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Letter

Time-dependent changes in serum concentrations of acyclovir and its metabolite, 9-carboxymethoxymethylguanine, in a patient with suspected acyclovir encephalopathy

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ABSTRACT — Valacyclovir, a prodrug of acyclovir, may cause adverse drug reactions, so called acyclovir encephalopathy. The acyclovir encephalopathy may not be explained simply by acyclovir blood concentrations, because recent reports suggest the involvement of 9-carboxymethoxymethylguanine (CMMG), a major metabolite of acyclovir. The present study demonstrates changes in serum concentrations of acyclovir and CMMG in a patient with suspected acyclovir encephalopathy. A 63-year-old male was prescribed loxoprofen and valacyclovir for herpes zoster. Seven days after the start of medication, he showed signs of confusion. The next morning, he was emergently transported to hospital for a suspected stroke. There was no stroke lesion but evidence of acute kidney injury, so the patient was given emergency dialysis. With daily hemodialysis sessions performed for three days, the serum concentrations of acyclovir and CMMG decreased, and his state of consciousness improved accordingly.The metabolite CMMG, as well as acyclovir, is efficiently removed by hemodialysis and symptoms of acyclovir encephalopathy improved with decreased serum concentrations. Therefore, if other organic diseases can be ruled out in a patient with suspected acyclovir encephalopathy, it is advisable to introduce hemodialysis immediately.

Key words: Valacyclovir, Acyclovir, 9-Carboxymethoxymethylguanine, Encephalopathy, Hemodialysis

INTRODUCTION

Valacyclovir, a L-valyl ester of acyclovir, is hydrolyzed to acyclovir mainly by the hepatic first-pass effect after oral administration (Fig. 1). Acyclovir (ACV) is phosphorylated by thymidine kinase in the herpes virus to form active acyclovir triphosphate, resulting in inhibition of viral DNA strand formation. Because it is not phosphorylated in host cells, it exhibits selective toxicity to viruses. The neuropsychiatric symptoms, so called acyclovir encephalopathy, include symptoms such as dysphoria, tremor, and disturbance of consciousness with hallucina-

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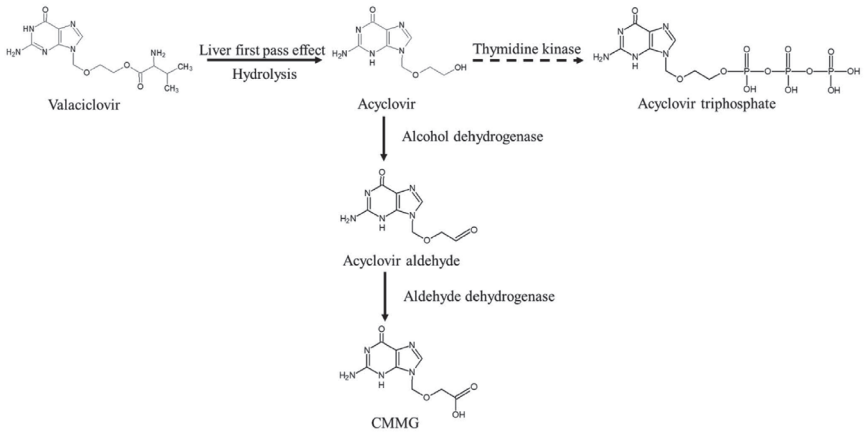

Fig. 1. Metabolic pathways of valacyclovir.

tions. Because acyclovir is a drug of urinary excretion, the blood concentrations tend to be higher in patients with impaired renal function. The dosage might be reduced according to renal function; however, acyclovir encephalopathy sometimes occurs in patients with renal dysfunction, the elderly, chronic kidney disease undergoing dialysis (Togawa *et al*., 2007).

The encephalopathy caused by ACV may not be explained simply by its blood concentrations, because recent reports have suggested the involvement of 9-carboxymethoxymethylguanine (CMMG), a major metabolite of acyclovir (Togawa *et al.*, 2007; Helldén *et al*., 2003). However, few cases have reported blood CMMG levels in ACV encephalopathy, and its time-dependent changes have not been reported at all.

