Association between Concomitant Use of Acyclovir or Valacyclovir with NSAIDs and an Increased Risk of Acute Kidney Injury: Data Mining of FDA Adverse Event Reporting System

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are likely to be used concomitantly with acyclovir or valacyclovir in clinical practice, but the study on the safety of such combinations was seldom reported. The objective of the study was to investigate reports of acute kidney injury (AKI) events associated with the concomitant use of oral acyclovir or valacyclovir with an NSAID by using the United States Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database between January 2004 and June 2012. The frequency of AKI events in patients while simultaneously taking either acyclovir or valacyclovir and an NSAID was compared using the Chi-square test. The effect of concomitant use of acyclovir or valacyclovir and individual NSAIDs on AKI was analyzed by the reporting odds ratio (ROR). The results showed that AKI was reported as the adverse event in 8.6% of the 10923 patients taking valacyclovir compared with 8.7% of the 2556 patients taking acyclovir (p =NS). However, AKI was significantly more frequently reported in patients simultaneously taking valacyclovir and an NSAID (19.4%) than in patients simultaneously taking acyclovir and an NSAID (10.5%) (p <0.01). The results also suggested that increased risk of AKI was likely associated with the concomitant use of valacyclovir and some NSAIDs such as loxoprofen, diclofenac, etodolac, ketorolac, piroxicam or lornoxicam. The case series from the AERS indicated that compared with acyclovir, valacyclovir is more likely to be affected by NSAIDs, and the concomitant use of valacyclovir with some NSAIDs might be associated with increased risk of AKI. The drug interactions with this specific combination of medications are worth exploring further.

Key words acyclovir; valacyclovir; nonsteroidal anti-inflammatory drug (NSAID); acute kidney injury; data mining; FDA Adverse Event Reporting System (FAERS)

Acyclovir and valacyclovir (the L-valyl ester of acyclovir, converted into acyclovir in vivo) are widely used to treat herpes simplex virus (HSV) and herpes zoster virus (HZV) infections. Clinical trials have shown that acyclovir and valacyclovir can lessen the symptoms of the infection and reduce the formation of new lesions.1,2 Whereas nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of acute or chronic conditions where pain and inflammation are present. Due to the current use profile of NSAIDs, either as prescription or OTC drugs, NSAIDs are likely to be used concomitantly with acyclovir or valacyclovir in clinical practice such as rheumatoid arthritis and herpes zoster virus infection, while the study on the safety of such combinations was hardly reported.

It is known that both oral acyclovir (or valacyclovir) and NSAIDs have the potential to affect kidney function, and in rare instances these drugs may cause more severe renal conditions such as acute kidney injury (AKI).3,4 Our previous research has revealed that the concomitant use of loxoprofen (a non-selective NSAID) and valacyclovir might lead to an increase in reports of AKI.5 However, it is not known whether the combination therapy of other NSAIDs with acyclovir or valacyclovir is associated with increased risk of AKI, and we also need to know the differences of drug interactions between acyclovir and valacyclovir.

In the present study, we examined the United States Food and Drug Administration (FDA) database to determine the frequency of AKI adverse events in patients taking both acyclovir or valacyclovir and an NSAID, and the differences of drug interactions between acyclovir and valacyclovir.

METHODS

We used the public release of the FDA’s Adverse Event Reporting System (AERS) database6 which covers the period from January 2004 to June 2012. The AERS contains reports of adverse drug events spontaneously submitted by physicians, pharmacists, other health care professionals, manufacturers, and consumers from the U.S. 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 and adverse events coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology—REAC file for the reported drugs were considered. A unique ISR number allows linking all information from different tables. As the AERS database has some duplicate reports, we removed the older ones from duplicate reports by sorting case identification numbers.7

All reports containing oral acyclovir or valacyclovir were included in the analysis, no matter whether the drug was reported as suspect (“Primary Suspect Drug (PS)" or “Secondary Suspect Drug (SS)”, interacting (“I”) or concomitant (“C”) in causing the adverse event. We excluded intravenous acyclovir because our focus was on outpatient-dispensed

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preparations.

