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Articles based on Case Reports

Clozapine-induced gastrointestinal hypomotility (CIGH)

by Nurul Aimi binti Mohd. Reduzan

Case Report 1

A 51-year-old female patient was taking tablet clozapine 125 mg twice daily and later increased to 125 mg OM and 250 mg ON for resistant schizophrenia. She has been on treatment for the past nine (9) years. She was reported to experience **constipation**, which subsequently escalated to **colitis** and **ileus paralytic**. Clozapine was suspected and withdrawn from treatment, and the patient was reported to be recovering from the adverse reaction.

Case Report 2

A male patient of an unknown age was started on tablet clozapine 150 mg twice daily for resistant schizophrenia. The patient was reported to have developed **intestinal obstruction** associated with perforated viscus after 15 days of treatment. The patient was reported to have died due to that and it was unknown whether or not an autopsy was performed.

Discussion

Clozapine is an atypical antipsychotic, derived from the tricyclic dibenzodiazepine family.[1] It possesses weak dopamine receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic and sedative properties. Clozapine has also been shown to have antiserotonergic properties. It is the drug of choice to treat resistant schizophrenia in patients who are intolerant or non-responsive to classical neuroleptics. It has desirable outcomes in terms of improvement in mental health, quality of life and life expectancy.[2,3]

Gastrointestinal hypomotility is a condition of reduced contraction forces of the gut smooth muscles or prolonged transit time in the gastrointestinal tract.[2] It may be genetic in nature, acquired from extrinsic factors (e.g. sedentary

lifestyle, overweight, a lacking in fluids and fibre intake) or induced by drugs.[2,4,5] These contributing factors render the CIGH to be under-detected and under-reported.[5] A patient with gastrointestinal hypomotility may not only present with a variety of symptoms, but may also have compromised nutritional absorption and bowel output.[2] It may develop to other gastrointestinal complications such as dyspepsia, gastroparesis, chronic constipation, irritable bowel syndrome (IBS), or more severely, intestinal pseudo-obstruction or ileus.

Clozapine is commonly associated to a spectrum of gastrointestinal adverse events that has been attributed to clozapine-induced gastrointestinal hypomotility (CIGH), ranging from constipation to faecal impaction, intestinal obstruction and paralytic ileus.[1,6,7] Previous studies show clozapine delays colon transit, mostly due to its anticholinergic and antiserotonergic properties.[3] CIGH may be potentially life-threatening, and is associated with a high mortality rate.[5-7]

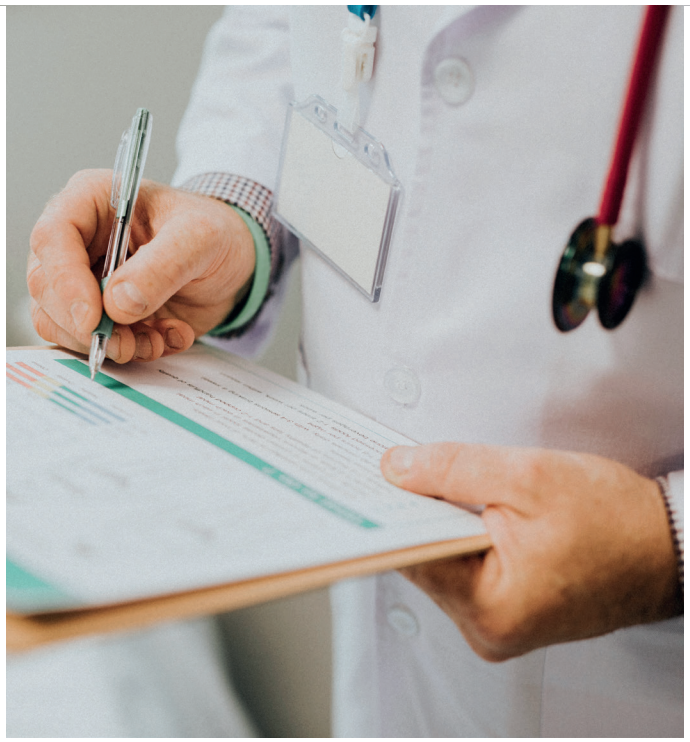
In a 22-year retrospective pharmacovigilance study in Australia and New Zealand to investigate serious or fatal CIGH, the analysis identified 160 out of 43,132 subjects receiving clozapine were associated with serious CIGH, where 29 subjects (18%) have died from CIGH.[3] The reported prevalence of serious CIGH was estimated to be 37 in 10,000 clozapine users, but it is thought that this figure is an underestimation of the true prevalence.

