MADRAC Bulletin

For healthcare professionals only
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In this issue

The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

Articles Based on Case Reports

What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that health care providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.

Tenofovir Disoproxil Fumarate-Induced Fanconi Syndrome in a Patient with Hepatitis B

By Ng Jia Mean

Case Report[1]

A 35-year-old male presented to the emergency department with **muscle weakness** and **a four-day history of intermittent upper and lower limb cramps**, along with worsening palpitations. The patient had been taking tenofovir disoproxil fumarate (TDF) 300 mg once daily for hepatitis B for three (3) years. He was also receiving oral amlodipine 10 mg once daily for underlying hypertension and oral potassium chloride 1,200 mg once daily for hypokalaemia. Laboratory investigations during the hospital stay indicated **hypochloraemic metabolic acidosis, glycosuria, hypokalaemia, hypophosphataemia,** and **hypocalcaemia.** The patient's renal profile is shown in ***Table 1***. Further review of past medical records revealed that the patient's **serum creatinine raised** from 78 umol/L at baseline to 96 umol/L, 10 months following TDF initiation, and later increased to 134 umol/L and 149 umol/L approximately two (2) and three (3) years post TDF initiation, respectively.

The patient was suspected of having **type 2 renal tubular acidosis secondary to Fanconi syndrome**. TDF was discontinued on Day 3 hospital admission, followed by a switch to entecavir on Day 4. Additionally, the patient was started on oral calcitriol 0.25 mcg once daily to treat concomitant vitamin D deficiency. The patient's clinical condition improved by Day 5, and he was discharged. In view of the presence of underlying medical conditions and concomitant drugs, a C3 possible drug-reaction causal relationship was assigned to this case.

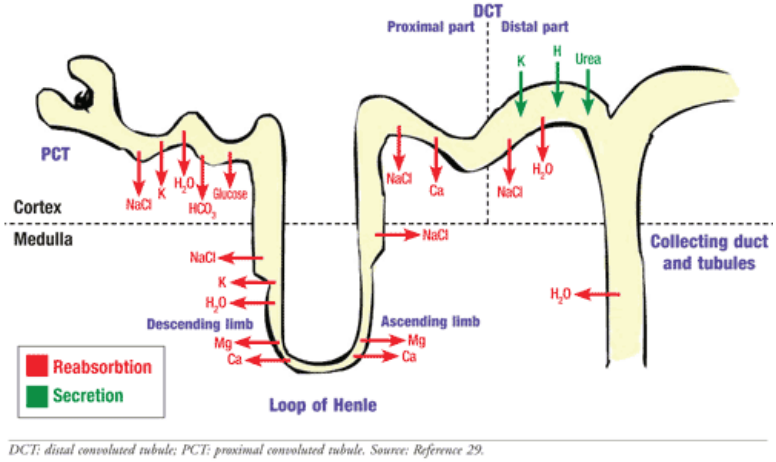
Table 1: Patient's renal profile during hospital admission

BUSE	Normal Range	Admission Day			
		D1	D2	D3	D4
Urea	1.7 -8.3 mmol/L	3.7	4.7	3.8	3.6
Na+	135 -145 mmol/L	134	135	134	134
K+	3.5 -5.0 mmol/L	2.4	3.2	3.2	3.6
Cl-	96 -106 mmol/L	110	115	116	118
SCr	64 -122 umol/L	152	136	125	130
CrCl	105 -150 ml/min	45	50.3	54.7	52.6
Ca2+	2.1 -2.6 mmol/L	1.94		1.96	2.04
Mg2+	0.7 -1.3 mmol/L	0.94	0.94	0.92	
PO4 -	0.8 -1.45 mm ol/L	0.21		0.52	0.66

Discussion

Tenofovir disoproxil fumarate (TDF) belongs to the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class of antiretroviral drugs.[2] It is used for the treatment of human immunodeficiency virus (HIV)-1 infection in adults and paediatric patients over 12 years of age in combination with other antiretroviral agents, as well as chronic hepatitis B in adults. TDF is a prodrug of the active metabolite tenofovir, which inhibits virus replication by competitively incorporating into the viral DNA chain and terminating the chain. In Malaysia, there are currently 17 registered products containing TDF in the form of tablets.[3] Six (6) of these products contain TDF as a single active ingredient, while the rest are in combination with one or more antiretroviral agents.

