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Ministry of Health, Malaysia

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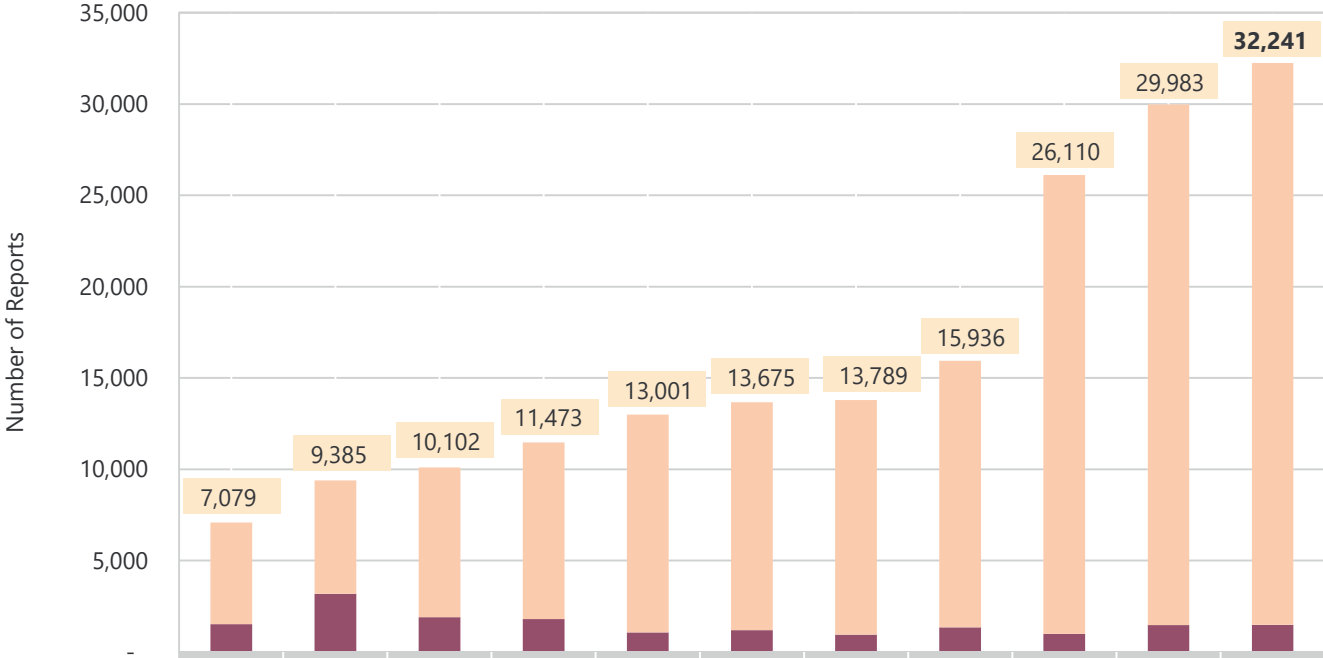
In this Issue

Features

Adverse event reports for 2010-2020

In 2020, the Centre for Adverse Drug Reaction Monitoring, NPRA received 32,241 adverse drug reaction (ADR) and adverse events following immunisation (AEFI) reports (Figure 1). The reports are processed and evaluated before they are sent to the World Health Organisation (WHO) Uppsala Monitoring Centre for inclusion into the WHO ADR database.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ADR Reports	5,550	6,202	8,199	9,678	11,921	12,489	12,834	14,590	25,127	28,505	30,746
AEFI Reports	1,529	3,183	1,903	1,795	1,080	1,186	955	1,346	983	1,478	1,495

DISCLAIMER:
Figure 1 shows the total reports received by NPRA before the full evaluation was carried out. These adverse events are not necessarily causally related to the product/vaccine.

Features

NPRA updates on reports of kidney-related and liver-related adverse reactions after consumption of ganoderma (lingzhi / reishi) products

by Nurul Aimi Mohd. Reduzan and Lee Sing Chet

The National Pharmaceutical Regulatory Agency (NPRA) wishes to advise the public on the risks of kidney-related and liver-related adverse reactions related to ganoderma which is also known as lingzhi or reishi.

