Use of therapeutic drug monitoring in the long-term valaciclovir therapy of relapsing herpes simplex virus encephalitis in children

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Sir,

Adequate therapy of herpes simplex virus (HSV) encephalitis relies upon good central nervous system (CNS) delivery of aciclovir and adequate duration of treatment as shorter courses of treatment have been associated with relapse of disease.1 The current paediatric practise is to treat with 3 weeks of intravenous (iv) aciclovir at 1500 mg/m²/day. Despite this, relapses have been reported that may represent either frank viral relapse or a post-infectious movement disorder.2 Long-term oral aciclovir therapy like that used in neonatal HSV-2 disease3 may benefit children with HSV-1 encephalitis. Valaciclovir is rapidly metabolized to aciclovir producing plasma concentrations three to five times higher than oral aciclovir4 and may thus provide a better alternative to oral aciclovir. Its use in children in a variety of herpes virus infections has been reviewed,3,5 but is confined mainly to non-CNS disease.6,7

Here, we report our experience in the therapeutic monitoring of plasma and cerebral spinal fluid (CSF) aciclovir concentrations in five children. Three very young children aged 20 months (patient 1), 11 months (patient 2) and 6 months (patient 3) with relapsing HSV-1 encephalitis were treated with long-term oral valaciclovir after completing a course of iv aciclovir at relapse. Two children (patients 4 and 5) with suspected viral encephalitis were treated with iv aciclovir. CSF aciclovir concentrations were only measured when a lumbar puncture was clinically indicated. Parental consent was obtained for the procedures and long-term oral valaciclovir therapy.

Our therapeutic plan was to achieve a trough level that is twice the maximum published IC₅₀ of aciclovir for HSV-1 [0.022–0.22 mg/L (0.1–1 μM)]8 to account for the CNS penetration, which is estimated at 50%.9 The initial dose of oral valaciclovir was selected from published paediatric data on its use in other conditions,6,7 to achieve our theoretical trough target concentration of 0.44 mg/L. Trough aciclovir concentrations were taken prior to the administration of either oral valaciclovir or iv aciclovir. Peak aciclovir concentrations were taken 1 h after the end of a 1 h infusion of iv aciclovir or 2 h after oral valaciclovir administration according to Eksborg et al.7

Aciclovir concentrations were measured by a simple isocratic HPLC assay9 at the Bristol Centre for Antimicrobial Research and Evaluation. Intra-assay and inter-assay percentage coefficients of variation were <10% and <3.2%, respectively. Patients on long-term oral valaciclovir were monitored clinically and with regular measurement of haematological and biochemical parameters and renal ultrasound scanning.

Table 1 summarizes the plasma and CSF concentrations measured in our patients. At doses of 25–40 mg/kg 8 hourly of oral valaciclovir, plasma trough concentrations of aciclovir ranged from 0.1 to 0.8 mg/L (mean 0.52, SD 0.23); whilst peak plasma aciclovir concentrations of 2.5–10.2 mg/L (mean 5.5, SD 2.4) were achieved. Our data were comparable to two other studies evaluating the pharmacokinetics of valaciclovir in children, where at doses of 10 mg/kg 8 hourly, 20 mg/kg 8 hourly and 40 mg/kg 8 hourly of oral valaciclovir, mean peak aciclovir concentrations of 2.61 mg/L, 7.517 mg/L and 7.5 mg/L, respectively, were achieved.6,7 The target trough concentration (0.44 mg/L) was achieved in all three patients on oral aciclovir, either on initial dosage or following dose titration. The low trough level in the final measurement of patient 2 is attributable to a missed dose of valaciclovir. Trough and peak concentrations following oral valaciclovir administration of up to 40 mg/kg 8 hourly in our patients approached published values in adults (trough mean 0.7, SD 0.3; and peak mean 9.8, SD 2.6) and children (peak mean 10.3, SD 4.3) treated with 5–6 mg/kg 8 hourly (250 mg/m² 8 hourly) of iv aciclovir.9 Our patients treated with iv aciclovir also achieved aciclovir concentrations similar to published adult (trough mean 2.3, SD 1.4; peak mean 20.7, SD 10.2) and paediatric (peak mean 20.7, SD 5.0) data, allowing for the recognized wide inter-subject variability.8