Fanconi syndrome is a condition characterised by multiple defects in renal proximal tubular cell transport and reabsorption (Figure 1), which leads to renal losses of various substances and electrolytes with subsequent hyperaminoaciduria, glucosuria, hypouricemia, hypophosphatemia, hypokalemia, and/or hypercalciuria.[4-6] Renal tubular acidosis type 2 is



DCT: distal convoluted tubule; PCT: proximal convoluted tubule. Source: Reference 29.

Figure 1: Normal physiology of the kidney, including the proximal tubule[16]

another common finding of Fanconi syndrome, which is caused by defective bicarbonate reabsorption in the proximal tubule and leads to a hyperchloremic metabolic acidosis.[4-5] Polyuria, polydipsia, dehydration, muscle weakness, and osteomalacia are reported clinical manifestations of Fanconi syndrome. Common acquired causes of Fanconi syndrome include multiple myeloma, light-chain deposition disease, renal transplantation, and medications (such as certain NRTIs and chemotherapeutic agents).

Renal adverse effects, including Fanconi syndrome, have been documented to be associated with TDF use.[2,7] Tenofovir is extensively excreted by the kidney through glomerular filtration and active tubular secretion in the proximal tubule mostly through organic anion transporter 1 (OAT-1).[2,7-8] While the exact pathophysiology by which TDF induces Fanconi syndrome is not fully understood, it has been suggested to be related to cellular accumulation of TDF through OAT-1, which causes mitochondrial toxicity in proximal tubular cells via inhibition of mitochondrial DNA polymerase.[6-9] The reduced mitochondrial adenosine triphosphate (ATP) production may disturb sodium potassium-adenosine triphosphatase (Na+/K+-ATPase) pumps on the basolateral membrane of proximal tubular cells, resulting in impaired active transport and reabsorption of of various substances and electrolytes.

Despite their rarity, the risks of Fanconi syndrome associated with TDF use in HIV-infected patients have been well described in published clinical studies and case reports.[6-8,10] Several case reports of Fanconi syndrome in chronic hepatitis B-monoinfected patients treated with TDF have been reported in the literature.[11-12] Fanconi syndrome can occur at any time during TDF treatment, usually detected within the first 1–29 months after exposure to the medication and is reversible with early detection and prompt management.[2,6,8,13]

To date, the NPRA had received 254 adverse drug reaction (ADR) reports with 438 adverse events associated with TDF including combination products.[1] Rash including rash maculopapular (64 cases), pruritus (30), vomiting (23), and dizziness (22) were the most frequently reported adverse events. A total of 30 local reports involving System Organ Class (SOC) Renal and Urinary Disorders were received by the NPRA for TDF, with acute kidney injury (7 cases) and **Fanconi Syndrome (7)** topping the class (including the case discussed above). As of November 2022, a search of the World Health Organisation (WHO) global ADR database (VigiBase)* revealed 1,046 global cases of Fanconi syndrome suspected to be associated with TDF.[14]

Tenofovir alafenamide (TAF), the newer prodrug of tenofovir, has been approved for use in Malaysia since 2018.[3] To date, there are seven (7) products containing TAF registered. While TAF is reported to have a more favourable renal safety profile than TDF, NPRA would also like to remind health care professionals of a previous safety communication issued in March 2022 on the possible risk of renal adverse effects associated with TAF use.[15] Thus far, no reports of renal adverse effects related to TAF have been received locally.[1]

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Health Care Professionals

1 Be aware of the risk of Fanconi syndrome associated with TDF use, especially in patients
- with underlying renal disease or at risks for renal impairment, OR
- taking concomitant nephrotoxic drugs, OR
- with smaller body stature or low body weight.

