Diuretics in Acute Kidney Injury in critically ill patients

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GUMS

- In many studies, oliguric AKI has been associated with worse outcomes than non oliguric AKI.

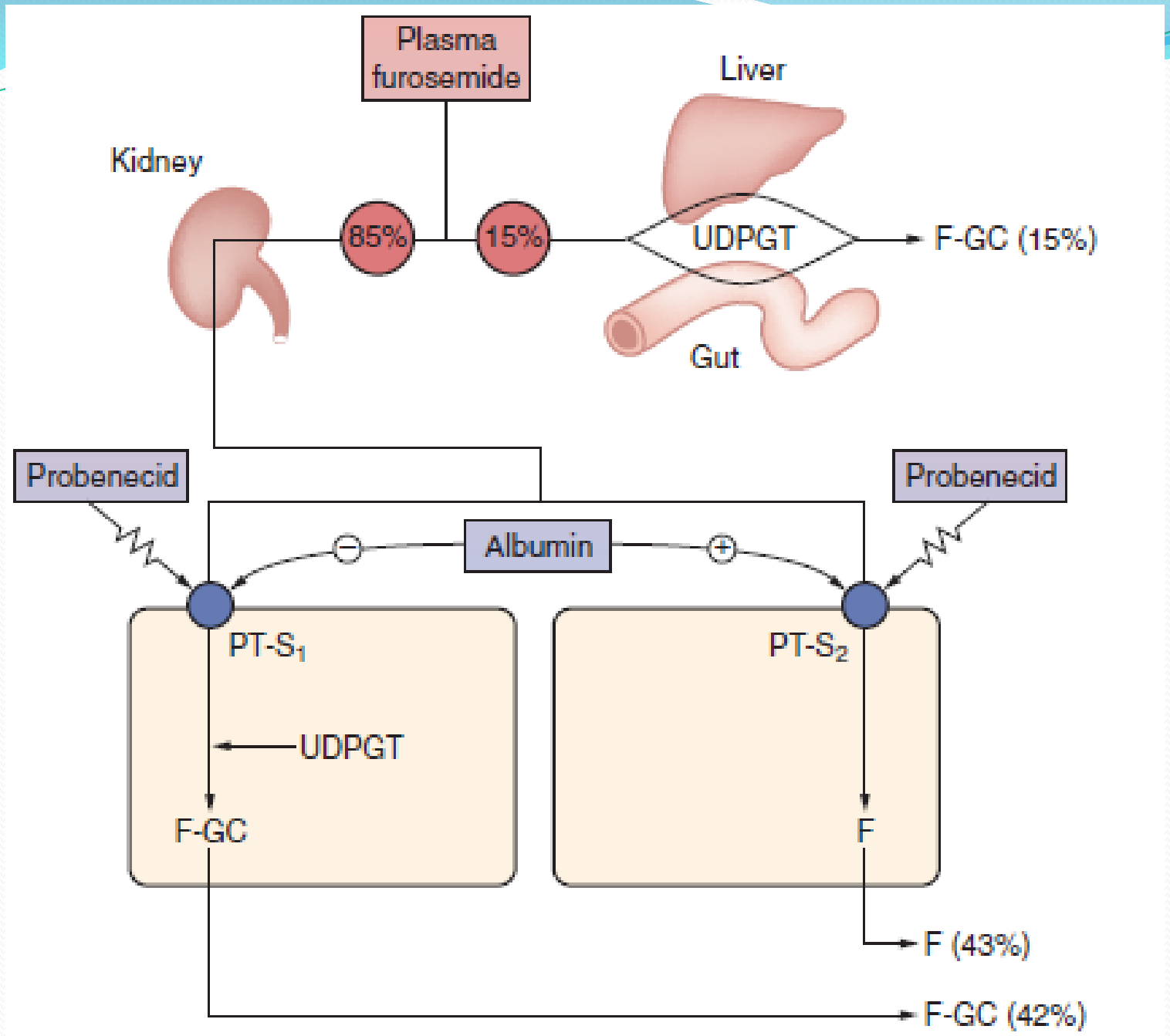
The use of diuretics in oliguric AKI?

The loop diuretics are clearly the most effective diuretics in the acute care setting.

The most common loop diuretics used clinically are furosemide, bumetanide and torsemide.

Furosemide is a weak organic acid.

A highly protein bound drug (>98 %), which facilitates tubular secretion and its action.