Background

Ganoderma lucidum (image), an oriental fungus, is a large, dark mushroom with a glossy exterior and a woody texture. In China, *G. Lucidum* is commonly known as lingzhi, and in Japan, reishi or mannentake.[1] It has a long history of use for promoting health and longevity in China, Japan, and other Asian countries.[2] However, there are no clinical studies in humans supporting its effectiveness or safety.[2,3] A variety of commercial *G. Lucidum* products are available in various forms, such as powders, tablets, capsules and tea. In Malaysia, there are 81 registered products of *G. Lucidum* or lingzhi as single ingredients that are available in the tablets, capsules, and powder forms.[4]

The National Centre for Adverse Drug Reactions Monitoring, NPRA has detected an **increase in the number of adverse reaction reports related to consumptions of ganoderma/ lingzhi** with 11 cases in the past one (1) year.[5]

Case reports related to the safety issue

Nine (9) reports of kidney-related adverse reactions

NPRA has received **nine (9) local reports of kidney-related adverse reactions** suspected to be associated with ganoderma-containing products in the last one (1) year. The reactions reported were **increased in creatinine and urea in the blood**, **acute interstitial nephritis** and also **worsening of existing kidney impairments**. The adverse reactions were reported to occur as early as six (6) days and up to four (4) months after the consumption of ganoderma-containing products.

The patients were between 30 to 60 years of age. Most of them were also concurrently taking other medications and were reported to have underlying medical conditions, including chronic kidney impairments, diabetes, coronary artery disease.

Out of the nine (9) patients that experienced the adverse reactions, seven (7) were hospitalised. Six (6) were reported to have recovered or were recovering (at the time of reporting) after stopping the suspected products, whereas the remaining three (3) did not recover.

Two (2) reports of liver-related adverse reactions

Within the same time period, NPRA has also received **two (2) local reports of liver-related adverse reactions** suspected to be associated with ganoderma-containing products. The symptoms included **liver enzymes impairment**, **jaundice** and **acute liver failure**. These adverse reactions occurred as early as four (4) days and up to one (1) month after taking the ganoderma-containing products.

Both patients, aged 55 and 61 years old, were hospitalised. One patient had history of taking other traditional medications, while the other has underlying hypertension, gout, rheumatic heart disease and chronic kidney disease.

After stopping the intake of the suspected products, one (1) patient was reported to have recovered and the other patient were recovering (at the time of reporting).

Safety concerns

Although currently there is no scientific data on the risks of kidney- or liver-related adverse reactions from taking ganoderma, NPRA would like to advise on exercising caution when considering the use of ganoderma-containing products. This is particularly important in patients with underlying medical conditions including reduced kidney and/or liver functions.

NPRA will continue to closely monitor this safety issue and update the public of any other significant findings.

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Advisory

1 Be aware that a number of local cases of kidney- and liver-related adverse reactions have been reported in some individuals following the consumption of ganoderma-containing products (which is also known as lingzhi or reishi). This risk could be higher in those with underlying medical conditions.

2 Advise patients to consult a doctor as soon as possible if they feel unwell or develop any of the signs and symptoms of kidney- or liver-related adverse reactions when taking ganoderma.

References

1. Wachtel-Galor S, Yuen J, Buswell JA, et al. Ganoderma lucidum (Lingzhi or Reishi): A Medicinal Mushroom. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 9. Available from https://www.ncbi.nlm.nih.gov/books/NBK92757/
2. Joob B., Wiwanitkit V. Linzhi (Ganoderma lucidum); evidence of its clinical usefulness in renal diseases. Journal of Nephropharmacology. 2016;5(1):9.
3. Lin Z, Yang B, editors. Ganoderma and Health: Pharmacology and Clinical Application. Springer Nature; 2019 Nov 27.
4. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). 2021 [Cited 2021 February 6]. Available from https://www.npra.gov.my
5. National Pharmaceutical Regulatory Agency. The Malaysian National ADR Database [Internet]. 2021 [Cited 2021 February 8]. Available from https://www.npra.gov.my

Articles based on Case Reports

Chlorpheniramine: A very rare incidence of dystonia

by Wo Wee Kee

Case Report

A 23-year-old female patient was given an injection of chlorpheniramine 10 mg stat and an injection of hydrocortisone for the treatment of rash, and was later discharged with chlorpheniramine tablet 4 mg. Two (2) days later, the rashes resolved but she developed a locked jaw instead. Unable to chew or swallow, she sought treatment at the hospital and was diagnosed with dystonia that is possibly secondary to chlorpheniramine. After receiving an injection of procyclidine 2.5 mg stat, the adverse event resolved. The causality of 'possible' was given for this drug-reaction pairing.

