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Review Article

Use of Oral Valacyclovir Instead of IV Acyclovir in Treatment of Herpes Simplex Encephalitis (Hse) in Resources- Poor Country: A Review Article

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Abstract:

Viral encephalitis remains a significant public health problem worldwide including Bangladesh. The recommended treatment for herpes simplex encephalitis (HSE) remains intravenous acyclovir. In resource-poor countries, however, intravenous formulations are usually unavailable or unaffordable. Efficacy of treatment depends upon cerebrospinal fluid (CSF) level of acyclovir. Main concern of use of valacyclovir is central nervous system penetration of drugs. This study reports the comparison of penetration of acyclovir into the cerebrospinal fluid (CSF) in patients with HSE, treated with the oral pro drug valacyclovir at a dose of 1,000 mg three times daily. The oral therapy achieved adequate acyclovir concentrations in the CSF and may be an acceptable early treatment for suspected HSE in resource-limited settings. In our country treatment of HSE by IV acyclovir is costly and needs about 45000 BDT per person to complete treatment and is not available in rural areas, on the other hand it is 10 times cost effective in treatment with oral Valacyclovir.

Key words: Acyclovir, Valacyclovir, HSE, Viral meningitis.

Introduction:

Encephalitis implies inflammation of the brain substance, parenchyma, which may coexist with inflammation of the meninges (meningoencephalitis) or spinal cord (encephalomyelitis). Encephalitis may be mild and self-limited, or may produce a devastating illness[1]. Herpes simplex virus type 1 (HSV-1) is the etiological agent in 10% of all viral encephalitis cases. HSV-1 is the most common cause of encephalitis in adults worldwide, with a high acute-case fatality rate and devastating neurological squeal in a significant proportion of survivors[2]. The recommended treatment is intravenous acyclovir, 10 mg/kg of body weight, three times daily for 21 days[3].

Acyclovir is a purine nucleoside analogue with activity against human herpes viruses, including HSV. Oral acyclovir has poor oral bioavailability (approximately 15 to 30%) and low penetration into the central nervous system (CNS). Hence, the treatment of HSV encephalitis, which requires higher drug levels to achieve antiviral efficacy, is dependent on the use of intravenous acyclovir. However, this regimen is unavailable and unaffordable for most patients in resource-limited settings like Bangladesh.

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Valacyclovir, the prodrug l-valyl ester of acyclovir, is converted *in vivo* to acyclovir by hepatic and plasma esterase. Oral bioavailability of acyclovir is 3- to 5-fold higher (about 54%) when given as the pro drug than when given as acyclovir[4]. Orally administered valacyclovir is very well tolerated, with few reported adverse events, even at a dose of 2,000 mg four times daily. Valacyclovir is 10 times less expensive than intravenous acyclovir and is readily available in pharmacies in countries with limited resources. Some authors investigated the pharmacokinetics of orally administered valacyclovir in the plasma and cerebrospinal fluid (CSF) of patients with herpes simplex encephalitis (HSE).

Review of articles:

A study was done in Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam[5] where they included adult patients aged ≥18 years with a presumptive clinical diagnosis of encephalitis. All patients underwent routine diagnostic investigations that included CSF cell count, chemistry, microscopy with Gram, Ziehl-Neelsen, and India ink stains, and routine culture for bacterial and fungal pathogens. Patients were excluded when an alternative microbiological diagnosis was made or renal impairment was proven. Treatment was initiated immediately upon enrollment at 1,000 mg three times daily for a total of 21 days and was stopped if 2 consecutive HSV PCR tests were negative after 5 days.Venous blood samples (1.5 ml) were obtained

prior to and 1, 2, 3, 4, 6, and 8 h after dose administration on day 0. On days 2, 10, and 20, blood samples were collected at predose and at 2 h postdose. Acyclovir concentrations in plasma and CSF were measured by high-performance liquid chromatography (HPLC) with UV detection after solid-phase extraction according to standard methods. Nine patients (5 males, 4 females) were enrolled in the study. Two patients had negative CSF HSV PCR tests, and valacyclovir was discontinued. One patient withdrew from the study. Two patients died on days 2 and 3 after study enrollment (both had positive HSV-1 PCR, and acyclovir CSF concentrations were not different from those of other patients). The other four patients had a positive PCR for HSV-1 and received the full 21-day course of valacyclovir. No serious adverse events were observed in the four patients. Routine hematology and biochemistry tests were within normal ranges, and no drug-related adverse events were observed throughout the study. In all patients, the 2-h-postdose concentrations of acyclovir in plasma remained stable from day 2 to the end of the treatment, with the mean steady-state concentration around 28.1 ± 9.8 mM, whereas the 2-h-postdose concentrations in CSF reached maximum levels on day 2 (6.5 ± 4.5 mM) and then on days 10 (4.2 ± 3.8 mM) and 20 (3.5 ± 1.7 mMmM) decreased to concentrations similar to andlower than that of the first day of treatment (3.6 ± 1.7 mM).