2 Assess the baseline renal risk before initiating TDF in all patients and periodically monitor their renal profiles at least every three (3) months in the first year of TDF use and every six (6) months thereafter if no deterioration. Patients at risks for renal impairment may require closer monitoring.

3 Advise patients to see medical attention if they develop clinical signs and symptoms of Fanconi syndrome such as thirsty, frequent urination, muscle weakness, and bone pain.

4 Carefully consider a differential diagnosis of acquired Fanconi sydrome in patients who develop proximal renal tubular acidosis and metabolic abnormalities during TDF therapy. If required, obtain consultation with a nephrologist.

5 When Fanconi syndrome is suspected and no other cause has been identified, consider adjustment of dosing interval or discontinuation of TDF followed by a switch to an alternate retroviral therapy, along with replacement of lost substances and electrolytes. Damage to the proximal tubules is usually reversible with early detection and prompt management.

6 Report any adverse drug reactions suspected to be related to the use of tenofovir to the NPRA.

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Reminder on the Risk of Diplopia with High Dose and Prolonged Use of Carbamazepine

By Jeevenraj Rajagopal

Case Report[1]

A 49-year-old male patient with an underlying complex partial seizure was started on antiepileptic treatment of carbamazepine 400 milligrams controlled-released (CR) tablets twice daily in 2016. The carbamazepine dose was subsequently raised to 600 milligrams twice daily in 2018. Two years later, patient experienced **diplopia about 8 to 9 times in a month** but **no dose adjustments were made at this point.** In March 2022, the dose was further increased to 800 milligrams twice daily, and then raised to 1000/800 milligrams twice daily. A month later, the patient experienced diplopia again, **but this time at a higher frequency of about 15 times a month**. The suspected medication, carbamazepine, was then reduced back to a dose of 800 milligrams twice daily, and the patient reported that he was no longer experiencing diplopia episodes. Other reported concomitant antiepileptics were valproic acid and phenobarbitone, but the timeline of the introduction was unknown. Figure 2 depicts the timeline of carbamazepine use and the reported event.

Discussion

Carbamazepine is a widely used first generation antiepileptic drug to treat certain types of seizures and psychiatric conditions, neurological diseases like trigeminal neuralgia and alcohol withdrawal syndrome.[2] In Malaysia, there are currently eight (8) registered products containing carbamazepine.[3] Carbamazepine stabilises hyperexcited neural membranes and inhibits repetitive neuronal firing by inhibiting voltage-dependent sodium channels, thus decreasing propagation of synaptic impulses.[2] The antiepileptic effects may be explained by the reduction in glutamate release and stabilisation of neuronal membranes, while carbamazepine's antimanic properties may derive from its depressive effect on dopamine and noradrenaline.

Diplopia, often known as double vision, is the perception of two images of a single object seen overlapping or adjacent to each other (horizontally, vertically, or obliquely).[4] Diplopia is usually binocular (double vision is seen only when both eyes are open) and less commonly monocular (double vision persists even after closing one eye). Diplopia may be a benign condition, but it may lead to functional difficulties

