DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Ninth, Jan– Mar 2023

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights analgesic nephropathy, orphan drugs, recent drug approvals, and few recent potential research papers. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Kidney Day: 09 Mar 2023; Theme: Kidney Health For All

Analgesic Nephropathy: A glimpse

Analgesic nephropathy is chronic tubule-interstitial nephritis caused by chronic use of analgesics such as acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). The presentation can be variable from asymptomatic hematuria, sterile pyuria, or proteinuria, to symptomatic anemia with features of chronic kidney disease or acute urinary tract infection. Hypertension, anemia, and impaired urinary concentration occur as renal insufficiency develops.

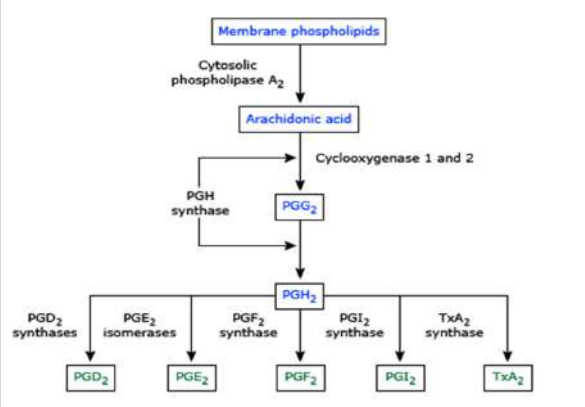
Risk factors for NSAID-induced kidney injury

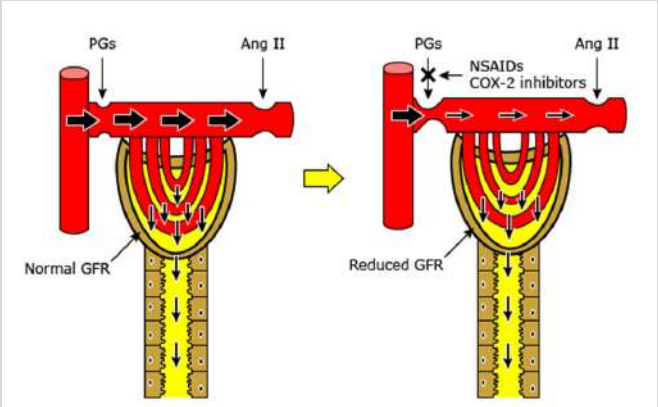
- Volume depletion: Emesis, diarrhea, sepsis, hemorrhage
- Medications: Diuretics, ACE inhibitors, ARBs, Calcineurin inhibitors
- Cirrhosis, Congestive heart failure, Nephrotic syndrome, Hypercalcemia (severe)
- Chronic kidney disease, Renal artery stenosis, Older age

Mechanism of Acute Kidney Injury

- Cyclooxygenases (COXs) are locally produced at many sites, including glomerular and vascular endothelium, the medullary and cortical collecting tubules, and medullary interstitial cells.
- COX-1 is expressed ubiquitously , while COX-2 expression is low at basal levels but increases with stimulation in setting of acute or chronic inflammation and other physiologic challenges.
- The tubules predominantly synthesize PGE2, while the glomeruli synthesize both PGE2 and PGI2. Kidney PGs are primarily local vasodilators.
- In the setting of hypotension and reduced kidney perfusion from vasoconstriction stimulated by angiotensin II, norepinephrine, vasopressin, or endothelin, PG synthesis is increased to maintain kidney perfusion and minimize ischemia. In addition to modulating renal hemodynamics, PGs also increase renin secretion, antagonize the water-retentive effects of arginine vasopressin, and enhance sodium excretion.

- NSAID inhibition of (COX) enzymes with subsequent reduction in prostaglandin (PG) synthesis can lead to reversible kidney ischemia, a decline in glomerular hydraulic pressure (the major driving force for glomerular filtration), and acute kidney injury (AKI).





Reference: UpToDate

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Analgesic Nephropathy...

