常見門診腎毒性藥品評估

蘇建豪 臨床藥師
高雄長庚紀念醫院藥劑部

May 09,2021

1

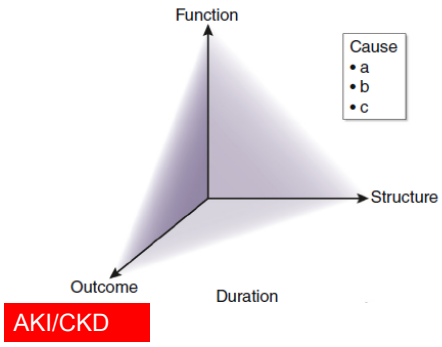
大綱

- 腎毒性藥品定義
  - 藥物相關急性腎損傷
  - 流行病學
  - 危險因子
- 常見門診腎毒性藥品
  - 血液動力學相關
    - ACEI/ARB、NSAID、SGLT2 inhibitor、contrast
  - 急性腎小管壞死與間質性腎炎
    - Antiviral agent、cotrimoxazole
  - 藥物相關腎結石
  - 常見中藥相關腎毒性

2

腎毒性藥品定義

- Nephrotoxicity is the development of functional or structural kidney damage
  - Kidney dysfunction: systemic renal/glomerular hemodynamic effects
    - impairment of blood pressure control
    - systemic hypotension and/or altered intraglomerular hemodynamics
      - afferent arteriole constriction, efferent arteriole dilation
    - renal endocrine function
    - glomerular or tubular dysfunction
      - Electrolyte imbalance
  - kidney injury: tubular or structural damage
    - glomerular and/or tubular abnormalities
    - morphologic lesions(small kidneys + chronic renal failure)
    - glomerular or tubular cell injury
      - filtered toxins
      - tubular obstruction
      - endothelial dysfunction
      - allergic reaction



J Pediatr Hematol Oncol 2011;33:128–134
Kidney Int 2020;98(2):294-309.

腎毒性藥品定義

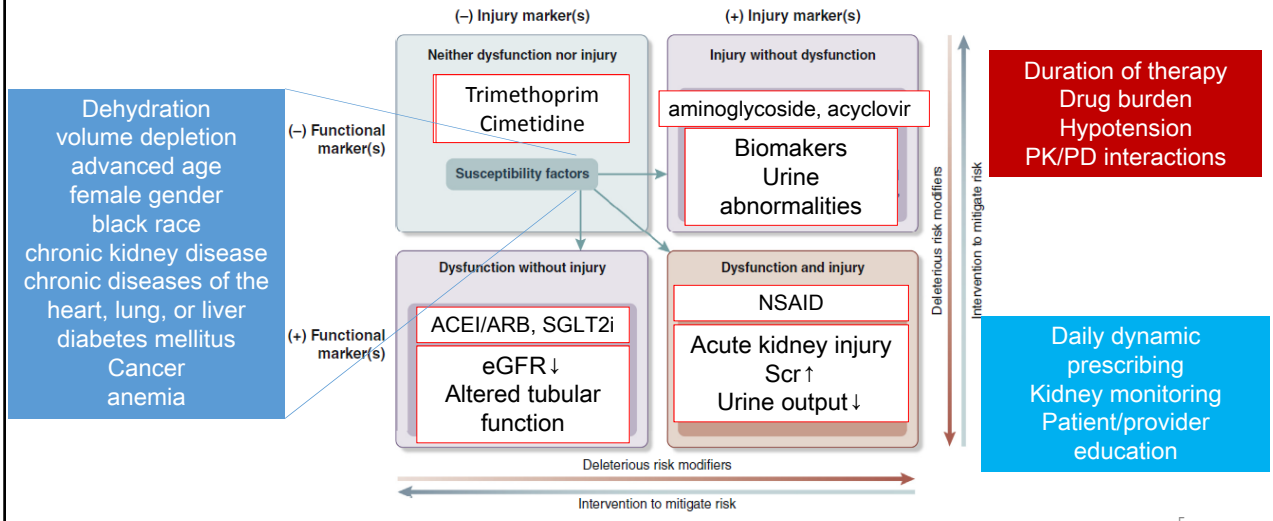
- Second nephrotoxic classification (Broad)
  - Directly harmful to kidney function
  - Eliminated by the renal route
    - harm from accumulation of parent drug or metabolites in the setting of AKI and AKD.
- New nephrotoxic definition(emerging)
  - kidney dysfunction without direct glomerular or tubular cell damage??
  - expression of physiologic effects of the drug
    - serum creatinine rising →renoprotective→improved outcomes
      - ACEI/ARB
      - SGLT2 inhibitor in diabetic nephropathy

4

Kidney Int 2020;98(2):294-309.

潛在腎毒性藥品分類

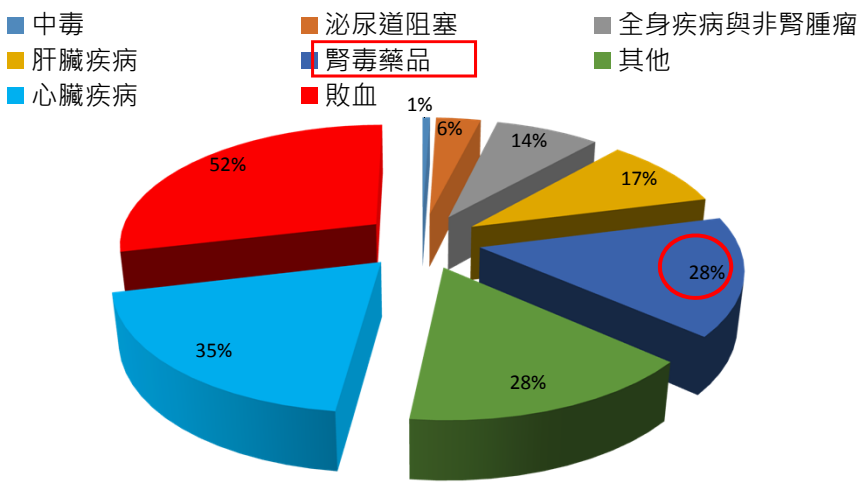
Drug related AKI
17-26%



5

Kidney Int 2020;98(2):294-309.