CSF aciclovir concentrations in four children (patients 2, 3, 4 and 5) on iv aciclovir and two children (patients 1 and 2) on oral valaciclovir were measured. When peak concentrations were measured, CSF penetration was 9% on two occasions in patient 2 compared with trough CSF penetrations of 80% in the same patient (Table 1). The discrepancy when measuring CNS distribution using peak concentrations is almost certainly related to the lag phase of the CSF peak. Single point measurements to reflect peak concentrations are extremely susceptible to such lag effects and are less reliable than trough values. Only multiple sampling and area under the curve (AUC) measurement can provide accurate data. Nevertheless, using CSF aciclovir trough measurements in four patients confirmed that a CSF concentration of at least 60% of plasma values could be achieved, adding more confidence to the current estimate of CSF penetration of 50%, which to the best
of our knowledge is derived from data on three patients (two adults and one child).8

Oral valaciclovir was well tolerated in our very young children and can be considered for long-term treatment such as in relapsing HSV encephalitis or disease with focal destruction lesions on neuroimaging where prolonged iv aciclovir therapy is not practical and oral aciclovir has poorer bioavailability. Provided aciclovir concentrations are monitored and the administration of valaciclovir tolerated, the valaciclovir dose can be titrated upwards either to achieve plasma concentrations equivalent to those reported after a particular iv aciclovir administration dose or to a theoretically calculated target dose, as in our cohort.

Acknowledgements

We thank Steve Tomlin, Head of Paediatric Pharmacy, Guy’s & St Thomas’ Hospitals NHS Foundation Trust, for providing the initial guidance on the administration of valaciclovir and his help with the early drafts of the manuscript. We are grateful to our neuroradiology colleague Dr Wajanat Jan for interpreting the MRI brain scan changes and to Dr Eithne MacMahon for virological support.

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This study was carried out as part of our routine clinical work.

Transparency declarations

None to declare.

References


Table 1. Plasma and CSF aciclovir concentrations in patients treated with iv aciclovir and/or oral valaciclovir

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration into illness</th>
<th>iv aciclovir (8 hourly dose)</th>
<th>Oral valaciclovir (8 hourly dose)</th>
<th>Trough plasma (mg/L)</th>
<th>Peak plasma (mg/L)</th>
<th>Trough CSF (mg/L)</th>
<th>Peak CSF (mg/L)</th>
<th>CSF penetration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 weeks</td>
<td>250 mg (30 mg/kg)</td>
<td>0.6</td>
<td>4.9</td>
<td></td>
<td>0.5</td>
<td>2.5</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>4 months</td>
<td>250 mg (28 mg/kg)</td>
<td>0.8</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 weeks</td>
<td>500 mg/m²</td>
<td>1.2</td>
<td>1</td>
<td></td>
<td>0.3</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>250 mg (30 mg/kg)</td>
<td>0.3</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6 weeks</td>
<td>375 mg (40 mg/kg)</td>
<td>0.7</td>
<td>10.2</td>
<td>0.9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 months</td>
<td>375 mg (38 mg/kg)</td>
<td>0.4</td>
<td>5.9</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3 months</td>
<td>375 mg (38 mg/kg)</td>
<td>0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 weeks</td>
<td>500 mg/m²</td>
<td>0.3</td>
<td>4.3</td>
<td>0.6</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 weeks</td>
<td>500 mg/m²</td>
<td>0.3</td>
<td>5.8</td>
<td>0.6</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 months</td>
<td>260 mg (30 mg/kg)</td>
<td>0.7</td>
<td>7.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>day 4</td>
<td>500 mg/m²</td>
<td>0.7</td>
<td>9.2</td>
<td>1.4</td>
<td>85</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>day 14</td>
<td>500 mg/m²</td>
<td>2.2</td>
<td>9.2</td>
<td>1.4</td>
<td>64</td>
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</table>

NB. The theoretical plasma trough target concentration was 0.44 mg/L.
<sup>a</sup>Missed dose prior to measurement.