Discussion

Dystonia is characterised muscle contractions that could be persistent or occurring at irregular intervals, which results in involuntary muscle twisting, repetitive movements or abnormal postures.[1,2] Oculogyric crisis, torticollis, trismus and spasticity are a few examples of its manifestation.[2,3] Dystonic reaction is associated with dopaminergic depletions, thus it is commonly caused by administration of drugs that disrupt dopamine concentration in the central nervous system, such as dopamine receptor antagonist or selective serotonin reuptake inhibitors (SSRI).[1,4]

Chlorpheniramine is a first-generation antihistamine that works by competitively attaching to H1 receptors, thus preventing histamine-mediated allergic reactions.[5] Owing to its lipophilic nature, chlorpheniramine can cross the blood brain barrier and initiate a variety of dopaminergic and serotonergic effects. Although antihistamines such as chlorpheniramine are reported to be effective in treating drug-induced dystonia[6], it is also documented in multiple references that it may in turn cause a dystonic reaction.[5,7,8] Theoretically, this may be attributed to its serotonin reuptake and dopaminergic inhibitory action.

In Malaysia, there are currently 62 registered products containing chlorpheniramine, as a single agent or as a combination product.[9] To date, NPRA has received 522 ADR reports with 992 adverse events associated with products containing chlorpheniramine products (all single and combination products). From this total, there are two (2) reports of dystonia and one (1) report for oculogyric crisis.[10] Globally, based on the World Health Organisation (WHO) ADR database, as of February 2021, there are eight (8) reports of dystonia associated with chlorpheniramine, seven (7) reports for oculogyric crisis,

and one (1) report each for torticollis, trismus and muscle spasticity.[11]*

*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

1. Although dystonic reactions are commonly a complication of an antipsychotic, antidepressant or antiemetic drug, it may also be caused by antihistamines such as chlorpheniramine.
2. Exercise caution when prescribing chlorpheniramine for the treatment of dystonia as in rare cases, the treatment itself is reported to cause dystonia.
3. Please report any ADRs suspected to be related to chlorpheniramine to the NPRA.

References

1. Loonen AJ, Ivanova SA. Neurobiological mechanisms associated with antipsychotic drug-induced dystonia. Journal of Psychopharmacology. [Internet]. 2020 Sep 9:0269881120944156. [Cited 2021 February 2]. Available from https://doi.org/10.1177/0269881120944156
2. Shah SM. Everything That Shakes is not a Seizure: A Primer of Movement Disorders for Emergency Physicians. Emergency Medicine Reports. [Internet]. February 25, 2001. [Cited 2021 February 2]. Available from https://www.reliasmedia.com/articles/68408-everything-that-shakes-is-not-a-seizure-a-primer-of-movement-disorders-for-emergency-physicians
3. Campbell D. The management of acute dystonic reactions. Aust Prescr [Internet]. 2001;24:19-20. [Cited 2021 January 13]. Available from https://doi.org/10.18773/austprescr.2001.011
4. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. Annals of Pharmacotherapy. [Internet]. 2002 Feb;36(2):251-4. [Cited 2021 February 7]. Available from https://doi.org/10.1345/aph.1A145
5. Chahal H. Antiallergics and Medicines Used in Anaphylaxis. World Health Organization [Internet]. [Cited 2021 January 13]. Available from https://www.who.int/selection_medicines/committees/expert/19/applications/Histamine_3_AC_R.pdf
6. Babatola AO, Taiwo AB, Ogundare EO, et al. Pattern and Outcome of Drug Induced Dystonia at the Paediatric Emergency Room of a Teaching Hospital in Southwestern Nigeria. Journal of Medical Sciences. [Internet]. 20: 13-17. [Cited 2021 February 7]. Available from https://scialert.net/abstract/?doi=jms.2020.13.17
7. Du Buske LM. Clinical comparison of histamine H1–receptor antagonist drugs. Journal of allergy and clinical immunology. [Internet]. 1996 Dec 1; 98(6):S307-18. [Cited 2021 January 13]. Available from https://doi.org/10.1016/S0091-6749(96)80116-3
8. Joseph MM, King WD. Dystonic reaction following recommended use of a cold syrup. Annals of emergency medicine. [Internet]. 1995 Dec 1; 26(6):749-51. [Cited 2021 January 13]. Available from https://doi.org/10.1016/S0196-0644(95)70050-1
9. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). 2021 [Cited 2021 February 6]. Available from https://www.npra.gov.my
10. National Pharmaceutical Regulatory Agency. The Malaysian National ADR Database [Internet]. 2021 [Cited 2021 February 8]. Available from https://www.npra.gov.my
11. VigiLyze, World Health Organisation Uppsala Monitoring Centre [Internet]. 2020 [Cited 2021 February 8]. Available from https://vigilyze.who-umc.org/

