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Ministry of Health, Malaysia

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Features

NPRA's ADR Workshop For Pharmacists

In February and March 2019, the Centre for Adverse Drug Reaction Monitoring, NPRA organised two adverse drug reaction (ADR) workshops for fellow pharmacists in Malaysia. The workshops aimed to improve the quality of ADR reports as well as to heighten the understanding and awareness of ADR and adverse events following immunisation (AEFI) reporting. A total of 80 pharmacists from Ministry of Health facilities, private hospitals, university hospitals as well as the Ministry of Defence had participated in this programme. It is hoped that the understanding of ADR reporting and its relevance will be passed down to fellow colleagues in their respective health settings.

Articles based on Case Reports

Zidovudine: Higher Occurrence of Anemia in Malaysia?

by Ng Wan Ning

Case Report 1

A 43-year old male patient, who was an active drug abuser on methadone replacement therapy, was prescribed with zidovudine 300 mg twice daily (combination product) and other antiretroviral agents for retroviral infection. After three weeks of antiviral treatment, the patient developed shortness of breath, on and off fever, pleuritic chest pain, respiratory rate of more than 30 breaths per minute, and reduced lung volume over the left side with an opportunistic lung infection. Patient was admitted to hospital and tests revealed his haemoglobin levels had dropped from 10 g/dL (before antiviral therapy initiation) to 5.8 g/dL. The patient was diagnosed with **zidovudine-induced anaemia**. The suspected drug was stopped and patient was given a blood transfusion. Although the haemoglobin levels increased after the blood transfusion, the patient passed away as a result of advanced retroviral infection and acute kidney impairment secondary to sepsis or dehydration. As there were multiple concomitant medications that coincided with the suspected drug in the onset of the adverse event, this case was assigned a causality of possibly related to the drug.

Discussion

Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI) that acts by competitively inhibiting the Human Immunodeficiency Virus (HIV) reverse transcriptase, halting viral DNA synthesis[1]. It was the first NRTI that was approved for antiretroviral therapy in Malaysia in 1987[2]. Currently, there are a total of **16 registered products containing zidovudine** as single agents and in combination with other antiretroviral drugs.

Although haematological abnormalities have also been highly linked to HIV infection[3], anaemia following administration of zidovudine has been identified as a common adverse reaction[4] and is well-documented in the product package insert. However, it was noted in June 2019 through the World Health Organisation (WHO) VigiBase analytics that the reaction of anaemia with zidovudine in Malaysia is **higher** (IC value= 6.4) as compared to the global data (IC value= 4.2)[5]. [Information Component (IC) is an **indicator value for disproportionate reporting** developed by WHO's Uppsala Monitoring Centre (UMC) for disproportionality analysis. It is a tool used to relate the observed and expected values to find drug–adverse effect combinations that have been reported more often than one would expect. These values change over time as more reports are received and processed by WHO.] This indicator may suggest that the occurrence of anaemia with zidovudine use in Malaysia is above average when compared globally, however, it does not take into account zidovudine usage or the severity of the disease in the country.

To date, NPRA has received **272 ADR reports with 517 adverse events** suspected to be related to zidovudine-containing products[6]. There are **149 adverse**

events related to anaemia (108 events, 20.9%) and **decreased haemoglobin (41 events, 7.9%)** that have been associated with zidovudine. Based on the cases reported, most patients required blood transfusion and recovered from the adverse event, except for three (3) fatal cases reported to be due to complications of the underlying retroviral infection.

A search in the WHO global ADR database, VigiLyze, revealed a total of 23,778 reports suspected to be related to zidovudine-containing products, with **7,886 reports of anaemia** and **112 reports of decreased haemoglobin**[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.

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Advice to Healthcare Professionals

1 Zidovudine should not be initiated in patients with baseline haemoglobin <8.0 g/dL[8].
2 Anaemia has been reported to occur more frequently in:
- Patients who are taking zidovudine at high doses (1200-1500mg/day).
- Patients with advanced HIV disease
- Patients with CD4 cell counts of less than 100/mm^3.

3 Haematological parameters should be carefully monitored. These haematological effects are not usually observed before 4–6 weeks of therapy.
4 For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy, and at least monthly thereafter. Depending on the overall condition of the patient, blood tests may be performed less often, for example, once every 1-3 months[4].
5 Moderate or severe toxicities may require substitution of the drug with another of the same antiretroviral class, but with a different toxicity profile[8].
6 Any adverse events associated with the use of zidovudine should be reported to NPRA.

