Use of oral valaciclovir in a 12-year-old boy with herpes simplex encephalitis

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We report on a 12-year-old boy with herpes simplex encephalitis, in whom a severe localised skin reaction developed following the infusion of intravenous acyclovir. Oral valaciclovir was given as continuation therapy to complete the 3-week course of antiviral treatment and resulted in complete recovery without side effects. This report illustrates the advantage of using the polymerase chain reaction to diagnose herpes simplex encephalitis and the potential use of newer antiviral agents, such as valaciclovir, as continuation therapy in the management of the infection. The higher oral bioavailability of newer antiviral agents allows part of the extended treatment period of patients with herpes simplex encephalitis to be carried out as an ambulatory oral regimen.

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Introduction

Acyclovir is very effective in inhibiting the replication of herpes simplex virus (HSV). Although acyclovir is the standard antiviral drug used to treat most herpesvirus infections, its poor oral bioavailability (15%-20% of the administered dose) has led to the development of newer nucleoside analogues and prodrugs that have a better oral bioavailibity. Valaciclovir hydrochloride (Valtrex; GlaxoWellcome, Manchester, United Kingdom) is the l-valyl ester of acyclovir and is well absorbed when given orally. It is rapidly converted to acyclovir by hepatic metabolism, which results in more than 50% of the drug's bioavailability: a three- to five-fold increase when compared with the oral administration of acyclovir. When valaciclovir is given orally at a dosage of 1000 mg three times a day to healthy adult volunteers, the plasma acyclovir levels are comparable to those achieved by the intravenous infusion of acyclovir at 5 mg/kg body weight.[1] This prodrug of acyclovir may thus provide a more convenient oral regimen to treat HSV infections and would be particularly useful when a high level of plasma acyclovir is required. Clinical experience with valaciclovir is currently limited to the treatment of herpes genitalis and herpes zoster in immunocompetent adults.[2,3] However, valaciclovir may also be useful as continuation therapy after initial intravenous acyclovir treatment for more serious infections. In this paper, we present the first report of using valaciclovir in a child with herpes simplex encephalitis (HSE).

Case report

A 12-year-old Chinese boy was admitted to the Yan Chai Hospital in March 1997 for a history of left-hand weakness, slurring of speech and dripping of saliva from the left angle of the mouth that had lasted 1 day, and generalised convulsions. He had no recent history of head injury or change in behaviour. Physical examination showed the patient to have claw-hand of the left hand, which had a motor power of grade 2. The proximal part of left upper limb, right upper limb, and both lower limbs were normal. The left facial muscles showed weakness, whereas other cranial nerves were normal. The body temperature was 36°C, peripheral white blood cell count was 14.2 x 10^9 /L and erythrocyte sedimentation rate was 47 mm/h (normal range, 0-20 mm/h). Computed tomography showed an ill-defined hypodense lesion over the right temporal lobe. Electroencephalography revealed intermittent

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runs of irregular slow-wave activity over the right central region; activity was enhanced during hyperventilation. The cerebrospinal fluid (CSF) that was taken on the day of admission showed pleocytosis—that is, a white blood cell count of $9x10^6$/L, and a red blood cell count of $22x10^6$/L. Protein and glucose concentrations were within the normal range; oligoclonal proteins were found in the CSF. Microbiological investigations of the CSF included virus isolation and the complement fixation test to detect anti-HSV antibodies, and gave negative results.

Empirical treatment with intravenous acyclovir 10 mg/kg every 8 hours, phenytoin, and cefotaxime was started on the day of hospital admission, while awaiting results of further investigations. On the day of admission, the patient experienced two episodes of generalised tonic-clonic convulsion and loss of consciousness lasting approximately 1 minute each, as well as frequent attacks of focal convulsion of the left upper limb that lasted approximately 1 minute each. Weakness of left facial and hand muscles subsided completely on day 4, and no more convulsions occurred. Polymerase chain reaction (PCR) analysis [4] of the CSF specimen confirmed the diagnosis of HSE on day 7. The dosage of acyclovir was increased and was intended as 3-week maintenance therapy in accordance with recently published guidelines.[5] However, the patient developed a significant local skin reaction—namely, erythema, tenderness, and blistering over the infusion sites—on day 2, which became progressively worse despite the slow infusion of acyclovir with normal saline and the frequent change of infusion site. In view of the clinical improvement and the severe skin reaction after 11 days of intravenous acyclovir, antiviral therapy was changed to oral valaciclovir 1000 mg three times a day. After 2 days of valaciclovir treatment, the patient was discharged home and completed the remaining 8 days of the oral valaciclovir regimen at home. The 10-day course of oral valaciclovir was well tolerated and no new skin lesions developed. There was no clinical relapse of encephalitis, and no residual neurological deficits were detected on follow-up visits at 1 week and 1 month after discharge.