Plasma furosemide
Liver
Kidney
85%
15%
UDPGT
F-GC (15%)
Gut
Probenecid
Probenecid
Albumin
PT-S1
PT-S2
UDPGT
F-GC
F
F (43%)
F-GC (42%)

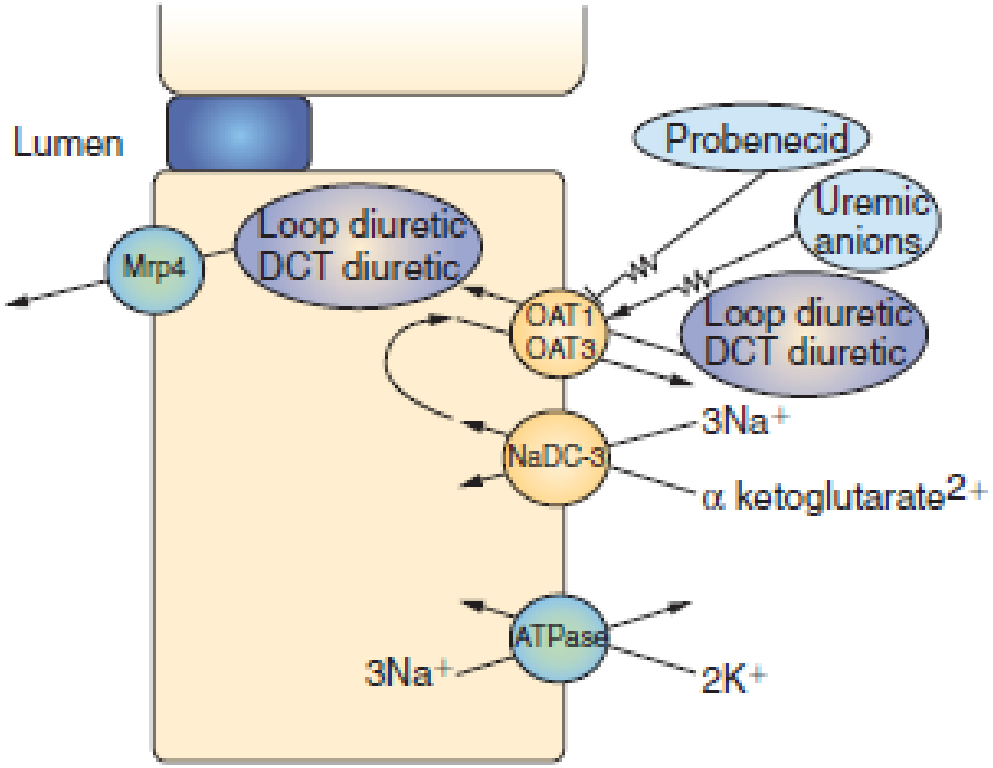
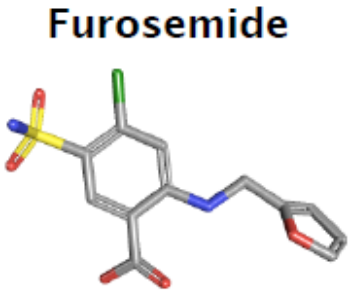
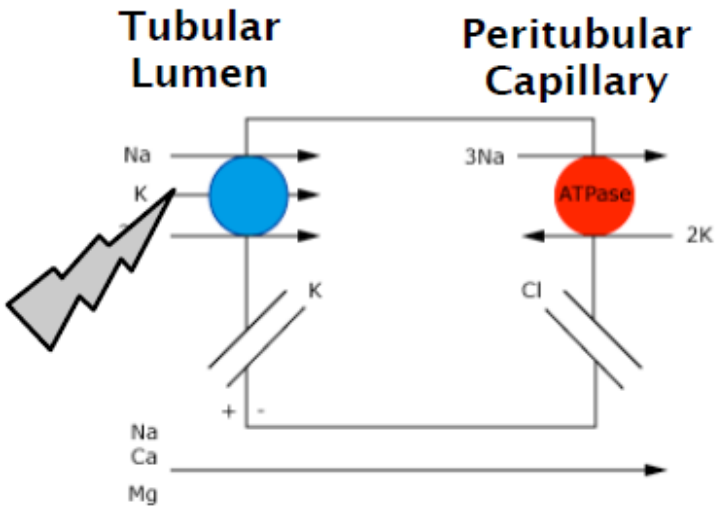


Figure 51.5 Mechanisms of diuretic secretion by proximal tubule cells. Cell diagram of the S2 segment of the proximal tubule showing secretion of anionic diuretics, including loop diuretics and distal convoluted tubule (DCT) diuretics. Peritubular uptake by an organic anion transporter (primarily OAT1, although OAT3 may play a smaller role) occurs in exchange for α-ketoglutarate, which is brought into the cell by the Na^+-dependent cation transporter NaDC-3. Luminal secretion can occur via a voltage-dependent pathway or in exchange for luminal hydroxyl (OH^-) or urate. A portion of the luminal transport traverses multidrug resistance–associated protein 4 (Mrp4). ATPase, adenosine triphosphatase.

