MADRAC Bulletin

For healthcare professionals only
Volume 43 | Issue 04/2023

In this issue

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

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

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

Signals

Features

What's New

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

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2]. The signals presented below are intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.*

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition[3], refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

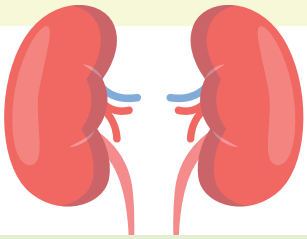
Drug-induced Nephrotoxicity

Written by Lee Sing Chet; Reviewed by Nora Ashikin Mohd Ali

Introduction

Drug-induced nephrotoxicity refers to any changes in the structure or function of the kidney caused directly or indirectly by drugs.[4] It can manifest in various forms, ranging from minor reversible renal injury to severe renal disorders. The mechanisms of nephrotoxicity are complex and multifactorial, including direct toxicity to renal tubular cells, obstruction of the tubular or interstitium, immune-mediated nephritis such as glomerulonephritis or interstitial nephritis, and alterations of renal haemodynamics such as renal blood flow and glomerular filtration rate (GFR).[5-6] Antimicrobial agents, antineoplastics, analgesics, immunosuppressants, and contrast agents are among the commonly known nephrotoxic drugs.[7-8]

During our routine signal detection activity, we have identified **two (2) nephrotoxic drugs** that have shown a disproportionate reporting of renal adverse events.[1-2] This reporting trend has also been observed to be on an upward trend. While we acknowledge that the change in trend could be influenced by increased usage of the drugs or heightened awareness of adverse drug reaction (ADR) reporting, we deemed it necessary to conduct a review to assess the characteristics of these potential signals, and identify any new aspects of the known association.



Signal #1 Colistin (Polymyxin E) – Acute kidney injury (AKI)

Colistin, also known as Polymyxin E, is an antibiotic administered in the form of its inactive prodrug called colistimethate sodium (CMS).[9-10] Approximately 30% of CMS undergoes hydrolysis to convert into the active ingredient, colistin. CMS is mainly eliminated by the kidneys via glomerular filtration, with 60% to 70% of CMS excreted unchanged in the urine within 24 hours in healthy subjects. In cases of renal impairment, dose adjustment is required to prevent renal accumulation. For the remainder of this document, the term 'colistin' will be used to denote CMS or polymyxin E.

In our recent routine signal detection analysis, NPRA has identified a disproportionality in the reporting of acute kidney injury (AKI) associated with colistin (intravenous), as indicated by an IC_{025} value of 3.5.[1-2] The disproportionality value based on global data in VigiBase was 4.3. Besides, a notable rise in the number of AKI cases associated with colistin was observed, with cases increasing from 2 in 2020 to 9 in 2021.

Background

Colistin is indicated for the treatment of certain serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents are contraindicated or may be ineffective due to bacterial resistance.[9] Colistin is a cyclic polypeptide antibiotic belonging to the polymyxin group, which selectively target aerobic Gram-negative bacteria that possess a hydrophobic outer membrane, disrupting their cell membrane and leading to lethal physiological effects. In Malaysia, there are two registered products containing colistin, both in injectable form.[11]

Colistin-associated nephrotoxicity, including AKI, has been reported in retrospective studies in Saudi Arab, Thailand, and Korea, with incidence rates spanning between 32% and 69%.[12-14] Factors associated with colistin-induced AKI were age (65 years and older), high blood bilirubin levels, AKI presentation prior to colistin administration, higher daily colistin dosages, and concomitant use of nephrotoxic drugs.[13]

Reports in QUEST[1]

As of May 2023, NPRA had received a total of 18 reports concerning AKI associated with colistin use. The patients' ages ranged from 25 to 81 years, with a median age of 55 years, and 61% were males. The time-to-onset ranged from < 1 to 22 days. Improvement following dose reduction and/or drug withdrawal was reported in ten (10) cases, while six (6) had observed no improvement at the time of reporting. In the remaining two (2) cases, the dose was not changed in one case, and the action taken was unknown in the other. Ten (10) cases were confounded by the concomitant use of nephrotoxic drugs and underlying health conditions. Causality assessment was C3 possible for all reports.

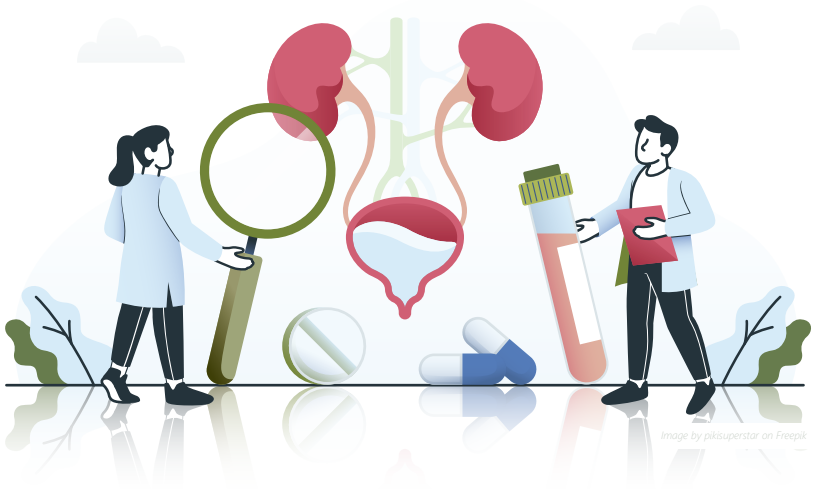
Reports in VigiBase[2]

