.

Table 4. *ROR of specific neuropsychiatric terms frequently reported with anti-herpesvirus drugs.*

Specific neuropsychiatric terms	N	ROR	95% two-sided CI
Depressed level of consciousness			
IV acyclovir	46	13.50	10.03-18.16
Oral acyclovir	27	7.59	5.18-11.14
Valacyclovir	231	10.98	9.62-12.54
Famciclovir	7	5.47	2.59-11.56
Confusional state			
IV acyclovir	68	6.55	5.12-8.38
Oral acyclovir	47	4.33	3.23-5.81
Valacyclovir	185	2.76	2.38-3.20
Famciclovir	21	5.50	3.53-8.54
Altered state of consciousness			
IV acyclovir	31	30.36	21.19-43.49
Oral acyclovir	16	15.05	9.17-24.69
Valacyclovir	211	35.28	30.62-40.66
Famciclovir	10	26.67	14.21-50.07
Encephalopathy			
IV acyclovir	45	28.92	21.41-39.06
Oral acyclovir	14	8.48	5.00-14.38
Valacyclovir	195	20.47	17.70-23.68
Famciclovir	4	6.76	2.52-18.13
Dysarthria			
IV acyclovir	35	12.05	8.60-16.90
Oral acyclovir	26	8.68	5.88-12.83
Valacyclovir	251	14.32	12.60-16.28
Famciclovir	5	4.62	1.91-11.17
Hallucination			
IV acyclovir	36	7.75	5.55-10.82
Oral acyclovir	33	6.94	4.90-9.82
Valacyclovir	189	6.58	5.68-7.61
Famciclovir	13	7.69	4.42-13.38
Hallucination, visual			
IV acyclovir	18	12.54	7.86-20.00
Oral acyclovir	21	14.39	9.33-22.20
Valacyclovir	72	8.11	6.42-10.25
Famciclovir	0	N. A.	N. A.
Neurotoxicity			
IV acyclovir	36	59.78	42.73-83.65
Oral acyclovir	20	31.74	20.34-49.53
Valacyclovir	25	6.42	4.32-9.53
Famciclovir	0	N. A.	N. A.
Ataxia			
IV acyclovir	1	N. A.	N. A.
Oral acyclovir	20	23.88	15.31-37.25
Valacyclovir	16	3.07	1.88-5.03
Famciclovir	3	9.87	3.16-30.76

Abbreviations: ROR,reporting odds ratios; CI, confidence intervals; IV, intravenous; N. A., not available.

For the mapped neuropsychiatric reactions, disproportionality analysis found significant ROR signals only for famciclovir (ROR 2.93, 95%CI 2.37-3.62), while the ROR values for IV acyclovir (ROR 2.10, 95%CI 1.85-2.40), oral acyclovir (ROR 1.86, 95%CI 1.63-2.12) and valacyclovir (ROR 1.82, 95%CI 1.72-1.92) failed to reach the threshold as safety signals. (Figure 2)

Neuropsychiatric reactions associated with IV acyclovir, oral acyclovir, valacyclovir and famciclovir showed stronger signals in the VZV group (ROR 4.13, 95% CI 3.22–5.31; ROR 4.81, 95% CI 3.69–6.26; ROR 6.48, 95% CI 5.85–7.19; ROR 4.66, 95% CI 3.46–6.28, respectively) compared with the HSV group (ROR 1.63, 95% CI 1.16–2.29; ROR 1.21, 95% CI 0.89–1.64; ROR 1.22, 95% CI 1.07–1.40; ROR 1.56, 95% CI 0.91–2.29, respectively). The ROR signals were not consistent for VZV and HSV groups, and valacyclovir ranked first in showing a safety signal for VZV group in the four anti-herpes agents.

The patients with neuropsychiatric events in VZV group were 70.5±15.5 years old (mean±S.D.) and females accounted for 55.8%. On the other hand, the patients in HSV group with neuropsychiatric events were 48.9±19.8 years old and females were 69.3%. It revealed that neuropsychiatric events reported in VZV group were more often elderly patients (>=65 years) or male patients ($p < 0.001$) compared to those in HSV group.

4. Discussion

We used the public release version of the FDA AERS database to explore potentially serious adverse events i.e. acute kidney injury (AKI) and neuropsychiatric reactions with acyclovir (IV and oral route of administration), valacyclovir and famciclovir. Although our analysis based on AERS data does not demonstrate causal relationships [15], it helps to focus on more narrowly defined groups of adverse events in a systematic way. In part, our analysis confirms the relative rate of adverse events previously reported in the literature by using the AERS methodology.