A result from a study on the effects of clozapine in the gut by adopting a wireless motility capsule technology, showed that 82% of the subjects prescribed with clozapine (n = 17) were found to experience reduced bowel motility in at least one region of the gastrointestinal tract - stomach, small intestine or colon.[8] While 59% of the subjects experienced multiregional gastrointestinal dysmotility, half of the subjects experienced delayed colon transit (50%), others were diagnosed with delayed small bowel transit (71%) and delayed gastric emptying (41%).

In Malaysia, there are currently seven (7) registered products containing clozapine.[9]

NPRA has received 333 adverse drug reaction (ADR) reports with 571 adverse events related to clozapine.[10] Adverse events related to CIGH include constipation (27), intestinal obstruction (9), abdominal pain (6), ileus paralytic (6), abdominal distension (4), and gastrointestinal hypomotility (3) and chronic constipation (2).

From the World Health Organisation (WHO) global ADR database, there were 170,891 cases reported adverse reactions linked to clozapine.[11] A total of 4,694 cases were



CIGH-related adverse reactions such as constipation (3,134), intestinal obstruction (1,002), ileus (543), ileus paralytic (360) and gastrointestinal hypomotility (76).*

In January 2020, the United States Food and Drug Administration (US FDA) has issued a drug safety communication on the risk of serious bowel complications associated with clozapine, and a new warning on this risk is required to be updated in the prescribing information of clozapine products.[12] This requirement was concluded following a safety review on the FDA Adverse Event Reporting System (FAERS) Database. In the 10-year review (2006 – 2016), there were 10 cases describing constipation that later progressed to serious gastrointestinal complications, resulting in hospitalisation, the need for surgery, or death.

The National Pharmaceutical Regulatory Agency (NPRA) has completed a safety review on the risk of serious bowel complications caused by constipation associated with clozapine. A safety alert on this risk has been communicated to healthcare professionals and a directive [Ref. No.: NPRA.600-1/9/13 (13)] has been released in the NPRA website for product registration holders to add new warnings and updates on this risk in the clozapine package inserts as well as consumer medication information leaflets (*Risalah Maklumat Ubat untuk Pengguna*).[13]

*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.

Advice to Healthcare Professionals

- Assess the patient's bowel habit before initiating clozapine. Remind patients and their caretakers to monitor on the frequency and quality of their bowel movements throughout clozapine treatment.
- Use lowest effective clozapine dose and avoid co-prescribing clozapine with other drugs that may induce constipation or gastrointestinal hypomotility (e.g. opiates, anticholinergic drugs).
- In high-risk patients and patients with previous history of chronic constipation or bowel obstruction, consider the use of laxatives as a prophylaxis during clozapine therapy.
- Inform patients and their caretakers to see a doctor if they are having symptoms of reduced bowel movement such as (e.g. low stool frequency, lack of urge to defecate, hard or dry stools, difficulty passing gas, nausea, bloating, abdominal pain, and vomiting).
- Advise patients and their caretakers not to stop taking clozapine without first talking to the doctor, as stopping treatment may trigger symptoms of schizophrenia or cause relapse.
- Educate patients and their caretakers on the importance of high fibre dietary intake such as fruits, vegetables and grains, as well as maintaining good hydration and daily physical activity to prevent constipation.
- Report all ADRs suspected to be related to clozapine to NPRA.

