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Ministry of Health, Malaysia

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In this Issue

Features

Preliminary report: Local adverse drug reactions associated with drugs used for COVID-19 infections

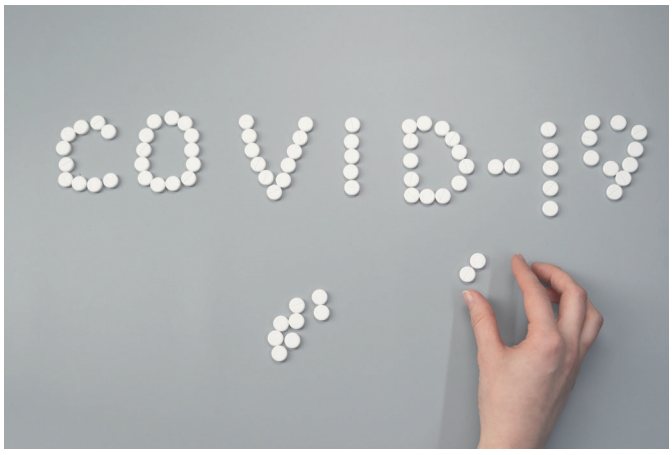
by Norleen Mohamed Ali

Introduction

On 30th January 2020, the novel coronavirus disease known as COVID-19 outbreak has been declared as a public health emergency of international concern by World Health Organisation (WHO).[1] On 11th March 2020, WHO characterised COVID-19 as a global pandemic.[2] It is a highly infectious disease with human to human transmission. Patients infected by the virus may experience symptoms that range from mild to severe or life threatening respiratory symptoms.[2,3]

To date, there are no drugs or vaccines that have been clinically approved for prevention or treatment of COVID-19.[3,4] Several drugs such as hydroxychloroquine, lopinavir/ritonavir combination drug, remdesivir, atazanavir, favipiravir and anti-inflammatory drugs (such as dexamethasone) have been tried and have showed some potential in treating COVID-19 patients. However, these treatment options are still in the exploratory stage and more studies are needed to fully understand their efficacy and adverse event profiles in COVID-19 conditions.[3,5]

The off-label use of these drugs for COVID-19 infection exposes patients to experience drug-related adverse



reactions. The fact that the elderly (over 60 years old) and patients with underlying illnesses (such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer) are at higher risk of getting severe COVID-19 disease than other population groups, this situation acutely makes treatment plans to be more complex and drug-related events became more prevalent. While ensuring the efficacy of these potential treatment is greatly desired, drug safety and adverse drug events monitoring should not be sidetracked.[4]

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Local ADR Report

Since March 2020, the National Pharmaceutical Regulatory Agency (NPRA) has been actively monitoring and collecting adverse drug reactions (ADR) data for the drugs used for the treatment of COVID-19 infections. Up to June 2020, NPRA has received a total of **111 ADR reports with 183 adverse events** associated with hydroxychloroquine, atazanavir, lopinavir/ritonavir, ritonavir, tocilizumab and interferon (refer to Table 1). As treatment of COVID-19 infection often involves combination therapy, the majority of these ADR reports contained multiple suspected drugs.[5]

The most frequently reported adverse events were **electrocardiogram QT prolonged (41 events)**, **blood bilirubin increased (31 events)** and **transaminases increased (19 events)**. Table 2 provides the details of the drugs that caused the events.

Table 1:

Number of ADR Reports

FOR DRUGS USED FOR THE TREATMENT OF COVID-19 INFECTIONS

1 HYDROXYCHLOROQUINE	
44 ADR reports	51 adverse events
2 LOPINAVIR / RITONAVIR	
44 ADR reports	58 adverse events
3 ATAZANAVIR	
32 ADR reports	36 adverse events
4 RITONAVIR	
13 ADR reports	14 adverse events
5 TOCILIZUMAB	
10 ADR reports	21 adverse events
6 INTERFERON	
1 ADR report	3 adverse events

Table 2:

MOST FREQUENTLY REPORTED

Adverse Events

1 Electrocardiogram QT prolonged **(41 adverse events)**	Hydroxychloroquine (27)
	Lopinavir / Ritonavir (12)
	Atazanavir (1)
	Ritonavir (1)
2 Blood bilirubin increased **(31 adverse events)**	Atazanavir (17)
	Ritonavir (8)
	Lopinavir / Ritonavir (4)
	Hydroxychloroquine (2)
3 Transaminases increased **(19 adverse events)**	Hydroxychloroquine (7)
	Lopinavir / Ritonavir (6)
	Atazanavir (3)
	Ritonavir (2)
	Tocilizumab (1)
4 Hyperbilirubinaemia **(13 adverse events)**	Atazanavir (9)
	Lopinavir / Ritonavir (2)
	Hydroxychloroquine (1)
	Ritonavir (1)
5 Alanine aminotransferase increased **(9 adverse events)**	Tocilizumab (3)
	Lopinavir / Ritonavir (3)
	Atazanavir (2)
	Interferon (1)
6 Diarrhoea **(8 adverse events)**	Lopinavir / Ritonavir (6)
	Hydroxychloroquine (2)
7 Bradycardia **(7 adverse events)**	Hydroxychloroquine (3)
	Lopinavir / Ritonavir (2)
	Atazanavir (1)
	Ritonavir (1)
8 Hyperglycaemia **(5 adverse events)**	Lopinavir / Ritonavir (3)
	Atazanavir (1)
	Ritonavir (1)
9 Aspartate aminotransferase increased **(4 adverse events)**	Tocilizumab (3)
	Interferon (1)
10 Nausea **(4 adverse events)**	Hydroxychloroquine (2)
	Lopinavir / Ritonavir (2)

The most reported events for hydroxychloroquine were electrocardiogram QT prolonged (27 events), transminases increased (7 events) and bradycardia (3 events). While for lopinavir/ritonavir the most reported events were electrocardiogram QT prolonged (11 events), diarrhoea (6 events) and transaminitis (5 events). Tocilizumab most reported adverse events were alanine aminotransferase increased (3 events) and aspartate aminotransferase increased (3 events).

All local ADR reports received by NPRA are shared with the WHO global ADR database, VigiBase. The WHO Uppsala Monitoring Centre COVID-19 monitoring team publishes periodic reports from the analysis of spontaneous reports of drugs used for the treatment COVID-19 infections, which were received from national ADR monitoring centres worldwide through VigiBase. From 1st November 2019 to 2nd August 2020, WHO has cumulatively received a total of 4,739 reports from six (6) WHO regions, where the majority of the reports were from the European region (50.1%).[7] The highest number of reports received by WHO was for hydroxychloroquine (2,192 reports, 46.2%) where frequently reported terms were electrocardiogram QT prolonged, gastrointestinal symptoms such as diarrhoea, nausea and vomiting, as well as hepatic adverse events particularly cholestasis, hepatocellular injury, hepatotoxicity, and increases of liver enzymes (gamma-glutamyl transferase, transaminases). For adverse events globally reported for lopinavir/ritonavir, the most commonly reported adverse events were diarrhoea (176 reports), nausea (66 reports), electrocardiogram QT prolonged (62 reports), hepatocellular injury (54 reports) and hypertriglyceridemia (51 reports).*

Conclusion

The local data shown in this report is no more than a preliminary overview of cases and reported ADRs. The adverse events associated with drugs used for COVID-19 infections observed locally were found to be consistent with the events being reported worldwide.

The NPRA is vigilant and will continue to closely monitor any new or emerging safety signals of the drugs used in patients with COVID-19 infection. The NPRA shall take regulatory actions or any appropriate measures to communicate any risks associated with the drugs used in the treatment of COVID-19 infections, when necessary.

Advice to Healthcare Professionals

Report any adverse event suspected to be associated with drugs used in suspected or confirmed COVID-19 patients. This may provide valuable evidence on the safe and effective use of these products as the pandemic of COVID-19 evolves.

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* This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.

Articles based on Case Reports

Hydrochlorothiazide: Risk of hearing disorder

by Ng Wan Ning

Case Report 1

A 59-year old female patient with hypertension was prescribed with hydrochlorothiazide 12.5 mg once daily. After seven days of treatment, she experienced hearing problem which she described that she was unable to hear people talking clearly and had required people to talk loudly and repeatedly. After the patient stopped taking the medication, she claimed that her hearing gradually improved and recovered.