Loop Diuretics

- Act in TAL LOH
- Inhibit Na–K–Cl carrier
- Compete with Cl site
- Reduce net re-absorption
  - Na, Cl, K, Mg, Ca
  - H20
- Action dependent on delivery to site of action:





Probenecid, Ciprofloxacin and Cephalosporins.

reduced response to furosemide due to; multiple mechanisms including a ;

reduced tubular secretion of furosemide

and

blunted response of Na-K-Cl2 co-transporters at TALH

BENEFITS

1/ Decrease O2 Demand

2/ improve urine flow by flushing out debris and denuded epithelium, thus avoiding intratubular obstruction.

3/ reduce the back leak of glomerular filtrate into the renal interstitium which tends to worsen acute kidney injury.

4/ decrease renal vascular resistance and therefore increase renal blood flow.(PGE2)

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Review Article

Furosemide in Acute Kidney Injury – A Vexed Issue

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Abstract

Loop diuretics have been traditionally used to enhance renal excretion of excess salt and water. Loop diuretics have numerous reno-protective properties that may help improve the management of Acute kidney injury and subsequently patient outcomes. Given the improved prognosis of non-oliguric acute kidney injury, it may be tempting to use loop diuretics in oliguric acute kidney injury to improve the urine output. A review of literature shows that the use of loop diuretics in patients with acute kidney injury has been associated with inconclusive results despite the theoretical benefits. Here we review the concerns pertaining to the use of furosemide in patients with Acute kidney injury.

Keywords: Furosemide; Acute kidney injury; Outcomes

Conversion from Oliguric to Nonoliguric Renal Failure

makes fluid and electrolyte management easier,

But

might perpetuate the renal insult if given after the onset of ATN.

Diuretic therapy can reduce the ECV too much and add a prerenal insult on top of the established ATN.

2) **TGF** may well be an adaptive mechanism, which autoregulates the medullary oxygen balance.

Inhibition of it could predispose to renal medullary ischemia.

However, if volume status is monitored closely, diuretics can be useful in the conversion to nonoliguric ARF, making patient management easier in the ICU.

In theory, avoidance of volume overload, by diuresis, may decrease the duration of mechanical ventilation in critically ill patients and thereby reduce lung injury.

torsemide may be the best agent for use in renal impairment, since ;it has a longer half-life independent of renal function, a favorable side effect profile and apparently less influence on calciuresis.

The loop diuretics may be more effective and less toxic when given as a **continuous infusion** rather than as a bolus .

Large boluses of loop diuretics may cause transient ***renal vasoconstriction***, adversely affecting renal medullary oxygenation.

the kidney is a highly vascular organ.

Most of the blood flow to the kidney is diverted to the renal cortex to optimize glomerular filtration.

The medulla by contrast has reduced blood flow, possibly to preserve osmotic gradients and enhance urinary concentration .

The medullary partial pressure of oxygen is in the range of 10 to 20 mm Hg, contrasting with the partial pressure of oxygen in the cortex, which is about 50 mm Hg .

Potential roles of furosemide in AKI.

As a part of the strategy to avoid fluid retention in patients with co-existing acute lung injury reduce the risk of AKI, duration of mechanical ventilation, and length of intensive care unit stay

Using urinary response to furosemide as a prognostic test to predict the risk of requiring RRT

Concurrent use of furosemide with octreotide improves GFR, urine output and portal HTN in patients with portal HTN and ascites when compared to octreotide alone.

Potential pitfalls of using furosemide

in patients who are at risk of, or with established AKI.

1/ improvement in renal function, delaying the diagnostic and therapeutic process .

2/ Induces hypovolaemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, and metabolic alkalosis

3/ Limits the use of urinary sodium concentrations to differentiate

4/ Delaying renal replacement therapy may increase mortality

5/ Induces ototoxicity

6/ High doses can induce systemic vasoconstriction.

6/ Reduces mucociliary transport and sputum clearance by inhibiting Na-K-Cl2 co-transporters of the respiratory tract

7/ Acidifies urine and reduces solubility of myoglobin and haemoglobin in patients with rhabdomyolysis and intravascular haemolysis (including cardiopulmonary bypass).

8/ Aciduria may also promote free radical formation in the urine by radiocontrast agents .

Drug interactions:

(i) reduces clearance of theophylline, gentamicin, and other organic acids (benzylpenicillin, cephalosporins, oxypurinol, bumetanide, active metabolite of oseltamivir);

(ii) increases the risk of amphotericin-induced hypokalaemia, anti-epileptic effect of valproate,

hypotensive effect of angiotensin-converting-enzyme inhibitors;

(iii) reduces therapeutic effect of warfarin, but warfarin also reduces the diuretic effect of furosemide

The Furosemide Stress Test and Predicting AKI Outcomes

there is a role for a diuretic challenge (in contrast with continued administration) in the management of AKI.

When faced with the patient with persistent oliguric AKI, administration of a single dose of furosemide was thought to be informative.