The number of patients with adverse events while simultaneously taking either acyclovir or valacyclovir and an NSAID was determined. We selected the most widely used NSAIDs as follows: propionic acid derivatives (ibuprofen, naproxen, Ketoprofen, flurbiprofen, loxoprofen, oxaprozin), acetic acid derivatives (diclofenac, indomethacin, ketorolac, sulindac, etodolac, nabumetone and tolmetin) enolic acid derivatives i.e. Oxicams (meloxicam, piroxicam, lornoxicam and tenoxicam) and selective Cyclooxygenase (COX)-2 inhibitors i.e. Coxibs (cecloxic and rofecoxic). Aspirin was excluded in this study because many people take aspirin for disease prevention.

The Standard MedDRA Queries (SMQs) are groupings of PT terms, which relate to defined medical conditions or areas of interest.8) In this study, acute kidney injury (AKI) cases were represented by 17 narrow Preferred Terms (PTs) in the SMQ [20000003]: “Acute phosphate nephropathy,” “Acute prerenal failure,” “Anuria,” “Azotaemia,” “Continuous haemodialfiltration,” “Dialysis,” “Haemodialysis,” “Neonatal anuria,” “Nephropathy toxic,” “Oliguria,” “Peritoneal dialysis,” “Pre-renal failure,” “Renal failure,” “Renal failure acute,” “Renal failure neonatal,” “Renal impairment” and “Renal impairment neonatal.” Non-cases were defined as reports that did not contain such PTs.

The effect of concomitant use of acyclovir or valacyclovir and individual NSAIDs on AKI was analyzed by the reporting odds ratio (ROR) which was based of case/non-case methodology.9,10) ROR estimates >1 depict exposure-event safety signals and was considered reliable if the number of cases was ≥3.

Frequencies for categorical variables were compared using the Chi-square test, and a p value <0.05 was considered statistically significant. The statistical analysis was performed using R version 2.15.2 software.

RESULTS

From January 2004 to June 2012, AERS included almost 3 million case reports. A total of 2556 patients were reported to have had an adverse event while taking acyclovir and a total of 10923 patients were reported to have had an adverse event while taking valacyclovir. AKI was reported as the adverse event in 8.7% of the 2556 patients taking acyclovir compared with 8.6% of the 10923 patients taking valacyclovir (p=NS).

The number of patients with adverse events while simultaneously taking either acyclovir or valacyclovir and an NSAID was shown in Table 1. Coadministration of an NSAID was found concomitant use of certain NSAIDs (such as loxoprofen, diclofenac etodolac, ketorolac, piroxicam or lornoxicam) and valacyclovir might be suggestive of drug interactions. As shown in Table 4, patients who used valacyclovir and those individual NSAIDs concomitantly had significantly higher RORs for the risk of AKI than patients who used the NSAID or valacyclovir alone. No interaction was observed between use of valacyclovir and other NSAIDs (data was not shown).

Table 1. Percentage of Patients with an Adverse Event While Taking Either Acyclovir or Valacyclovir Who Were Also Taking an NSAID

| Exposure                               | Acyclovir (n=2556) | Valacyclovir (n=10923) | p Value |
|----------------------------------------|--------------------|------------------------|---------|
| Patients taking NSAIDs concomitantly*  | 200                | 1155                   | <0.001  |
| Propionic acid derivatives              | 128                | 705                    | 0.006   |
| Acetic acid derivatives                 | 45                 | 250                    | 0.100   |
| Enolic acid derivatives (Oxicams)       | 11                 | 91                     | 0.034   |
| Selective COX-2 inhibitors (Coxibs)     | 33                 | 227                    | 0.009   |