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Articles based on Case Reports

Dapsone-induced methaemoglobinaemia

by Ng Jia Mean

Case Report

A 28-year-old male patient with newly diagnosed retroviral disease and previous history of co-trimoxazole allergy was given oral dapsone 100 mg daily for the prophylaxis of Pneumocystis carinii pneumonia (PCP). Two (2) days after the initiation of dapsone, he developed multiple spikes of fever and dry cough. On investigation, his temperature was 38.9°C and SpO_2 87-90% in room air. He was well-perfused with warm peripheries but had dusky appearance with bluish nails. The patient remained cyanosed despite receiving oxygen supplementation via nasal prong. His arterial blood gas showed increased methaemoglobin level at 10.4% (normal range: 1-3%). The patient was diagnosed with **dapsone-induced methaemoglobinaemia**. The drug was withdrawn and the patient received supportive treatment with oxygen and activated charcoal. Three (3) days after the diagnosis, the patient achieved full recovery with methaemoglobinaemia level normalised to 1.2%.

Discussion

Dapsone is a synthetic sulfone that is used as an antimicrobial agent in treating leprosy, mycetoma, toxoplasmosis and in the prophylaxis of malaria.[1] It exerts its bacteriostatic effect by interfering with folate synthesis, an essential step in the production of DNA in bacterial cell division.[1-3] Dapsone is also used as an anti-inflammatory agent in other medical conditions, such as dermatitis herpetiformis and other dermatoses. Although the exact mechanism of action has not been fully elucidated, the anti-inflammatory action of dapsone is thought to be associated with decreasing neutrophil migration to the lesion site and the moderation of the level of damage by neutrophils when treating inflammatory conditions. In Malaysia, there is currently one (1) registered product containing dapsone.[4]

Methaemoglobinaemia is a known adverse event induced by dapsone.[1,2,3,5,7] Metabolites of dapsone are potent oxidants that may trigger the conversion of ferrous [Fe^{2+}] ion in the haemoglobin to its oxidised ferric [Fe^{3+}] state.[6,7] The adverse event itself is a potentially life-threatening condition, as the oxidation of Fe^{2+} reduces the oxygen-carrying capacity of the haemoglobin, leading to decreased oxygen delivery to the body tissues, resulting in hypoxia.

The severity of the presenting signs and symptoms of

methaemoglobinaemia is related to the levels of methaemoglobin in blood[8], as shown in Table 1 below:

Methaemoglobin Level (%)	Clinical Presentation
< 15	Generally asymptomatic
15-30	Cyanosis, anxiety, light-headedness, fatigue, headache
30-50	Tachypnoea, confusion, syncope
50-70	Seizures, arrhythmias, metabolic acidosis, coma
> 70	Death

Table 1: Symptoms based on methaemoglobin level

NPRA has received 232 adverse drug reaction (ADR) reports with 431 adverse events associated with dapsone use.[9] Some of the common adverse events reported include skin reactions such as rash (90), pruritus (32) and drug reaction with eosinophilia and systemic symptoms (DRESS) (28). Currently, there are 12 ADR reports of methaemoglobinaemia associated with the use of dapsone (including the case report discussed above). As of March 2021, a search in the World Health Organisation (WHO) global ADR database revealed a total of 486 reports of methaemoglobinaemia, 106 reports of cyanosis, and eight (8) reports of tachypnoea, suspected to be associated with dapsone.[10]*

*DISCLAIMER

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Advice to Healthcare Professionals