References

1. Rathbun, Liedtke, Miller et al. (2019, April 18). Antiretroviral Therapy for HIV Infection. Retrieved from https://emedicine.medscape.com
2. NPRA (2019, June 3). QUEST 3+ database. Retrieved from https://www.npra.gov.my
3. Edwards MT et al. (2005). Characterization of anaemia in HIV-infected (HIV+) subjects treated with antiretroviral therapy (ART) with and without zidovudine (+/- ZDV) in 54 clinical trials. Third International AIDS Society Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, abstract TuFo0106, 2005.
4. Zidovudine Malaysian product package insert [Last revision: July 2018]
5. VigiLyze Uppsala Monitoring Centre, World Health Organisation (2019, June 4). Analytics in Vigilyze. Retrieved from https://www.who-umc.org/vigibase/vigilyze/analytics-in-vigilyze
6. The Malaysian Adverse Drug Reactions Database, NPRA [Accessed May 2019].
7. Vigilyze Uppsala Monitoring Centre, World Health Organisation [Accessed June 2019].
8. Ministry of Health (2017). Malaysian Consensus Guidelines on Antiretroviral Therapy 2017. The Malaysian Society for HIV Medicine.

Articles based on Case Reports

Colchicine: Reminder on the Risk of Rhabdomyolysis

by Soon Vi Vian

Case Report 1

A 54-year-old man with medical history of hypertension, dyslipidaemia, chronic kidney disease and gouty arthritis presented with back pain, pain over both thighs, persistent bilateral lower limb weakness, and passing dark-coloured urine. Prior to this, the patient was taking simvastatin and amlodipine for over a year, and occasionally took colchicine during acute gout attacks. Laboratory investigations showed marked increases in creatine kinase, potassium, ALT and ALP. The patient was diagnosed with acute **rhabdomyolysis** secondary to the cumulative effect of prolonged combination of amlodipine and simvastatin, precipitated by concomitant use of simvastatin andcolchicine. The suspected drugs were withdrawn, and the patient recovered following treatment. As he had underlying medical conditions as well as multiple concomitant drugs, this case was assigned a possible drug-reaction causal relationship.

Case Report 2

A 63-year-old man developed **rhabdomyolysis** with acute chronic kidney disease secondary to colchicine therapy. He had underlying hypertension, diabetes, gout and dyslipidaemia. It was found that his creatine kinase levels were high. Upon withdrawal of colchicine, the patient eventually recovered. This case was also assigned a possible drug-reaction causal relationship.

(please see next page)

Discussion

Colchicine is known for its anti-inflammatory effects in the prevention and treatment of acute gout. It inhibits the migration of granulocytes into the inflamed area, which in turn reduces the release of lactic acid and proinflammatory enzymes that occurs during phagocytosis, thus acts against the inflammatory response to urate crystals[1].

Rhabdomyolysis is a complex medical condition where damaged muscles breakdown rapidly and release their contents into the bloodstream, which may lead to kidney damage. The common symptoms of rhabdomyolysis are: (1) shoulders, thighs, or lower back muscle pain; (2) trouble moving limbs or muscle weakness; and (3) dark red/brown urine or reduced urination. Other symptoms include nausea, vomiting, abdominal pain, fever, confusion, dehydration and rapid heart rate. Rhabdomyolysis may also cause hyperkalaemia, which may lead to irregular heart rate, cardiac arrest or kidney damage. With prompt treatment, recovery from rhabdomyolysis is expected[2].

Although the frequency is rare, rhabdomyolysis may occur following the use of colchicine[1,3]. It is suggested that the pathogenesis of colchicine-induced myopathy may be linked to the disruption of a cytoskeletal microtubular network that interacts with lyposomes[3].

There are **three (3) registered products containing colchicine** in Malaysia. Since 2000, NPRA has received **99 ADR reports with 169 adverse events** suspected to be related to colchicine use[4]. The most commonly reported adverse events were diarrhoea, pruritus, maculopapular rash, urticaria and vomiting. To date, NPRA has received **two (2) ADR reports** of rhabdomyolysis associated with colchicine, as discussed above.

As of May 2019, the World Health Organisation (WHO) global ADR database revealed a total of **217 reports for rhabdomyolysis** suspected to be associated with colchicine[5]*.

*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. Patients on colchicine should be monitored for symptoms of neuromuscular toxicity, which may present as muscle pain, weakness, and tingling or numbness in the fingers or toes. This may occur with colchicine alone or when used with certain other drugs known to cause this effect, such as statins[6].
2. Advise patients to immediately seek medical attention if any symptoms of rhabdomyolysis (such as muscle pain, muscle weakness, dark red or brown urine or decreased urination) develop after taking colchicine.
3. Due to the narrow therapeutic index, caution should be taken on the dosing of colchicine, even in the presence of normal renal function.
4. Please **report** any adverse events suspected to be associated with the use of colchicine to the NPRA. When reporting ADRs, it is advisable to include clinically indicated measurements, such as creatine kinase.

References

1. Malaysian Package Insert for colchicine [Accessed: April 2019]
2. WebMD (2019, March 19). Rhabdomyolysis. Retrieved from https://www.webmd.com/
3. I Chattopadhyay, H G M Shetty, P A Routledge *et al.* (2001). Colchicine induced rhabdomyolysis. Postgrad Med J; 77: 191-192.
4. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: May 2019].
5. VigiLyze Uppsala Monitoring Centre, World Health Organisation [Accessed: May 2019].
6. RxList (2019). Colchicine. Retrieved from https://www.rxlist.com [Accessed: July 2019].

