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BRIEF REPORT

Use of High-Dose Oral Valacyclovir During an Intravenous Acyclovir Shortage: A Retrospective Analysis of Tolerability and Drug Shortage Management

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ABSTRACT

Introduction: In late 2011, a shortage of IV acyclovir led to the need to empirically substitute high-dose oral valacyclovir (HDVA) to conserve IV acyclovir for patients with confirmed herpes simplex virus (HSV) meningitis or encephalitis. This report describes the management of the most recent national IV acyclovir shortage by the Antimicrobial Stewardship Program (ASP) at Northwestern Memorial Hospital (NMH), Chicago, IL, USA, and the use of HDVA. Secondarily, we assessed the safety and tolerability of HDVA as an alternate to IV acyclovir during this shortage.

Methods: We report the step-wise management, restrictions, and guidelines implemented at NMH during a protracted IV acyclovir shortage. The assessment of HDVA was a retrospective, observational cohort study of hospitalized patients receiving HDVA between 1 January 2012 and 31 December 2013. Appropriate demographic and treatment variables were collected. The primary outcome was percentage of patients experiencing an adverse event.

Results: There were 15 adult patients included in the study on a median daily dose of HDVA of 3 g (IQR 2–8). There were four patients with microbiologically confirmed viral CNS infections ($n = 1$ HSV-1, $n = 2$ HSV-2, $n = 1$ VZV encephalitis) and eleven patients with unknown causative pathogens. Six (40%) patients experienced at least one adverse drug reaction (ADR) to HDVA (thrombocytopenia, 33.3%, $n = 5$; headache, 6.7%, $n = 1$; nausea, 6.7%, $n = 1$; rash, 6.7%, $n = 1$). One patient (6.7%) was readmitted within 30 days with a suspected non-CNS infection. There were no treatment discontinuations or symptomatic therapy necessary to treat any of the ADRs.

Conclusions: The shortage of IV acyclovir was successfully managed by the ASP and HDVA appeared to be well tolerated when used as an alternative to IV acyclovir.

Keywords: Acyclovir; Shortage; Valacyclovir; Viral encephalitis; Viral meningitis

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INTRODUCTION

Drug shortages continue to be a problem in the United States, causing numerous difficulties for

clinicians, health-care facilities, patients, and federal regulators [1, 2]. As a generic injectable agent, intravenous (IV) acyclovir is vulnerable to drug shortage due to a variety of reasons including manufacturing difficulties, supply and demand issues, regulatory issues, and raw material shortage [2–4]. In late 2011, a severe shortage of IV acyclovir led to the decision by the Antimicrobial Stewardship Program (ASP) to empirically substitute high-dose oral valacyclovir (HDVA) to conserve IV acyclovir for patients with confirmed herpes simplex virus (HSV) meningitis or encephalitis [5]. Pharmacokinetic data suggest similar serum concentrations to IV acyclovir doses can be achieved with HDVA [6, 7]; however, little data exist regarding the safety and tolerability of HDVA for viral central nervous system (CNS) infections. Here, we describe the management of the most recent national IV acyclovir shortage by the ASP at Northwestern Memorial Hospital (NMH), Chicago, IL, USA, and the replacement with HDVA. Secondarily, we assessed the safety and tolerability of HDVA as an alternate to IV acyclovir during this shortage.

METHODS

IV Acyclovir Shortage Management

The restrictions on IV acyclovir were progressively intensified as supplies dwindled over the 11-month shortage. As of October 2012, ASP pharmacists performed next-day review of new medication starts to assess for appropriateness. Restrictions were added in late November 2012 due to dwindling supplies. IV acyclovir was reserved for patients with HSV disseminated disease, neurological or eye involvement, and neonatal HSV. As the shortage continued, a mandatory next-day infectious disease (ID) consult was required in mid-December 2012 for all IV acyclovir use. In February 2013, restrictions for IV acyclovir use were tightened to diseases with high morbidity and mortality: HSV or varicella zoster virus (VZV) encephalitis documented by cerebrospinal fluid (CSF) polymerase chain reaction (PCR) and neonatal HSV.

