

Lessons of the month 2: A case of inappropriate drug–drug interaction in kidney transplant

Authors: Min-Hui Tan,^A Seow-Yeing Yee^A and Rosnawati Yahya^A

ABSTRACT

Carbamazepine remains a first-line antiepileptic medication for the treatment of partial seizures. Despite its widespread use, carbamazepine has significant neurotoxicity and hypersensitivity reactions. We report a case of a patient post-kidney transplant who was on regular carbamazepine for childhood epilepsy and developed nystagmus, diplopia and a broad-based gait after receiving diltiazem. Understanding of the interaction between diltiazem and carbamazepine is necessary to prevent the neurotoxic effects.

KEYWORDS: carbamazepine, diltiazem, drug interaction, kidney transplant, neurotoxicity

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Introduction

Carbamazepine is a commonly used first-line agent for treatment of epilepsy. However, it can cause significant neurotoxicity and hypersensitivity reactions due to high concentrations of its active metabolite in response to co-administration of other medications. Here, we report a case of inappropriate co-administration of diltiazem leading to carbamazepine toxicity in a patient post-kidney transplant.

Case presentation

A 49-year-old man was admitted urgently for symptoms of lethargy, tinnitus and blurring of vision over 4 days. He was a recipient of a living-unrelated kidney transplant 27 years ago with his primary renal disease being lupus nephritis. His other medical history included childhood epilepsy, hypertension, old lacunar infarct and history of pulmonary tuberculosis (in which he had completed treatment 11 years previously).

He was a chronic smoker of 1 pack per day. He denied any allergies. His medications were prednisolone, cyclosporin, carbamazepine, sodium valproate, metoprolol, felodipine, Cardiprin and simvastatin. He claimed compliant to these medications.

A week prior to this, he was admitted for acute allograft dysfunction (his creatinine level rose from 186 to 236 $\mu\text{mol/L}$). His allograft biopsy showed borderline rejection for which he received intravenous methylprednisolone and his immunosuppression regimen was augmented. His cyclosporin was changed to tacrolimus and felodipine was changed to diltiazem to help achieve adequate trough levels of tacrolimus, as part of cost-saving measures.

During this admission, he was haemodynamically stable and afebrile. His cardiovascular and respiratory examinations were unremarkable. His abdomen was soft with no graft tenderness and there was no organomegaly. He had bilateral bidirectional nystagmus but no papilloedema on funduscopy. His other cranial nerves examination was normal. He had broad-based gait but had no past-pointing, no dysidiadochokinesia and Romberg's test was negative. Examination of his bilateral upper and lower limbs revealed normal tone and power with intact reflexes and sensation.

Initial differential diagnoses included central nervous system pathology or drug toxicity. An urgent computed tomography of the brain showed old lacunar infarcts with no evidence of haemorrhage, thus excluding acute intracranial pathology. A brief review of his blood results revealed normal electrolytes but high trough carbamazepine level. His serial investigations are shown in Table 1. Therefore, he was diagnosed with carbamazepine toxicity due to cytochrome P450 inhibition by co-administration of diltiazem.

His carbamazepine was withheld for a day and restarted at lower dose after that. The neurological symptoms improved during the hospital stay after reduction of carbamazepine dose, and he was discharged well with regular therapeutic drug monitoring. His visual impairment and tinnitus resolved completely during the outpatient clinic review.

Discussion

Tacrolimus has become a central part of the modern immunosuppression regimen for kidney transplants since the publication of the ELITE SYMPHONY trial.¹ Despite its high intra- and inter-individual variability, the high cost of tacrolimus puts tremendous pressure on the healthcare expenditure. Administration of diltiazem is known to increase concentrations of tacrolimus in kidney transplant recipients, thus resulting in a tacrolimus-sparing effect. This occurs via two mechanisms, namely either through diltiazem-induced inhibition of cytochrome P450 3A4-mediated presystemic tacrolimus metabolism or through inhibition of transport by P-glycoprotein.^{2,3}

Authors: ^Aconsultant nephrologist, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Table 1. Serial investigations trend