In this study, we report changes in blood concentrations of ACV and CMMG in a patient with neuropsychiatric symptoms and suspected ACV encephalopathy due to valacyclovir treatment.

Case

A 63-year-old male with hypertension, who showed normal renal function eight months ago, was prescribed loxoprofen 60 mg twice a day and valacyclovir 500 mg three times a day by a local doctor for herpes zoster. Seven days after the start of medication, he showed signs of confusion, such as shouting, soliloquy, and inconsistent words and deeds. The next morning, his symptoms did not improve, and he was emergently transported to hospital for a suspected stroke. There was no stroke lesion but evidence of acute kidney injury (AKI), so the patient was transported to our hospital for emergency dialysis.

The Glasgow Coma Scale (GCS) was 10 (E4V2M4) for the patient on the first hospital day, and no stroke lesions were found on CT or MRI. On the other hand, BUN, Cr, FENa and FEUN were 85.4 mg/dL, 12.9 mg/dL, 20.3% and 62.4%, respectively (Fig. 2). Therefore, considering the possibility of rapidly progressive glomerulonephritis (RPGN), anti-glomerular basement membrane antibodies (anti-GBM antibodies), anti-neutrophil cytoplasmic antibodies (ANCA), and other collagen disease markers were measured, but all were negative.

Based on these results and the history of neuropsychiatric symptoms within a week after valacyclovir administration, we considered acyclovir encephalopathy to be the most likely cause and decided to perform hemodialysis (HD) for three days. Dexmedetomidine and propofol were administered to treat restlessness. Fentanyl was added on hospital Day 2, as dexmedetomidine and propofol were no longer effective. On Day 3, GCS was E4VTM6 and the disorientation improved. His BUN and Cr were 36.8 mg/dL and 6.75 mg/dL, respectively, indicating that renal function was improving (Fig. 2). On Day 7, BUN and Cr were 49.6 mg/dL and 3.40 mg/dL, respectively, indicating that Cr showed a tendency to improve, and the patient started walking (Fig. 2).

Consent for publication of this case was obtained.

MATERIALS AND METHODS

Reagents

Acyclovir and penciclovir were purchased from Tokyo Chemical Industry Co., LTD. (Tokyo, Japan). The 9-carboxymethoxymethylguanine (CMMG) was purchased from Toronto Research Chemicals (Ontario, Canada). Human serum was purchased from Cosmo Bio Co., LTD. (Tokyo, Japan). All other reagents used were of the highest grade commercially available.

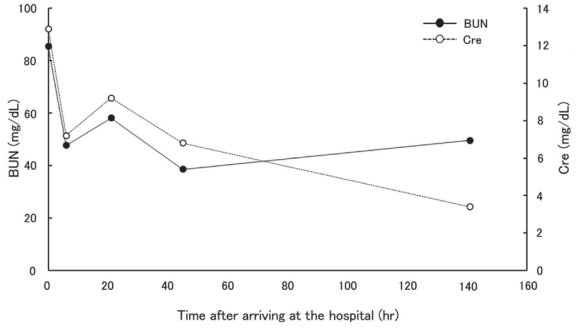

Fig. 2. Changes in serum concentration of BUN, creatinine in patient serum.

Sample preparation

Calibration standards were prepared by mixing appropriate amounts of standard solutions and drug-free human serum. The concentration range of the calibration curve was 0.1–25 mg/mL for acyclovir and 0.1–50 mg/mL for CMMG.

Serum samples (calibration standards or patient samples; 150 mL) were mixed vigorously with 100 mg of ammonium sulfate and 50 mL of 7% [v/v] aqueous perchloric acid solution (containing 500 ng of pencyclovir as an internal standard) for 30 sec and were then centrifuged at 15,000 × g at 4°C. The supernatant was filtered and subjected to HPLC analysis.