藥物相關急性腎損傷之流行病學

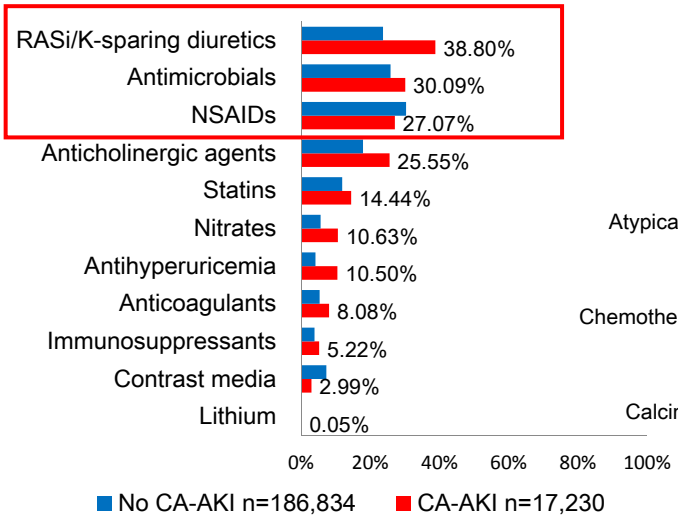


6

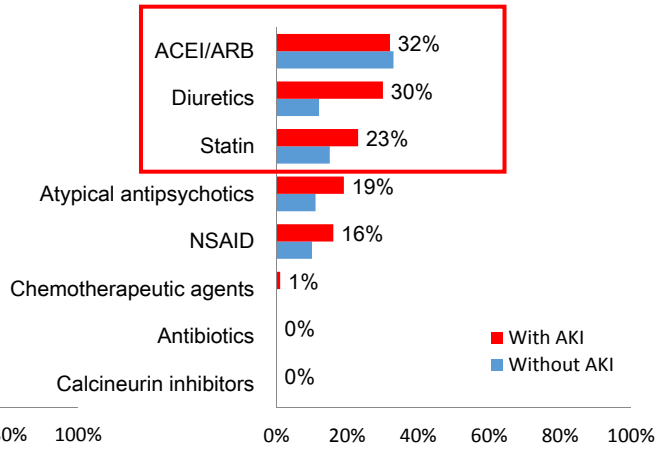
Medicine (2016) 95:39(e4987)

社區型AKI發生前腎毒性藥品分布

2010~2016, CGMH, ,3個月前門診廣義腎毒性藥品分布



每增加一類心血管用藥
OR 1.30 (95% CI 1.03–1.64)



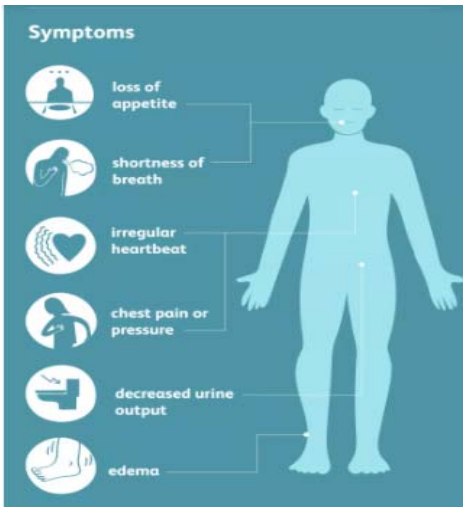
JMIR2020;22(8):e16903.
Medicine (Baltimore). 2015;94(31):e1251.

7

藥物相關腎毒性臨床表現

Sign

- Decreased urine output
  - progression to volume overload and hypertension.
- Proximal tubular injury
  - Metabolic acidosis with bicarbonaturia
  - glycosuria in the absence of hyperglycemia
  - reductions in serum phosphate, uric acid, potassium, and magnesium due to increased urinary losses.
- Distal tubular injury:
  - Polyuria from failure to maximally concentrate urine
  - metabolic acidosis from impaired urinary acidification
  - hyperkalemia from impaired potassium excretion.



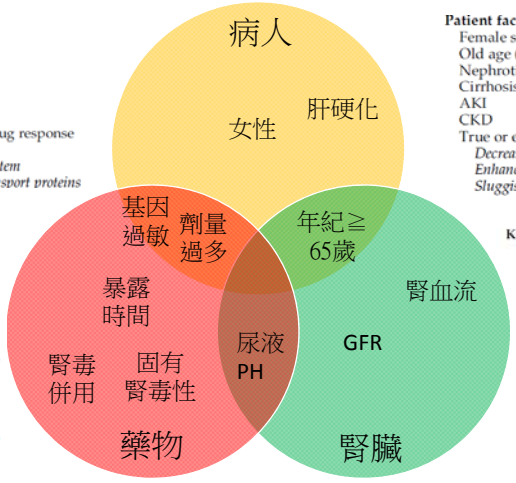
8

Pharmacotherapy, a pathophysiologic approach 2019

藥物腎毒性危險因子

Patient factors
Metabolic perturbations
Hypokalemia, hypomagnesemia, hypercalcemia
Alkaline or acid urine pH
Immune response genes increasing allergic drug response
Pharmacogenetics favoring drug toxicity
Gene mutations in hepatic and kidney P450 system
Gene mutations in kidney transporters and transport proteins

Drug factors
Prolonged dosing periods and nephrotoxic drug exposure
Potent direct nephrotoxic drug effects
Combinations of toxins/drugs promoting enhanced nephrotoxicity
Competition between endogenous and exogenous toxins for transporters, increasing drug accumulation within the tubular cell
Insoluble drug and/or metabolite with intratubular crystal precipitation
Drug that accumulates in lysosome due to lack of enzymes to metabolize the drug



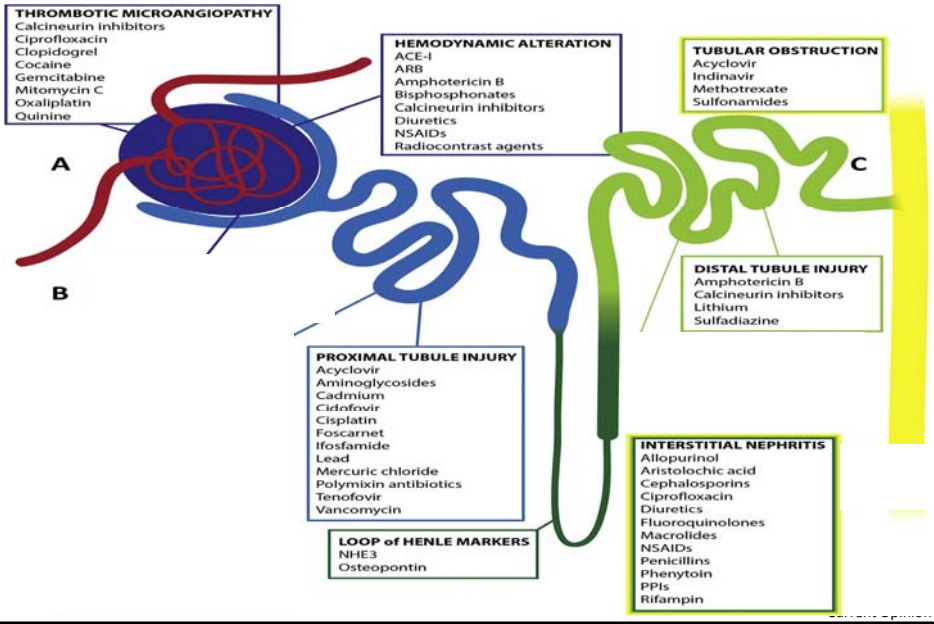
Patient factors
Female sex
Old age (>65 yr of age)
Nephrotic syndrome
Cirrhosis/obstructive jaundice (nephrotoxic bile acids)
AKI
CKD
True or effective volume depletion (kidney hypoperfusion)
Decreased GFR
Enhanced proximal tubular toxin reabsorption
Sluggish distal tubular urine flow rates

Kidney factors
High rate of blood delivery to the kidneys (approximately 25% of cardiac output)
Increased drug concentrations within the kidney medulla and interstitium
Biotransformation of drugs to nephrotoxic metabolites and reactive oxygen species
High metabolic rate of tubular cells (*i.e.*, loop of Henle) within a hypoxic environment
Proximal tubular uptake of drugs
Apical drug uptake via endocytosis or pinocytosis with drug accumulation
Basolateral drug transport via hOAT or hOCT with drug accumulation
Reduced drug efflux via apical transporters with drug accumulation

9

Clin J Am Soc Nephrol.2018;13(12):1897-1908.