In brief, this diuretic challenge was developed in the setting of early AKI and consists of a one-time dose of 1.0–1.5 mg/kg . IV .....a 200-ml increase in urine output over the next 4 hours in an oliguric euvolemic patient in critically ill patients with stage 1 or 2 AKI

The primary outcome ; stage 3 AKI (need for RRT, increased serum creatinine three times baseline, or urine output 0.3 ml/h per kg 24 hours) within 14 days of the diuretic challenge.

AUC for total urine output within 2 hours after the diuretic challenge was 0.87 for predicting progression to stage 3 AKI.

Perhaps most telling, the reported pilot study results did not demonstrate any statistically improved risk prediction when a biomarker panel was added to the FST results, but when FST was combined with the other biomarkers of AKI there was in improvement in risk prediction for all outcomes.

There are important limitations to obtaining urine flow rates.

Although the most accurate assessment of urine flow is readily available in the critical care setting, the reality is that most patients with less severe AKI occur outside of the critical care setting.

An important strength of the FST is that it can be performed outside of a critical care unit .

Realizing the FST is more than a test of renal reserve, but an assessment of integrated renal function (blood flow, organic acid secretion, thick ascending function, luminal patency, etc.),

it seems likely that prior exposure to furosemide may affect the sensitivity or dose response of the FST.

When diuretics are used in the acute care setting, the loop diuretics are clearly the most effective.

However, addition of a thiazide diuretic may augment the effectiveness of such therapy.

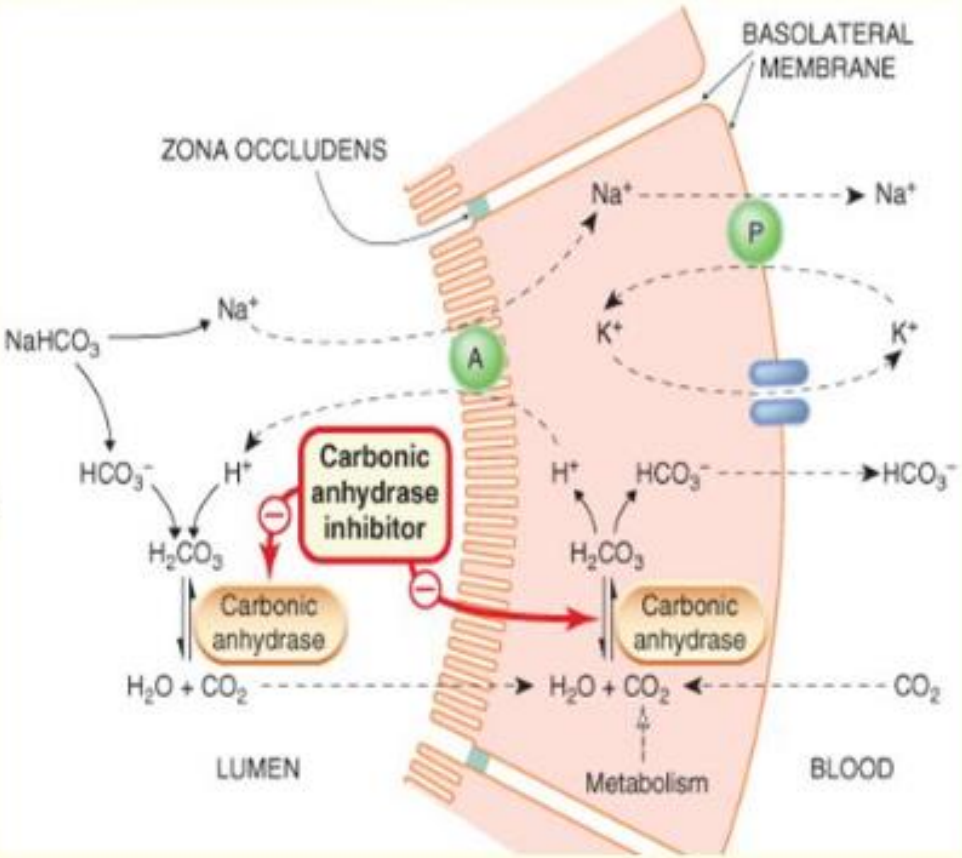
DCT DIURETICS

mineralocorticoid receptor antagonists

K SPARING DIURETICS

Carbonic Anhydrase Inhibitors

- *Acetazolamise & Dichlorphenamide*
- **Site of action?**
- **Mechanism of action?**
- **CA inhibition**→ ↑luminal PCT H^+→↓ bicarbonate reabsrobtion → ↓ Na^+ /H^+ transporter activity
- Only mild natriuresis (1-3%)
- Increased bicarbonate in urine



Anuric Acute Kidney Injury Induced by Acute Mountain Sickness Prophylaxis With Acetazolamide

Journal of Investigative Medicine High Impact Case Reports
1–5

DOI: 10.1177/2324709614530559
hic.sagepub.com
SAGE

Javier A. Neyra, MD[1], James Castle Alvarez-Maza, MD[2], and James E. Novak, MD, PhD[3]

Acetazolamide is a sulfonamide derivative that is the mainstay for prevention and treatment of acute mountain sickness .