We stratified our analysis by VZV and HSV condition. We evaluated reports for VZV and HSV conditions separately, and we found indication-related differences for both AKI and neuropsychiatric reactions. AKI and neuropsychiatric reactions were more frequently reported in patients with VZV than with HSE, and the results were consistent with the findings of Anders Helldén [16] who reported that neuropsychiatric reactions were more common in patients with herpes zoster. The signals for AKI and neuropsychiatric reactions were both specific to patients with varicella zoster virus (VZV) infection, and this suggested potential confounding by indication, although the reasons remain unknown.

AKI induced by intravenous (IV) acyclovir is well known. The proposed mechanism of injury is precipitation and crystallization of the drug in the renal tubules, resulting in obstruction and possible cellular necrosis [17, 18]. Our analysis of FDA AERS data indicated that AKI ADRs were reported at least 15 times more often with IV acyclovir than would be expected. Previous meta-analysis and observational studies have also reported an increased risk of AKI with oral acyclovir, valacyclovir and famciclovir. In the analysis we identified an increased risk of AKI for all the oral anti-herpesvirus drugs (the lower limit of the 95% CI

exceeded 2.0). According to a recent retrospective population-based cohort study [6], oral acyclovir and valacyclovir use were not associated with a higher risk of AKI compared to famciclovir. Our results were consistent with the study although we found a significantly strong signal for AKI with valacyclovir in VZV group.

Evidence from randomized, controlled trials has suggested the potential for increased risk of neuropsychiatric reactions with anti-herpesvirus medications. Our analysis indicated that neuropsychiatric ADRs were most commonly reported representing 34.7% of overall reactions with the anti-herpesvirus drugs. Although we identified an increased risk of neuropsychiatric reactions with famciclovir (ROR 2.93), the relative rate of reporting of neuropsychiatric reactions did not exceed our signal threshold with IV acyclovir (ROR 2.10), oral acyclovir (ROR 1.86)or valacyclovir (ROR 1.82). In this analysis, we mapped 66 MedDRA terms representing neuropsychiatric reactions to a single term (Table 5). The practice of combining terms generally might be problematic because the relative reporting rate might decline if the wrong terms are combined [15]. To explore the potential for this, we evaluated ROR values for individual terms mapped to neuropsychiatric reactions. The analysis revealed significantly strong signals for depressed level of consciousness, altered state of consciousness, encephalopathy and hallucination with all these anti-herpesvirus drugs.

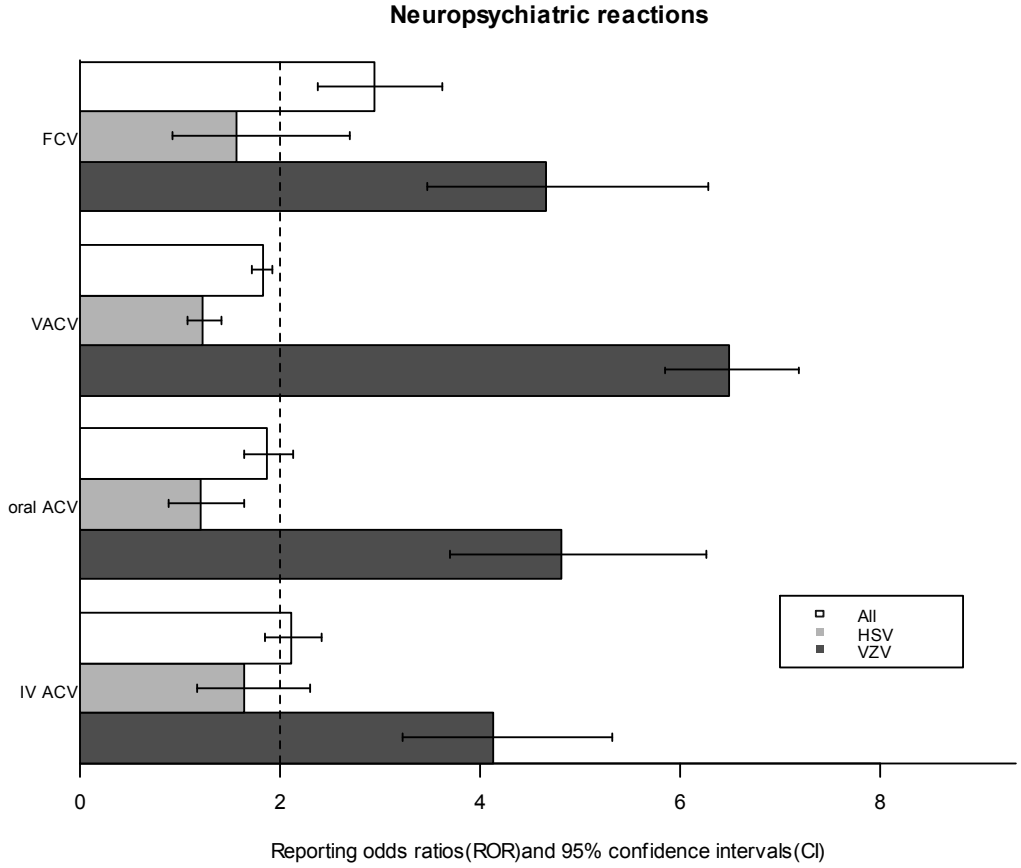

Figure 2. *ROR and 95% CI for neuropsychiatric events with anti-herpesvirus drugs stratified by indications.*

