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Ratnapala DUS
Teaching Hospital, Badulla, Sri Lanka

Wijesekara HP
Teaching Hospital, Badulla, Sri Lanka

Corresponding Author:
Ratnapala DUS
Teaching Hospital, Badulla, Sri Lanka

Drug prescription in kidney disease: Essential knowledge

Ratnapala DUS and Wijesekara HP

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Abstract
Kidney disease is a significant global health burden. Drug-induced renal toxicity contributes to acute kidney injury and chronic kidney disease worldwide. Conversely, altered kidney function affects the pharmacokinetics of drugs. Hence, causing drug toxicity. In this review, we discuss prescription of common nephrotoxic drugs in patients with underlying renal impairment, focusing on the pathophysiology of toxicity and preventive strategies available to avoid toxicity.

Keywords: Kidney disease, nephrotoxic drugs, metabolism, NSAIDs

Introduction
Many drugs and their metabolites necessitate normal renal function for metabolism and excretion. Hence, pharmacokinetics of drugs excreted via the kidney are influenced by kidney disease. These pharmacokinetic alterations range from absorption of drug, plasma protein binding, distribution within tissues, to renal elimination, ultimately causing drug toxicity from accumulation [1]. Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (Aminoglycosides, beta-lactam antibiotics, and quinolones), anticancer drugs and proton pump inhibitors (PPIs) are common nephrotoxic drugs which should be cautiously used in patients with underlying kidney disease [2]. Pathophysiological mechanisms of nephrotoxicity leading to acute kidney injury (AKI) include direct tubular toxicity, vasoconstriction causing impaired renal perfusion, interstitial nephritis, and intrarenal crystallization [3]. In this review, we discuss a few commonly prescribed nephrotoxic drugs, their pathophysiology of toxicity, and preventive measures to avoid toxicity.

NSAIDs
NSAIDs are a well-known nephrotoxic drug [2, 4, 5]. Nevertheless, NSAIDs are highly prescribed for pain management in patients with underlying chronic kidney disease (CKD) worldwide [2, 6–9]. NSAIDs inhibit cyclooxygenase (COX) enzymes and reduce prostaglandin synthesis, hence providing analgesic, anti-inflammatory, and antipyretic effects [10, 11].
The common renal adverse effects of NSAIDs include AKI, acute on chronic kidney disease, fluid retention, acute interstitial nephritis and analgesic nephropathy. There are rare complications such as nephrotic syndrome and acute or chronic papillary necrosis were reported [10, 12-16]. There is a significant association between high doses of NSAIDs exposure and incident of CKD in the literature [17]. Furthermore, there is an independent association between recent use of NSAIDs and emergency dialysis start in patients with end-stage kidney disease (ESKD) [18]. Hence, NSAIDs are contraindicated in advanced CKD and AKI. It should be prescribed very cautiously even in early CKD [12].
Patients with underlying renal impairment, volume-depleted status, older age, concomitant use of ACEI, and ARBs are at higher risk for nephrotoxicity [10, 15]. Because renal toxicity can occur in the early course of treatment in high risk ill patients, serum creatinine and urine output should be monitored daily until the treatment is over [5, 13, 15]. furthermore, long-term therapy and high daily doses of NSAIDs should be avoided, even with normal renal function [13, 16].

It is recommended to avoid concomitant use of diuretics or Renin Angiotensin Aldosterone System (RAAS) inhibitors, maintain adequate hydration, and consider alternative analgesics with low prostaglandin activity such as acetaminophen [12, 14, 15, 19]. The current recommendation is to avoid prolonged use of NSAIDs if glomerular filtration rate (GFR) <60 ml/min/1.73 m2 and discontinuation of NSAIDs if GFR <30 ml/min/1.73 m2 [12, 14, 17-19].

Aminoglycosides

Aminoglycosides are bactericidal antibiotics with a narrow therapeutic index, used in the treatment of infections caused primarily by gram negative microorganisms [20, 23]. The important side effects of aminoglycosides include ototoxicity from accumulations in inner ear and AKI due to tubular toxicity [12, 21, 24]. Furthermore, aminoglycosides exert a complex tubular, glomerular, and vascular effects on the kidney contributing to nephrotoxicity [16, 25]. Its primary site of damage is proximal tubular cells [26]. The level of nephrotoxicity decreases from neomycin to gentamicin, tobramycin, amikacin, netilmicin, and streptomycin, with only a marginal variation in toxicity in the middle four drugs [26]. The main risk factors for aminoglycoside nephrotoxicity include dehydration, diabetes mellitus, CKD, prolonged therapy (> 7 days), high trough concentrations (> 2 mcg per mL), co-existing liver disease, hypoalbuminemia and concomitant use of nephrotoxic drugs and iodinated contrast media [15].