Case Report 2

A 51-year old male hypertensive patient has been taking hydrochlorothiazide 25 mg once daily with amlodipine 10mg once daily and lovastatin 40 mg at night. When he was dispensed with an alternate brand of hydrochlorothiazide, he complained that his hearing was impaired after 30 minutes of taking the first dose of the drug. He described that his hearing was "blocked" and is alleviated by hitting the ears gently for a few times. The patient claimed that when he omitted the drug, he found that his hearing got better. When he consumed the medication again, the same event occurred. During his follow-up appointment, the patient consulted his doctor and the suspected drug was withdrawn and changed to a different antihypertensive medication. The patient had recovered after the withdrawal of hydrochlorothiazide.

Both of these cases were assigned with a possible drug-adverse event causal relationship.

Discussion

Hydrochlorothiazide (HCTZ) is a thiazide diuretic and it acts by inhibiting sodium and chloride reabsorption in distal renal tubules, resulting in increased of water, sodium, potassium and hydrogen ions loss.[1] It is indicated for the management of hypertension and as an adjunctive therapy in oedema associated with congestive heart failure, hepatic cirrhosis, corticosteroid and oestrogen therapy, as well as oedema of renal origin.[2]

HCTZ has been reported to cause vertigo and tinnitus.[3,4] However, it is not documented to cause hearing disorder.[2] In a case series research article, 94 case reports of hearing disorder associated with HCTZ use were identified between 1972 to August 2017 in the World Health Organisation adverse drug reaction (ADR) database, VigiBase.[5] The reaction terms that were extracted from the data pool and selected in the inclusion criteria were decreased hearing (916), tinnitus (50), deafness (23), vestibular disorder (4), and deafness nerve (1). It was found that 28% of the 94 cases reported HCTZ as the sole suspected drug and there were no concomitant drugs. The study has also observed that in 75% of the cases collected, the adverse events were reported even at normal therapeutic doses of 12.5 – 50 mg/day, suggesting that HCTZ-related hearing loss may occur at normal doses, and could even put patients with a higher risk at hearing loss when co-administered with ototoxic drugs.

Despite these findings, the study acknowledged that hearing disorder may be affected by various factors such as age, hypertension, and concomitant drugs. While the study has stated that age-related hearing loss is progressive and possibly irreversible, the reversibility of hearing loss seen in 66.7% of the cases in the study showed that the effect of age was questionable.

There were several limitations to the study, such as environmental and genetic factors, occupational hazard exposure, lacking in denominator data, as well as the possibility of inaccurate incidence rate due to underreporting. Overall, the study concluded that there is a suggestive causal relationship between HCTZ and hearing disorder and warrants further studies to validate the safety signal through epidemiological studies.[5]

In Malaysia, there are 62 registered products containing HCTZ which six (6) products are available as a single agent and 56 products are in combination with other antihypertensive agents.[6]

To date, NPRA has received 1,492 ADR reports with 2,574 adverse events associated with HCTZ use. The most commonly reported adverse events were dizziness, hyponatraemia, and headache, followed by hypokalaemia and pruritus. At the time of this publication, there are six (6) reports of tinnitus, nine (9) reports of vertigo and two (2) reports of hearing disorder associated with HCTZ use (as discussed above).[3]

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Advice to Healthcare Professionals

1. Be aware on the possible association of HCTZ with hearing disorder and consider recommending hearing assessments for patients prescribed with HCTZ.
2. Exercise caution in prescribing ototoxic drugs concomitantly with HCTZ, and advise patients to minimise the use of other drugs which are known to be ototoxic, like non-steroidal anti-inflammatory drugs when taking HCTZ.
3. Report any adverse events associated with any drugs including HCTZ to NPRA.

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Articles based on Case Reports

Peripheral neuropathy associated with amlodipine

by Soon Vi Vian

Case Report 1

A 54-year-old man with hypertension complained of numbness in both upper and lower limbs after 30 minutes of consuming amlodipine tablet. The numbness was said to resolve after three (3) hours. He claimed to experience the same adverse reactions for the next three (3) days before he stopped taking amlodipine. The patient consulted his doctor and was diagnosed as **peripheral neuropathy**. He was prescribed with a different antihypertensive drug and did not experience the adverse event after the change.

Case Report 2

A 57-year-old woman with a history of non ST segment elevation myocardial infarction (NSTEMI) and hypertensive emergency was started on amlodipine on top of her other cardiovascular medications. After consuming amlodipine tablet, she complained of bilateral foot numbness. She was diagnosed with **peripheral neuropathy** and amlodipine was substituted with an alternate antihypertensive drug. At the time of reporting, the patient was reported to be recovering from the adverse event.

