Viral encephalitis masking acyclovir neurotoxicity? A case report

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Abstract - Neurotoxicity of acyclovir is an often reported side effect, especially in critically ill patients with renal failure, but this diagnosis is often overlooked due to overlapping pathological symptoms. To illustrate this we present a 69-year-old woman on immunosuppressive therapy for a kidney transplant with a deteriorating clinical course of Epstein Barr virus encephalitis who was transferred to the intensive care unit and died after developing acute renal failure during treatment with high dose (10 mg/kg tid) intravenous acyclovir. Acyclovir serum concentrations were measured (trough 2.9 – 5.1 mg/L) indicating that at least part of the patient’s encephalopathy may have been the result of acyclovir neurotoxicity, thus complicating the clinical decision making on the intensive care unit. Although no threshold for acyclovir trough concentrations has been established to assess the risk of neurotoxicity, the contribution of this adverse effect to the neurological findings in our patient cannot be excluded. Further efforts to investigate the relationship between acyclovir exposure and neurotoxicity are warranted.

Keywords - acyclovir, neurotoxicity, renal failure, encephalitis

Introduction

Intravenous acyclovir and its oral pro-drug valacyclovir are both used for prophylaxis and treatment of specific viral infections (herpes simplex virus, varicella zoster virus, Epstein Barr virus). After phosphorylation by viral thymidine kinase in infected cells, acyclovir inhibits viral DNA polymerase activity preventing further replication of the virus. Acyclovir is eliminated from the circulation predominantly by glomerular filtration and tubular secretion in the kidney. In patients with normal renal function a half-life of about three hours is observed [1].

Although therapy with acyclovir or valacyclovir is generally associated with a favourable drug safety profile, serious adverse events such as acute renal failure and neurotoxicity may develop in specific clinical situations.

Cases of neurotoxicity related to treatment with acyclovir or valacyclovir are regularly reported and include intensive care patients [2-7]. Moreover, several reviews have addressed the risk factors associated with acyclovir neurotoxicity [7, 8]. Nevertheless, in clinical practice this adverse drug effect can be easily overlooked due to an overlap with pathological symptoms of viral infections of the brain (e.g. agitation, psychosis, encephalopathy, coma). To illustrate this we present a patient who was particularly at risk for this adverse drug reaction and may be typical of patients in a critical care setting.

Case report

A 69-year-old female (62 kg) was admitted to our hospital with dysphagia, severe oral herpes stomatitis, diarrhoea, loss of weight, poor nutritional status, dehydration and drowsiness. She had undergone kidney transplantation six years earlier for which she was being treated with immunosuppressive drugs (mycophenolate mofetil, prednisolone). In the year before admission she underwent an anterior vaginal wall plasty for cystocele. In the first few days after admission her condition deteriorated and signs of encephalopathy developed (delirium, loss of consciousness, disorientation, lethargy). A computer tomography scan revealed right temporal and frontal hypodensity and intravenous acyclovir 600 mg (10 mg/kg) tid was started on day three for suspected herpes encephalitis (estimated creatinine clearance: 43 ml/min). Cerebrospinal fluid tested negative (polymerase chain reaction) for herpes simplex virus, varicella zoster virus and cytomegalovirus, but highly positive for Epstein Barr virus, upon which acyclovir was continued as the only treatment option. For atrial fibrillation digoxin and acenocoumarol were started. Due to a large bleeding leg wound and rectal blood loss, acenocoumarol was stopped after three days. Over the next week the patient’s level of consciousness first seemed to improve but then progressively developed into a coma. She also developed hypotension and respiratory insufficiency and 16 days after admission she was transferred to the intensive care department (ICU). There she was stabilized, ventilated and treated with antibiotics for sepsis. Antiepileptic treatment (phenytoin/valproic acid) was started based on a pattern suspect for temporal epileptiform activity on the encephalogram. This activity had resolved when the encephalogram was repeated three days later.

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During the first few days on the ICU the patient’s coma worsened (Glasgow coma scale score decreased from 10 to 3) in the absence of sedative medication. Renal function rapidly decreased and continuous renal replacement therapy (CVVH) was started on day 20. The acyclovir dosage was not reduced according to renal function leading to serum trough concentrations (determined in venous blood samples drawn just before dosing) ranging from 2.9 to 5.1 mg/L (Figure 1). On day 21 the acyclovir was stopped. Five consecutive acyclovir concentration measurements after the acyclovir dose showed a high peak (35.9 mg/L) followed by a slow elimination rate with a calculated half-life of 19.4 hours.