- Be aware on the possible association between dapsone use and methemoglobinemia.
- Consider the possibility of methaemoglobinaemia in patients receiving dapsone who have presented with cyanosis and decreased saturation levels on pulse oximetry. Further investigations such as arterial blood gas analysis and methaemoglobin level may be required to confirm the diagnosis and severity of the adverse event.
- Educate patients on the symptoms of methaemoglobinemia, and advise patients to immediately seek a doctor if signs and symptoms of methaemoglobinemia developed.
- Initial management of methaemoglobinaemia includes discontinuation of the offending drug and provision of supportive care. Treatment with methylene blue intravenously at 1 to 2 mg/kg of body weight over 5 minutes can be given to patients who are symptomatic or with a methaemoglobin level of 30% and above. In patients who do not respond to treatment with methylene blue alone, activated charcoal, exchange transfusions and hyperbaric oxygen therapy may be considered.
- Report any ADRs suspected to be related to the use of dapsone to NPRA.

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Articles based on Case Reports

Gastrointestinal adverse effects associated with immune checkpoint inhibitors

by Yeoh Hee Sheong

Local Case Study

A 74-year old male with non-small cell lung cancer was managed with pembrolizumab and radiotherapy. The patient caregiver's complained that patient has developed diarrhoea of more than 10 times per day, stomach ache, flatulence, changes in mood, skin thinning, rash and increased tendency of bruising. Pembrolizumab was continued despite of the adverse reactions and the outcome of the reaction was unknown.

International Case Study

A 44-year old male with metastatic non-small cell lung cancer was receiving treatment with pembrolizumab for one (1) year. His past medication history includes omeprazole, duloxetine, and pregabalin. He presented with symptoms of bloating, dysphagia, regurgitation, vomiting and weight loss for the past eight (8) weeks. Patient's esophagogastroduodenoscopy revealed diffusely active gastroduodenitis, and an immunohistochemistry investigation for *Helicobacter pylori* and cytomegalovirus detection were negative, suggesting the possibility of **immune checkpoint inhibitor-induced gastroduodenitis**. Pembrolizumab treatment was withdrawn and the patient was treated with oral prednisolone. His condition eventually improved.

Discussion

Immune checkpoint inhibitors (ICI) are monoclonal antibodies designed to target immune checkpoints such as programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4).[1,2] Tumour cells evade the body's self-defense mechanisms by activating these immune checkpoints, as this inhibits T-cell response and other immune-mediated responses. Through the inhibition of immune checkpoints, ICIs restore the immune system that leads to destruction of tumour cells.[2]

There are currently four (4) ICIs registered in Malaysia, which are atezolizumab, durvalumab, nivolumab and pembrolizumab. ICIs are indicated for a variety of cancers, including non-small cell lung cancer, melanoma, advanced renal cell cancer and squamous cell cancer of the head and neck (for full prescribing information, please refer to the product package insert).[3-6]

The unique mechanism of action of ICIs is by enhancing the immune system and act as double edge sword due to its potential to tilt the balance between tolerance (of the immune system towards its own cell) and immunity (towards antigens). As the adoption of ICIs for the treatment of cancer progresses, there has been a significant increase in immune-related adverse events (irAE) as well.[1,7] The onset of irAE varies from days to more than a year, and the adverse event may still develop for a long period of time even after the treatment has ended (delayed onset).[1]

IrAE are adverse events similar to an autoimmune response which may affect multiple organs of the body.[1,8] After skin, gastrointestinal adverse effects are the second most

common IrAEs associated with ICIs, such as oral ulcers, esophagitis, gastritis and enteritis.[9] ICI-associated colitis (ICIAC) or immune-mediated colitis is the most common among the severe IrAE associated within this drug group.[10] It is a documented adverse event in ICI product package inserts.[3-6] In addition, enterocolitis may lead to intestinal perforation which could be fatal, again reinforcing the suggestion of an early investigation.[11]

NPRA has received a total of 388 adverse drug reaction (ADR) reports with 552 adverse events suspected to be related to ICIs.[12] Reported adverse events related to the gastrointestinal system were diarrhoea (6), colitis (4), mucositis (2), nausea (2) and vomiting (2). Based on the World Health Organisation (WHO) international ADR database, there were reports of ulcerative colitis (149), gastric ulcer (49), duodenal ulcer (40), and gastrointestinal ulcer (9) associated with the use of ICIs.*[13]