Both case reports were given a causality of possibly-related to the drug.

Discussion

Amlodipine is a calcium channel blocker indicated for the treatment of hypertension and chronic stable angina.[1,2] Amlodipine dilates the peripheral arteries of the vascular smooth muscles causing a reduction in peripheral vascular resistance, which leads to a reduction in blood pressure.

Peripheral neuropathy refers to the conditions that involve damage or disorder of the peripheral nerves and may present with paraesthesia, which may be accompanied with pain, weakness, or autonomic symptoms.[3,4] Clinical presentation include myelopathy, radiculopathy, muscle disease or even hyperventilation.[3] There are many common causes to peripheral neuropathy such as diabetes, vitamin deficiency, excessive alcohol use, traumatic injury and drugs.[4] Drugs that are commonly associated with peripheral neuropathy include cardiovascular agents such as statins, chemotherapeutic agents, certain antimicrobial agents, and immunosuppressants.[5]

Although rare, peripheral neuropathy has been documented with amlodipine use and is observed in the post-marketing setting.[2,6] The pathophysiology has not been fully elucidated and due to the limited studies, the association of amlodipine to peripheral neuropathy is not widely recognised. As the drug is not usually suspected during treatment and mild forms of peripheral neuropathy are easily overlooked, the incidence of drug-induced peripheral neuropathy (DIPN) is difficult to establish.[7]

Since year 2000, NPRA has received 12,336 adverse drug reaction (ADR) reports with 12,353 adverse events suspected to be related to amlodipine use.[8] There are **three (3) reports** of amlodipine associated with **peripheral neuropathy**, including the two (2) cases described above.

Advice to Healthcare Professionals

1. With wide usage of amlodipine and high incidence of diabetes-induced peripheral neuropathy in Malaysia, be alert on the risk of peripheral neuropathy associated with the use of amlodipine products.
2. During follow-up appointments, peripheral neuropathy should be ruled out especially if patient complains of pain, weakness, numbness, tingling or other abnormal sensation of the hands or feet.
3. Consider an alternative if the condition affects patient's quality of life.
4. Advise patients to be cautious of symptoms of peripheral neuropathy.
5. Remind patients not to stop taking amlodipine and consult their doctors if they develop any symptoms to an adverse event.
6. Report any adverse events suspected to be associated with the use of any medicines including amlodipine to NPRA.

A search in the World Health Organisation (WHO) database revealed a total of 87,818 case reports associated with amlodipine use, of which 216 case reports of peripheral neuropathy were associated with amlodipine.[9]*

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* This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.

Articles based on Case Reports

Ceftazidime: Risk of acute generalised exanthematous pustulosis (AGEP)

by Jeevenraj Rajagopal

Case Report 1

A 69-year-old female patient with underlying end-stage renal failure (ESRF) was diagnosed with catheter-related bloodstream infection caused by methicillin-resistant *Staphylococcus Aureus*. She was prescribed with intravenous ceftazidime 1 gram once a day concomitantly with intravenous vancomycin 1 gram every alternate day. Four (4) days after drug administration, she developed mild erythematous scaly skin at both upper eyelid and cheek, generalised small pustules with underlying erythematous skin on the neck, trunk, upper limbs and both thighs. In some areas, the pustules coalesced together, forming lakes of pus that presented mainly over both axilla and flexural areas and the back. Laboratory investigations showed an increased count of eosinophils.

The patient was diagnosed with **acute generalised exanthematous pustulosis (AGEP)** secondary to ceftazidime. The suspected drug was discontinued and patient was treated with potassium permanganate spray and dressing of the pustular areas with lint cloth. The patient later recovered with sequelae. Given that other factors such as concomitant drug may have contributed to the adverse event, this case was assigned to be possibly-related to the drug.

Case Report 2

A 54-year-old female patient with ESRF on regular haemodialysis was administered two (2) antibiotics, intravenous ceftazidime and vancomycin for line-related sepsis. On day eight (8) after drug initiation, she developed rashes on the trunk, extending to the back and limbs that worsened to form pustules. She was seen by a dermatologist and was diagnosed with **acute generalised exanthematous pustulosis (AGEP)**. Both ceftazidime and vancomycin were

withdrawn and replaced with another antibiotic. The patient was then treated with chlorpheniramine, prednisolone, and diluted potassium permanganate and aqueous cream for topical application at the pustular area. At the time of reporting, the patient was reported to be recovering from suspected adverse event. This case was assigned a possible drug-reaction causal relationship.

