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Views and Practice

Acyclovir dosing adjustment in a chronic kidney disease patient with continuous ambulatory peritoneal dialysis

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Introduction

Herpes Zoster (HZ) is a viral infection caused by latent VZV (Varicella Zoster Virus) reactivation from the sensory ganglia.[1] Several risk factors can trigger the reactivation, either by disruption of the immune system due to the natural ageing process or due to immunosuppressive conditions such as diabetes, genetic vulnerability, mechanical trauma, psychological stress, malignancy, and kidney failure.[2] Furthermore, in patients with kidney failure or chronic kidney disease (CKD), the use of various dialysis modalities such as haemodialysis (HD), peritoneal dialysis (PD) or kidney transplant also increases the risk of HZ.

Generally, long-term HD has a higher risk of HZ compared to the normal population and patients with PD have a higher risk of HZ compared to HD patients.[3] According to the data from a Taiwan National Health Insurance Research Database cohort study between 1999-2009 in which 843 CKD patients underwent HD, more than 30% of patients were reported to have had HZ, compared to >15% in subjects without CKD.[3] Continuous ambulatory peritoneal dialysis (CAPD) is one of the modalities in maintaining kidney function in CKD patients. In contrast to HD, which is machine-based, CAPD uses peritoneal membrane as a substitute for kidney function. CAPD uses a glucose-contain dialysate solution that is inserted into the body through a catheter implanted in the abdominal cavity, in which diffusion and filtration by the blood vessels occur.[4]

Dose regulation in CKD patients is crucial, considering limited kidney excretion and the risk of neurotoxicity due to excess acyclovir metabolites. However, inadequate acyclovir dosing can also increase the risk of encephalitis. The clinical symptoms of neurotoxicity caused by acyclovir and herpes encephalitis are similar, making these two entities a diagnostic challenge. Immediate management of both diagnoses is imperative and is completely contradictory, thus requiring special medical expertise.

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Case report

A 38-year-old woman presented to the emergency department with throbbing pain on the left back which had spread to her left breast over the previous six days. Clustered blisters were found in the painful area. There was no response to antibiotic and antiviral ointments. There was six-year history of CKD due to hypertension, for which she had undergone HD during the first two years and was currently on CAPD for the past four years. She was taking medications for hypertension and hyperuricemia, vitamin and iron supplements from her internist. There was a past history of chickenpox.

Physical examination showed erythematous clustered vesicles with multiple erythematous papules on the left-back, lateral side, and lower left breast area (Figure 1a). Routine investigations were as follows: haemoglobin 7.5 g/dL, haematocrit 22%, erythrocytes 2.8 ml/µL, leukocytes 2930/µL, urea 11.6 mg/dL, and creatinine 115 mg/dL. A Tzanck test from a vesicle was positive in which multinucleated giant cells and squamous epithelial cells with an underlying PMN infiltrate were seen (Figure 2). Creatinine Clearance (CrCl) was also conducted to determine the proper acyclovir dosing in this case. The CrCl was 1.43 mL/min (normal range: 75-125 mL/min).

The history and clinical findings were consistent with herpes zoster. As her CrCl was reduced, she received 800 mg oral acyclovir every 12 hours for 7 days, 500 mg paracetamol for pain relief, salicylic powder to the intact vesicles, and mupirocin ointment to ruptured vesicles and erosions. The patient was subsequently discharged. The next day, the patient returned to the outpatient clinic with complaints of nausea and dizziness after consuming acyclovir. The throbbing pain and skin lesions had not improved. Acyclovir was resumed with a lower dose of 800 mg every 24 hours for 7 days.

When seen on the sixth day, there was clinical improvement of the lesions and decreased pain in the affected area, with erythematous crusts and multiple pustules on the left-back, lateral side and lower left breast. There were no new vesicles (Figure 1b). Oral acyclovir 800 mg every 24 hours was continued for another seven days.

Discussion

The kidney functions as an excretory organ and also as an immunomodulator.[5] Several studies have shown that a decreased glomerular filtration rate in CKD patients affects the circulation of dendritic cells, naive T-cell, and CD4 central memory cells.

