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Case Report Open Access

PRES Induced by Cyclosporin with Normal Blood Concentrations in a Bone Marrow Recipient

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Abstract

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinic neuroradiological entity. This syndrome occurs in complex conditions as allogenic bone marrow transplantation, organ transplantation and immunosuppressant therapy such as cyclosporin (CsA). The occurrence of PRES is favored by a high concentration of CsA. Therefore, therapeutic monitoring of CsA is necessary to effects due to overdose. The therapeutic range of CsA is between 150-300 ng/mL. We aimed to present a case PRES induced by CsA in bone marrow transplantation with normal cyclosporine blood concentrations.

Case: A 26 years old man received an allogenic bone marrow for bone marrow aplasia in January 2013. He was treated by CsA. Mean CsA dose was 2.57 mg/kg/day. CsA mean blood concentration was 295 ng/mL. After 20 days, our patient presented a complex partial seizure and cortical abnormal. He had no history of head injury, epilepsy or hypertension and there was no family history of neurological or psychiatric disorders. Patient's blood pressure wasn't measured. CsA was stopped. He received mycophenolate acid and clonazepam. Seizure and abnormal vision vanished 10 days later. Whereas, the patient developed graft-versus-host disease (GVHD). Then, mycophenolate acid was stopped 1.5 month later and CsA taken back. CsA mean dose was 1.1 mg/kg/day. Mean CsA blood concentration was 167.71 ng/mL. After two months, the patient developed general seizures and in Magnetic Resonance Imaging (MRI) there was a low-density in the subcortical white matter areas. So, CsA was stopped once and for all and the seizures vanished few days later.

Conclusion: PRES is responsible for various and no specific neurological symptoms. These symptoms are usually reversible but sometimes fatal. Therapeutic monitoring of CsA was necessary to avoid neurotoxicity depending of concentration but we must remain cautious even if patients have CsA blood concentrations in the therapeutic range.

Keywords: PRES; Bone marrow allograft; Cyclosporin; Therapeuti drug monitoring; Blood concentrations

Introduction

Posterior reversible encephalopathy syndrome (PRES) or hypertensive encephalopathy is a clinico-neuroradiological entity. PRES is neurotoxic state due to a failure of the cerebrovascular autoregulation in response to acute changes in blood pressure, which in turn results in a brain vasogenic edema most commonly in the parieto-occipital regions. It can present with focal neurologic deficits, mimicking a stroke and can often represent a diagnostic challenge when presenting atypically. Clinical presentation included seizures, encephalopathy, headache and visual disturbances. Fugate JE and al. identified etiologies of PRES. It included hypertension, cytotoxic medications, sepsis, preeclampsia or eclampsia, and multiple organ dysfunctions [1]. This syndrome is frequently recognized in complex conditions as allogeneic bone marrow transplantation, organ transplantation or immunosuppressant therapy such as cyclosporin (CsA). Imaging, clinical and laboratory features of this toxic state are becoming better elucidated. The occurrence of PRES is favored by high concentrations of CsA [2]. Therefore, therapeutic monitoring of CsA is necessary at least to avoid toxic adverse reactions. Trough concentration is more correlated to rejection and toxicity because peak concentration varied with the absorption and factors affecting this one [3]. The therapeutic range of CsA is between 150 – 300 ng/mL [4]. We aimed to present a case of PRES with normal trough blood concentrations of CsA. Case: A 26 years old man who received an allogenic bone marrow for bone marrow aplasia in January 2013. He was treated by intravenous injection of CsA, methyl prednisolone hemisuccinate, imipenem and amikacin. Mean CsA dose was 2.75 mg/kg/day (1.64 – 3.88 mg/kg/day). CsA mean tough blood concentration was 307.9 ng/mL (270.2 – 421.5 ng/mL). Bioavailability expressed by the ratio concentration/dose ranged from 84.34 to 164.58 ng.kg/mg.Ml (Table 1, Graph 1). Twenty days Later, our patient presented a complex partial seizure and a cortical abnormal vision. The patient's blood pressure wasn't measured at this moment. CsA was highly suspected in the occurrence of these neurological troubles and then was stopped. He received mycophenolate acid and clonazepam. Seizures and abnormal vision vanished ten days later. Our patient developed a graft-versus-host disease (GVHD). Mycophenolate acid was stopped after 1.5 month and CsA taken back. CsA mean dose was 1.14 mg/kg/day (1.04–1.34 mg/kg/day). He was taken intravenous injection of CsA. Mean CsA blood concentration was 141.1 ng/mL (40.4–421.5 ng/mL). Bioavailability expressed by the ratio concentration/dose ranged from 33.8 to 179.63 ng.kg/mg.mL (Table 1, Graph 1). Two months later, the patient developed general seizures and in MRI (Magnetic Resonance Imaging) there was a low-density in the subcortical white matter areas. CsA was stopped once and for all. Naranjo scale was 6. Thus, in this case, induction of PRES syndrome by CsA was probable.