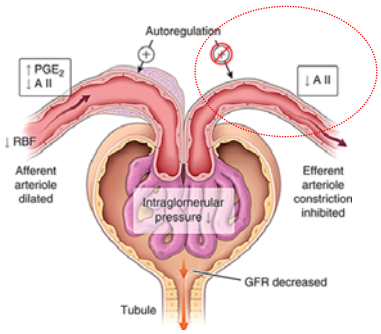
腎毒性藥品分類



10

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

- Incidence: 6-38% (LoE: B)
  - renal artery stenosis, volume depletion, and congestive heart failure and those with pre-existing kidney disease, including diabetic nephropathy
- Pathogenesis
  - reduced renal blood flow or effective arterial blood volume
  - prerenal settings (congestive heart failure)
- Clinical presentation
  - increase in Scr of up to 30% within 3 to 5 days of initiating therapy
  - typically stabilizes within 1 to 2 weeks
  - is usually reversible upon stopping the drug
  - Scr threshold for discontinuation of ACEI or ARB therapy is unclear.



11
Pharmacotherapy, a pathophysiologic approach 2019

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

- Risk factor
  - bilateral renal artery stenosis or stenosis in a single kidney
  - decreased effective arterial blood volume
    - decompensated congestive heart failure
    - volume depletion from excess diuresis or GI fluid loss
    - hepatic cirrhosis with ascites
  - nephrotic syndrome
  - patients with pre-existing kidney disease
  - nephrotoxic drugs (NSAID, Triple whammy)
- Prevention
  - started on low doses of long-acting ACEIs→ dose titration every 2 to 4 weeks
  - Use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (NSAIDs, diuretics) should be discouraged and dehydration avoided

12
Pharmacotherapy, a pathophysiologic approach 2019

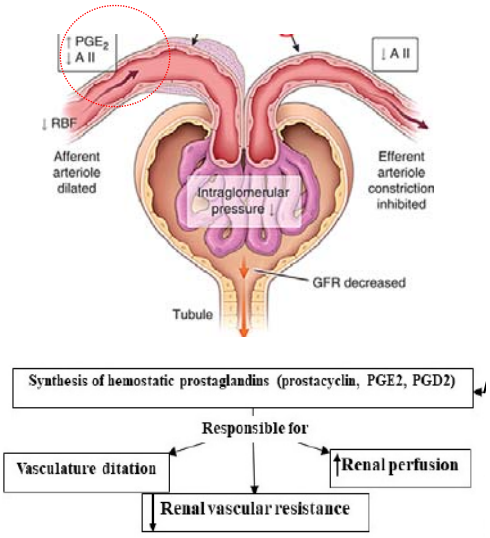
Nonsteroidal Anti-Inflammatory Drugs

- Incidence: 1-7% (LoE: A)
  - NSAID- and COX-2-induced AKI usually occurs within 2 to 7 days of initiating therapy
- **Clinical Presentation**
  - diminished urine output, weight gain, and/or edema
  - Urine sodium concentrations (<20 mEq/L) and fractional excretion of sodium (<1%)
  - BUN, Scr, potassium, and blood pressure are typically elevated.
- Risk factor
  - age more than 60 years
  - pre-existing kidney disease
  - hepatic disease with ascites
  - congestive heart failure
  - intravascular volume depletion/dehydration
  - systemic lupus erythematosus
  - Triple whammy

13

Pharmacotherapy, a pathophysiologic approach 2019

NSAID相關腎損傷機轉



14

COX1 VS.. COX2 inhibitor

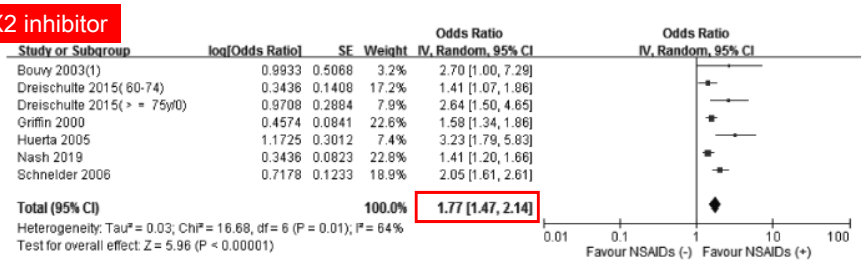


圖 2. 老年人使用NSAIDs與未使用者產生急性腎損傷的綜合優勢比[註1]和95%信賴區間

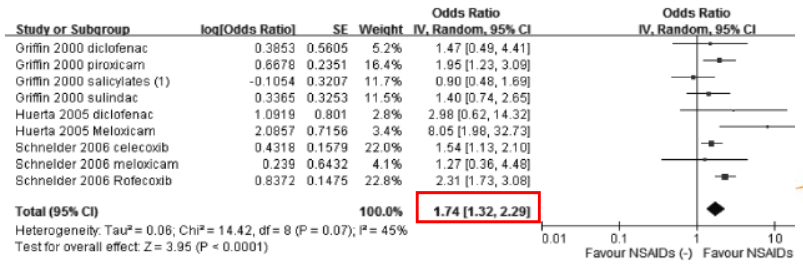


圖 3. 老年人使用選擇性Cox-2 抑制劑與未使用者產生急性腎損傷的綜合優勢比[註1]和95%信賴區間

15

台灣急性腎損傷處置共識 2020

其他腎毒性表現

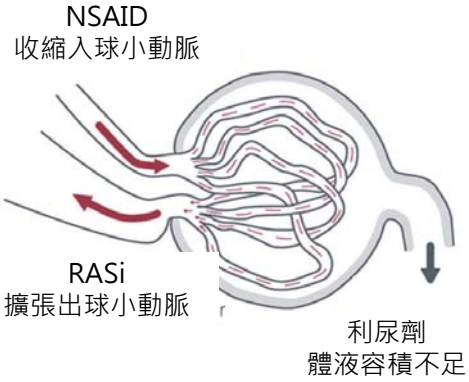
*Nephrotoxicity**	Stage 1-2 CKD	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD, No KRT
AKI	Low risk, similar to general population†.	Low risk, similar to non-elderly general population†, mildly increased in elderly.	At least moderately increased risk compared with general population.	High risk compared with general population.
	Risk posed by concurrent RAASi and/or diuretic use greater than in general population.			
Hyperkalemia	Low risk, similar to general population†.	Low risk, similar to general population†.	Moderately increased risk compared with general population.	High risk compared with general population.
Hyponatremia	Low risk, similar to general population†. Risk may be increased with DM.	Low risk, similar to general population†. Risk may be increased with DM.	Risk may be elevated compared with general population, but data lacking.	Risk may be elevated compared with general population, but data lacking.
Hypervolemia	Risk similar to general population†.	Risk similar to general population†.	Increased risk due to risk for Na+ and water retention and reduced GFR.	High risk due to risk for Na+ and water retention and reduced GFR.
Hypertension	Likely increased risk compared with general population based on level of underlying hyporeninemia.	Mildly increased risk compared with general population based on level of underlying hyporeninemia.	Increased risk due to risk for precipitating hypervolemia and systemic vasoconstriction.	High risk due to risk for precipitating hypervolemia and systemic vasoconstriction.
Progression of CKD	No increased risk with NSAID use†.	No increased risk with NSAID use†.	Likely moderate increased risk.	Moderate to high increased risk.
Data Strength	Strong-moderate	Moderate	Weak	Weak
Recommen-dations	Short-term use for ≤5 days acceptable**. Long-term use also acceptable on case-by-case basis**, with close monitoring for nephrotoxicity and for development of risk factors for nephrotoxicity as in Table 3.		Consider short-term, low-dose NSAID use on a case-by-case basis with close monitoring**. In patients with underlying hyperkalemia, should consider NSAIDs contraindicated	Would consider NSAIDs as absolutely contraindicated except under circumstances of palliative care.