*DISCLAIMER

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Advice to Healthcare Professionals

- Be vigilant on the risk of immune-related adverse events following the use of immune checkpoint inhibitors (ICIs).
- Monitor the patient's bowel habit changes after initiating ICI treatment, especially patients under anti-tumour combination therapy (anti PD-1/PD-L1 agent with anti CTLA-4), with elevated BMI or steroid refractory disease.
- Counsel patients on the signs and symptoms of colitis, such as diarrhoea, vomiting, fever of more than 38.2˚C, abdominal pain and bloody stool and advise patients to seek medical attention immediately. Early detection of colitis is vital as it may reduce the duration of symptoms, complications and hospitalisation rates.
- Discontinue the ICI if the condition is life-threatening. Consider switching to a different class of ICI once the adverse events have resolved.
- Please report any adverse events suspected to be associated with the use of ICI to the NPRA.

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Articles based on Case Reports

Ophthalmic preparations of vascular endothelial growth factor (VEGF) inhibitors: Risk of myocardial infarction

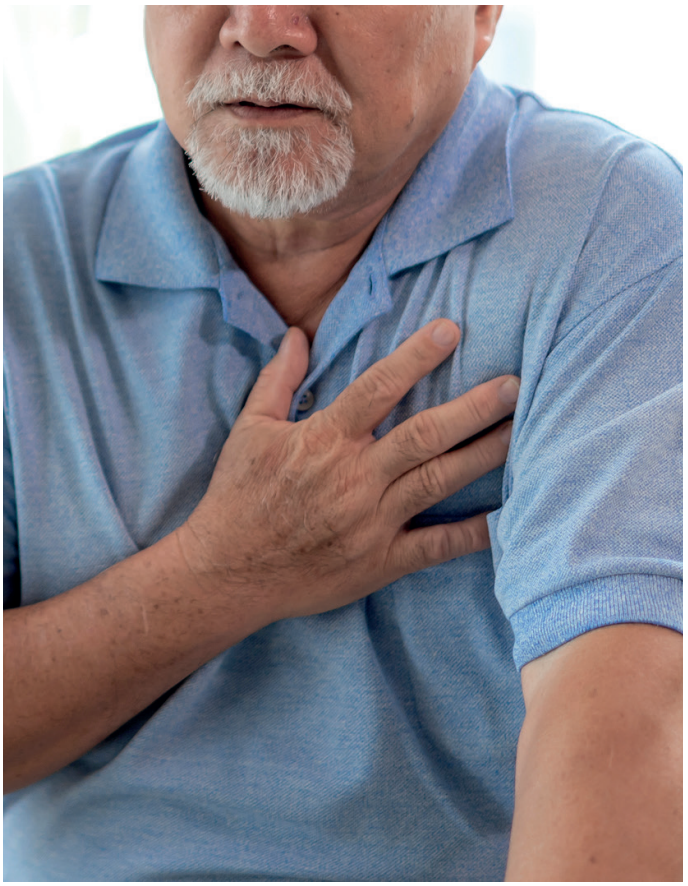
by Goh Pui Yen

Case Report 1

A 60-year-old male patient was diagnosed with age-related macular degeneration and was started on ranibizumab injection therapy. He has no medical history of hypertension or diabetes, and all investigation values were within normal limits. Other relevant history were cataract operation and a vascular graft bypass surgery. After receiving six (6) doses of ranibizumab during his 14 months of therapy, the patient had developed **myocardial infarction** and underwent a bypass surgery. It was unknown whether or not ranibizumab was withdrawn from treatment. At the time of reporting, the outcome of the adverse event was not provided.

Case Report 2

A 73-year-old male patient was diagnosed with age-related macular degeneration and was initiated with ranibizumab therapy. Prior to his appointment for second dose of ranibizumab, the patient informed his doctor that he had experienced **myocardial infarction**. Information on the patient's medical history and concomitant drugs was not reported, and the outcome of the adverse event was unknown.



