

Coma secondary to aciclovir neurotoxicity

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Introduction

Aciclovir is an anti-viral nucleoside analogue discovered in 1972. Since its introduction into clinical practice in 1982 very few adverse effects have been reported. Renal dysfunction and central nervous system disturbance are the two major adverse effects. The neurological manifestations of aciclovir toxicity include agitation, hallucinations, disorientation, tremors, and coma. Neurotoxicity can occur following oral or intravenous administration of aciclovir, but is usually associated with intravenous dosing regimes. However, the exact mechanism of this effect remains unknown. Neurological dysfunction is also a feature of encephalitis; the patient may be receiving therapy for this.

Case report

A 77-year-old woman was admitted with a 24-hour history of confusion, slurred speech and leg weakness. Past medical history included anuric end-stage renal failure, essential hypertension and mild chronic obstructive airways disease. She was on thrice-weekly haemodialysis. Her medications were sustained release nifedipine 20mg per day, fluoxetine 20mg per day, omeprazole 40mg per day, erythropoietin and iron. Oral aciclovir 800mg twice daily had been introduced 48 hours previously for a painful herpes zoster infection.

On examination, she was afebrile with normal vital signs. She was drowsy and disorientated with a Glasgow coma scale (GCS) of 11/15. No focal neurological signs were elicited. She had a blistering herpes zoster rash over the right chest wall.

Laboratory results were: white cell count (WCC) $10.5 \times 10^9/l$ (normal diff.); haemoglobin (Hb) 10.1g/dl; MCV 88 fl; normal coagulation screen, urea 14.7mmol/l; creatinine 736 μ mol/l; sodium 134mmol/l; potassium 3.5mmol/l; glucose 6.3mmol/l; and albumin 30g/l. Also, liver biochemistry was normal. An electrocardiogram (ECG) showed left ventricular hypertrophy by voltage criteria. Brain computerised tomography (CT) was normal. A lumbar puncture revealed clear cerebrospinal fluid (CSF) with negative Gram stain, and glucose content of 3.1mmol/l, protein content of 60mg/dl and no white cells. A diagnosis of viral encephalitis was made. Parenteral aciclovir 5mg/kg t.i.d. and parenteral cefotaxime 750mg eight hourly was administered to treat possible aspiration pneumonia.

Within 24 hours her GCS deteriorated to 3/15. Tone increased in all four limbs and knee reflexes became brisk bilaterally but there were no focal neurological signs. She was intubated in the Intensive Care Unit (ICU). A diagnosis of aciclovir neurotoxicity was considered and it was discontinued. A random serum aciclovir level was 24.3mg/l while the CSF aciclovir on admission was 2.1mg/l. She received haemodialysis on four consecutive days. On the fourth day, she commenced spontaneous eye opening and was moving all limbs spontaneously. Her GCS was 14/15. An EEG showed some left hemispheric

slow wave activity. One week later, she was orientated and mobilising with minimal assistance. She returned to baseline condition one month later.

Discussion

Neurotoxicity can follow oral or intravenous administration of aciclovir, but is usually associated with intravenous regimes. There is only one other reported case of coma following oral administration.¹ Absorption of oral aciclovir is slow with a bioavailability of 15-30%. Patients with impaired renal function are at greater risk of drug accumulation and it is excreted 85% unchanged in the urine. Following intravenous administration, the half-life is three hours, whereas in anuric patients the half-life is 20 hours.² There is negligible clearance from peritoneal dialysis but it is cleared by haemodialysis.

Neurological symptoms occurred after a short period despite appropriately adjusted dosage for renal failure.³ The total consumed dose was 3,200mg over 48 hours. Intravenous dosing schedule was higher than the 5mg/kg per 24 hours recommended in dialysis patients.⁴ The mean steady state plasma range of aciclovir following multiple oral dosing of 800mg capsules in normal adults is 1.6mg/l. Steady state mean plasma concentration following intravenous doses of 5mg/kg eight hourly is 10mg/l. CSF levels are normally 50% of serum levels.⁵ Our patient had neurological side-effects at a relatively low level of CSF aciclovir (2.1mg/l). Slow blood and brain equilibration may explain lack of correlation between CSF levels and toxicity.⁶ This lag⁷ has been termed 'anti-clockwise hysteresis'.⁸ Bataille et al⁹ noted CSF aciclovir concentrations twice that of serum levels following haemodialysis. Severe symptoms at serum levels of 24.3mg/l are consistent with the findings of others.¹⁰ The area under the concentration curve, rather than peak concentration, correlates best with side-effects.

Oral administration of aciclovir accelerates healing and reduces the severity of acute neuritis in immunocompetent patients with herpes zoster infection. Nucleoside analogues do not reduce post-herpetic neuralgia¹¹ but are effective in reducing zoster-associated pain. As many patients with herpes zoster

are elderly, caution should be exercised when prescribing orally-administered acyclovir. Caution should also be extended to other anti-viral nucleoside analogues.^{12,13}

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