16

Am J Kidney Dis.76(4):546-557

Triple whammy effect

- Incidence of AKI
  - patients taking either an ACE inhibitor/ARB or a diuretic with a NSAID
    - NNH over one year : >300
  - all three classes of medicine were taken together
    - NNH:158
    - risk of AKI: ↑31%
    - risk of AKI was highest (nearly two-fold increased risk) within the first 30 days
  - counteract antihypertensive medicines and diuretics
- Symptoms and signs of AKI due to hypovolemia
  - Reduced urine output, Thirst, Lethargy, Orthostatic hypotension, Tachycardia, Dry mucous membranes, Decreased skin turgor



17

https://bpac.org.nz/2018/triple-whammy.aspx

指引建議

Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities:

亞太胃腸道學會/亞太風濕病學會聯盟/亞太消化道內視鏡學會/亞太高血壓學會/亞太腎臟學會/PoA

RENAL EFFECTS OF NSAID THERAPY

Guideline statements

3.1 We recommend a NSAID be avoided in patients with severe CKD (eGFR <30 mL/min/1.73 m^2), or patients with moderate CKD (eGFR 30–59 mL/min/1.73 m^2) receiving ACE inhibitors, ARBs or diuretics. [1C]

3.2 If NSAID is to be given to patients at high risk of CKD, we recommend a renal function test be performed if it has not been done in the past 6 months. [2D]

3.3 If a NSAID is necessary for patients with CKD, evidence does not favour the recommendation of any specific drug. (not graded)

3.3.1 We recommend monitoring of renal function 1 week after initiation of a NSAID. [1C]

3.3.2 Regular monitoring of renal function during chronic NSAID therapy is desirable. [2C]

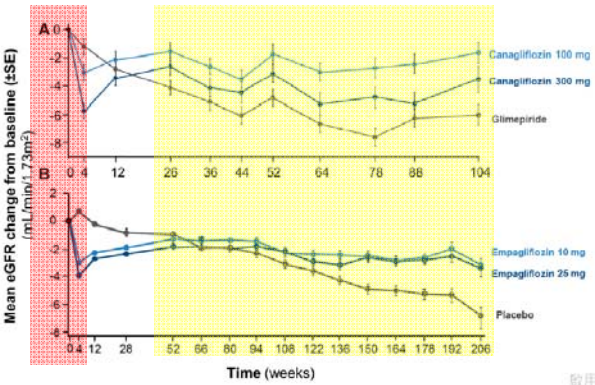
3.3.3 We recommend renal function be checked if fluid retention develops or there are clinical features of renal function deterioration during NSAID therapy. [1D]

18

Gut 2020;0:1–13

SGLT2 inhibitor

SGLT2 inhibitors induce stabilization of eGFR trajectory



Summary of the effects of SGLT2 inhibition on major kidney outcomes

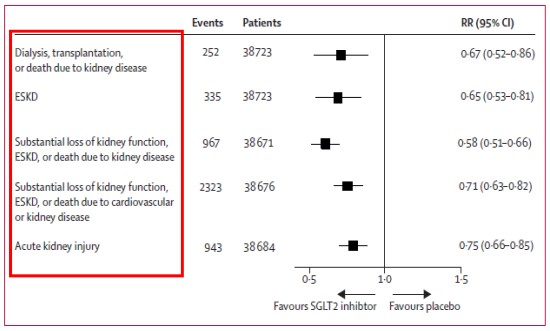


Figure 4: **Summary of the effects of SGLT2 inhibition on major kidney outcomes**
ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

Lancet Diabetes Endocrinol 2019;7(11):845-854

TABLE 1 Practical Considerations With Use of SGLT2 inhibitors

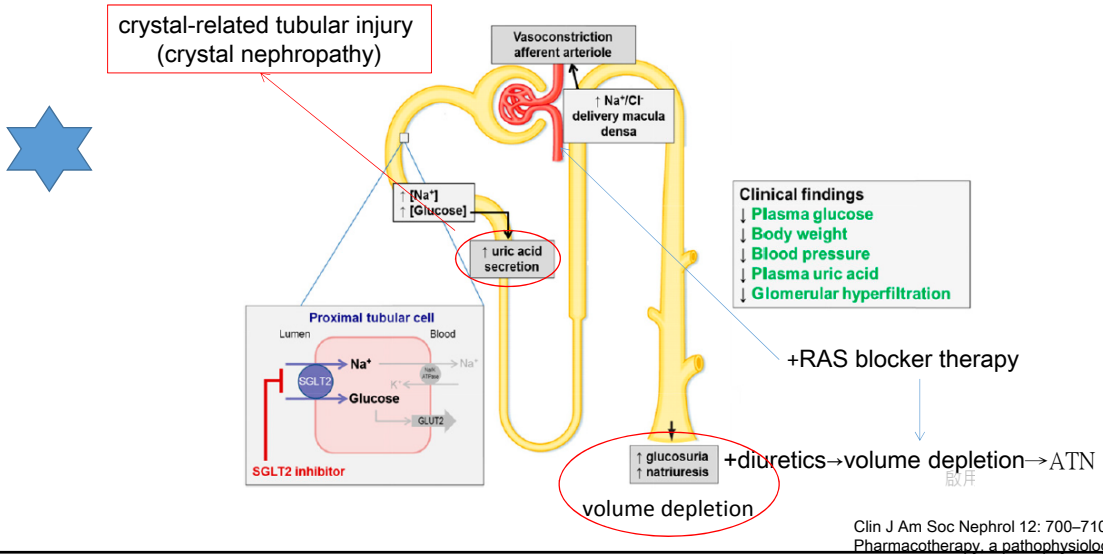
Potential Adverse Effect	Practical Considerations
Adverse drug-drug interaction	Pharmacokinetic drug-drug interactions are minimal Canagliflozin is a P-glycoprotein substrate (modest inhibition); co-administration with digoxin may increase plasma levels of digoxin; monitor digoxin levels and for signs and symptoms of toxicity when both are used together
Genital and urinary infections	Mycotic infections more common among females and in uncircumcised males Reinforce importance of adequate hygiene Counsel patients to urgently report genital/perineal tenderness, redness, or swelling No significant increase in risk of urinary tract infections
Hypoglycemia	Uncommon; risk increased with concomitant use of sulfonylureas and insulin
Diabetic ketoacidosis	Avoid pre-emptive substantial reductions in insulin dose Hold dose if acutely ill with limited oral intake, and 3 days before major surgery Use caution with low carbohydrate diets to minimize excessive ketosis Discourage excessive alcohol intake Asymptomatic elevations in beta-hydroxybutyrate are frequent with SGLT2 inhibitors, but only a fraction lead to overt diabetic ketoacidosis Counsel patients regarding potential symptoms of diabetic ketoacidosis (fruity odor on breath, thirst, polyuria, nausea, vomiting, abdominal pain, confusion, and fever)
Renal injury	Baseline and periodic monitoring of renal function is recommended, especially if used in chronic kidney disease Modest decrease in eGFR (3 to 4 ml/min/1.73 m^2) is expected with initiation Currently being investigated in eGFR <30 ml/min/1.73 m^2 Cases of acute kidney injury are rare, except in concert with volume depletion
Volume depletion	Increased risk with concomitant diuretic use; consider diuretic dose adjustment Educate patient about potential for orthostatic hypotension and necessity to monitor daily weights and blood pressure, particularly in the first week of therapy Anticipatory guidance to call healthcare provider if home weight decreases by 3 or more pounds over 24 h, or 5 or more pounds in a week, or in the setting of symptomatic hypotension
Lower limb amputations	Predominantly toe and metatarsal More apparent with canagliflozin Increased risk among those with previous amputations or in patients with peripheral artery disease Remind patients to perform regular foot exams and to see a podiatrist annually

eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter 2.

20

JACC Heart Fail 2019;7(2):169-172

SGLT2 inhibitor機轉



Clin J Am Soc Nephrol 12: 700–710, 2017
Pharmacotherapy, a pathophysiologic approach 2019

SGLT2 inhibitor使用建議

Table 4 Recommendations for initiation and monitoring of SGLT2 inhibitor therapy

1. Optimize volume status and avoid hypotension prior to SGLT2 inhibitor initiation
2. Concurrent RAAS inhibitor and /or diuretic use are not contraindications to SGLT2 inhibitor initiation, however, caution should be taken to minimize other risk factors for AKI prior to SGLT2 inhibitor initiation
3. Cautious initiation of SGLT2 inhibitors in patients exposed to NSAIDs or other nephrotoxic agents
4. Close monitoring should be undertaken in patients with stage 3b CKD and other risk factors for AKI (nephrotoxic drugs, contrast exposure, N/V, diarrhea, etc.) started on a SGLT2 inhibitor
5. Employ a "sick day strategy" of holding SGLT2 inhibitors with acute illness, trauma, or major surgery when adequate fluid intake may be compromised or patients are otherwise prone to AKI

RAAS renin-angiotensin aldosterone system, *CKD* chronic kidney disease, *AKI*: acute kidney injury, *NSAIDs* nonsteroidal anti-inflammatory drugs, *N/V* nausea and/or vomiting

- Management
  - volume depletion on exam, holding the SGLT-2 inhibitor (and RAS blocker and diuretic if also prescribed) and giving intravenous fluids typically resolve AKI
  - The SGLT-2 inhibitor can likely be restarted in patients where kidney function recovers to baseline and eGFR is above the FDA-recommended threshold.

J Nephrol . 2020 Feb 18. doi: 10.1007
Pharmacotherapy, a pathophysiologic approach 2019

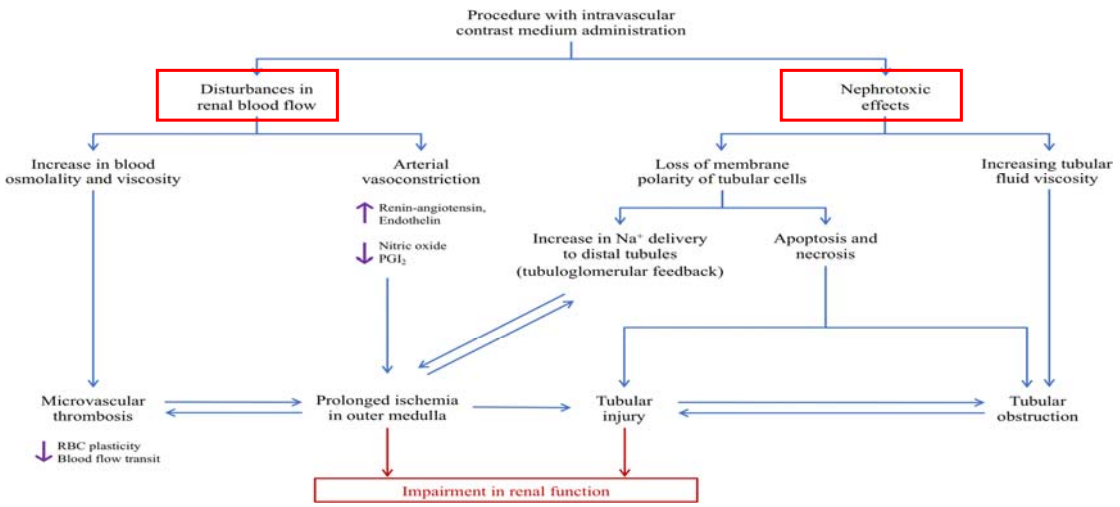
顯影劑腎病變

- Incidence (LoE: A)
  - No diabetes or pre-existing chronic kidney disease: 0-10%(<2%)
  - Diabetes:8-20%
  - pre-existing chronic kidney disease: 15-55%
  - pre-existing chronic kidney disease and diabetes: 27-81%
- Clinical presentation
  - nonoliguria with kidney injury apparent within the first 24 to 48 hours
  - S_{cr} usually peaks between 3 and 4 days after exposure, with recovery after 7 to 10 days
  - irreversible oliguric (urine volume less than 500 mL/day) AKI requiring dialysis

23

Pharmacotherapy, a pathophysiologic approach 2019

顯影劑相關腎病變機轉



24

Cardiovascular Intervention and Therapeutics (2020) 35:209–217

哪些病人應該採取預防措施降低AKI發生

- 適用族群
  - AKI or an eGFR <30 mL/min/1.73 m^2 and are not undergoing maintenance dialysis
    - The risks of prophylaxis (heart failure, other hypervolemic conditions)
  - eGFR of 30–44+(numerous risk factors, recent AKI, borderline eGFR)
    - at the discretion of the ordering clinician

❖ 常見預防方法-1

- *N-acetylcysteine*
  - intra-arterial iodinated contrast: not shown to be effective versus placebo
  - Intravenous contrast not recommended
  - PRESERVE用法：血管攝影術前、後1小時分別給與口服N-acetylcysteine 1200 mg(2#)，之後每12小時給與 1200 mg(2#) ，持續使用4天。