Articles based on Case Reports

Is there a risk of erectile dysfunction associated with the use of atorvastatin?

by Ng Wan Ning

Case Report 1

A 43-year-old male patient was prescribed atorvastatin for hyperlipidaemia. Over the course of one (1) year while he was on atorvastatin therapy, the patient complained of reduced libido and **erectile dysfunction (ED)**, which was described as taking a longer time to achieve full erection and unable to maintain it for a successful intercourse. Upon consultation with his doctor, the suspected drug was changed to simvastatin. The patient had no complaints of the adverse event when he was on simvastatin. However, as the patient's cholesterol level was not well-controlled with simvastatin, he had to be put back on atorvastatin, following which the adverse event reappeared.

Case Report 2

A 50-year-old male patient with diabetes and hyperlipidemia developed erectile dysfunction after one (1) month since atorvastatin was introduced to his treatment management. The doctor subsequently switched the drug to a different statin following which he ceased to complain of the adverse event.

Discussion

Atorvastatin is approved as an adjunct to diet for the treatment of hyperlipidaemia, hypercholesterolaemia and prevention of cardiovascular disease.[1] It acts by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which is the enzyme that converts HMG-CoA to mevalonate, a precursor of sterols – including cholesterol.

Atorvastatin is not known and not documented to cause erectile dysfunction. However, the potential association of ED to statins has been described in a few retrospective and prospective studies.[2-4] Several hypotheses were suggested to explain this association. First, the decrease in cholesterol levels as a result of statin use may inhibit the production of testosterone hormone, therefore be partly responsible for decreased libido in males.[5] The second postulated mechanism was the lipophilicity of statins. It was described that statins that have high lipophilic factor could act centrally or cause peripheral neuropathy in the penile nerves.[2,4] As atorvastatin has high lipophilicity, there could be an association of the drug to ED.

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On the contrary, more recent publications have suggested otherwise; a meta-analysis concluded that statin use does not appear to be associated with a new onset of ED.[6] Instead, statin use was associated with a reduced risk of erectile dysfunction incidents and in turn, an improvement of erectile dysfunction.[7-10]

Statins may contribute in reducing the risk of ED by lowering LDL levels and enhancing the vascular endothelial function via their pleiotropic effects, including reducing inflammation, oxidative stress and increased plasma nitric oxide concentrations.[7] In rat models with ED, it was demonstrated that the statin may interfere with penile RhoA and its effector Rho kinase signaling leading to the restoration of erection, mainly through the reduction of geranyl pyrophosphate, an essential step in RhoA activation.[9] This may explain the use of statins in improving the quality of erection in patients with ED. Another possible mechanism for statin efficacy on erectile function is through the activation of endothelial nitric oxide synthase as nitric oxide and cyclic guanosine monophosphate increased penile blood flow and relaxed smooth muscle, leading to improved erectile function.[8]

In Malaysia, there are 61 registered products containing atorvastatin, which are available as a single agent (51) and in combination with other antihypertensive agents (10).[11]

To date, NPRA has received 934 ADR reports with 1,483 adverse events associated with atorvastatin use.[12] The most commonly reported adverse events were pruritus, dizziness, myalgia, followed by rash and headache. At the time of this publication, there were 11 reports of erectile dysfunction (including the cases described above) which were associated with atorvastatin use, affecting male patients between the age of 40 to 70 years old. In seven (7) of the reports, the onset of erectile dysfunction was reported to be between several days to six (6) months, while the remaining four (4) reports did not disclose the time to onset of ED. The majority of the patients (9) were reported to recover from the adverse event after drug withdrawal. Based on the WHO database, as of March 2021, there were a total of 127,120 adverse events reported, associated with atorvastatin use globally.[13]* Out of this, there were 590 cases of erectile dysfunction and 143 cases of reduced libido.