Synergistic toxicity of analgesics in the renal inner medulla

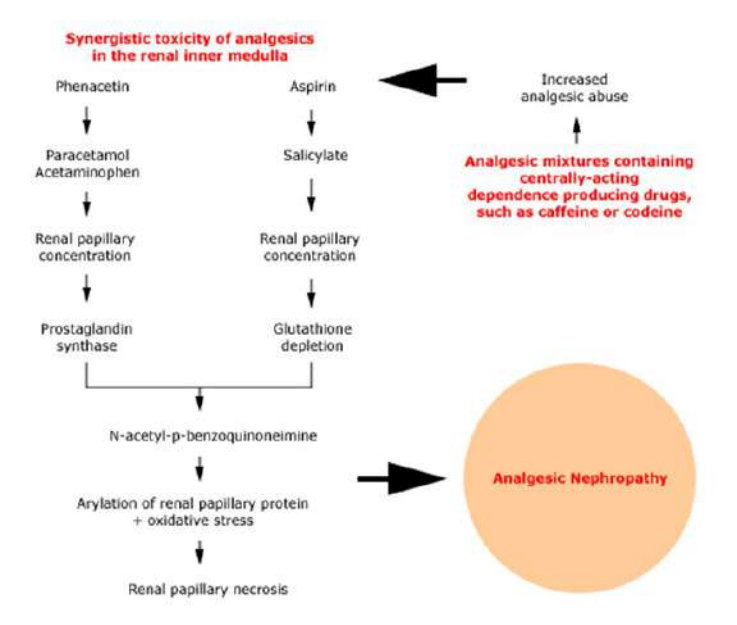
When phenacetin or acetaminophen is ingested with aspirin, there is a potentiating nephrotoxic effect.

-Aspirin is converted to salicylate, which becomes highly concentrated and depletes glutathione in both the cortex and papillae of the kidney.

-With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.

-Patients taking analgesic mixtures that contain aspirin, acetaminophen, and/or phenacetin plus potentially addicting compounds, such as codeine and caffeine, are more likely to abuse such drugs, thereby further enhancing risk of analgesic nephropathy.

-Combination should be avoided.



Medications To Be Avoided in Acute Kidney Injury (AKI)

-Stop medications such as NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and other drugs causing nephrotoxicity (eg, aminoglycoside antibiotics, piperacillin-tazobactam, amphotericin, tenofovir, nephrotoxic chemotherapy), at least in the acute phase of AKI.

-Drugs that are renally cleared and can accumulate leading to serious adverse effects in the setting of AKI should also be discontinued or undergo dose adjustment, even though they may not directly impact kidney function (eg, metformin, gabapentin, cefepime, morphine).

-If available, the patient should be switched to alternative agents that are not renally cleared.

-Where applicable, therapeutic drug level monitoring should be sought.

Dose Adjustments in Acute Kidney Injury (AKI)

-All medications should be carefully reviewed for appropriate dose adjustments according to the presumed estimated glomerular filtration rate (eGFR).
-Medication doses may be changed multiple times during the course of AKI depending on the eGFR:

Parameters	Remarks
Serum creatinine is rising briskly (or if only a single initial value is available)	GFR should be presumed to be 0 mL/min, and drugs should be dosed accordingly.
If serum creatinine is falling, the eGFR based on the serum creatinine likely underestimates the true GFR.	Medications should be dosed according to a GFR greater than the calculated eGFR, with re-evaluation of dosing on a daily basis depending upon the trajectory of improvement.
If the creatinine has reached a plateau and is stable for several days or more.	Serum creatinine may be used to estimate GFR (using an estimating equation) and dosed accordingly.
For medications that have a clear physiologic response (eg, vasopressors), the dose should be titrated to the desired clinical endpoint.	