Aminoglycosides display concentration dependent pharmacodynamics. Concentration of the antibiotic relative to the minimum inhibitory concentration of the bacteria determine the potency of the antibiotic [27]. Interval method of drug dosing is preferred for drugs with concentration dependent pharmacodynamics, where the dose is kept constant while the time interval between doses is lengthened [19, 28]. This class of drugs is contraindicated in AKI [13, 21]. The therapeutic drug level monitoring and use of correct dose according to the eGFR should be carried out in all patients [12, 19, 21, 23].

Cotrimoxazole

Cotrimoxazole, a combination of trimethoprim and sulfamethoxazole, is an antibiotic that inhibits folic acid synthesis [29]. It has both gram-negative and positive cover [29]. Although cotrimoxazole is generally safe, it is associated with well-defined adverse effects [29, 30].

The important renal insults are hyperkalemia [10, 24, 30, 31] and AKI due to acute interstitial nephritis (AIN) [30-33], which are dose-dependent side effects [29, 31]. Other uncommon renal effects include obstructive tubulopathy and hyponatremia [30]. CKD, old age, high prescribed doses, combined use of ACEI, ARBs, spironolactone or NSAIDs, diabetes mellitus (DM), and acquired immunodeficiency syndrome (AIDS), further increases the risk for hyperkalemia [30]. Therefore, dosing adjustment is indicated if GFR < 30 mL/min/1.73 m2 [34]. Furthermore, it is advised to monitor the serum creatinine and potassium within the first 2-4 days of treatment, since any acute elevations predict drug-induced AKI and hyperkalemia, respectively [30, 31, 33]. It would direct immediate interventions such as early drug discontinuation.

Amphotericin B

Amphotericin B is a gold standard antifungal for severe fungal infections. Among its adverse effects, nephrotoxicity occurring generally within the first 2weeks of therapy is the most serious effect [35]. Underlying CKD, rapid infusion, large daily doses, deoxycholate formulations, and prolonged therapy increases the risk for nephrotoxicity [15, 24]. The preventive measures include adequate hydration with 0.9% saline before and after administration [sodium loading], dose reduction, giving as a continuous infusion over 24 hours, regular electrolyte monitoring (Na+, K+, Ca 2+, Mg2+), using the liposomal formulation over deoxycholate preparation, and avoiding prolonged therapy with high doses [15, 24, 36]. The current recommendation is to avoid amphotericin B unless no other option when GFR <60 ml/min/1.73 m2 [19].

Proton pump inhibitors (PPI)

PPI are another commonly prescribed class of drugs with a perceived favorable safety profile. PPI inhibit gastric acid secretion by blocking the H+/K+ ATPase enzyme in gastric wall cells [37]. Hence, increases the pH of gastric juice. A high prevalence of prescribing PPI for CKD patients is evident in the literature [37, 38]. One of the common indications is acid-related gastrointestinal disorders prevalent among CKD patients [37, 39]. Untoward common renal adverse events of long term PPI use include AIN and, CKD progression [38, 42, 44, 45].

Therefore, long term PPI should be avoided in CKD. But alternative treatment such as H2 receptor inhibitors can be considered.

Acyclovir

Acyclovir is an antiviral agent and a major amount of it is eliminated via kidneys [16]. Acyclovir is less soluble in urine causing drug crystallization [15, 16]. Hence, deposit in distal renal tubules, obstruct the tubules, and provide foci for interstitial inflammation, ultimately leading to AKI [15, 24, 49]. Other medications causing crystal nephropathy are antibiotics (e.g., ampicillin, ciprofloxacin, sulfonamides), antivirals (e.g., foscarnet, ganciclovir), indinavir, methotrexate, and triamterene [15, 24].