AKI is not well recognized as a complication of ACZ ingestion, especially when low doses are used for short periods of time.

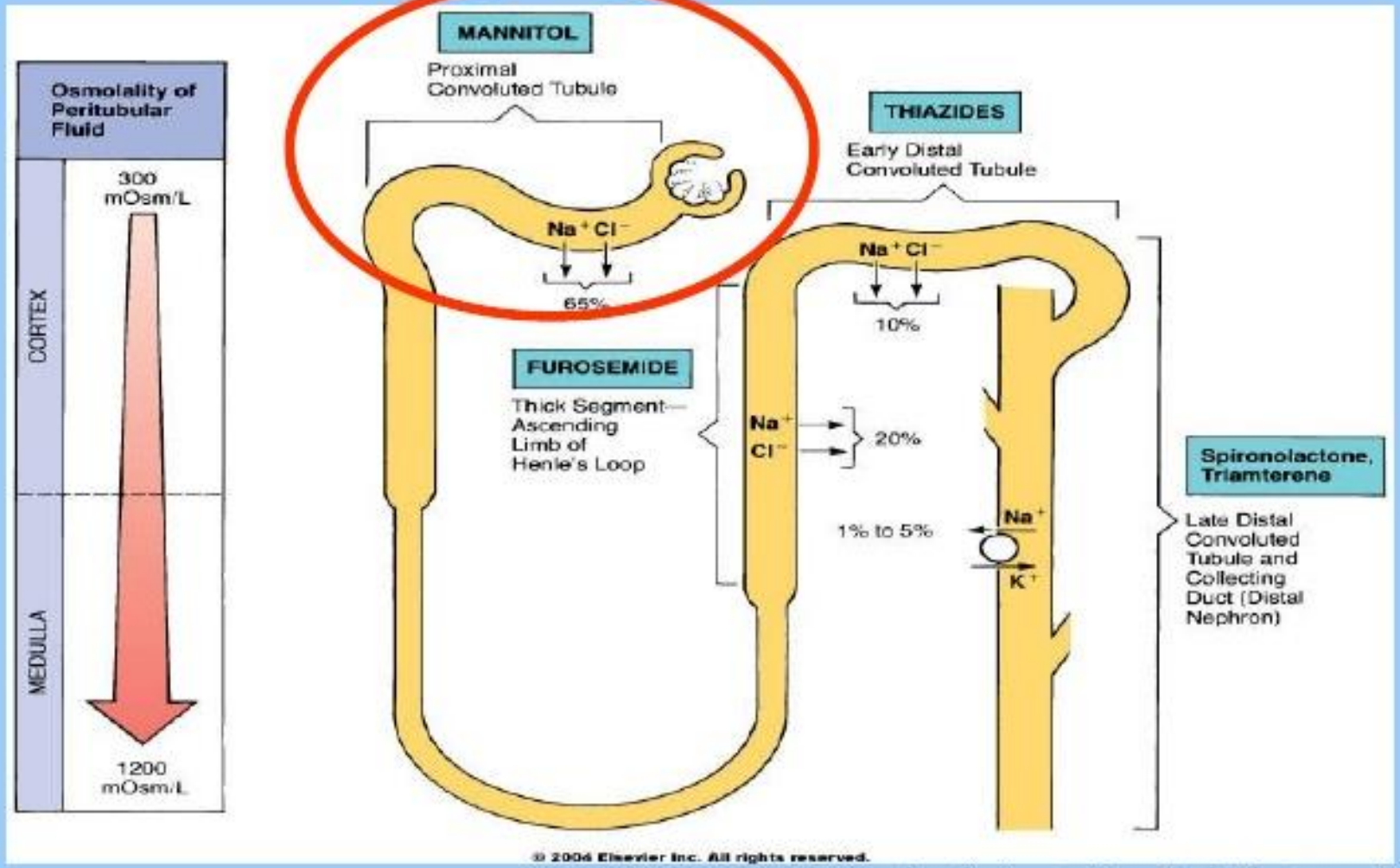
studies highlight the risk of adverse renal outcomes following ACZ ingestion even in previously healthy individuals and suggests that increased fluid intake and avoidance of NSAID may be advisable in travelers taking ACZ prophylaxis.

AKI….intratubular sulfonamide crystalluria

calcium phosphate kidney stones …… chronic use of ACZ.

For this reason, it is crucial to differentiate sulfonamide crystalluria.

Osmotic Diuretics -Mannitol



Lehne, 2009, *Pharmacology for Nursing Care, 7th ed., Elsevier, p. 445*

Prevents re-absorption of <u>water</u> from the proximal tubule.