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Calculation of drug dose in renal dysfunction: Simplified approach

Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago .
Rudolph Bucheim

Stepwise approach: 03 steps

Step 1: Calculation of creatinine clearance from serum creatinine

-For children (between 1 to 20 years): Clcr = 0.48 X H/Scr X (W/70)0.7

-For adult (> 20 years) Male: (140-Age)X W/ 72-Scr

Female: (140-Age)X W/ 85-Scr = 0.9 of Clcr of Male

Clcr: Creatinine clearance in ml/min
Scr : Serum creatinine in mg%
W: Weight in Kg
H: Height in cms
Age is measured in years

Step 2: Calculation of renal function (RF) from creatinine clearance (Clcr)

Clcr (ml/min)	Kidney status
120-130	Normal kidney
20-50	Moderate renal failure
<10	Severe renal failure

Renal funtion (RF) = Clcr of patient/ Clcr of a normal person e.g. 30/120 = 0.25
Dosage regimen need not be changed in following cases: RF > 0.7 ;
Fraction of drug excreted unchanged is <0.3

Ms. Patel (45-year-old, wt – 70kg) with a history of type 2 diabetes and stage 3 chronic kidney disease with a creatinine clearance of 45 ml/min , has been admitted to the hospital for management of a urinary tract infection. The physician has prescribed ceftriaxone, an anti-biotic used to treat bacterial infections. The normal dose of ceftriaxone is 2 grams once daily. How would you calculate the appropriate dose of ceftriax-one for Ms. Patel?
(Hint: Appropriate dose of ceftriaxone for Ms. Patel would be 750 mg once daily.)

Step 3: Adjustment of dosage regimen based on renal function (RF)

Option 1	Option 2
Reduce the dose (Dose interval constant)	Increasing the dose interval (Dose constant)
Patient dose = Normal dose X RF	Patient dose interval = Normal dose interval/ RF

-If the drug is excreted non-renally, then
Patient dose = Normal dose (RF X Fraction excreted in urine + Fraction excreted non-renally)

Note : Medication doses may need to be adjusted frequently in patients with renal disease, as kidney function can change rapidly.

Role of Diuretics in Acute Kidney Injury (AKI)

-Diuretics may be used to relieve hypervolemia among patients with AKI who are not anuric.

-Loop diuretics are the preferred agents as they provide a greater natriuretic effect than thiazide diuretics.

-Dosing of loop diuretics varies inversely with GFR (high doses needed for patients with impaired GFR).

-Diuretics are generally given intravenously rather than orally since the absorption of oral agents is variable in patients with decreased intestinal perfusion and motility and in those with mucosal edema.

-Diuretic-naïve patients: start with 80 mg of intravenous (IV) furosemide, or equivalent, and assess for response.

-Patients on diuretics prior to AKI onset: should receive a dose that is at least double their prior (home) dose.

-If no definite augmentation in the urine output within two hours of an IV diuretic dose, then administer double the initial dose (maximum of 200 mg in a single dose of IV furosemide or equivalent).

-Addition of a thiazide diuretic such as chlorothiazide (500 to 1000 mg IV) is sometimes given in conjunction with furosemide to augment urine output.

-Lack of response to a 200 mg dose of IV furosemide or equivalent, with or without a thiazide diuretic, may suggest the need for extracorporeal removal of excess volume.

-Patients who respond to diuretics: Continue to give repeated doses to avoid hypervolemia if kidney function is improving or improvement is thought to be imminent.

-If improvement not imminent: Initiate renal replacement therapy.

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ORPHAN DRUGS

Rare Disease Day: 25 Feb 2023; Theme: Share Your Colors

- Orphan drugs are the pharmaceutical product aimed for the therapy of rare diseases.
- A rare disease is any disease that affects fewer than 200,000 people (U.S.A.) , < 5,00,000 people (India).
- Speeding and increasing the development of effective and safe treatment options to address the unmet needs of patients with rare diseases is the vision of regulatory agencies.
- Despite the vision, the vast majority of rare diseases still do not have approved therapies.
- Challenges in orphan drug development: Low disease prevalence, disease severity, difficulties in patient recruitment, limited knowledge of the natural history of disease, phenotypic diversity and genetic subsets.

FDA Orphan Drug Act,1983: Provision for granting special status (orphan designation/orphan status) to a drug or biological product to treat a rare disease or condition upon request of a sponsor.