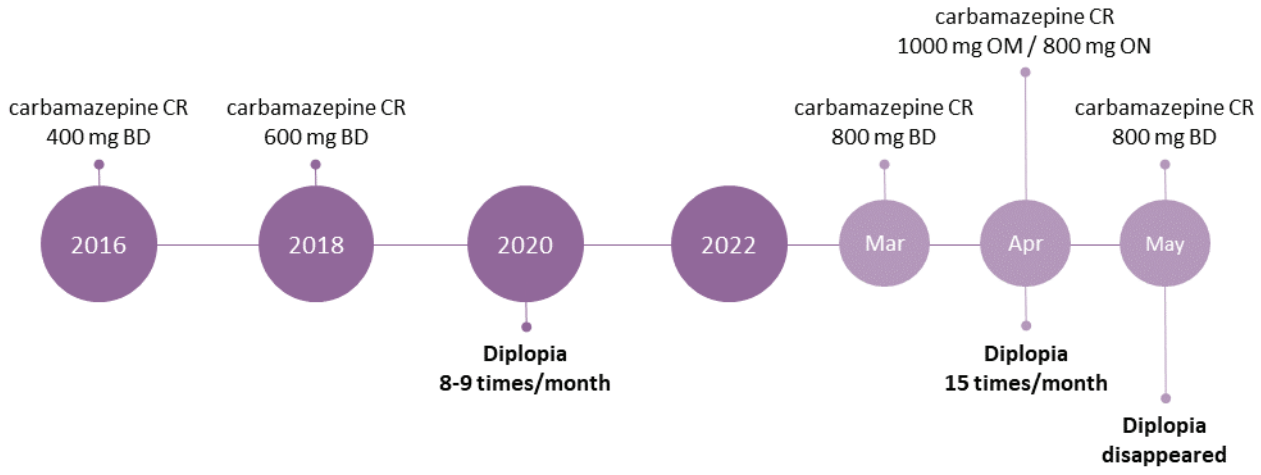

Figure 2: Timeline of carbamazepine use and reported event. BD: twice daily; OM: once in the morning; ON: once at night
Timeline of the introduction of concomitant antiepileptics (valproic acid and phenobarbitone) was unknown.

with daily activities, such as reading, driving and walking.[4-6] At times, it may indicate a significant underlying condition that requires further investigation and treatment.

Diplopia has been documented as a very commonly seen central nervous system (CNS)-related adverse event for carbamazepine, particularly during drug initiation, when an initial dose is excessively high, in elderly patients, or with prolonged treatment.[3,7] The effects of carbamazepine on saccadic and smooth muscle eye movements have been considered in the occurrence of diplopia.[7] These ocular motility dysfunctions are dose-dependent and usually resolve within a few days, either spontaneously, following a transient dose reduction, or after withdrawal.[3,6]

To date, NPRA has received a total of 1,262 reports with 2,298 adverse events suspected to be related to carbamazepine-containing products.[1] Adverse events involving the System Organ Class (SOC) Skin and Subcutaneous Tissue Disorders were the most frequently reported, which include Stevens-Johnson syndrome (SJS), rash, rash maculo-papular, and pruritus. Of the 69 local cases of SOC Eye Disorders suspected to be related to carbamazepine use, there were **six (6) cases of diplopia** (including the case discussed above) and six (6) cases of vision blurred. As of November 2022, VigiBase*, the World Health Organisation (WHO) global database of individual case safety reports (ICSRs), had recorded 3,005 cases of SOC Eye Disorders suspected to be associated with carbamazepine, including 785 cases of diplopia and 453 cases of vision blurred.[8]

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Advice for Health Care Professionals

1. Be aware of the potential risk of diplopia associated with carbamazepine, especially during drug initiation or dose escalation, in situations of excessively high dose, prolonged treatment, or in elderly patients.
2. Start carbamazepine at low initial dose and gradually adjust the dose to establish the optimum dose. If diplopia persists or worsens, consider splitting the daily dose or switching to an alternative treatment.
3. Use carbamazepine with caution in patients receiving concomitant medications that may affect plasma levels of carbamazepine, such as inhibitors of CYP3A4, inhibitors of human microsomal epoxide hydrolase, or abrupt discontinuation of CYP3A4 inducers.
4. Educate patients receiving carbamazepine to monitor symptoms of double vision and other visual disturbances.
5. Advise patients who have recently experienced double vision to avoid driving and operate dangerous machinery as well as seek medical attention.
6. Report all adverse events suspected to be related to the use of carbamazepine-containing products to the NPRA.

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What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Pholcodine	Risk of Anaphylaxis to Neuromuscular Blocking Agents (NMBAs)	9-Mar-2023; [Updated] 23-Mar-2023	-
2	Topiramate	Neurodevelopmental Disorders in Children Exposed to Topiramate During Pregnancy	17-Mar-2023	-

How to report adverse events?

NPRA encourages all health care professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit **www.npra.gov.my**
2. Report ADR **as Health Care Professional**
   a) Choose **Online Reporting** or
   b) Download the **ADR manual form** and submit the completed form via email or post:

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