In order to implement these restrictions, the ASP partnered with the microbiology department to have the CSF PCR specimens tested on a daily basis rather than only Monday through Friday, the previous routine schedule. This collaboration highlights the importance of engagement of all parties involved in shortage management and communication. HDVA was used as an alternative to IV acyclovir if clinicians desired treatment for a suspected viral syndrome and the patient did not meet criteria for IV acyclovir use. A dose of at least 6 g of valacyclovir per day (adjusted for renal function) was targeted for CNS infections to achieve expected therapeutic CNS concentrations. These restrictions on IV acyclovir remained in place until September 2013 when an ample supply of IV acyclovir was able to be ordered from warehouses.

HDVA Study Design

This was a retrospective, observational cohort study of hospitalized patients receiving HDVA between 1 January 2012 and 31 December 2013. This elongated timeline was meant to capture any patients past the date of the resolution of the shortage who may have received HDVA after restrictions had been lifted. Subjects eligible for review were male or female $\geq$18 years of age receiving treatment for suspected viral meningitis or encephalitis with HDVA per the patient's medical record. HDVA was defined as any dose and length of therapy exceeding the Food and Drug Administration (FDA) recommendations (e.g., 3 g/day for regimens lasting >1 day for normal renal function). Subjects were assessed for demographics, renal function status, liver function status, steroid use, modified APACHE II score, duration of HDVA treatment, IV acyclovir use, duration of hospital stay, intensive care unit (ICU) transfer, use of symptomatic treatment, adverse drug events, whether ID consultation occurred, time from neurological symptoms to first dose, readmission within 30 days, and neurological sequelae. Patients were also assessed for results of viral microbiological tests. The primary outcome was percentage of patients experiencing an adverse event. This study was approved by

the Northwestern and Midwestern University Institutional Review Boards. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. Descriptive statistics were compiled using Intercooled Stata, v.13 (Statacorp, College Station, TX, USA).

RESULTS

There were 15 patients on HDVA who were included in the study. The average patient in the study was a 45-year-old (IQR 35–60), immunocompromised (66.7%, $n = 10$), Caucasian (46.7%, $n = 7$), male (66.7%, $n = 10$), with a modified APACHE II score of 13.5 (IQR 8–24; Table 1). The most common presenting symptom suggestive of viral CNS disease was altered mental status ($n = 13$) followed by nuchal rigidity ($n = 7$). All patients had a lumbar puncture. There was 1 patient with microbiologically confirmed HSV-1 encephalitis, 2 patients with confirmed HSV-2 ($n = 1$ encephalitis, $n = 1$ meningitis), 1 patient with confirmed VZV encephalitis, and 11 patients with unknown causative pathogens ($n = 5$ meningioencephalitis, $n = 3$ encephalitis, $n = 2$ meningitis, $n = 1$ unknown). In total, 8 patients received at least one dose of IV acyclovir and there were 2 patients who had neurological sequelae. The average length of hospital stay per patient was 7 (IQR 4–44) days, including 6 patients (40%) transferred to the ICU (Table 2). One patient (6.7%) was readmitted within 30 days with a diagnosis of *Enterococcus faecalis* and *Staphylococcus epidermidis* blood stream infection; his symptoms included chills, somnolence, and generalized weakness.

The median daily dose of HDVA given to the patients was 3 g (IQR 2–8) with median total length of therapy 11 days (IQR 4–16; Table 3). Six (40%) patients experienced at least one adverse drug reaction (ADR) to HDVA with thrombocytopenia being the most common (33.3%, $n = 5$) followed by headache (6.7%, $n = 1$), nausea (6.7%, $n = 1$), and rash (6.7%, $n = 1$). There were no treatment discontinuations or symptomatic therapy necessary to treat any of the ADRs.

Table 1 Patient demographics

	***n* = 15**
Age, years (median, IQR)	45 (35–60)
	Range: 28–73
Race (*n*, %)	
Caucasian	7 (46.7)
African American	4 (26.7)
Hispanic	3 (20)
Asian	1 (6.7)
Gender, male (*n*, %)	10 (66.7)
Weight, kg (median, IQR)	72.9 (59.3–92)
	Range: 52–96.6
Baseline serum creatinine, mg/dL (median, IQR)	0.89 (0.70–1.46)
	Range: 0.42–8.16
Highest serum creatinine, mg/dL (median, IQR)	0.94 (0.75–1.46)
	Range: 0.44–10.28
Valacyclovir renal adjustment necessary (*n*, %)	4 (26.7)
Immunocompromised (*n*, %)	10 (66.7)
Neutropenic (*n*, %)	1 (6.7)
Modified APACHE II, day 0 (median, IQR)	13.5 (8–24)
	Range: 6–26
Intravenous acyclovir given (*n*, %)	8 (53.3)
Infectious diseases consult obtained (*n*, %)	13 (86.7)