Mannitol

Volume depletion and hypernatremia

Volume expansion, hyponatremia, hyperkalemia, hypokalemia, and metabolic acidosis

Acute kidney injury (65 mosm/kg, above 1080 mg/dL ,200 to 300 g of mannitol per day).

The plasma osmolal gap should not *be allowed to exceed* ***55*** *mosmol/kg and the mannitol dose should not exceed* ***250 mg/kg every 4 hours*** *when mannitol is used in the treatment of* ***cerebral edema or glaucoma;***

higher doses can cause reversible acute renal failure.

Patients who develop renal failure appear to recover renal function rapidly if treated with hemodialysis to remove the excess mannitol.

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PLOS ONE

Intravascular Administration of Mannitol for Acute Kidney Injury Prevention: A Systematic Review and Meta-Analysis

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Abstract

Background: The effects of mannitol administration on acute kidney injury (AKI) prevention remain uncertain, as the results from clinical studies were conflicting. Due to the lack of strong evidence, the KDIGO Guideline for AKI did not propose completely evidence-based recommendations on this issue.

Methods: We searched PubMed, EMBASE, clinicaltrials.gov and Cochrane Controlled Trials Register. Randomized controlled trials on adult patients at increased risk of AKI were considered on the condition that they compared the effects of intravascular administration of mannitol plus expansion of intravascular volume with expansion of intravascular volume alone. We calculated pooled risk ratios, numbers needed to treat and mean differences with 95% confidence intervals for dichotomous data and continuous data, respectively.

Results: Nine trials involving 626 patients were identified. Compared with expansion of intravascular volume alone, mannitol infusion for AKI prevention in high-risk patients can not reduce the serum creatinine level (MD 1.63, 95% CI −6.02 to 9.28). Subgroup analyses demonstrated that serum creatinine level is negatively affected by the use of mannitol in patients undergoing an injection of radiocontrast agents (MD 17.90, 95% CI 8.56 to 27.24). Mannitol administration may reduce the incidence of acute renal failure or the need of dialysis in recipients of renal transplantation (RR 0.34, 95% CI 0.21 to 0.57, NNT 3.03, 95% CI 2.17 to 5.00). But similar effects were not found in patients at high AKI risk, without receiving renal transplantation (RR 0.29, 95% CI 0.01 to 6.60).

Conclusions: Intravascular administration of mannitol does not convey additional beneficial effects beyond adequate hydration in the patients at increased risk of AKI. For contrast-induced nephropathy, the use of mannitol is even detrimental. Further research evaluating the efficiency of mannitol infusions in the recipients of renal allograft should be undertaken.

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Cancer Chemother Pharmacol (2016) 77:19–26
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REVIEW ARTICLE

The ability of mannitol to decrease cisplatin-induced nephrotoxicity in children: real or not?

Antonio Ruggiero[1] · Daniela Rizzo[1] · Giovanna Trombatore[1] · Palma Maurizi[1] · Riccardo Riccardi[1]

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Intravascular administration of mannitol does not convey additional beneficial effects beyond adequate hydration in the patients at increased risk of AKI.

Its use for AKI prevention is not scientifically justified, and for contrast-induced nephropathy prevention is even detrimental.

Natruretic peptide

CJASN™

Clin J Am Soc Nephrol. 2009 Feb; 4(2): 261–272.
doi: 10.2215/CJN.03780808

PMCID: PMC2637582
PMID: 19073785

Atrial Natriuretic Peptide for Management of Acute Kidney Injury: A Systematic Review and Meta-analysis

Sagar U. Nigwekar,* Sankar D. Navaneethan,† Chirag R. Parikh,‡ and John K. Hix§

Author information ► Article notes ► Copyright and License information ► Disclaimer

- **Natriuretic Peptides and Their Analogs**
- increase GFR ;
- Glomeruluar effect,
- tubular effect
- Urodilatin

human trials ….

can not be recommended for the use in prevention or treatment of ATN.

In conclusion, there are a limited number of high quality studies to make any definite statement about the role of ANP in management of AKI.

Current available evidence suggests that the use of ANP may be associated with beneficial clinical effects when administered in patients undergoing major surgery such as cardiovascular surgery.