Considering the wide use of atorvastatin and the possible under-reporting of this adverse event in the local setting, ED could be impacting a larger number of patients. However, based on the data observed in literature and spontaneous reports, ED in most cases seems to be reversible after drug withdrawal.[3,5,6,12] While more epidemiological studies and randomised trials are required to affirm this association, healthcare professionals' vigilance of this effect in patients undergoing statin therapy could contribute to their patients' quality of life.

Advice to Healthcare Professionals

1. Consider the possible association of erectile dysfunction with atorvastatin.
2. Consider advising patients taking atorvastation on the possible risk of erectile dysfunction and to seek medical advice if necessary.
3. Please report any adverse events associated with atorvastatin to the NPRA.

References

1. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). Lipitor local package insert [Internet]. Last revision date: 2021 February 10 [Cited 2021 January 15]. Available from https://www.npra.gov.my
2. Nurkalem Z, Yildirimtürk Ö, Özcan KS, Kul Ş, Çanga Y, Satılmış S, Bozbeyoğlu E, Kaya C. The effect of rosuvastatin and atorvastatin on erectile dysfunction in hypercholesterolaemic patients. Kardiologia Polska (Polish Heart Journal). 2014;72(3):275-9.
3. Carvajal A, Macias D, Sáinz M, Ortega S, Arias LH, Velasco A, Bagheri H, Lapeyre-Mestre M, Montastruc JL. HMG CoA Reductase Inhibitors and Impotence. Drug safety. 2006 Feb 1 [Cited on 2021 January 15];29(2):143-9. Avaliable from https://europepmc.org/article/med/16454541
4. Do C, Huyghe E, Lapeyre-Mestre M, Montastruc JL, Bagheri H. Statins and erectile dysfunction [Internet]. Drug safety. 2009 Jul 1 [Cited 2021 January 15];32(7):591-7. Available from https://link.springer.com/article/10.2165/00002018-200932070-00005
5. De Graaf L, Brouwers AH, Diemont WL. Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? British journal of clinical pharmacology. 2004 Sep [Cited on 2021 January 15];58(3):326-8. Available from https://www.doi.org/10.1111/j.1365-2125.2004.02128.x
6. Elgendy AY, Elgendy IY, Mahmoud AN, Al-Ani M, Moussa M, Mahmoud A, Mojadidi MK, Anderson RD. Statin use in men and new onset of erectile dysfunction: a systematic review and meta-analysis [Internet]. The American journal of medicine. 2018 Apr 1 [Cited on 2021 January 15];131(4):387-94. Available from https://www.doi.org/10.1016/j.amjmed.2017.10.043
7. Chou CY, Yang YF, Chou YJ, Hu HY, Huang N. Statin use and incident erectile dysfunction - a nationwide propensity-matched cohort study in Taiwan. International journal of cardiology. 2016 Jan 1;202:883-8. Available from https://www.sciencedirect.com/science/article/pii/S0167527315305763
8. Cai X, Tian Y, Wu T, Cao CX, Bu SY, Wang KJ. The role of statins in erectile dysfunction: a systematic review and meta-analysis. Asian journal of andrology. 2014 May [Cited on 2021 January 15];16(3):461. Available from http://www.asiaandro.com/Abstract.asp?doi=10.4103/1008-682X.123678
9. Cui Y, Zong H, Yan H, Zhang Y. The effect of statins on erectile dysfunction: A systematic review and meta-analysis. The journal of sexual medicine. 2014 Jun 1 [Cited on 2021 January 15];11(6):1367-75. Available from https://www.doi.org/10.1111/jsm.12497
10. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. The Journal of urology. 2004 Jul 1 [Cited on 2021 January 21];172(1):255-8. Available from https://www.doi.org/10.1097/01.ju.0000132368.10458.66
11. National Pharmaceutical Regulatory Agency. Product Search (Quest 3+) [Internet]. 2021 [Cited 2021 January 15]. Available from https://www.npra.gov.my
12. National Pharmaceutical Regulatory Agency. The Malaysian National ADR Database [Internet]. 2021 [Cited 2021 February 5]. Available from https://www.npra.gov.my