IQR interquartile range

DISCUSSION

Through the application of restrictions, guidelines, and expanded microbiological testing, the available inventory of IV acyclovir was adequate to sustain the institution through the shortage

Table 2 Patient outcomes

	$n = 15$
Length of hospital stay, days (median, IQR)	7 (4–44)
	Range: 2–76
Transferred to ICU (n, %)	6 (40)
ICU length of stay, days, $n = 6$ (median, IQR)	9.5 (4–24)
	Range: 4–32
Time to first dose from admission, h (median, IQR)	10 (6–53)
	Range: 1.75–600
Time from symptoms to first dose, h (median, IQR)	25.5 (5.5–48)
	Range: 0–96
Neurological sequelae (n, %)	2 (13.3)
Readmission within 30 days with suspected infection (n, %)	1 (6.7)

IQR interquartile range, *ICU* intensive care unit

Table 3 Dosing characteristics and adverse effects associated with HDVA

	$n = 15$
Valacyclovir grams per day (median, IQR)	3 (2–8)
	Range: 1–8
Highest AST, IU/L (median, IQR)	24 (18–49)
	Range: 12–326
Highest ALT, IU/L (median, IQR)	24 (13–48)
	Range: 6–286
Highest total bilirubin, mg/dL (median, IQR)	0.7 (0.4–1)
	Range: 0.3–2.3
Duration of valacyclovir, days (median, IQR)	11 (4–16)
	Range: 2–34
Adverse reaction to valacyclovir (n, %)	6 (40)
Headache (n, %)	1 (6.7)
Nausea (n, %)	1 (6.7)
Vomiting (n, %)	0 (0)
Rash (n, %)	1 (6.7)
Thrombocytopenia (n, %)	5 (33.3)
Nephrotoxicity (n, %)	0 (0)
Symptomatic therapy needed (n, %)	0 (0)

IQR interquartile range

period. An important drug management strategy includes identifying alternative or therapeutically equivalent drugs; however, safety and efficacy data for alternatives may be limited. In this study, HDVA appeared to be well tolerated and may be an option when IV acyclovir is unavailable for viral meningitis.

When implementing restrictions during drug shortages, ASPs should consider relevant treatment guidelines, current primary literature should be utilized to guide evidence-based decisions, and appropriate hospital committees and administration should be involved. As an example, in a review article regarding neonatal treatment for CNS or disseminated HSV infections during an acyclovir shortage, foscarnet and ganciclovir were both considered unsafe to use due to ADRs and very little safety data [8]. As such, one of the allowed indications for IV acyclovir at NMH was neonatal HSV. ASPs have also successfully managed antibiotic shortages using a prospective audit approach and without restrictions [9].

Orally administered valacylovir for various CNS infections has been well tolerated in previous studies with few reported adverse events or drug-related abnormalities [10, 11]. The most common ADRs in these studies were mild headache and low back pain ($n = 19$ total patients; dose 1 g by mouth three times daily). The most common ADRs using HDVA in a previous study for episodic treatment of HSV cold sores were headache, nausea, and diarrhea ($n = 310$ patients treated with HDVA) [7]. This is similar to the current findings and supports potential use outside of FDA dose recommendations when necessary for patient care.

Limitations of this study include a small sample size, retrospective review, and a limited

follow-up period. However, the entire shortage period was analyzed to increase the sample size and larger studies are needed to confirm safety and provide data on the efficacy of HDVA for viral meningitis when specifically used due to a shortage of IV acyclovir. As the focus of this study was tolerability and safety, a larger cohort of a more homogenous population would be necessary to comment on the observed effects of efficacy from the use of high-dose valacyclovir. As generic injectable shortages may repeat, this is an area of interest for future study.

CONCLUSION

The shortage of IV acyclovir was successfully managed through guidelines and restrictions by the ASP. As the shortage intensified, the ASP implemented a policy of reserving IV acyclovir for PCR-confirmed HSV and VZV encephalitis and neonatal HSV disease. HDVA appeared to be well tolerated as initial and directed therapy for HSV meningitis and may be an option when IV acyclovir is unavailable.

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Disclosures. Milena McLaughlin, Sarah Sutton, Ashley O. Jensen and John Esterly have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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