These observations need to be confirmed in a prospective multi-center study using low dose ANP preparations

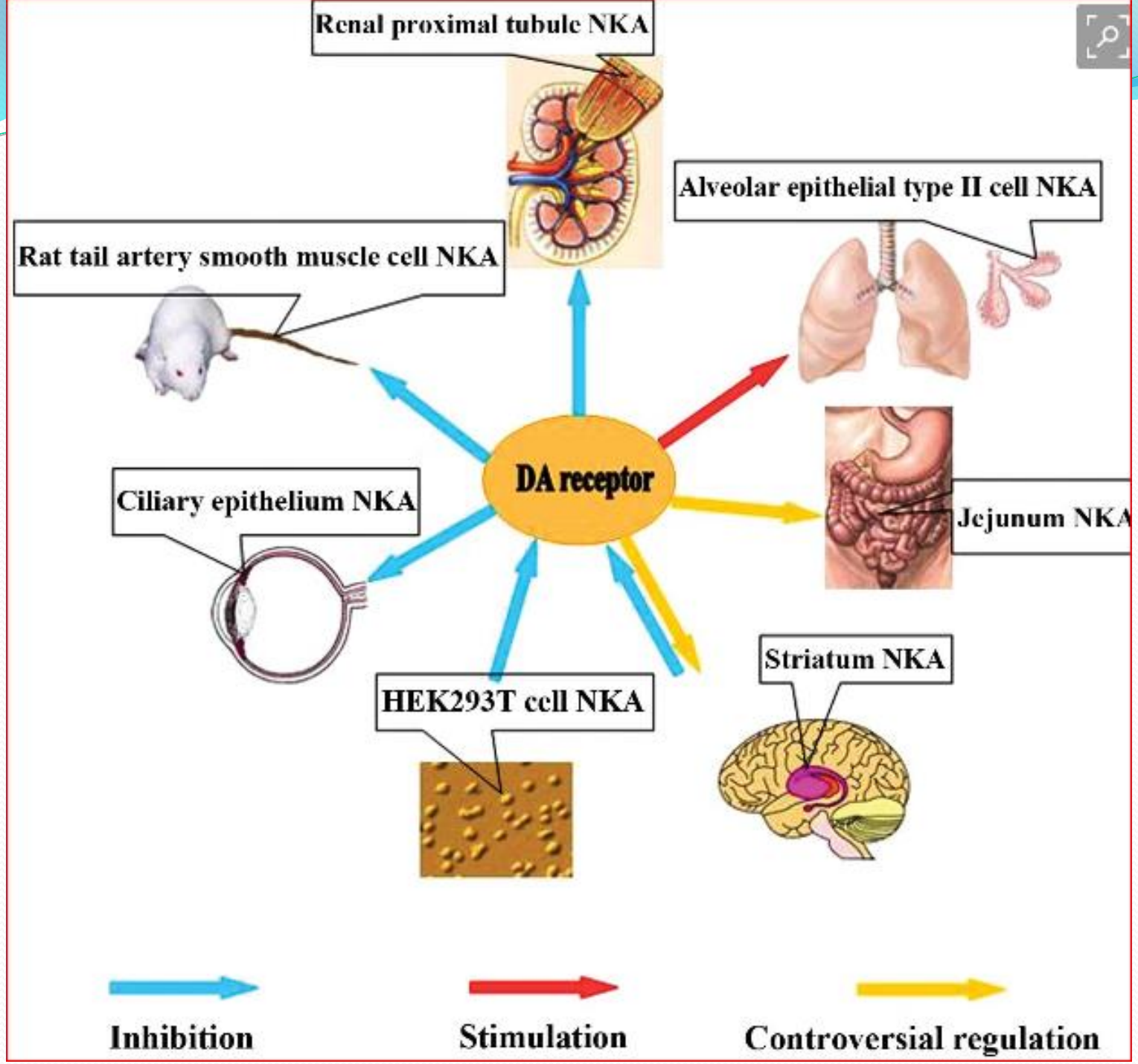
- **Dopamine and Dopamine-Receptor Agonists**