25

Radiology 2020; 294:660–668

水要怎麼給

❖ 常見預防方法-2

表 1. 國際相關醫學會提供的靜脈輸液補充參考方式

加拿大放射醫學會共識指引
從治療處置前 12 小時到結束後 12 小時，提供 0.9% 生理食鹽水輸液 1 ml/kg/hr。另一種方式為治療處置前至少 1 小時到處置後 6 小時，提供生理食鹽水或碳酸氫鈉溶液 3 ml/kg/hr。輸液補充量必須依照病人體重，注射顯影劑前至少提供 300~500 ml 的輸液。
歐洲心臟醫學會心血管重建工作小組
1. 進行心導管檢查前 12 小時到處置結束後至少 24 小時，輸液補充等張生理食鹽水 1 ml/kg/hr（射出分率＜ 35% 或美國紐約心臟協會分類第二級以上的心衰竭病人，則輸液補出等張生理食鹽水 0.5 ml/kg/hr）。 2. 進行心導管檢查前 1 小時，快速靜脈注射 0.84% 碳酸氫鈉溶液（體重 kg×0.462 mEq）；處置結束後，靜脈輸液補充 0.84% 碳酸氫鈉溶液（體重 kg×0.154 mEq / hr）至少 6 小時。

26

台灣急性腎損傷處置共識 2020

常見預防方法-3 中斷不必要腎毒性藥品

- In patients with AKI or eGFRs<30 mL/min/1.73 m^2
  - it may be prudent to withhold nonessential potentially nephrotoxic medications if clinically feasible for 24 to 48 hours before and 48 hours after exposure
    - Nonsteroidal anti-inflammatory drugs (NSAID)
    - Diuretics
    - Aminoglycosides
    - Amphotericin
    - Platins
    - Zoledronate
    - Methotrexate
  - If CA-AKI develops, then nonessential nephrotoxic medications should continue to be withheld until kidney function has recovered
- RAASi(-pril,-sartan結尾的藥品)
  - lack of strong evidence demonstrating that continuing RAASi is beneficial
    - should consider withholding RAASi in patients at risk for at least 48 hours before elective contrast-enhanced CT (靜脈打顯影劑)
    - RAASi may be restarted if CA-AKI does not occur or following the return of kidney function to baseline

27

Radiology 2020; 294:660–668

常見門診腎毒性藥品與追蹤

藥品	機轉	臨床表現	降低腎毒性方式	追蹤
ACEI/ARBs	出球小動脈擴張			開始使用2周內監測血中肌酸酐與血鉀
Calcineurin inhibitors	引起入球與出球小動脈收縮			當合併腎毒性藥品時監測血清肌酸酐
Trimethoprim/ sulfamethoxazole	肌酸酐分泌受阻 形成結晶	急性間質性腎炎、 肌酸酐偽性上升 高血鉀	＊避免對該藥有過敏史的病人 ＊導致血清肌酸酐偽性上升（25%），中斷後回到正常值	當Clcr<15 ml/min時監測血清肌酸酐與血鉀
Acyclovir	腎小管內結晶沉積 直接腎小管細胞毒性	腎結石 急性間質性腎炎	＊給藥前維持適當水分補充與尿量 ＊降低輸注速率	三個月內監測血中肌酸酐
Ganciclovir、valganciclovir	腎小管內結晶沉積		＊給藥期間維持適當水分補充與尿量	
Tenofovir disoproxil fumarate	近端腎小管細胞毒性	Fanconi-like 症候群 急性腎小管壞死 腎性尿崩症	＊ Tenofovir alafenamide 腎毒性較低	

28

Prim Care Clin Office Pract 47 (2020) 691–702

Trimethoprim/sulfamethoxazole 相關急性腎損傷

Table 1. Characteristics of patients with and without AKI

11.17%

Category	AKI patients, N=64	Non-AKI patients, N=509	P value
>2 tablets/day[a]	4 (6.3)	24 (4.7)	0.59
>10 days of treatment	23 (35.9)	174 (34.2)	0.78
Age >60 years	36 (56.3)	263 (51.7)	0.49
Race			
white	32 (50.0)	295 (58.0)	0.23
black	23 (35.9)	149 (29.3)	0.31
Hispanic	4 (6.3)	33 (6.5)	1.0
other/undocumented	5 (7.8)	32 (6.3)	0.59
Gender			
male	64 (100)	493 (96.9)	0.24
female	0 (0)	16 (3.1)	—
Diabetes mellitus	40 (62.5)	169 (33.2)	<0.001
well controlled	26 (40.6)	131 (25.7)	0.01
poorly controlled	14 (21.9)	38 (7.5)	<0.001
Hypertension	49 (76.6)	256 (50.3)	<0.001
Hypertension and well-controlled diabetes	20 (31.2)	88 (17.3)	0.007
Hypertension and poorly controlled diabetes	11 (17.2)	27 (5.3)	<0.001
Chronic kidney disease	22 (34.4)	104 (20.4)	0.01
stage 1	1 (4.5)	0 (0)	—
stage 2	8 (36.4)	47 (45.2)	0.45
stage 3	13 (59.1)	54 (51.9)	0.54
stage 4	0 (0)	2 (1.9)	—
stage 5	0 (0)	1 (1.0)	—
HIV	6 (9.4)	58 (11.4)	0.63
CD4 >200 cells/mm^3	2 (3.1)	15 (2.9)	1
CD4 <200 cells/mm^3	4 (6.3)	43 (8.4)	0.81
Indication			
bacteraemia	0 (0)	9 (1.8)	0.28
osteomyelitis	3 (4.7)	6 (1.2)	0.07
PCP prophylaxis	4 (6.3)	57 (11.2)	0.23
PCP pneumonia	2 (3.1)	13 (2.6)	0.79
pneumonia	4 (6.3)	33 (6.5)	0.94
skin and soft tissue	28 (43.8)	183 (36.0)	0.22
urinary tract infection	16 (25)	139 (27.3)	0.70
miscellaneous/ undocumented	7 (10.9)	69 (13.6)	0.56

Table 3. Urinalysis findings after documentation of AKI

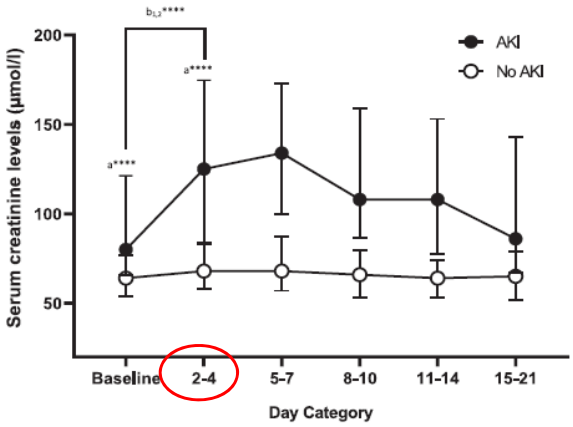
Study findings	Number of patients
≥5 WBCs/HPF	12 (32.4)
≥5 RBCs/HPF	11 (29.7)
Urine pH ≥6	14 (37.8)
Urine crystals	4 (10.8) 結晶尿
Calcium oxalate	2 (5.4)
Uric acid	2 (5.4)
Sulpha	0 (0)
RBC casts	0 (0)
WBC casts	0 (0)
Coarse granular casts	0 (0)
Renal epithelial cells	0 (0)
Urine eosinophils[a]	0 (0)

Data are shown as the number (%) of abnormal findings in 37 patients for whom a urinalysis was obtained.
[a]Urine eosinophils were obtained in 18 patients.