Discussion

Ceftazidime is a broad-spectrum third-generation cephalosporin indicated for the treatment of severe infections (such as septicaemia, bacteraemia, peritonitis, meningitis), respiratory tract infections, urinary tract infections, skin and soft tissue infections and infections associated with dialysis. In Malaysia, there are 12 registered products containing ceftazidime.[1]

AGEP is characterised by an acute generalised rash followed by widespread non-follicular sterile pustules occurring on erythematous and oedematous skin, which is frequently presented with systemic fever and leucocytosis.[2-5] It is a type IVd hypersensitivity reaction that is usually a drug-related skin reaction, in which the drug or its metabolite stimulates the activation and proliferation of cytotoxic T cells that migrate to the skin tissues to cause keratinocytes apoptosis, resulting in subcorneal vesicles formation. Subsequently, the release cytokines and other inflammatory mediators which would further propagate neutrophils accumulation and the formation of pustules. As AGEP is generally a rare adverse drug reaction and has similarities to other skin reactions, its occurrence may be overlooked and underreported.[2]

NPRA has received a total of 378 ADR reports with 711 adverse events suspected to be related to ceftazidime. Out of this number, 259 adverse events are associated with skin and subcutaneous disorders, which **four (4) reports of AGEP** [including two (2) cases discussed above].[6] As of June 2020, the World Health Organisation (WHO) global ADR database (VigiLyze) has identified 11,635 skin reaction cases suspected to be associated with ceftazidime. Among them, there were 35 cases of AGEP.[7]*

* This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.

Advice to Healthcare Professionals

1. Advise patients to be wary of signs and symptoms of AGEP and inform medical personnel promptly if any symptoms of AGEP appear.
2. If AGEP is suspected, monitor patient's haematological parameters like neutrophils, leucocytes and C-reactive proteins.
3. AGEP is benign and self-limiting, thus supportive treatments of topical costicosteroids and disinfectant solutions during the pustular phase and rehydrating lotions during the desquamative phase, as well as antipyretics, is usually sufficient.
4. Report any adverse events suspected to be associated to the use of any drugs including ceftazidime to the NPRA.

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What's New?

List of directives related to drug safety issues (May - August 2020)

NPRA reviews and presents drug safety issues at MADRAC meetings 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 of all products containing the affected active ingredients are updated with the required safety information. The following are DCA directives issued between May to August 2020, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Diclofenac (excluding topical products)	(i) Risk of anastomotic leakage (ii) Kounis syndrome	12 May 2020	[Ref: (4) dlm.BPFK/PPP/07/25 Jilid 4]
2	Gabapentin	Risk of dysphagia	12 May 2020	[Ref: (5) dlm.BPFK/PPP/07/25 Jilid 4]
3	Domperidone	New safety information in use in paediatric patients	12 May 2020	[Ref: (6) dlm.BPFK/PPP/07/25 Jilid 4]
4	Proton pump inhibitors	Microscopic colitis	12 May 2020	[Ref: (7) dlm.BPFK/PPP/07/25 Jilid 4]
5	Topiramate	Risk of uveitis	17 August 2020	[Ref: NPRA.600-1/9/13(5)]
6	Parenteral nutrition containing amino acids and/or lipids	Risk of toxic degradations of ingredients when exposed to light	17 August 2020	[Ref: NPRA.600-1/9/13(6)]
7	Propofol	Risk of priapism	17 August 2020	[Ref: NPRA.600-1/9/13(7)]

For Healthcare Professionals

How to report adverse drug reactions?

NPRA encourages the reporting of all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, as well as traditional and health supplements.

To report adverse drug reactions:
1. Visit www.npra.gov.my
2. Click on Reporting ADR
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Completed hardcopy forms may be submitted via post or email to:

The Pharmacovigilance Section,
Centre of Compliance & Quality Control,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Universiti,
46200 Petaling Jaya, Selangor.

fv@npra.gov.my

*To join the **NPRA Safety Information Mailing List**, please send an email with your details to **fv@npra.gov.my***

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