As of May 2023, VigiBase recorded a total of 1,783 reports of renal adverse events associated with colistin, with AKI being the most commonly reported term (782 cases). The highest number of reports (33%) came from Thailand, followed by India and Korea (8% each). Malaysia contributed 1.8% of global reports. The cases had a mean age of 59 years, ranging from <1 to 96 years, and the majority (64%) were males. Time-to-onset was inconsistent and ranged from <1 day to 9 months. At the time of reporting, recovery was reported in approximately half of the cases (46%). There was limited information on underlying diseases, concomitant drugs, and causality in most reports.

Conclusion & Advice

The current package inserts for colistin has addressed its potential for nephrotoxicity and emphasised the need for adjusting the dose and interval for patients with moderate to severe renal impairment based on creatinine clearance.[9]

Healthcare professionals are reminded to monitor renal function at the start and periodically during colistin treatment for all patients. Increased risks of nephrotoxicity have been observed in patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs. Additionally, some studies have reported an association between nephrotoxicity and the cumulative dose and treatment duration of colistin. Therefore, healthcare professionals should carefully weigh the benefits of prolonged colistin treatment against the potential increased risk of renal toxicity.



Signal #2 Imatinib – Renal disorders

Imatinib is documented to be potentially associated with renal disorders, including a decline in renal function and acute kidney injury (AKI).[15] A screening of local reports in QUEST, the national pharmacovigilance database, detected disproportionalities in the reporting of renal adverse events associated with imatinib.[1] These include renal impairment (IC_{025} = 2.5), renal failure (IC_{025} = 1.6), chronic kidney disease (CKD) (IC_{025} = 0.8), and decreased blood creatinine (IC_{025} = 0.3).[8-9] Comparatively, an assessment of global cases in VigiBase, the World Health Organisation (WHO) global ADR database, identified lower disproportionality values for renal impairment (IC_{025} = 1.2), renal failure (IC_{025} = 1.0), and CKD (IC_{025} = -0.4), but a higher value for decreased blood creatinine (IC_{025} = 1.7).[2] Notably, we observed an increasing cumulative number of reports on imatinib-associated renal disorders over the last five (5) years, rising from 14 cases in 2017 to 45 cases in 2022.[1]

Background

Imatinib is a first-generation tyrosine kinase inhibitor (TKI) indicated for chronic myeloid leukaemia (CML) and chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in both adults and paediatrics.[15] In adults, its indications also encompass gastrointestinal stromal tumours (GIST), Philadephia myelodysplastic / myeloproliferative diseases (MDS/MPD), hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL), dermatofibrosarcoma protuberans (DFSP), and aggressive systemic mastocytosis (ASM). Imatinib acts by inhibiting the BCR-ABL tyrosine kinase and several receptors, including the platelet-derived growth factor receptors alpha and beta (PDGFR-α and PDGFR-β). Imatinib and its metabolites are mainly eliminated in faeces, and to a lesser extent, in urine. In Malaysia, there are 23 registered products containing imatinib, available in tablet or capsule forms.[11]

AKI and increased blood creatinine have been reported to occur at an uncommon frequency (≥ 1/1000 to < 1/100) in clinical studies where imatinib was indicated for CML and GIST.[15] A decline in GFR and the development of CKD have also been reported with imatinib therapy.[16-18] Additionally, the decline in estimated GFR (eGFR) was significantly associated with the duration of imatinib therapy.[19] Older age and a lower eGFR value at the initiation of imatinib treatment were also found to have a significant association with the development of renal dysfunction.[16]

Reports in QUEST[1]

As of March 2023, NPRA had received a total of 49 reports containing 61 adverse events relating to renal disorders following the use of imatinib. The terms reported include renal impairment (23 reports), increased blood creatinine (12), AKI (9), renal failure (7), CKD (4), hydronephrosis (2), renal atrophy (1), bladder calculus (1), decreased creatinine clearance (1), and decreased urine output (1).

These patients had a mean age of 67.5 years, ranging from 19 to 89 years, and the majority (55%) were males. The time-to-onset, which was reported in only four (4) cases, varied from one (1) month to four (4) years. Imatinib was mainly indicated for GIST (49%) and CML (43%), while the rest did not specify its indication. Most reports lacked information about underlying diseases or the use of concomitant drugs, which impeded further case evaluation. Nevertheless, considering the plausible mechanism, all reports were assigned a C3 possible causality.