The risk for crystal nephropathy is augmented in the presence of CKD, metabolic disturbances (metabolic acidosis, alkalosis, or renal tubular acidosis), combined therapy with other nephrotoxic drugs, and volume-depleted status [15, 49]. Prevention of crystal nephropathy can be achieved by adjusting drug dose to GFR, adequate pre and post intravenous hydration with N saline and avoiding concomitant nephrotoxic drugs [15, 16, 49]. Acyclovir should be given as slow intravenous infusion [16, 49].

Opioids

Chronic pain is a common burdensome symptom in CKD patients [50]. Hence, adequate pain management is crucial to improve the quality of life of the patient. Opioids are a commonly used drug modality in pain management. Opioids primarily undergo hepatic metabolism and the metabolites are excreted via kidneys [51]. With impaired renal function, the metabolites which are more potent than parent drug accumulates and become toxic [51]. Furthermore, increased gastric pH, delayed gastric emptying, and gastrointestinal edema in CKD patients increase opioid absorption [50]. Frequent adverse effects of opioids include gastrointestinal side effects such as constipation, nausea, and vomiting, central nervous system effects, and respiratory depression

[51, 52]. Patients with CKD stage 5 are more prone to experience adverse effects of opioids [13].

There are no universally accepted evidence-based guidelines on the prescription of opioids [50]. However, an opioid prescription is recommended if nonpharmacologic interventions and nonopioid analgesics fail to achieve adequate pain management [53]. Furthermore, it is suggested to prescribe opioids along with acetaminophen and/or its adjuvant, rather than being prescribed alone [53]. Use of Screen-Quantify-Use opioids -Adjust-Reassess-Engage (SQUARE) strategy is recommended to follow when prescribing opioids [50, 51].

It is recommended to start the lowest effective dose for a short duration, combining non-pharmacological pain management interventions, and patient education of possible overdose [50, 51]. Drug-drug interaction and comorbid diseases should be taken into consideration [50]. If opioids are indicated, the recommended first-line opioids are oral hydromorphone, transdermal fentanyl, and transdermal buprenorphine [50, 51].

Lithium

Lithium is a renally excreted drug with a narrow therapeutic index [27]. AKI, Nephrogenic diabetes insipidus and interstitial nephritis and CKD are some renal side effects of lithium [12, 24]. The pathophysiological mechanisms include chronic interstitial nephritis, glomerulonephritis, and rhabdomyolysis [15, 24]. Underlying CKD, dehydration, diuretic use, and high doses further augment the risk for nephrotoxicity [24].

Therefore, it is necessary to maintain drug levels at the therapeutic range, avoid concomitant thiazide diuretics or NSAIDs and maintain euvolemia, especially during intercurrent illnesses to avoid nephrotoxicity [12, 15, 19]. Currently, it is recommended to monitor GFR, serum electrolytes, and lithium levels at every 3-6month interval or more often if the dose is modified or the patient is critically ill [19].

Conclusion

The clinicians should be cautious in prescribing drugs to patients with underlying renal impairment, as drugs can further exacerbate the renal impairment. Using alternative medicine if possible, assessing baseline renal function, adjusting doses, avoiding concomitant use of other nephrotoxic drugs, adequate hydration, using for a short period of time, monitoring drug levels, serum creatinine, and urine output, and increasing prescriber and patient awareness are all generally applicable preventive strategies.