Discussion

Vascular endothelial growth factor (VEGF) inhibitors that are administered intravitreally has been used for the treatment of neovascular age-related macular degeneration (AMD).[1] They are also indicated for treatments of visual impairment due to macular oedema, choroidal neovascularisation, and proliferative diabetic retinopathy *(for full prescribing details, please refer to product packaging insert)*.[2] VEGF inhibitors act by preventing VEGF from binding to the receptor tyrosine kinases present on the surface of endothelial cells.[2,3] This inhibition results in the suppression of endothelial cell proliferation, neovascularisation as well as vascular leakage.

In Malaysia, there are currently three (3) products of VEGF inhibitors registered for intravitreal use, which are ranibizumab (1), brolucizumab (1) and aflibercept (1).

Although intravitreal administration of VEGF inhibitor doses are smaller as compared to systemic use, detectable levels of VEGF inhibitors in the systemic circulation have been found.[4,5] Moreover, the blood-ocular barrier is often impaired in patients with neovascular diseases. This increases the absorption of anti-VEGF drugs into the systemic circulation, therefore causing potential systemic adverse events. The risk of systemic adverse events including myocardial infarction, non-ocular haemorrhages, arterial thromboembolic events, and stroke associated with the use of intravitreal VEGF inhibitors has been documented in the local product package insert.[2]

To date, NPRA has received 62 adverse drug reaction (ADR) reports with 101 adverse events associated with the use of aflibercept, brolucizumab and ranibizumab.[6] A total of five (5) reports of myocardial infarction have been reported with ranibizumab (3) and aflibercept (2). A search in the World Health Organisation (WHO) ADR database revealed a total of 1,389 case reports of myocardial infarction associated with VEGF inhibitors, involving ranibizumab (584), bevacizumab (541), aflibercept (259) and brolucizumab (5).[7]*

*DISCLAIMER

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Advice to Healthcare Professionals

- VEGF inhibitors for eye application such as ranibizumab, brolucizumab and aflibercept have been reported to cause myocardial infarction and this risk has been documented in the products' packaging insert.
- VEGF inhibitor therapy for ocular diseases are not recommended for use in patients with recurrent thromboembolic phenomena or a history of recent thromboembolic phenomena, including myocardial infarction or stroke in the past three (3) months.
- Take precautions when administering intravitreal injections of VEGF inhibitors to patients with high baseline vascular risk and monitor for symptoms of cardiovascular diseases.
- Advise patients to be cautious of symptoms of cardiovascular disease and seek immediate medical attention if any symptoms appear.
- Report all ADRs suspected to be related to the use of VEGF inhibitors to the NPRA.

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What's New?

List of directives related to drug safety issues

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 table below shows the DCA directives that were recently issued, which is available on the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Ref. Number
1	Vascular Endothelial Growth Factor (VEGF) Inhibitors (excluding eye preparations)	Risk of artery dissections and aneurysms	12 April 2021	[NPRA.600-1/9/13 (20)]
2	Rocuronium	Risk of Kounis syndrome	12 April 2021	[NPRA.600-1/9/13 (21)]
3	Mirtazapine	Risk of amnesia and risk of drug reaction with eosinophilia and systemic symptoms (DRESS)	12 April 2021	[NPRA.600-1/9/13 (22)]
4	Ceftriaxone	Risk of encephalopathy	14 June 2021	[NPRA.600-1/9/13 (24)]

How to report adverse drug reactions?

NPRA encourages all healthcare professionals to report 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. Report ADR as healthcare professional.
   a) Choose Online Reporting; or
   b) Download the ADR manual form and submit the completed form via email or post:

fv@npra.gov.my

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

NPRA Safety Information Mailing List

To join the mailing list, please send an email with your details to fv@npra.gov.my

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