Abbreviations: IV, intravenous; ACV, acyclovir; VACV, valacyclovir; FAC, famciclovir; VZV, varicella zoster virus; HSV, herpes simplex virus

Our analysis provided additional, up-to-date evidence supporting the risk of AKI and neuropsychiatric reactions with anti-herpesvirus drugs, demonstrating relatively strong signal scores for blood creatinine increased, blood urea increased, as well as depressed level of consciousness, altered state of consciousness, encephalopathy and hallucination. In addition, we were able to confirm the increased risk of neuropsychiatric reactions in patients with VZV infections documented by Anders Helldén [16]. In our analysis, the relative reporting rate of neuropsychiatric reactions with valacyclovir in VAV group was nearly 6.5 times greater than the expected reporting rate.

Disproportionality analysis is limited in that it only provides the relative rate of reporting of adverse events in the post-marketing setting rather than the incidence of adverse events. Disproportionality analyses can be used as a method to explore signals, as we have done here, but they should not be viewed as establishing causal relationships. Future studies are needed to validate the hypotheses generated by disproportionality analyses by reviewing individual cases behind signals or using causal study designs (e.g., case-control study) to test hypotheses [19–22]. In addition, differences in the rate of reporting for specific drugs or events are known to be influenced by product age, targeted surveillance, selective prescribing, stimulated reporting or source of reporting (e.g., U.S. vs foreign reports). These differences might have influenced the results of our analysis [15].

One strong point of our analysis compared with other studies that we have used the timeliness of FDA AERS data. We found the relative rate of reporting of AKI and neuropsychiatric terms with the anti-herpesvirus drugs such as blood creatinine increased, blood urea increased, depressed level of consciousness, altered state of consciousness, encephalopathy and hallucination to be consistent with previous analyses. We also found AKI and neuropsychiatric reactions are more common in patients with VZV infections. However, this potential risk needs to be studied further with well-conducted epidemiologic studies. In the meantime, clinicians should stress this risk in the shared decision-making process.

Supplementary

Table 5. *Mapping of MedDRA terms to events of interest.*

Event ategory	Events of interest (MedDRA preferred terms)
Acute kidney injury	Acute phosphate nephropathy, acute prerenal failure, anuria, azotaemia, continuous haemodiafiltration, dialysis, haemodialysis, neonatal anuria, nephropathy toxic, oliguria, peritoneal dialysis, prerenal failure, renal failure, renal failure acute, renal failure neonatal, renal impairment, renal impairment neonatal, albuminuria, blood creatinine abnormal, blood creatinine increased, blood urea abnormal, blood urea increased, blood urea nitrogen/creatinine ratio increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, creatinine urine abnormal, creatinine urine decreased, crystal nephropathy, glomerular filtration rate abnormal, glomerular filtration rate decreased, hypercreatininaemia, nephritic syndrome, nephritis, oedema due to renal disease, protein urine present, proteinuria, renal function test abnormal, renal transplant, renal tubular disorder, renal tubular necrosis, tubulointerstitial nephritis, urea renal clearance decreased, urine output decreased
Neuropsychiatric reactions	Dizziness, headache, depressed level of consciousness, confusional state, dysarthria, hallucination, encephalopathy, altered state of consciousness, somnolence, disorientation, nervous system disorder, delirium, speech disorder, gait disturbance, tremor, restlessness, hallucination, visual, convulsion, agitation, insomnia, abnormal behavior, paraesthesia, loss of consciousness, dyslalia, muscular weakness, neurotoxicity, vision blurred, dyskinesia, coma, anxiety, hypoaesthesia, aphasia, depression, incoherent, psychiatric symptom, abasia, burning sensation, coordination abnormal, dysstasia, aggression, delusion, mental status changes, vertigo, lethargy, balance disorder, myoclonus, eating disorder, ataxia, hallucination, auditory, psychotic disorder, dysgeusia, syncope, toxic encephalopathy, memory impairment, mental disorder, amnesia, irritability, nightmare, mental impairment, hallucinations, mixed, movement disorder, partial seizures, nystagmus, hypersomnia, dysphonia, neurological symptom

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