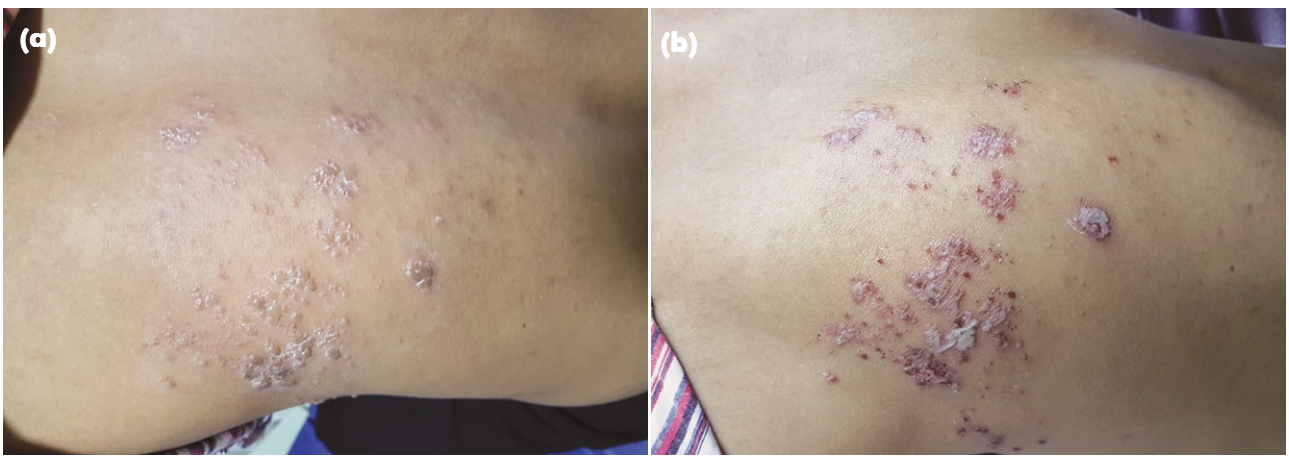

Figure 1. (a) Multiple clusters of vesicles with an erythematous base on the left posterior and lateral thorax at the first visit. (b) Follow-up on the sixth day, improvement of the lesions with multiple crusted vesicles and residual pustules.

Furthermore, a disturbed immune response can also be caused by uraemic toxin accumulation in CKD patients, thus affecting chemotaxis, phagocytosis, antigen exposure, antibody production, cytokine regulation, and T cell balance.[6] In our case, the patient had a history of CKD. Several studies have reported that patients with PD experienced loss of macrophages and immunoglobulin due to dialysate solution, thus affecting humoral immunity. Also, a decrease in VZV specific T-cell is a risk factor of HZ, whereas patients with PD had more disturbed cell-mediated response compared to HD patients.[6]

Acyclovir and its main metabolite (9-CMMG) are excreted through the kidney, therefore acyclovir dose should be adjusted in CKD patients to prevent neurotoxicity due to reduced excretion.[7] In patients with kidney dysfunction, the half-life of acyclovir is increased from 2-3 hours to 14 hours. The protein that acts in regulating substance transport between the brain and cerebrospinal fluid (CSF) barriers is inhibited by acyclovir and 9-CMMG, which leads to metabolite accumulation, which in turn decreases metabolism and CSF secretion in the brain.[8]

Acyclovir dosing should be modified to the glomerular filtration rate (GFR) and CrCl can be calculated using a GFR estimate using the *Cockcroft Gault* formula or a more precise calculation using 24 hour urine. Dosing adjustment based on British Medical Association Royal Pharmaceutical Society of Great Britain in 2015, is as follows; CrCl >50 mL/min: 800 mg 5 times daily, CrCl 30-50 mL/min: 800 mg every 8 hours, CrCl 10-29 mL/min 800 mg every 12 hours, and CrCl <10 mL/min: 800 mg daily.[9] Gilmartin et al. stated dosing adjustment for oral acyclovir as follows: CrCl ≤10 mL/min: 800 mg every 12 hours, CrCl 10-25 mL/min: 800 mg every 8 hours, and CrCl >25 mL/min: 800 mg every 4 hours (no adjustment).[10]

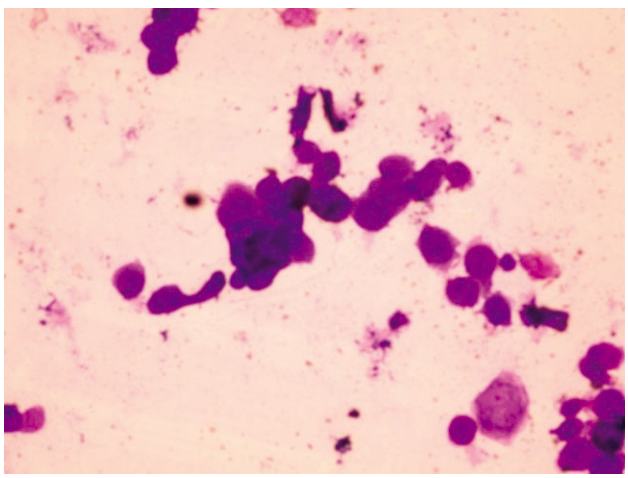

Figure 2. Tzanck smear: multinucleated giant cells (Giemsa stain).

In our case, as the patient complained of nausea and dizziness with oral acyclovir 800 mg every 12 hours, but was able to tolerate treatment after reducing the dose was reduced to 800 mg every 24 hours for 7 days. Symptoms like nausea and dizziness should not be underestimated since these may indicate neurotoxicity and encephalitis. Neurotoxicity caused by acyclovir is an emergency that should be immediate management. It is vital to distinguish neurotoxicity this from herpes encephalitis since they have similar clinical symptoms but the management is the reverse of each other. History taking, clinical presentation, neurological examination, radiological examination of the head, serum 9-CMMG examination and lumbar puncture can help differentiate these two entities.[11]

In neurotoxicity, mental status changes, hallucinations, delusions, and involuntary motor movement often occur, while high fever, severe headache, and convulsion are found in herpes encephalitis.[8] When neurotoxicity due to acyclovir is suspected, diagnosis can be established from a lumbar puncture, with an increase of 9-CMMG in CSF or an increase of 9-CMMG serum level. Acyclovir neurotoxicity commonly shows no neurological deficit, with acellular CSF, normal CT scan, normal EEG and significant clinical improvement following discontinuation of acyclovir treatment and HD.[11] Several cycles of HD are necessary for severe neurotoxicity, in which HD for 3-4 hours can decrease acyclovir serum levels to 58% and 9-CMMG to 64%.[12]

Conflict of interest statement

The authors have no conflicts of interest to declare.

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