HPLC analysis

The 20 mL portion of samples were analyzed by using the HPLC-SPD-M20A at 255 nm and a Prodigy 5u ODS column (150 x 4.6 mm, 5 m particle size; Phenomenex, Torrance, CA, USA). The column temperature was set at 25°C. Gradient elution was performed with (A) 0.08% [v/v] trifluoroacetic acid solution (pH 2.3) and (B) methanol at a flow rate of 1 mL/min. The initial elution condition was set at 4% B for 7 min, then immediately changed to 60% B and held for 3 min. Afterwards, the gradient went back to 4% B, which was held for another 10 min.

RESULTS

Under the present HPLC conditions, the retention times of acyclovir, CMMG, and pencyclovir (IS) were 6.3 min, 6.8 min, 7.3 min, respectively (Fig. 3A). The chromatogram of the patient's serum on Day 1 is shown in Fig. 3B. The concentrations of ACV and CMMG in patient serum calculated from the calibration curve are shown in Fig. 3C. The ACV and CMMG concentrations before HD on Day 1 were 11.2 μg/mL and 36.4 μg/mL, respectively, well above the reported blood concentrations at which ACV encephalopathy develops. The ACV and CMMG concentrations before HD on Day 2 were 5.39 μg/mL and 16.37 μg/mL, respectively, which were still in the levels of intoxication. Before HD on Day 3, GCS scored E4VTM6, disorientation had improved, and blood ACV concentration had decreased to 2.26 μg/mL, although it was still higher than the effective blood concentration. In addition, the blood CMMG concentration was 7.22 μg/mL. On Day 7, blood ACV and CMMG levels were below the detection limit (0.1 μg/mL).

DISCUSSION

Acyclovir causes crystallization when the concentration of ACV in the renal tubules exceeds the solubility level due to overdose or decreased urine output. The ACV crystals cause nephrogenic damage by obstructing the intratubules. Loxoprofen causes drug-induced kidney injury but induces pre-renal kidney injury due to decreased renal blood flow. However, values of FENa and FEUN of this patient ruled out the possibility of loxoprofen-induced pre-renal AKI. This patient was considered to have AKI due to ACV.

Renal dysfunction due to ACV occurs 24–48 hr after initiation of medication but is often overlooked due to poor subjective symptoms. As a result, ACV may accumulate and cause encephalopathy three to five days after starting ACV medication. In the patient, symptoms suggesting ACV encephalopathy developed seven days after the start of administration.

Valacyclovir, a prodrug of acyclovir, shows improved gastrointestinal absorption; bioavailability of valacyclovir is about 54% whereas acyclovir is about 10–20%. Therefore, an oral dose can be reduced compared with the active drug, but the ACV blood concentration could be increased by valacyclovir treatment. The mean of maximum plasma concentration for a single oral dose of 800 mg acyclovir is 0.94 μg/mL (Sasa and Hayashi, 1990), whereas the mean of maximum plasma concentration for a single oral dose of 500 mg valacyclovir is 3.66 μg/mL (Azuma *et al*., 1998).

Although ACV encephalopathy may generally occur when ACV blood levels exceed 4 μg/mL, there is a report that ACV encephalopathy arose even at 2 μg/mL (Helldén *et al*., 2006; Iijima *et al*., 2003). In addition, previous reports suggest that ACV encephalopathy develops in patients with blood CMMG concentrations of approximately 6 to 10 μg/mL or higher (Togawa *et al*., 2007; Helldén *et al*., 2006). The blood levels of ACV and