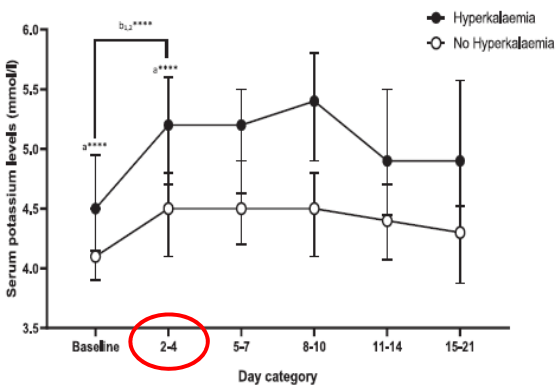
J Antimicrob Chemother 2012; 67: 1271 –1277

Trimethoprim/sulfamethoxazole腎毒性表現

AKI incidence: 11.2-19.6%
OR 3.65, 95% CI 1.73-7.41, p 0.001



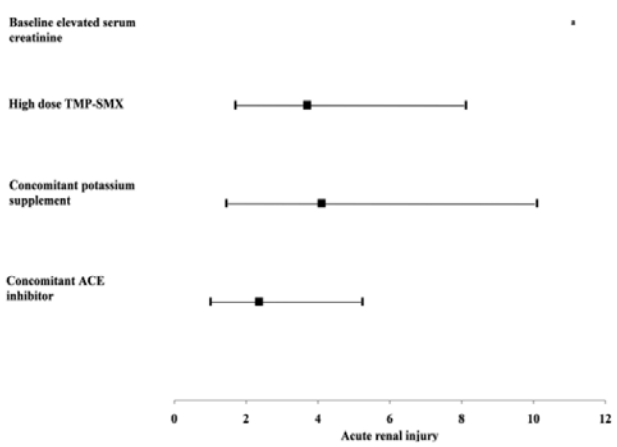
Hyperkalemia incidence: 15.4%,
OR 2.47, 95% CI 1.14-5.27, p 0.0236



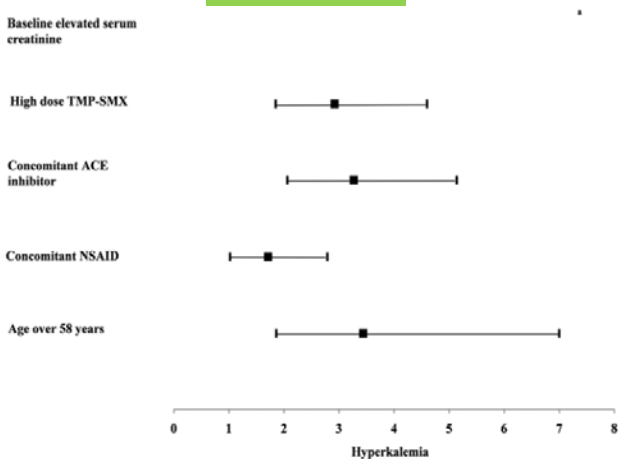
Clin Microbiol Infect.2020;26(12):1651-1657
J Antimicrob Chemother 2012; 67: 1271 –1277

不同劑量cotrimoxazole與併用藥品影響

Acute kidney injury



Hyerkalemia



[a]Baseline elevated serum creatinine had the following statistics for hyperkalemia: odds ratio [OR] = 45.1; 95% CI = 21.7-93.2; $P < .0001$. Baseline elevated serum creatinine had the following statistics for acute renal injury: OR = 2110; 95% CI = 724-7980; $P < .0001$.

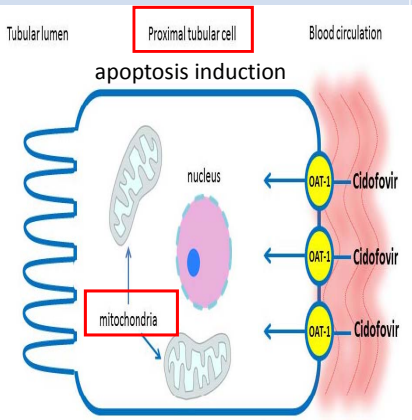
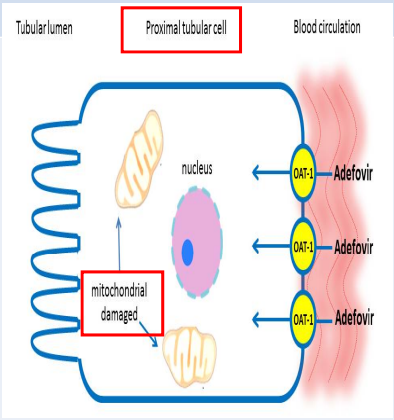
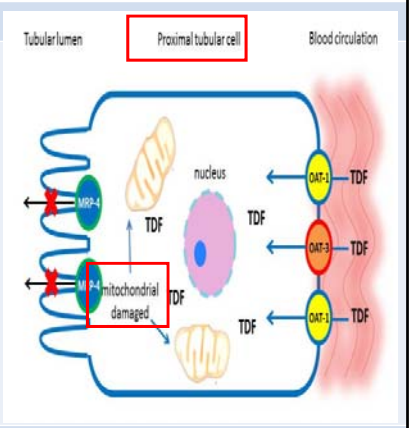
31

Annals of Pharmacotherapy47(12) 1618–1626

抗病毒用藥相關腎毒性

Mechanisms	Antiviral Drugs	Clinical Finding
Acute tubular necrosis (ATN)	Cidofovir、Adefovir、Tenofovir	FENa> 2% UOsm< 350 mOsmol/kg water Urinary sediment contains -granular casts -renal epithelial cells
Allergic interstitial nephritis (AIN) (Idiosyncratic or allergic reaction)	Atazanavir	Rash ,Fever ,Eosinophilia, Eosinophiluria , Pyuria
Crystal nephropathy	Acyclovir, Indinavir, Foscarnet	Sediment might be benign despite obstruction

32

Cidofovir(IV)	Adefovir	Tenofovir
		
5 mg/kg for Q2 weeks: 10 – 15% has an increased serum creatinine.	Post 3 years:3-4% Scr↑>0.5 mg/dl	4.9 years:1.4% vs. 0.7% ARF/RRT
Co-administration of nephrotoxic agents are contraindicated, and at least days should elapse before initiation		1.adequately monitoring renal function with proper adjustment of dosages 2. Tenofovir alafenamide fumarate (TAF)

33

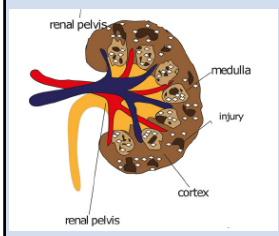
藥物相關腎結石

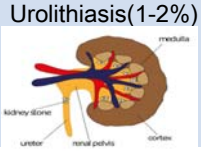
- Drug-induced renal calculi
  - Nephrolithiasis
  - Acute renal failure
    - crystalline obstruction of the urinary tract
    - crystal infiltration of the renal tubules and interstitium
    - direct (precipitation of the drug itself)
    - indirect(promoting release and precipitation of tissue-degradation products or cellular casts)
- Prevention
  - increased fluid intake
    - maintaining a high urine output throughout the duration of treatments with drugs of known lithogenic potency
  - modification of urine pH
    - when formation of calculi is pH dependent,.