The CSF/plasma concentration ratio was calculated to determine the blood/CSF levels of acyclovir over the treatment period. The concentrations of acyclovir in plasma remained stable from the beginning of steady state (day 2) to the end of the treatment, whereas the concentrations in CSF decreased after day 2. The 2-h-postdose CSF/plasma acyclovir concentration ratio was 22.9% on day 2, 14.5% on day 10, and 12.0% on day 20. The acyclovir CSF/plasma ratio dropped to approximately 50% within 18 days of steady state.

Another study was done by Lycke et al[6] where they shows the acyclovir CSF/plasma ratio 2 h postdose at steady state was 11%, and the mean CSF concentration was 2.5 ± 0.7 mM. The concentrations of acyclovir in serum and CSF were measured at steady state after 6 days of oral treatment with 1,000 mg of valacyclovir three times a day. Samples were obtained from 10 patients with MS. All patients had normal renal function, and none had signs of a damaged blood-CSF barrier. The maximum concentration of acyclovir in serum was reached after 1 to 3 h (mean +/- standard deviation [SD], 27.1 +/- 5.6 micro M), and the minimum concentration in serum was 3.1 +/- 1.1 micro M (mean +/- SD). The acyclovir concentrations in CSF at 2 and 8 h were essentially stable, with the mean +/- SD levels being 2.5 +/- 0.9 and 2.3 +/- 0.7 micro M, respectively.

Another study was done byTyring SK et al[7] in University of Texas Medical Branch, Texas. They showed that long-term use of acyclovir for up to 10 years for HSV suppression is effective and well tolerated. Safety monitoring data from clinical trials of valacyclovir, involving over 3000 immunocompetent and immunocompromised persons receiving long-term therapy for HSV suppression, were analyzed. Safety profiles of valacyclovir (</=1000 mg/day), acyclovir (800 mg/day), and placebo were similar. Extensive sensitivity monitoring of HSV isolates confirmed a very low rate of acyclovir resistance among immunocompetent subjects (<0.5%). The incidence of resistance among immunocompromised patients remains low at about 5%.

Pouplin and colleagues[8] evaluated valacyclovir 1000 mg 3 times daily in 9 patients, of which 4 completed the 21-day course. Two-hour post-dose levels on days 2, 10, and 20 were 6.5 ± 4.5 μM, 4.2 ± 3.8 μM, and 3.5 ± 1.7 μM, respectively. They found that this valacyclovir dose can achieve an IC_{50} higher than the target range for most clinical isolates of HSV-1 and -2. CSF levels were higher in the acute phase of infection (ie, at day 2) vs after 10 days and 20 days of treatment, which may be due to partial correction of altered blood-brain barrier permeability as treatment continues.

Milena M. McLaughlin et al[9] done a study 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, they assessed the safety and tolerability of HDVA as an alternate to IV acyclovir during this shortage. 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 was no treatment discontinuations or symptomatic therapy necessary to treat any of the ADRs. They concluded that use of HDVA appeared to be well tolerated when used as an alternative to IV acyclovir.

Conclusion:

In conclusion, valacyclovir orally administered at 1,000 mg three times daily for 21 days in patients with herpes encephalitis achieved therapeutic levels in the CSF throughout the course of treatment and well tolerated.The higher levels of acyclovir in CSF at the early stage of treatment potentially reflected an impaired and more permeable BBB. In resource-poor settings like Bangladesh, valacyclovir should be considered an alternative to intravenous acyclovir for treatment of herpes simplex encephalitis when the latter is not available or affordable. The maximum benefit of these drugs is when they are used early in the course of disease. Consideration should be given to making oral valacyclovir available and encouraging its use immediately after a patient presents with suspected encephalitis, particularly in rural settings where molecular diagnostic tests and intravenous acyclovir are not available.

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