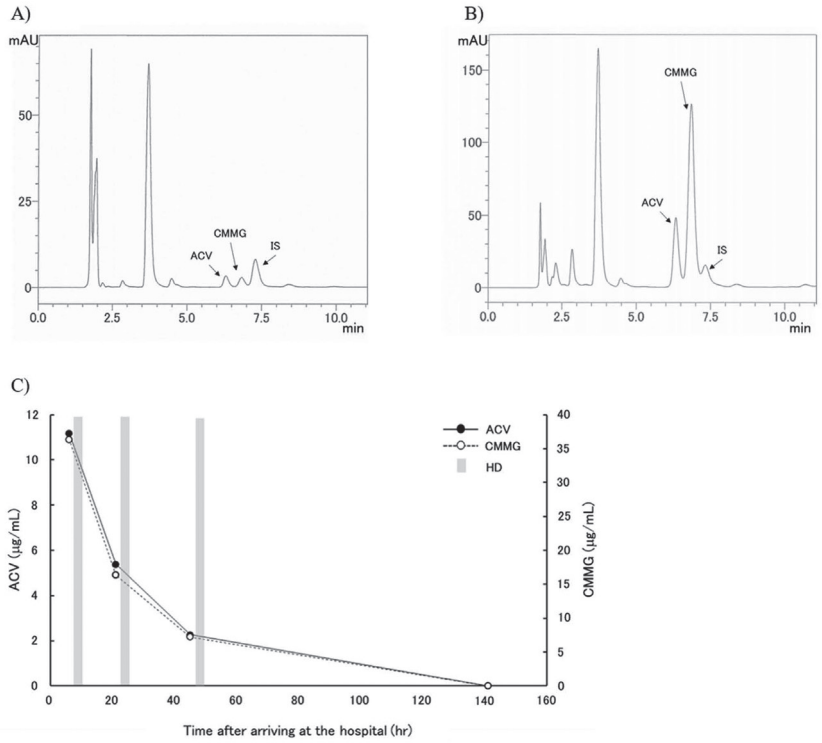

Fig. 3. HPLC chromatogram and changes in serum concentration of ACV and CMMG. A) HPLC chromatogram of calibration standard (ACV 1 μg/mL, CMMG 1 μg/mL, and pencyclovir (IS) 2.5 μg/mL). B) HPLC chromatogram of patient serum on Day 1. C) Acyclovir and CMMG concentrations changes in serum of the patient.

CMMG in the patient on Day 1 were 11.2 μg/mL and 36.4 μg/mL, respectively, which were substantially higher than the previously reported cases. No abnormalities in the brain on MRI scan or other tests ruled out the possibility of organic brain disease and the patient was considered to be an acyclovir encephalopathy patient.

The half-life of acyclovir is usually 2 to 3 hr but is prolonged to about 20 hr in patients with renal dysfunction (Laskin *et al.*, 1982). Individual differences in this regard are large; cases that exceeded 40 hr have been reported (Kokubo *et al*., 2004). Although there is no treatment specific for acyclovir encephalopathy, repeated dialysis is recommended for patients with impaired consciousness or respiratory distress. In the present patient, ACV was effectively eliminated by dialysis. The efficacy of dialysis for CMMG has not been reported previously. However, CMMG was effectively eliminated by dialysis in a similar manner with ACV in this case.

We have also experienced a case with comparatively low CMMG concentrations and mild symptoms of encephalopathy, although blood ACV concentrations were comparable to the present case. Blood concentrations of ACV do not correlate with those of CMMG (Togawa *et al*., 2007). In addition, ACV is transferred to the central nervous system, and its concentration in the cerebrospinal fluid is approximately 60% of that in the blood (Lindström *et al*., 2019). However, the blood-brain barrier penetration of CMMG is low (Lindström *et al*., 2019), making it difficult to measure the concentration of CMMG in cerebrospinal fluid. On the other hand, CMMG concentration in cerebrospinal fluid is increased in patients with neuropsychiatric symptoms (Helldén *et al*., 2006; Lindström *et al*., 2019). It can be inferred that CMMG contributes to the development of ACV encephalopathy.

This study showed that CMMG, as well as ACV, is efficiently removed by HD and that symptoms of ACV encephalopathy improved with a concomitant decrease in blood ACV and CMMG levels. Therefore, if other organic diseases can be ruled out in patients with suspected ACV encephalopathy, it is advisable to introduce HD as soon as possible.

Conflict of interest---- The authors declare that there is no conflict of interest.

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