	3 months prior	Acute rejection episode	1 week before current admission	Current admission	On discharge	10 days post-discharge	Normal range
Hb, g/dL	14.2	12.9	N/A	12.1	11.5	13.2	13.0–17.0
WBC, × 10 ⁹ /L	10.8	11.4	N/A	11.3	8.8	10.5	4.0–10.0
Platelet, × 10 ⁹ /L	351	306	N/A	251	265	298	150–410
Urea, mmol/L	11.7	17.2	17.8	14.5	15.5	16.4	2.8–8.1
Na, mmol/L	139	136	142	136	141	142	136–145
K, mmol/L	4.5	4.7	5.1	4.8	5.6	5.7	3.5–5.0
Creatinine, µmol/L	186	236	255	224	261	258	62–106
Albumin, g/L	41	37	N/A	32	30	37	35–52
ALT, U/L	11	13	N/A	29	26	33	0–41
ALP, U/L	65	62	N/A	60	65	80	40–130
Ca, mmol/L	2.46	2.23	N/A	2.12	2.13	2.26	2.15–2.50
PO ₄ , mmol/L	1.19	1.27	N/A	1.38	1.28	1.19	0.81–1.45
TDM carbamazepine, µmol/L	N/A	N/A	N/A	64.2	41.7	N/A	16.9–50.8
TDM tacrolimus, ng/mL	N/A	N/A	2.4	6.0	10.7	4.2	4.0–7.0
TDM valproic acid, µmol/L	N/A	N/A	N/A	281	N/A	N/A	346–693

ALP = alkaline phosphatase; ALT = alanine transaminase; Ca = calcium; Hb = haemoglobin; K = potassium; Na = sodium; PO₄ = phosphate; TDM = therapeutic drug monitoring; WBC = white blood cell.

Using diltiazem to minimise the dose of tacrolimus has been recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) 2009 guidelines, as part of the strategies to reduce drug costs.⁴ This has been proven to be effective in our local transplant setting. Co-administration of tacrolimus and diltiazem has also been shown to have a relatively safe adverse effect profile.⁵ As part of the treatment of borderline rejection in our patient, the immunosuppressive regimen has been optimised with co-administration of tacrolimus and diltiazem.

Unfortunately, our patient developed central nervous system (CNS) side effects that were attributed to carbamazepine toxicity, after excluding acute organic causes. Reduction of carbamazepine dose in this patient resulted in reversal of the neurological symptoms; thus, confirming the diagnosis.

Carbamazepine is largely protein-bound and its plasma half-life ranges from 30 to 40 hours. Co-administration of diltiazem is also known to inhibit carbamazepine metabolism via the cytochrome P450 pathway. Clinical features of carbamazepine toxicity include nystagmus, diplopia, ataxia, CNS depression, respiratory failure, seizures, cardiac arrhythmias and hypotension. There is no antidote for carbamazepine toxicity as the mainstay of management is supportive therapy. Haemodialysis or peritoneal dialysis have limited efficacy due to its high plasma protein binding and large volume of distribution.^{6,7}

Adverse drug–drug interactions have a significant impact on healthcare systems, leading to as high as 21% of hospital

admission as well as a major cause of mortality. The incidence is rising, owing to polypharmacy practices and newer drugs with a relatively poorly understood metabolism. Other factors that increase risks of interactions include interference of absorption of certain medicines in the gut and impaired renal function leading to poor clearance; for example, iron supplements are known to interfere with absorption of fluoroquinolones and tetracycline antibiotics. Meanwhile, elimination of the active form of morphine (morphine-6-glucuronide) is dependent on glomerular filtration.⁸

While it is impossible to remember all potentially life-threatening drug–drug interactions, a prescriber should strive to check all new prescriptions to consider for potential interactions. If a therapeutic drug monitoring service is available for medicines of concern, this should be utilised as well. The role of dedicated transplant pharmacists is crucial to counter-check individual prescriptions and such a service should ideally be available in every transplant centre.

Conclusion

Drug–drug interactions represent a common clinical problem in the management of a patient with complicated kidney transplant from multiple comorbidities. This case demonstrated that, although inhibition of tacrolimus metabolism with diltiazem helps with cost-saving, this unfortunately led to unwanted carbamazepine toxicity. Increased clinical vigilance will help avoid this adverse interaction. ■

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References

- Ekberg H, Tedesco-Silva H, Demirbas A *et al*. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Eng J Med* 2007;357:2362–575.
- Hebert MF, Lam AY. Diltiazem increases tacrolimus concentrations. *Ann Pharmacother* 1999;33:680–2.
- Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004;43:623–53.
- Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009;9:S1–155.
- Chong CL, Wong HS, Lee FY *et al*. Dose response relationship between diltiazem and tacrolimus and its safety in renal transplant recipients. *Transplant Proc* 2018;50:2515–20.
- Duzova A, Baskin E, Usta Y, Ozen S. Carbamazepine poisoning: treatment with plasma exchange. *Hum Exp Toxicol* 2001;20:175–7.
- Goktas U, Kati I, Yuce HH. Management of a severe carbamazepine overdose with continuous venovenous hemodiafiltration. *Am J Emerg Med* 2010;28:260.e1–2.
- Day RO, Snowden L, McLachlan AJ. Life-threatening drug interactions: what the physician needs to know. *Intern Med J* 2017;47:501–12.

**Address for correspondence: Dr Min-Hui Tan, Department of Nephrology, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Malaysia.
Email: tanminhui83@yahoo.com**