Articles based on Case Reports

Pembrolizumab: Reminder of the Risk of Pneumonitis

by Jeevenraj Rajagopal

Case Report 1

A 46-year-old female patient suffering from colon cancer with bilateral lung and ovarian cancer was receiving intravenous pembrolizumab 100 mg once in 3 weeks. After seven weeks of treatment, she developed progressive dyspnoea and was hospitalised. Results from a computed tomography (CT) scan showed ground glass pattern, and patient was diagnosed with **pneumonitis**. Pembrolizumab therapy was withheld and the patient was treated with prednisolone. At the time of the reporting, the outcome of the adverse event was not provided. Given that other factors such as patient's underlying condition may have contributed to the adverse event, this case was assigned a causality of possibly-related to the drug.

Discussion

Pembrolizumab is a monoclonal antibody that directly binds to programmed cell death protein-1 (PD-1) receptor on T cells, therefore blocking the interaction between PD-1 and its ligand PD-L1 on cancer cells[1]. This enhances T-cell responses and can lead to a range of unusual side effects called immune-related adverse events, involving several organs such as the skin, gastrointestinal and endocrine systems. **Immune-related pneumonitis**, a known complication of pembrolizumab therapy, is considered as a potentially lethal immune-mediated adverse event related to lung disorders. It is classified as a **common** adverse reaction and is documented in the pembrolizumab Malaysian package insert[2]. In clinical trials, the time to onset was reported to range from 2 days to 19 months (median 3.3 months).

Currently, there is **one (1) product containing pembrolizumab** registered with the Drug Control Authority (DCA). It is approved for the treatment of unresectable or metastatic melanoma, non-small cell lung carcinoma (NSCLC), recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), metastatic urothelial carcinoma, and relapsed or refractory classical Hodgkin lymphoma (cHL) *(for full prescribing details, please refer to the product package insert)*[2].

NPRA has received **49 ADR reports with 86 adverse events** suspected to be related to the use of pembrolizumab[3]. To date, **eight (8) cases of pneumonitis** have been reported (including the case described above). Other adverse events related to respiratory disorders include interstitial lung disease, lung disorder, lung infection, pneumonia, dyspnoea and cough.

As of July 2019, the WHO ADR database (VigiLyze) contains **642 reports of pneumonitis** suspected to be associated with pembrolizumab use, as well as reports of pneumonia (376 cases), interstitial lung disease (930), lung inflammation (2), lung infection (45), dyspnoea (406) and cough (209)[4]*.

Advice to Healthcare Professionals

1. Fatal and non-fatal cases of pneumonitis have been reported in patients receiving pembrolizumab[5].
2. Patients on pembrolizumab should be counselled on the signs and symptoms of pneumonitis (such as cough, dyspnoea, difficulty in breathing) and advised to seek medical attention promptly if these symptoms appear.
3. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes.
4. For moderate immune-mediated pneumonitis (Grade 2), withhold pembrolizumab until adverse reactions recover to Grade 0-1. For severe or life-threatening immune-mediated pneumonitis (Grade 3-4) or recurrent moderate (Grade 2), permanently discontinue pembrolizumab therapy**.
5. All adverse events related to pembrolizumab should be reported to the NPRA.

DISCLAIMER

*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.

**Please refer to pembrolizumab product package insert for full prescribing information on immune-mediated pneumonitis.

References

1. Leroy V, Templier C, Faivre J-B, *et al.* (2016). Pembrolizumab-induced pneumonitis. ERJ Open Res 2017; 3: 00081-2016.
2. Pembrolizumab Malaysian product package insert [Last revision date: May 2019]
3. The NPRA QUEST 3+ database [Accessed July 2019].
4. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: June 2019].
5. Vigilyze Uppsala Monitoring Centre, World Health Organisation [Accessed: July 2019].

What's New?

List of Directives Related to Drug Safety Issues (May - August 2019)

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 2019, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Fluoroquinolone antibiotics	(i) Deletion and restriction of indications (ii) Disabling and potentially permanent side effects (tendinitis, tendon rupture, peripheral neuropathy, and central nervous system/neuropsychiatric deffects)	19 July 2019	[Ref: (12) dlm.BPFK/PPP/07/25 Jilid 3]
2	Topiramate	Nephrocalcinosis	19 July 2019	[Ref: (13) dlm.BPFK/PPP/07/25 Jilid 3]
3	Lamotrigine	Risk of Brugrada-type ECG	19 July 2019	[Ref: (14) dlm.BPFK/PPP/07/25 Jilid 3]

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 reaction:

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

Completed hard copy forms may be submitted via post, email or fax at:

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

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

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