Orphan drug designation request criteria

-Rarity of the condition
-No reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug
-Severity of the condition in terms of life threatening or chronic debilitating nature
-Providing sufficient scientific rationale
-Clinical Superiority in condition of sameness of drugs

Prerequisites for approval

•Substantial evidence of effectiveness for treatment of the proposed indication
•Benefits of the drug must outweigh its risks for the patient population
•Adequate manufacturing methods to ensure product identity, strength, quality and purity
•Evidence-based drug labeling that adequately guides providers and patients on how to use the drug safely and effectively

Expedited Drug Development Programs

Fast Track Designation

A drug that is intended to treat a serious condition **AND** Nonclinical or clinical data demonstrate the potential to address unmet medical need **OR**

A drug that has been designated as a qualified infectious disease product

Breakthrough Therapy Designation

A drug that is intended to treat a serious condition **AND** Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies

Accelerated Approval Designation

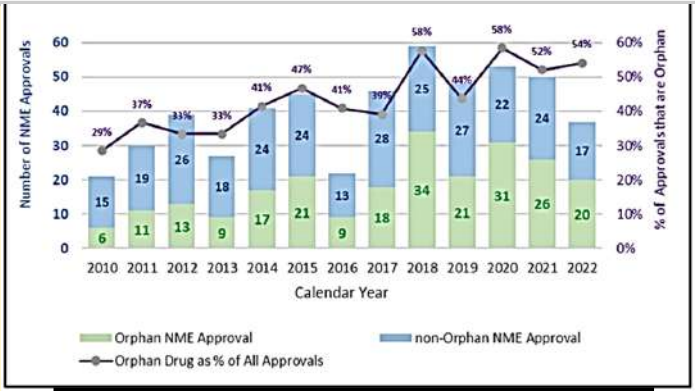
A drug that treats a serious condition **AND** Generally provides a meaningful advantage over available therapies **AND** Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., an intermediate clinical endpoint

Priority Review Designation

An application (original or efficacy supplement) for a drug that treats a serious condition **AND** if approved, would provide a significant improvement in safety or effectiveness **OR** Any supplement that proposes a labelling change pursuant to a report on a paediatric study **OR** An application for a drug that has been designated as a qualified infectious disease product **OR** Any application or supplement for a drug submitted with a priority review voucher

New drugs for Sickle cell anaemia

- **L glutamine**: Decrease the oxidative damage of sickled red blood cells by improving something called NAD, which is a common Redox cofactor.
- **Crizanlizumab**: IV monoclonal antibody, binds to P-Selectin on the surface of activated platelets and endothelial cells in the blood vessels and decreases the adhesion of the sickle cells, the platelets, and neutrophils.
- **Voxelotor**: First hemoglobin oxygen affinity modulator, decreases or inhibit the polymerization of Hemoglobin S, and prevent vaso-occlusive or pain crises.



No. of Orphan drug approvals between 2010-2022

New Drugs Corner

Lecanemab-irmb
MOA: An amyloid beta-directed antibody
Indication: To treat Alzheimer's disease

Bexagliflozin
MOA: A sodium-glucose co-transporter 2 (SGLT2) inhibitor
Indication: To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise

Pirtobrutinib
MOA: Kinase inhibitor
Indication: To treat relapsed or refractory mantle cell lymphoma in adults who have had at least two lines of systemic therapy, including a BTK inhibitor

Elacestrant
MOA: An estrogen receptor antagonist
Indication: To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced breast cancer with disease progression following at least one line of endocrine therapy

Daprodustat
MOA: Hypoxia-inducible factor prolyl hydroxylase (HIF PH)
Indication: To treat anemia caused by chronic kidney disease for adults on dialysis for at least four months

Velmanase alfa-tycv
MOA: A recombinant human lysosomal alpha-mannosidase
Indication: To treat non-central nervous system manifestations of alpha-mannosidosis

Sparsentan
MOA: An endothelin and angiotensin II receptor antagonist
Indication: To reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression

Omaveloxolone
MOA: Activates the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway
Indication: For treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older

Zavegepant
MOA: Calcitonin gene-related peptide receptor antagonist
Indication: To treat migraine

Trofinetide
MOA: Synthetic analog of the amino-terminal tripeptide of IGF-1
Indication: To treat Rett syndrome

Retifanlimab-dlwr
MOA: A programmed death receptor-1 (PD-1)–blocking antibody
Indication: To treat metastatic or recurrent locally advanced Merkel cell carcinoma