Reports in VigiBase[2]

In VigiBase, imatinib has been associated with a total of 2,675 cases of renal adverse events. The most frequently reported terms were renal failure (448), increased blood creatinine (432), renal impairment (388), AKI (358), renal disorder (174), and CKD (121). Nearly half of the cases (45%) were reported in the United States, followed by Japan (8%) and Germany (7%). Malaysia contributed 2% of the global reports. Similar to cases observed in Malaysia, the majority of global cases involved male

(55%), and imatinib was primarily indicated for CML (44%) and GIST (17%). However, the global patient demographic was slightly younger, with a mean age of 60 years old, ranging in age from two (2) months to 98 years. The time-to-onset varied considerably from one (1) day to 19 years. In most reports, information on underlying diseases, concomitant drugs, and causality was not provided.

Conclusion & Advice

The current package inserts for colistin has addressed its potential for nephrotoxicity and emphasised the need for adjusting the dose and interval for patients with moderate to severe renal impairment based on creatinine clearance.[9]

Health care professionals are reminded to monitor renal function at the start and periodically during colistin treatment for all patients. Increased risks of nephrotoxicity have been observed in patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs. Additionally, some studies have reported an association between nephrotoxicity and the cumulative dose and treatment duration of colistin. Therefore, healthcare professionals should carefully weigh the benefits of prolonged colistin treatment against the potential increased risk of renal toxicity.

*DISCLAIMER

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

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Key Messages

Our review did not uncover any new insights regarding colistin-associated AKI and imatinib-associated nephrotoxicity. We encourage healthcare professionals to continue reporting any suspected drug-induced nephrotoxicity, including those involving known nephrotoxic drugs. When reporting, it is crucial to provide as much information as possible, including the patient's medical history, any concomitant drugs, time-to-onset, laboratory findings, and any other relevant information. The availability of such data will aid in better signal detection.

Features

Publication Hearing loss and tinnitus associated with COVID-19 vaccines: An analysis from the national pharmacovigilance database in Malaysia

Sing Chet Lee, Wee Kee Wo, Hee Sheong Yeoh, Sim Mei Choo, Azuana Ramli

Objectives:

To compare the reporting pattern of hearing loss and tinnitus across different vaccines brands used in Malaysia (BNT162b2, CoronaVac, ChAdOx1, Ad5.CoV2-S and BBIBP-CorV).

Methods:

This retrospective study included all reports of hearing loss and tinnitus occurring after COVID-19 vaccination that were received in the national pharmacovigilance database, QUEST, from February 24, 2021 through July 31, 2022. Reports given causality consistent or indeterminate were included.

Results:

There were 21 cases on hearing loss, with overall reporting rate of 0.29 cases per million doses. The rate was similar across BNT162b2, CoronaVac and ChAdOx1. For tinnitus, 35 cases reported tinnitus, with the overall reporting rate of 0.49 cases per million doses, and the highest rate was reported for ChAdOx1. For both events, most aged 30 to 49 years. No gender disparity was observed. Both events were mainly reported to have occurred after the primary doses, with a median time-to-onset of two (2) days. There were no statistically significant differences in the reporting patterns for both events across BNT162b2, CoronaVac and ChAdOx1 by age group, gender, race, and dose number.

Conclusions:

Despite the low reporting rates and insufficient evidence to confirm its relationship, hearing loss and tinnitus following vaccinations should not be ignored due to its disabling potential and impact on one's quality of life. Continual reporting is encouraged for better signals characterisation in the future.

Significance

The reporting rates of hearing loss across mRNA vaccine (BNT162b2), inactivated vaccine (CoronaVac), and adenoviral vector vaccine (ChAdOx1) were similar, whereas for tinnitus, ChAdOx1 had approximately two times higher reporting rates compared to the other two vaccines. The reporting pattern of hearing loss and tinnitus by age, group gender, race, and dose number was similar for all vaccines.

Original Article

Asian Pacific Journal of Tropical Medicine

Hearing loss and tinnitus associated with COVID−19 vaccines: An analysis from the national pharmacovigilance database in Malaysia

For more information, read the full article published in the ***Asian Pacific Journal of Tropical Medicine.***

Lee SC, Wo WK, Yeoh HS, Choo SM, Ramli A. Hearing loss and tinnitus associated with COVID-19 vaccines: An analysis from the national pharmacovigilance database in Malaysia [Internet]. Asian Pacific Journal of Tropical Medicine. Elsevier BV; 2023 Jul;16(7):p 289-295. Available from: https://doi.org/10.4103/1995-7645.380718

SCAN HERE

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

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

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Terlipressin (Glypressin®)	Serious Fatal Respiratory Failure and Sepsis/Septic Shock in Patients with Type 1 Hepatorenal Syndrome	13-Jun-2023	-
2	Statins	Risk of Inducing or Aggravating Myasthenia Gravis	18-Jul-2023	-

How to report adverse events?

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

To report ADR/AEFI:

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

fv@npra.gov.my

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