*Numbers add up to greater than the total taking any NSAID because some patients were taking more than one NSAID.
Table 2. Comparison of Patients Who Had an Adverse Event While Taking Either Acyclovir or Valacyclovir in Combination with an NSAID

|                      | Acyclovir/NSAID (n=200) | Valacyclovir/NSAID (n=1155) | p Value |
|----------------------|--------------------------|-----------------------------|---------|
|                      | n | %    | n | %    |               |
| Sex                  |   |      |   |      |               |
| Female               | 100 | 50.0 | 822 | 71.2 | <0.001        |
| Male                 | 90  | 45.0 | 316 | 27.4 | <0.001        |
| Sex missing          | 10  | 5.0  | 17  | 1.5  | <0.001        |
| Age stage            |   |      |   |      |               |
| <45                  | 45  | 22.5 | 220 | 19.0 | 0.256         |
| 45–64                | 68  | 34.0 | 385 | 33.3 | 0.854         |
| ≥65                  | 48  | 24.0 | 345 | 29.9 | 0.091         |
| Age missing          | 39  | 19.5 | 205 | 17.7 | 0.552         |
| Reporter country     |   |      |   |      |               |
| United states        | 89  | 44.5 | 616 | 53.3 | 0.021         |
| Japan                | 54  | 27.0 | 339 | 29.4 | 0.499         |
| Other                | 42  | 21.0 | 79  | 6.8  | <0.001        |
| Reporter country missing | 22  | 11.0 | 128 | 11.1 | 0.973         |
| Type of reporter     |   |      |   |      |               |
| Physician or pharmacist | 118 | 59.0 | 604 | 52.3 | 0.079         |
| Other health professional | 28  | 14.0 | 145 | 12.6 | 0.572         |
| Consumer             | 35  | 17.5 | 264 | 22.9 | 0.092         |
| Lawyer               | 5   | 2.5  | 50  | 4.3  | 0.226         |
| Reporter missing     | 14  | 7.0  | 92  | 8.0  | 0.639         |
| Adverse drug reactions|   |      |   |      |               |
| Acute kidney injury  | 21  | 10.5 | 224 | 19.4 | 0.003         |

Table 3. The Frequency of AKI in the Patients Taking Either Acyclovir or Valacyclovir in Combination with Individual NSAIDs

| Concomitant use of NSAIDs | Acyclovir/NSAID | Valacyclovir/NSAID | p Value |
|---------------------------|-----------------|-------------------|---------|
|                           | AKI/all cases* | %                 | AKI/all cases* | %                 |         |
| Propionic acid derivatives | 15/128         | 11.7              | 156/705         | 22.1              | 0.006    |
| Ibuprofen                 | 4/59            | 6.8               | 21/287          | 7.3               | 0.885    |
| Naproxen                  | 1/26            | 3.8               | 9/157           | 5.7               | 0.695    |
| Ketoprofen                | 3/10            | 30.0              | 2/17            | 11.8              | 0.239    |
| Flurbiprofen              | 2/8             | 25.0              | 2/8             | 25.0              | 1.000    |
| Loxoprofen                | 7/37            | 18.9              | 124/271         | 45.8              | 0.002    |
| Oxaprozin                 | 0/0             | n.a.              | 1/6             | 20.0              | n.a.     |
| Acetic acid derivatives   | 6/45            | 13.3              | 55/250          | 22.0              | 0.186    |
| Diclofenac                | 3/25            | 12.0              | 37/147          | 25.2              | 0.150    |
| Indomethacin              | 0/8             | 0                 | 1/20            | 5.0               | n.a.     |
| Sulindac                  | 0/1             | 0                 | 0/9             | 0                 | n.a.     |
| Ketorolac                 | 2/7             | 28.6              | 5/21            | 23.8              | 0.801    |
| Etodolac                  | 1/6             | 16.7              | 12/33           | 36.4              | 0.347    |
| Nabumetone                | 1/1             | 100.0             | 2/26            | 7.7               | 0.188    |
| Tolfmetin                 | 0/0             | n.a.              | 0/1             | 0                 | n.a.     |
| Enolic acid derivatives (Oxicams) | 0/11        | 0                 | 19/91           | 20.9              | n.a.     |
| Meloxicam                 | 0/7             | 0                 | 10/68           | 14.7              | n.a.     |
| Piroxicam                 | 0/4             | 0                 | 5/15            | 33.3              | n.a.     |
| Lornoxicam                | 0/0             | n.a.              | 4/8             | 50.0              | n.a.     |
| Tenoxicam                 | 0/0             | n.a.              | 1/1             | 100.0             | n.a.     |
| Selective COX-2 inhibitors (Coxibs) | 3/33        | 9.1               | 18/227          | 7.9               | 0.819    |
| Celecoxib                 | 2/24            | 8.3               | 12/157          | 7.6               | 0.906    |
| Rofecoxib                 | 1/10            | 10.0              | 9/80            | 11.3              | 0.906    |