Articles based on Case Reports

Phenytoin: Risk of atrioventricular (AV) block

by Syifa' Izzati Mohd Zainul Arifien

Case Report 1

A 75-year-old male patient with a fitting episode was started on intravenous phenytoin with a loading dose of 1 g that was administered over 30 minutes. The treatment was continued with maintenance dose of intravenous phenytoin 100 mg three times daily. After a total of seven doses given, the patient developed a transient **third-degree heart block** secondary to phenytoin toxicity. The serum phenytoin level was found to be 36.3 mmol (normal range: 10 – 20 mmol). Phenytoin was discontinued and a substitute drug was given, and the patient gradually recovered. No other information on patient's medical history and concomitant medications were reported. The adverse event was given a causality of possibly-related to the drug.

Discussion

Phenytoin is a widely used anticonvulsant drug and is generally used for the prevention and management of certain types of seizure.[1,3] Phenytoin also possesses class B antiarrhythmic properties and it suppresses the automaticity of His-Purkinje fibres in the ventricle.[2] Due to this effect, the use of phenytoin is contraindicated in patients with sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular (AV) block and Adams-Stokes syndrome.[1,3] According to the 2017 Malaysian Consensus Guideline on The Management of Epilepsy, it was recommended that a cardiac assessment i.e. electrocardiogram (ECG) should be performed in all patients with epilepsy, as the risk of conduction block is exacerbated in patients taking phenytoin and other antiepileptic drugs such as carbamazepine.[4]

In a systematic review, it was observed that the infusion rate during intravenous administration of phenytoin was more critical in the development of cardiac adverse events compared to the total dose of phenytoin administered.[5] To minimise potential local and cardiac adverse events, it was suggested that the infusion rate of phenytoin should not exceed 50 mg/minute in adults, and not to exceed 1–3 mg/kg/minute in neonates and children (or 50 mg/minute, whichever that is slower).[1,3]

There are currently five (5) registered products containing phenytoin in Malaysia, available in capsule, oral suspension and parenteral formulations.[6] To date, NPRA has received 1,747 ADR reports with 3,027 adverse events suspected to be related to phenytoin. There are three (3) reported cases of complete AV block and one (1) case of second-degree AV block associated with phenytoin use.[7] At the time of this publication, the World Health Organisation (WHO) global ADR database contains 31 reports of AV block, 21 reports of complete AV block, nine (9) reports of first-degree AV block and four (4) reports of second-degree AV block suspected to be associated with phenytoin.[8]*

*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

1. Strictly follow the recommended infusion rate of intravenous phenytoin in the guidelines to minimise potential cardiotoxic adverse events. Rate reduction or discontinuation may be required if symptoms develop.
2. Cardiac monitoring is recommended during intravenous loading doses of phenytoin.
3. Take extra care when initiating intravenous phenytoin in patients with underlying cardiovascular diseases who are concurrently taking other epileptic drugs. **Note that there have also been post-marketing reports of cardiac adverse events in patients with no underlying cardiovascular diseases and comorbidities and at recommended doses and infusion rates.**
4. Report any adverse drug reactions suspected to be related to the use of phenytoin to the NPRA.

References

1. IBM Micromedex® Web Applications Access. Phenytoin: DRUGDEX Evaluations. IBM Corporation 2021 [Cited 2021 Feb 9]. Available from https://www.micromedexsolutions.com
2. Weng JT, Smith DE, Moulder PV. Antiarrhythmic Drugs: Electrophysiological Basis of Their Clinical Usage. The Annals of Thoracic Surgery. 1986 Jan 1 [Cited 2021 Feb 9];41(1):106-12.
3. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). Phenytoin local package insert [Internet]. Last revision date: 2019 Oct 16 [Cited 2021 Feb 9]. Available from https://www.npra.gov.my
4. Malaysian Society of Neurosciences. Consensus Guideline on the Management of Epilepsy [Internet]. Malaysia: Malaysian Society of Neurosciences; 2017 [Cited 2021 Feb 9]. Available from https://www.neuro.org.my
5. Guldiken B, Rémi J, Noachtar S. Cardiovascular Adverse Effects of Phenytoin. Journal of Neurology. 2016 May 1;263(5):861-70. [Cited 2021 Feb 10].
6. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). Product search: Phenytoin. 2021 [Cited 2021 Feb 8]. Available from https://www.npra.gov.my
7. National Pharmaceutical Regulatory Agency. The Malaysian National ADR Database [Internet]. 2020 [Cited 2021 Feb 8]. Available from https://www.npra.gov.my
8. VigiLyze, World Health Organisation Uppsala Monitoring Centre [Internet]. 2021 [Cited 2021 Feb 8]. Available from https://vigilyze.who-umc.org