Discussion

To confirm a diagnosis of HSE is a difficult challenge. The disease, particularly in its early stages, can mimic a variety of other neurological illnesses. The diagnosis requires a concerted clinical and laboratory team effort, but definitive aetiological diagnosis remains the task of the virus laboratory. The European Union's Concerted Action on Virus Meningitis and Encephalitis has produced a comprehensive review of various means of confirming the diagnosis of HSE.[5] Imaging and electroencephalography are neither sensitive nor specific, particularly in the diagnosis of HSE in its early stages. In contrast, biopsy examination of the brain is both sensitive and specific, and a reliable diagnosis can often be obtained 4 to 5 days after the onset of illness. The invasive nature of performing a brain biopsy, however, limits its application. The detection of intrathecal HSV-specific antibodies has been a valuable diagnostic test, but 10 to 12 days are usually needed to produce a detectable amount of antibody. As a result, the diagnosis is mainly retrospective and carries little influence on the management of individual cases.

The sensitivity of the detection of HSV in CSF by either isolation or antigen detection is far below the satisfactory level.[5] Fortunately, nested PCR provides a rapid, sensitive, specific, and less invasive method to detect HSV DNA in a sample of CSF. Although nested PCR is more susceptible to producing artefacts due to contamination than are traditional methods such as virus isolation or serology, diagnostic PCR has been successfully used by many clinical microbiology laboratories and is likely to be the gold standard for the diagnosis of HSE.[6] In this case, the positive PCR result was the only unequivocal finding, not only to confirm the diagnosis, but also to support the continuation of antiviral therapy when complications occurred. Molecular diagnosis of HSE, such as PCR analysis, is still not widely available in Hong Kong, and its development for use in routine clinical service should be encouraged.

The availability of PCR analysis as a routine diagnostic method has also redefined the spectrum of HSV infections of the central nervous system. The method has shown that some patients with HSE relapse within 2 to 3 weeks of an apparent recovery,[7] and in a series described by Kimura et al,[8] four of 15 children with HSE had a clinical relapse. The pathogenesis of clinical relapse of HSE is still controversial; possible causes are persistent infection, the reactivation of latent virus, or postinfectious encephalitis.[9] In the study by Kimura et al,[8] HSV DNA was detected in samples of CSF that were taken during relapse following a standard course of acyclovir treatment, thus indicating that the then recommended therapy of acyclovir 10 mg/kg every 8 hours for 10 to 14 days was insufficient. A longer duration of antiviral therapy has recently been recommended to prevent relapse.[5]

Although major side effects of acyclovir are uncommon, skin reactions (as observed in this case) have been reported.[10] In this case, intravenous infusion of acyclovir was changed to oral valaciclovir, which also allowed an earlier discharge from hospital. Owing to the lack of a readily available assay, the plasma levels of acyclovir following the intravenous infusion of acyclovir and oral administration of valaciclovir were not measured. Based on published data,[1] the dosage of oral valaciclovir that was used for this patient was expected to achieve a plasma acyclovir level equivalent to that due to intravenous infusion of acyclovir at a dosage of 5 mg/kg every 8 hours. With the increasing use of a higher dose and longer duration of intravenous acyclovir for HSE in particular, clinicians may encounter more cases of minor side effects, and more patients will have to remain hospitalised for intravenous therapy despite recovery from the acute illness. Hence, an alternative mode of continuation therapy may be required in certain circumstances, and oral valaciclovir therapy could be an option, especially because of the added benefit of allowing earlier discharge home if this is indicated.

In the treatment of infections of the central nervous system, drug bioavailability across the blood-brain barrier is more important than drug bioavailability in the plasma. Because valaciclovir (a prodrug of acyclovir) is rapidly converted to acyclovir by hepatic metabolism, the CSF penetration of valaciclovir should be equivalent to that of intravenous acyclovir (ie the concentration in the CSF is approximately 50% of that in the plasma).

In this case, the patient's condition improved by day 4 of hospital admission. This time course could represent the natural course of a mild case of HSE, or it could indicate a response to the initial acyclovir therapy. Although the efficacy of oral valaciclovir cannot be concluded from a single case report, the use of oral valaciclovir as continuation therapy and the subsequent complete recovery without clinical relapse and allergic reaction have been illustrated. It may be worthwhile to perform a controlled clinical trial to evaluate the efficacy of valaciclovir and other newer drugs in the treatment of HSE.

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