n.a., not available. * More cases are noted than the total number of reports as some patients were taking more than one NSAID.
It is considered that valacyclovir enhances acyclovir bioavailability compared with orally administered acyclovir, and the efficacy and side effect profiles for oral acyclovir and valacyclovir are quite similar. While it has been reported that there are some differences in drug interactions for acyclovir and valacyclovir. For example, valacyclovir is more likely to be affected by cimetidine, while phenytoin and valproic acid are more likely to have their effectiveness reduced by acyclovir.

In this study, we reviewed adverse events reported to the FDA in patients receiving either oral acyclovir or valacyclovir along with an NSAID. Although there were no differences in AKI adverse events between patients taking valacyclovir (8.6%) and those taking acyclovir (8.7%), we found that AKI was significantly more frequently reported in patients simultaneously taking valacyclovir and an NSAID (19.4%) than in patients simultaneously taking acyclovir and an NSAID (10.5%) ($p<0.01$). It’s revealed that compared with acyclovir, valacyclovir is more likely to be affected by NSAIDs.

Our previous research has revealed that the concomitant use of valacyclovir and loxoprofen might lead to an increase in reports of AKI. In this study, it is revealed that concomitant use of valacyclovir and some other NSAIDs such as diclofenac, etodolac, piroxicam, ketorolac or lornoxicam might also be associated with increased occurrence of AKI. The analysis of possible drug-drug interactions is based on the concept that a suspected ADR is more often reported on the combination of two drugs compared with the situation where either of these drugs has been used in absence of the other one. Our results showed that the chance of AKI being reported was slightly increased in patients who used these individual NSAIDs or valacyclovir alone, but the reporting rate was much higher when the NSAID and valacyclovir were used concomitantly. For this reason, the strong association between the concomitant use of these NSAIDs with valacyclovir and AKI therefore was suggestive of an interaction.

The mechanism underlying this suspected interaction remains to be explained. It has been reported that valacyclovir is a substrate of organic anion transporter 1 (OAT1), OAT2 and OAT3, and it might increase plasma valacyclovir concentrations by inhibiting the OAT-mediated tubular secretion of valacyclovir. An increase in the levels of valacyclovir might lead to increased occurrence of AKI. Nevertheless, we did not find the association between the concomitant use of valacyclovir with some other NSAIDs such as ibuprofen, naproxen or celecoxib and the increased occurrence of AKI. The reasons why AKI adverse effects involving drug interactions might vary between certain individual NSAIDs are not clear.

The main strength of the present study was the use of FDA AERS database, which collected standardized information on adverse reactions related to drug use in a “real-world” population. The database also provides a rich opportunity to detect novel post-marketed drug interaction adverse effects since in clinical trials patients on multiple drugs are usually excluded. However, there are limitations in the quality and scope of spontaneously reported databases such as reporting bias, underreporting, lack of information regarding drug therapy and clinical details. In addition, the analysis of spontaneously reported systems cannot provide incidence or quantify...
the increased risk because of a lack of information defining the “true” numerator and the “true” denominator.\textsuperscript{24,25} Hence, further confirmation of a cause—effect relationship between drug combination and adverse events pairs would require independent testing using clinical pharmacology studies or clinical trials.

**CONCLUSION**

Based on FDA AERS database between January 2004 and June 2012, this study suggested that compared with acyclovir, valacyclovir is more likely to be affected by NSAIDs. It revealed that the concomitant use of acyclovir and an NSAID such as loxoprofen, diclofenac, etodolac, ketorolac, piroxicam or lornoxicam might be associated with increased risk of AKI. However, we did not find the association between the concomitant use of acyclovir with an NSAID and an increased occurrence of AKI. The drug interactions with this specific combination of medications are worth exploring further.

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**Conflict of Interest**  The authors declare no conflict of interest.

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