Articles based on Case Reports

Azithromycin: A reminder of the risk of cardiac death

by Nurul Aimi Mohd. Reduzan

Case Report 1

A 15-year-old female patient was admitted to hospital for severe pneumonia. On admission, the patient had low potassium, calcium and magnesium levels. She was started on intravenous (IV) ceftriaxone and IV azithromycin. The next morning, the patient received a second dose of IV azithromycin. After a few hours, the patient had an episode of **ventricular tachycardia** and eventually suffered **cardiac arrest**. The patient was pronounced dead that afternoon.

Case Report 2

A 74-year-old male patient was admitted to hospital and was diagnosed with atypical pneumonia and acute coronary syndrome (ACS) with atrial flutter. After 1 hour of IV azithromycin infusion, patient complained of discomfort at the branula site as well as feeling unwell, giddiness and shortness of breath. Patient was then found to be unresponsive – presented with blank stare, not breathing, and asystole. Cardiopulmonary resuscitation (CPR) was carried out for 10 minutes and IV adrenaline was given. Patient subsequently recovered and was then diagnosed with **cardiac arrest** secondary to azithromycin-induced arrythmias.

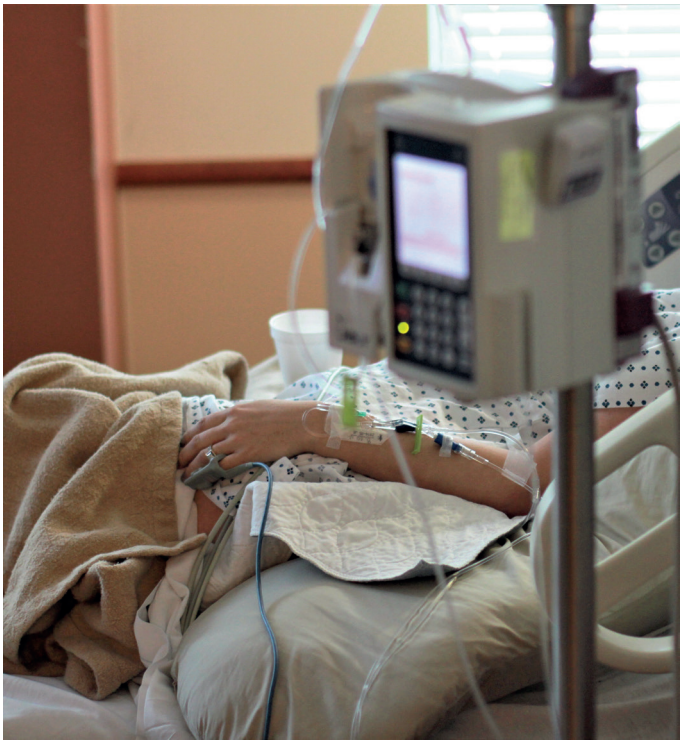
Both cases were assigned a possible drug-reaction causal relationship.

Discussion

Azithromycin is a broad-spectrum macrolide antibiotic which is used to treat or prevent a range of common bacterial infections including upper and lower respiratory tract infections as well as certain sexually transmitted diseases.

Previously, azithromycin was thought to be relatively free of cardiotoxic effects.[1] However, in 2012, a retrospective cohort study published in the New England Journal of Medicine suggested a higher risk of cardiovascular deaths (hazard ratio 2.88; 95% confidence interval [CI], 1.79 to 4.63; $p<0.001$) and deaths from any cause in patients receiving a 5-day course of azithromycin, compared to patients receiving other selected antibiotics or no antibiotics.[1,2]

An analysis of the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (FAERS) database showed that over an eight-year period



extending from 2004 to 2011, there were 203 reports of azithromycin-associated QT prolongation, *torsades de pointes*, ventricular arrhythmia, and sudden cardiac death resulting in a total of 65 fatalities.[3]

Since 2000, NPRA has received a total of 812 ADR reports involving 1,415 adverse reactions suspected to be associated with azithromycin use.[4] There are 44 adverse events related to cardiac disorders such as **palpitations (10)**, **electrocardiogram QR prolongation (6), tachycardia (4)**, **ventricular tachycardia (3,** including Case Report 1 above), **supraventricular tachycardia (3)**, **QT prolongation (3)**, ***torsades de pointes (2)*** and **cardiac arrest (1,** as discussed in Case Report 2).