Conflict of Interest

Not available

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References

1. Chahine B. Antibiotic dosing adjustments in hospitalized patients with chronic kidney disease: A retrospective chart review. Int Urol Nephrol. 2022;54:157-63. https://doi.org/10.1007/s11255-021-02834-6
2. Yameen MA, Tafseer M, Khan W, Anjum S, Raza-E-Mustafa, Chohan O. Trends in prescribing patterns and drug related problems of kidney disease patients. J Pak Med Assoc. 2021;71:2629-36.
3. Goldstein SL. Medication-induced acute kidney injury. Curr Opin Crit Care. 2016;22:542-5.
4. Tang KS, Shah AD. Nonsteroidal anti-inflammatory drugs in end-stage kidney disease: dangerous or underutilized? Expert Opin Pharmacother. 2021;22:769-77. https://doi.org/10.1080/14656566.2020.1856369
5. Hartmann B, Czock D, Keller F. Drug Therapy in Patients With Chronic Renal Failure. Dtsch Arztebl. 2010;107:647-56.
6. Ingrasciotta Y, Sultana J, Giorgianni F. The burden of nephrotoxic drug prescriptions in patients with chronic kidney disease: A Retrospective population-based study in Southern Italy. PLoS One. 2014;9:1-8.
7. Plantinga L, Grubbs V, Sarkar U, Hsu CY, Hedgeman E, Robinson B, *et al*. Nonsteroidal Anti-Inflammatory Drug Use Among Persons With Chronic Kidney Disease in the United States. Ann Fam Med. 2011;9:423-30.
8. Imai S, Momo K, Kashiwagi H, Miyai T, Sugawara M, Takekuma Y. Nonsteroidal anti-inflammatory drugs use in patients with chronic kidney disease are often prescribed from different clinicians than those who diagnosed them. Pharmacoepidemiol Drug Saf. 2020;29:873-80.
9. Guirguis-Blake J, Keppel GA, Holmes J, Force RW, Kriegsman W, Baldwin LM. Prescription of high-risk medications among patients with chronic kidney disease: A cross-sectional study from the washington, wyoming, Alaska, montana and idaho region practice and research network. Fam Pract. 2018;35:589-94.
10. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? Am J Kidney Dis. 2020;76:546-57. https://doi.org/10.1053/j.ajkd.2020.03.023
11. Sidorenkov G, Navis G. Safety of ACE inhibitor therapies in patients with chronic kidney disease. Expert Opin Drug Saf. 2014;13:1383-95.
12. Whittaker CF, Miklich MA, Patel RS, Fink JC. Medication safety principles and practice in CKD. Clin J Am Soc Nephrol. 2018;13:1738-46.
13. Charles C, Ferris AH. Chronic Kidney Disease. Prim Care - Clin off Pract. 2020;47:585-95.
14. Montgomery T, OwsianyChelsea E, Hawley, Laura K. Triantafylidis JMP. Opioid Management in Older Adults with Chronic Kidney Disease: A Review. Am J Med. 2019;132:1386-93. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958625/pdf/nihms960157.pdf
15. Bae E, Lee TW, Park DJ. Drug-induced nephrotoxicity. J Korean Med Assoc. 2020;63:30-5.
16. Wu H, Huang J. Drug-Induced Nephrotoxicity: Pathogenic Mechanisms, Biomarkers and Prevention Strategies. Curr Drug Metab. 2018;19:559-67.
17. Nelson DA, Marks ES, Deuster PA, O'Connor FG, Kurina LM. Association of Nonsteroidal Anti-inflammatory Drug Prescriptions with Kidney Disease among Active Young and Middle-aged Adults. JAMA Netw Open. 2019;2:e187896.
18. Pétureau A, Raffray M, Polard E, Couchoud C, Vigneau C, Bayat S. Analysis of the association between emergency dialysis start in patients with end-stage kidney disease and non-steroidal anti-