34

Drugs 2018:78:163201

Crystalline nephropathy	Renal	Disease	Source	Medication
Type 2 Intratubular Crystal formation	AKI	drug-induced crystal nephropathy		
		drug-induced crystalluria	drug crystal	sulfamethoxazole, indinavir, acyclovir….
		acute phosphate nephropathy (Nephrocalcinosis) incidence:1 in 1,000~5,000	Ca*P	Sodium phosphate
		tumor lysis syndrome	Uric acid	Chemotherapy
		Anticoagulant nephropathy (CKD 33% vs. nonCKD 16.5%)	RBC case	warfarin
	CKD	drug-induced crystal nephropathy	Uric acid	
Type 3: Urolithiasis(1-2%)	Colic (GFR is usually not decreased)	drug-induced crystalluria	drug crystal	antiretroviral agents
		Drug induced crystal nephropathy	CaOx, CaP	Massive ascorbic acid
		Hyperuricosuric syndromes	uric acid	Uricosuric drugs (benzbromarone、losartan)





	Urinary pH	Crystal-Induced Kidney Injury	Risk factor	Prevention
sulfamethoxazole, sulfasalazine, Acetazolamide	5.5	crystalluria and crystalline nephropathy	insoluble in acidic urine.	Intravenous fluids and urinary alkalization
Acyclovir/valacyclovir(rare)	5.5-7.0 relatively insoluble at physiologic urine pH	crystalline-induced AKI (within 24 to 48 hr)	high doses (>1,500 mg/m^2/d), bolus intravenous administration, preexisting kidney disease, and volume depletion(dehydrated oliguric)	establishing urinary output of 100 to 150 mL/h, avoiding rapid infusions, and large doses
Indnavir (7-15%)	5.5-7.0	Crystalluria, crystal nephropathy, nephrolithiasis, interstitial nephritis AKI(mild and reversible) or CKD	PK interacton with Trimethoprim-sulfamethoxazole, underlying liver diseases	Mandates ingest at least 2 – 3 liters of fluid per day.
Atazanavir	6.0-7.0 maximally soluble at pH of 1.9	crystalluria, nephrolithiasis, crystalline nephropathy, and acute and chronic interstitial nephritis.	prolonged duration of therapy (2-3 years), ritonavir boosting, previous nephrolithiasis with indinavir, and elevated bilirubin levels. pH becomes more alkaline.	adequate hydration to obtain a urinary output of at least 1,500 mL/day
Methotrexate(high-dose)	5.4-6.0 precipitate in acidic urine	AKI (2%) from crystalline nephropathy and direct toxic effects oligoanuric kidney injury	limited solubility in acidic urine Urine pH ↑6.0~7.0→6- to 8-fold more soluble	Intravenous fluids and urinary alkalization

中草藥腎病變的危險因子

用藥因素
1.過量，使用時間過長
2.中西藥交互作用

中草藥相關因素
1.中草藥本身的內在毒性
2.分辨不清種類
3.錯誤加工
4.錯誤儲存
5.摻雜其他物質
6.包含重金屬

病人因素
1.慢性腎病
2.藥物過敏

腎損傷

37

Clin J Am Soc Nephrol 13: 1605–1611, 2018

馬兜鈴酸事件(馬兜鈴酸腎病變)

2003年公告全面禁止使用

表一　歷年各國發生誤用馬兜鈴科植物為中藥材所導致腎病之個案數及時間

國家	比利時	中國	台灣	日本	英國	法國	美國	西班牙	德國	韓國
案數	128	116	33	6	4	4	2	1	1	1
時間	1993	2001, 2004	2000-2001	2000	1999, 2002	1994, 1998	2000	1996	2000	2004

	廣防己	青木香	關木通	馬兜鈴	天仙藤
用　途	利尿、清熱、治療關節發炎疼痛	行氣解鬱、治胸悶	利尿	止咳化痰	活血化鬱
副作用	腎衰竭	腎衰竭	腎衰竭	腎衰竭	腎衰竭
替代藥物	木防己 稀薄草	香附	車前子 豬苓、茯苓	麥門冬 天門冬	當歸、丹參

38

Table 2. Chinese herbal medicines associated with nephrotoxicity

Possible Toxic Compound	Latin Name	English Name/ Chinese Name	Indications	Kidney Manifestations	Refs.
Aristolochic acid	*Aristolochia* spp. 關木通	Aristolochia, Guan Mu tong, Han Fang Ji	To induce weight loss, liver disease, arthritis, headache, edema	Chronic interstitial nephritis, renal interstitial fibrosis, Fanconi syndrome, urothelial carcinoma	19–22,43
Flavonoid (sciadopitysin)	*Taxus cerebica* 紅豆杉(紫杉)	Chinese yew	Diabetes, vascular diseases	Acute tubular necrosis, acute interstitial nephritis	11
Flavonoid	*Cupressus funebris* Endl 柏木	Mourning cypress	Vascular diseases, instead of "yew"	Acute tubular necrosis, acute interstitial nephritis	14
Flavonoid oligomeric procyanthins	*Crataegus orientalis* 山楂	Hawthorn	Congestive heart failure, hypertension, hyperlipidemia	AKI	15
Ephedrine, norephedrine, pseudoephedrine	*Ephedra sinica* 麻黃	Ma huang	Cough, to induce weight loss, to cause sexual arousal	AKI, nephrolithiasis	32–34,44
Glycyrrhetinic acid, glycyrrhizic acid	*Glycyrrhiza glabra* 甘草	Licorice Gancao	Cough, sore throat, arthritis, to induce weight loss	Acute tubular necrosis, hypokalemic nephropathy, Fanconi syndrome	28–30,45
Anthraquinones, oxalic acid	*Rhizoma rhei* 大黃	Rhubarb	Laxative, anti-inflammatory	Interstitial fibrosis, tubular atrophy	31,45
Active moiety triptolide	*Tripterygium wifordii* 雷公藤	Lei Gong Teng	Arthritis, anti-inflammatory, immunosuppressant	Acute tubular necrosis	46
Oxidative degradation products	*Aloe capensis* 蘆薈	Cape aloe	Constipation, insect bites	Acute tubular necrosis, parenchymatous nephritis	31,45
Colchicine	*Colchicum autumnale* 秋水仙	Autumn crocus	Gout	AKI	47
Dioscorine, dioscine	*Discorea quarrhiana* 山藥(生)	Yam	Taken as food, to cause poisoning or induce suicide	Acute tubular necrosis	48
Irritant chemicals in the latex of the plant	*Euphorbia matabelensis, Euphorbia paralias* 大戟	Spurge	Edema, to induce abortion	Acute tubular necrosis	12,49
Andrographolide	*Andrographis paniculata* 穿心蓮	Chuan-Xin-Lian (heart piercing lotus)	Infectious disease, such as upper and lower respiratory tract infection, acute enteritis, bacillary dysentery	AKI, acute tubular necrosis	13

39

ephrol 13: 1605–1611, 2018

感謝您的聆聽

40