Cardiac disorders such as palpitations, arrhythmias, and ventricular tachycardia are documented in the Malaysian product information leaflet of azithromycin, including rare post-marketing reports of QT prolongations and *torsades de pointes*.[5] Information on this risk, including warnings and precautions, have been updated in the product information leaflets.[6] Although the pathophysiology between azithromycin and the risk of cardiac death is still not fully understood, healthcare professionals are advised to be mindful of this risk and vigilant when prescribing azithromycin.

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Advice to Healthcare Professionals

1 The risk of developing torsades de pointes and cardiac arrhythmias, which may be fatal, has been reported with azithromycin use.

2 Carefully weigh the risks and benefits when considering treatment with azithromycin. Groups at higher risk include:

- Patients with known risk factors for arrhythmias including congenital long QT syndrome (LQTS) and acquired QT interval prolongation.
- Patients with concurrent use of other medications known to prolong the QT interval, such as class IA (e.g. quinidine and procainamide), class III (e.g. amiodarone, sotalol, and dofetilide) and antiarrhythmics agents.
- Patients with electrolyte disturbances such as hypokalaemia and hypomagnesaemia.
- Patients with clinically relevant bradycardia, cardiac arrhythmias or cardiac insufficiency.
- Elderly patients.

3 Periodic monitoring with electrocardiography for patients with especially high risk of arrhythmias may offer an additional measure of safety.

4 Report any ADRs suspected to be related to azithromycin to the NPRA.

References

1. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. New England Journal of Medicine [Internet]. 2012 May 17 [Cited 2020 March 27];366(20):1881-90. Available from https://www.nejm.org/doi/full/10.1056/nejmoa1003833
2. FDA Drug Safety Communication. Safety announcement: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms [Internet]. 2013 Dec 3 [Cited on 2020 March 27]. Available from https://www.fda.gov/media/85787/download
3. Giudicessi JR, Ackerman MJ. Azithromycin and risk of sudden cardiac death: guilty as charged or falsely accused?. Cleveland Clinic journal of medicine. 2013 Sep [Cited 2020 March 27];80(9):539. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906667/
4. National Pharmaceutical Regulatory Agency. The Malaysian National ADR Database [Internet]. 2020 [Cited 2021 Feb 8]. Available from https://www.npra.gov.my
5. National Pharmaceutical Regulatory Agency. Malaysian Product Registration Database (Quest 3+). Azithromycin local package insert [Internet]. Last revision date: 2018 November [Cited 2020 March 27]. Available from https://www.npra.gov.my
6. National Pharmaceutical Regulatory Agency. *Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984. Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 3 Tahun 2016: Direktif untuk Semua Produk yang Mengandungi Azithromycin (Formulasi Sistemik): Pengemaskinian Sisip Bungkusan dengan Maklumat Keselamatan Berkaitan Kesan Advers* QT Prolongation *dan* Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Available from Ruj. Kami: (34) dlm. BPFK/dlm.BPFK/PPP/07/25.

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	Mesalazine and sulfasalazine	Risk of nephrolithiasis	15 January 2021	[NPRA.600-1/9/13 (11)]
2	Abiraterone	Risk of hypoglycaemia due to drug interaction	15 January 2021	[NPRA.600-1/9/13 (12)]
3	Clozapine	Risk of serious bowel complications caused by constipation	15 January 2021	[NPRA.600-1/9/13 (13)]
4	Efavirenz (including combination products)	Risk of late onset neurotoxicity	15 January 2021	[NPRA.600-1/9/13 (14)]
5	Ondasetron	Information updates on risk of birth defects	15 January 2021	[NPRA.600-1/9/13 (15)]
6	Oseltamivir	Thrombocytopenia	15 January 2021	[NPRA.600-1/9/13 (16)]

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

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NPRA Safety Information Mailing List

To join the 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.