Leniolisib
MOA: Inhibits PI3K-delta by blocking the active binding site of PI3K-delta
Indication: To treat activated phosphoinositide 3-kinase delta syndrome

Rezafungin
MOA: New β-glucan synthase inhibitor
Indication: To treat candidemia and invasive candidiasis

Reference: USFDA

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Recent updates in pharmacology & drug discovery

Finerenone (Kerendia) Lowers Cardiovascular Events, Chronic Kidney Disease Progression

-Patients with Type 2 diabetes mellitus (T2DM) are at an increased risk for both macrovascular and microvascular complications.

-Long term complications of T2DM include cardiovascular disease, diabetic kidney disease, neuropathy, and retinopathy. Current treatments available for T2DM help prevent long term complications of the disease but do not reverse disease progression.

-Finerenone inhibits mineralocorticoid receptor-mediated sodium reabsorption and overactivation in epithelial and nonepithelial tissues reducing fibrosis and inflammation.

-Sodium-glucose co-transporter 2 (SGLT2) inhibitors and finerenone (a nonsteroidal mineralocorticoid receptor antagonist) prevent important adverse kidney and cardiovascular outcomes in patients with diabetic kidney disease (DKD).

American Diabetes Association (ADA)- 2022 guidelines and the Kidney Disease: Improving Global Outcomes (KDIGO): Advise the use of SGLT2 inhibitors in all patients with DKD; use of finerenone in patients who have increased albuminuria despite treatment with an angiotensin inhibitor and an SGLT2 inhibitor, except when serum potassium is elevated (serum potassium >4.8 mEq/L or estimated glomerular filtration rate <25 mL/min/1.73 m2).

-Finerenone reduce the risk of cardiovascular death, sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, non-fatal myocardial infarction, and hospitalization for heart failure. Most common adverse effects—Hyperkalemia, hypotension, and hyponatremia.

Reference: Bakris, G. L., Agarwal, R., Anker, S. D., Pitt, B., Ruilope, L. M., Rossing, P., Kolkhof, P., Nowack, C., Schloemer, P., Joseph, A., & Filippatos, G. (2020). Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. New England Journal of Medicine, 383(23), 2219–2229

Immunotherapy

- Immunotherapy is a type of cancer treatment that helps your immune system fight cancer.
- Two subtypes: chimeric antigen receptor (CAR) T-cell and bispecific T-cell engager (BiTE) therapies.
- CAR is programmed to be able to target a specific antigen, and when those bind, the results are T cell activation and the proliferation of the CAR T cells. There's then a release of inflammatory cytokines and interleukins, ultimately resulting in tumor cell destruction.
- BiTE molecules come in a variety of different constructs and are unique antibodies that are able to recognize 2 different antigens. It is able to recognize the CD3 on the T cell and the target antigen on the tumor cells, and they're linked together with a little linker in between. So when they combine and are linked together, it results in the activation of the patient's own T cells releasing enzymes and proteins like perforin and granzyme B etc., resulting in apoptosis and tumor cell destruction.
- 10 immunotherapies (6 CAR T-cell therapies and 4 BiTE therapies) have been approved by the FDA (since 2014).
- 6 CAR T-cell therapies: tisagenlecleucel (Novartis) in August 2017, axicabtagene ciloleucel (Kite Pharma) in October 2017, brexucabtagene autoleucel (Kite Pharma) in July 2020, lisocabtagene maraleucel (Bristol Myers Squibb) in February 2021, idecabtagene vicleucel (Bristol Myers Squibb) in March 2021, and ciltacabtagene autoleucel (Janssen Pharmaceutical Companies) in February 2022.
- 4 BiTE therapies: blinatumomab (Amgen) in December 2014, tebentafusp (Immunocore) in January 2022, teclistamab (Janssen Biotech) in October 2022, and mosunetuzumab (Genentech) in December 2022.
- The average response rate of cancer patients to immunotherapy drugs is between **20 to 50%** .

The Pill Box Quiz: 09

Instructions:
Scan the QR code to access the quiz.

SCAN ME