Following sigmoidoscopy, showing a widely distended colon with ischaemia, a perforation occurred and a rectosigmoid resection was performed on day 22. Postoperatively, the patient did not recover from her coma, which was attributed to EBV encephalitis although the contribution of acyclovir neurotoxicity could not be excluded. On day 25 the patient died.

Discussion
This case report illustrates the need to carefully calculate the dose of acyclovir in patients with renal failure. The recommended dose for intravenous acyclovir ranges from 5-10 mg/kg every 8 hours in patients with normal renal function to the same dose every 24 hours in patients with end stage renal failure or on haemodialysis [1]. In our case, a schedule of 10 mg/kg tid was chosen to treat viral encephalitis in an immunocompromised patient. With approximately 50% of the serum concentration achieved in the cerebrospinal fluid this dose was appropriate for use as a starting schedule, but should have been reduced according to the patient’s renal function on the second treatment day to 10 mg/kg bid. When acyclovir was started, renal function was already impaired (plasma creatinine: 135 mmol/L), but improved somewhat before transfer to ICU. Moreover, considering the patient’s poor nutritional status and reduced muscle mass, renal function calculated on plasma creatinine values would likely be overestimated. Unexpectedly, the initial development of renal failure was not associated with a corresponding rise in acyclovir trough concentrations. Only after the last dose of acyclovir, when severe renal failure had led to the start of CVVH, were acyclovir concentrations very high and only slowly decreasing with elimination dependent on haemofiltration. Acyclovir is known to potentially induce acute renal failure especially when high doses are rapidly infused intravenously. This is due to the formation of crystals in the renal tubules and may be prevented by administration, as in case of our patient, at a slow infusion rate (max. 500 mg/h) and maintaining an adequate hydration status [9, 10]. Neurotoxicity is the most prominent but reversible side effect of acyclovir overdosage. The symptoms are related to the serum concentration and include symptoms such as headache, lethargy, tremor, agitation, ataxia, dysarthria, confusion, hallucinations, psychosis, encephalopathy and coma [1, 11]. Acyclovir may have a direct toxic effect in the brain, but other mechanisms have also been proposed [8]. A concentration-effect relationship has been suggested for acyclovir with anticlockwise hysteresis, reflecting the process of equilibration between blood and cerebrospinal fluid [11]. This may explain why toxicity is reported to occur at varying serum concentrations, even below the trough concentrations we observed in our patient [11, 12]. From this we can conclude that an established trough concentration threshold that predicts neurotoxicity cannot be given. Instead, other pharmacokinetic parameters that reflect exposure to acyclovir, such as the area under the concentration-time curve (AUC), may prove to have better predictive value [13]. To test this hypothesis additional collection of both concentration measurements and clinical data is required as part of routine clinical practice especially in patients at risk for acyclovir neurotoxicity, such as those with renal failure and patients with a critical illness. Preferably, the possible role of intracellular concentrations of phosphorylated acyclovir as well as the involvement of one of the metabolites of acyclovir (CMMG) in neurotoxicity should then also be taken into account [14].

In our patient acyclovir neurotoxicity was not considered until after the last dose of acyclovir, when a high serum peak concentration was measured and a slow concentration decrease was observed. To determine the patient’s prognosis, it was difficult to discriminate between EBV encephalitis as the cause of persisting coma or the masking effect of acyclovir neurotoxicity, because the symptoms mainly overlap [15]. Also, renal failure with uraemia could have contributed to the altered level of consciousness. Four days after discontinuation of acyclovir, plasma levels were low and it was concluded that remaining toxic effects of acyclovir were unlikely to contribute to the comatose state of the patient. Although the clinical

Figure 1

Measurements of acyclovir and creatinine concentrations during hospital admission. Acyclovir concentrations determined in venous samples just before dosing (●) and the concentration profile after the last dose (●) are indicated distinctively.
presentation of the patient can be solely attributed to the encephalopathy caused by the EBV in combination with the metabolic and epileptic activity, we cannot exclude that toxicity of acyclovir contributed to the earlier neurological findings during treatment. According to a method described by Naranjo et al to estimate the probability of the patient's symptoms being an adverse drug reaction we would classify the likelihood as 'possible (score 3)' [16].

References