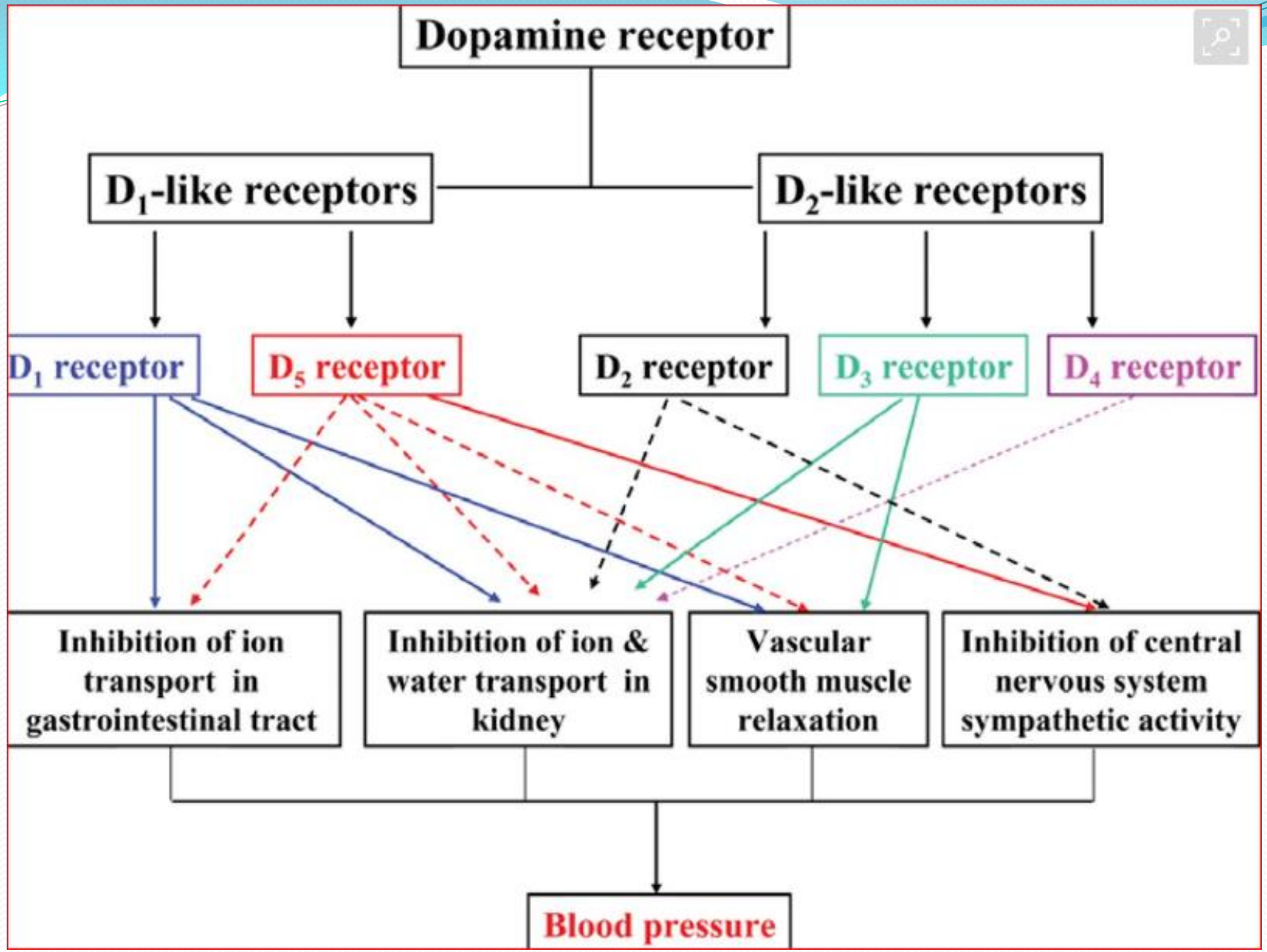
Chronic Congestive Heart Failure

American Heart Association
Fighting Heart Disease and Stroke

DOPAMINE AND DOBUTAMINE EFFECTS

	DA (µg / Kg / min)			Dobutamine
	< 2	2 - 5	> 5	
Receptors	DA_1 / DA_2	$ß_1$	$ß_1$ + α	$ß_1$
Contractility	±	++	++	++
Heart Rate	±	+	++	±
Arterial Press.	±	+	++	++
Renal perfusion	++	+	±	+
Arrhythmia	-	±	++	±


Renal proximal tubule NKA
Alveolar epithelial type II cell NKA
Rat tail artery smooth muscle cell NKA
DA receptor
Ciliary epithelium NKA
Jejunum NKA
Striatum NKA
HEK293T cell NKA
Inhibition
Stimulation
Controversial regulation


Dopamine receptor
D1-like receptors
D2-like receptors
D1 receptor
D5 receptor
D2 receptor
D3 receptor
D4 receptor
Inhibition of ion transport in gastrointestinal tract
Inhibition of ion & water transport in kidney
Vascular smooth muscle relaxation
Inhibition of central nervous system sympathetic activity
Blood pressure

Dopmaine is often used in ARF to increase urine output and in the hope of attenuating the renal insult.

low dose or renal dose 0.5 to 3 g/kg/min both to increase urine output and yo preserve renal function.

Dopamin generally has renal effects opposite to those of EPI & NEPI.

The lack of a consistent beneficial effect from dopamine in ARF may be partly attributed to its indiscriminate interaction with multiple receptors (dopamine- 1, dopamine-2, alpha -1 and alpha-receptors).

.

Such stimulation may offset any potential benefit of dopamine-1 (DA-1) receptor agonism.

This has prompted the consideration of the use of selective DA-1 agonists in the management of ARF.

For example, fenoldopam, a selective DA-1 receptor agonist even at high doses, produces only DA-1-mediated splanchnic and renal vasodilation . Fenoldopam has been shown to increase RBF and GFR.

Human studies with fenoldopam have been largely limited to normotensive and hypertensive human volunteers evaluating its effects on RBF, GFR, sodium excretion and urine output .Also, fenoldopam, like dopamine, is likely to increase RBF without actually improving renal medullary oxygenation.

THANK YOU

For your attention