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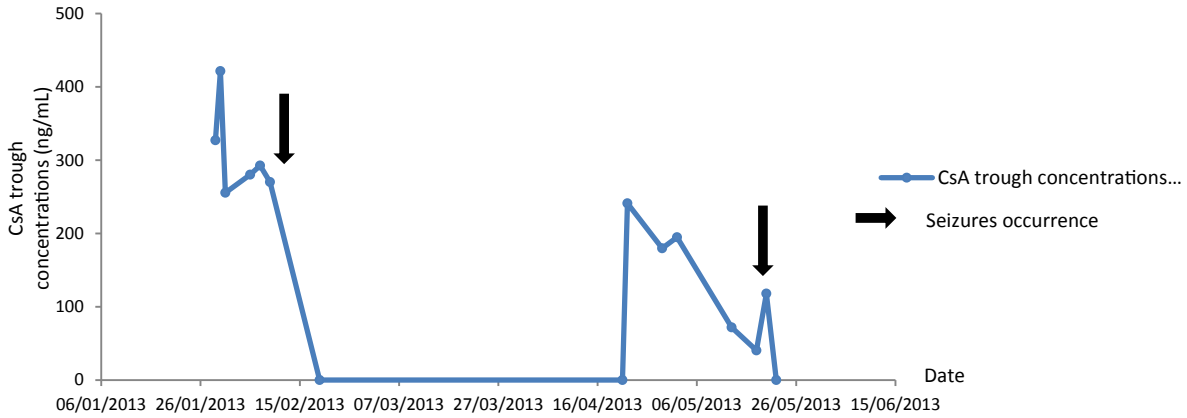

Graph 1: CsA trough blood concentrations in time

Date	Dose (mg/kg/d)	C0 (ng/mL)	C0/Dose
29/01	3.88	327.3	84.34
30/01	3.58	421.5	117.67
31/01	2.98	255.6	85.63
05/02	2.38	280.3	117.37
07/02	2.38	292.7	122.57
09/02	1.64	270.2	164.58
15/02	1st seizures and CsA withdrawal		
22/04	1.34	241.3	179.63
29/04	1.04	179.8	172.09
02/05	1.04	195	186.64
13/05	1.04	72	68.91
18/05	1.19	40.4	33.83
20/05	1.19	118.1	98.91
	2nd seizures and CsA withdrawal		

Table 1: Changes of doses, trough concentrations (C0) and bioavailability (C0/dose) of CsA in time

Discussion

CsA inhibits T-cell activation, proliferation and interleukin-2 production through inhibition of calcineurin pathway. CsA is associated with low-level neurotoxicity with an incidence of 10%–40% of the patients (tremors, anxiety and psychiatric dysfunction) [2]. The incidence of PRES after allogeneic bone marrow transplantation using myeloablative marrow preconditioning and CsA immune suppression is approximately 7–9% and appears to vary with the preconditioning regimen [2]. Bartynski concluded that immunosuppressant blood levels do not appear to correlate with severe neurotoxicity or PRES, but immunosuppressant discontinuation or switch usually results in clinical improvement [2]. But, Lier et al. suggested that when trough blood concentrations of CsA were supra therapeutic, risk of PRES increased [5]. According to Schwartz et al., CsA and neurologic toxicity is more frequent in patients who had a trend toward higher serum levels of CsA in the days preceding the onset of the syndrome [6]. In our case, CsA trough blood concentration was in the therapeutic range with a trend toward higher serum levels. Neurological toxicity can be explained by the ABCB1 gene polymorphism. In fact, this gene encodes for the synthesis of the P-glycoprotein which is present on the blood-brain barrier [7]. It contributes to the protection and detoxification of the central nervous system by limiting the entry of drugs. ABCB1 gene polymorphism multiplies intracerebral passage of CsA through 55 times [7]. *In vitro*, studies have shown that CsA has toxic effect on glial cells responsible for dendritic myelination and endothelial cells in culture and that the severity of the toxic damage was correlated with the duration of exposure [5]. Histologic evaluation of PRES demonstrated evidence of demyelination and myelin pallor along with evidence of ischemia, neuronal anoxic damage, laminar necrosis, or older hemorrhage in the white matter and cortex [2]. PRES occurs most commonly in the first month of CsA therapy [2]. Our patient developed PRES 20 days after. PRES is responsible for various and no specific neurological symptoms as confusion, coma, seizures and visual disturbances [8]. These symptoms are usually reversible but sometimes fatal [5]. In the study of Hinchey et al. about 15 patients, the neurologic deficits resolved within two weeks in all cases [9]. In our case, the symptom resolved in 10 days. PRES was associated with moderate to severe hypertension in 70% - 80% of patients [2] unlike our patient. PRES can be explaining by two mechanisms. The first is a dysfunction of autoregulation. The autoregulatory capacity of brain vasculature is exceeded in case of sudden elevation in systolic blood pressure. This results in a region of vasodilatation and vasoconstriction, especially in the arterial boundary zone (since cerebrovascular resistance and cerebral vascular flow changes passively follow cerebral perfusion pressure) causing a breakdown of the blood–brain barrier with subsequent transudation of fluid along with hemorrhage. The preferential involvement of the posterior circulation has been postulated as being due to the sympathetic innervation protecting the brain from sudden increase in blood pressure being relatively less in the arterioles supplied by the vertebrobasilar system than in the anterior circulation [10]. In the setting of normotensive PRES, the second mechanism may be based on an endothelial dysfunction, immune system activation and other systemic features. Although initially edema is vasogenic in nature, a failure to reverse the disease etiology will subsequently cause cytotoxic edema and eventually brain infarction, further emphasizing the importance of early disease recognition [11]. Reece et al. cited the following risk factors for neurotoxicity in case of CsA therapy: use of unrelated or HLA mismatched related donors, total body irradiation as part of conditioning, use of corticosteroids for prophylaxis or treatment of acute GVHD, or development of either acute GVHD or clinically significant microangiopathic hemolytic anemia post-BMT [12]. Our patient was taken corticosteroids and had GVHD. The MRI frequently objectified hypodensities at the subcortical white matter mainly parieto-occpital. These brain lesions are commonly grouped under the name “leuko encephalopathy associated with immune suppressants” [5].

Conclusion

We report a case of PRES with normal trough blood concentration of CsA. Therapeutic monitoring of CsA was necessary to prevent neurotoxicity concentration dependant but we must remain cautious even if patients have CsA blood concentrations in the therapeutic range.

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