inflammatory drugs, proton-pump inhibitors, and iodinated contrast agents. J Nephrol. 2021;34:1711-23. https://doi.org/10.1007/s40620-020-00952-5
19. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. Suppl. 2013;3:1-150.
20. Hassan Y, Al-Ramahi R, Abd Aziz N, Ghazali R. Drug use and dosing in chronic kidney disease. Ann Acad Med Singapore. 2009;38:1095-103.
21. Blanco VE, Hernandorena CV, Scibona P, Belloso W, Musso CG. Acute kidney injury pharmacokinetic changes and its impact on drug prescription. Healthc. 2019;7:1-9.
22. Clase CM, Carrero JJ, Ellison DH. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020;97:42-61.
23. Matzke GR, Aronoff GR, Atkinson AJ, *et al*. Drug dosing consideration in patients with acute and chronic kidney diseasea clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80:1122-37. http://dx.doi.org/10.1038/ki.2011.322
24. Olyaei AJ, Bennett WM. Drug Dosing in the Elderly Patients with Chronic Kidney Disease. Clin Geriatr Med. 2009;25:459-527.
25. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: An integrative point of view. Kidney Int. 2011;79:33-45. http://dx.doi.org/10.1038/ki.2010.337
26. Begg EJ, Barclay ML. Aminoglycosides--50 years on. Br J Clin Pharmacol. 1995;39:597-603. http://www.ncbi.nlm.nih.gov/pubmed/7654476%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1365070
27. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: Fundamental principles. Clin J Am Soc Nephrol. 2018;13:1085-95.
28. Aloy B, Launay-Vacher V, Bleibtreu A. Antibiotics and chronic kidney disease: Dose adjustment update for infectious disease clinical practice. Med Mal Infect. 2020;50:323-31. https://doi.org/10.1016/j.medmal.2019.06.010
29. Eyler RF, Shvets K. Clinical pharmacology of antibiotics. Clin J Am Soc Nephrol. 2019;14:1080-90.
30. Ho JMW, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ. 2011;183:1851-8.
31. Rajput J, Moore LSP, Mughal N, Hughes S. Evaluating the risk of hyperkalaemia and acute kidney injury with cotrimoxazole: a retrospective observational study. Clin Microbiol Infect. 2020;26:1651-7. https://doi.org/10.1016/j.cmi.2020.02.021
32. Rennie TJW, De Souza N, Donnan PT. Risk of acute kidney injury following community prescription of antibiotics: Self-controlled case series. Nephrol Dial Transplant. 2019;34:1910-6.
33. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012;67:1271-7.
34. Aloy B, Launay-Vacher V, Bleibtreu A. Antibiotics and chronic kidney disease: Dose adjustment update for infectious disease clinical practice. Med Mal Infect. 2020;50:323-31. https://doi.org/10.1016/j.medmal.2019.06.010
35. Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: A review. J Chemother. 2000;12:463-70.
36. Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. Rev Iberoam Micol. 2009;26:223-7.
37. Lee HJ, Lee H, Oh SH, Park J, Park S, Jeon JS, *et al*. Chronic kidney Disease (CKD) patients are exposed to more Proton Pump Inhibitor (PPI)s compared to non-CKD patients. PLoS One. 2018;13:1-10.
38. Liabeuf S, Lambert O, Metzger M, Hamroun A, Laville M, Laville SM, *et al*. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: The CKD-REIN cohort study. Br J Clin Pharmacol. 2021;87:2967-76.
39. Okoro RN, Farate VT. The use of nephrotoxic drugs in patients with chronic kidney disease. Int. J Clin Pharm. 2019;41:767-775. https://doi.org/10.1007/s11096-019-00811-9
40. Vengrus CS, Delfino VD, Bignardi PR. Proton pump inhibitors use and risk of chronic kidney disease and end-stage renal disease. Minerva Urol Nephrol. 2021;73:462-70.
41. Ito T, Jensen RT. Association of Long-term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium. Curr Gastroenterol Rep. 2010;12:448-57.
42. Al-Aly Z, Maddukuri G, Xie Y. Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe. Am J Kidney Dis. 2020;75:497-507. https://doi.org/10.1053/j.ajkd.2019.07.012
43. Lanas-Gimeno A, Hijos G, Lanas Á. Proton pump inhibitors, adverse events and increased risk of mortality. Expert Opin Drug Saf. 2019;18:1043-53. https://doi.org/10.1080/14740338.2019.1664470
44. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: A critical review. Ther Adv Drug Saf. 2019;10:1-13.
45. Lazarus B, Chen Y, Wilson FP. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176:238-46.
46. Perazella MA. Proton pump inhibitors and hypomagnesemia: A rare but serious complication. Kidney Int. 2013;83:553-6. http://dx.doi.org/10.1038/ki.2012.462
47. Roux-Marson C, Baranski JB, Fafin C. Medication burden and inappropriate prescription risk among elderly with advanced chronic kidney disease. BMC Geriatr. 2020;20:1-12.
48. Moledina DG, Perazella MA. Proton pump inhibitors and CKD. J Am Soc Nephrol. 2016;27:2926-8.
49. Perazella MA. Crystal-induced acute renal failure. Am J Med. 1999;106:459-65.

50. Zhuo M, Triantafylidis LK, Li J, Paik JM. Opioid Use in the Nondialysis Chronic Kidney Disease Population. Semin Nephrol. 2021;41:33-41.
51. Davison SN. Clinical pharmacology considerations in pain management in patients with advanced kidney failure. Clin J Am Soc Nephrol. 2019;14:917-31.
52. Coluzzi F, Caputi FF, Billeci D. Safe use of opioids in chronic kidney disease and hemodialysis patients: Tips and tricks for non-pain specialists. Ther Clin Risk Manag. 2020;16:82137.
53. Davison SN, Rathwell S, George C, Hussain S, Grundy K, Dennett L. Analgesic Use in Patients With Advanced Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Can J Kidney Heal Dis. 2020;7:205435812091032.

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