

# An Eye Opening Experience

Dr. Bonnie Kwan

Department of Medicine & Therapeutics

Prince of Wales Hospital

# History

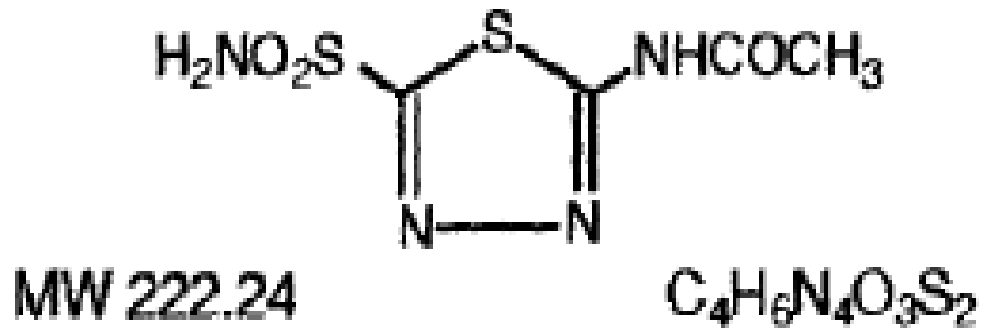
- 57-year-old woman
- DM / HT
- ESRD
- Tenckhoff catheter inserted 1 week ago
- currently on temporary HD
  
- admitted ophthalmology ward for sudden deterioration of left eye visual acuity
- diagnosed to have glaucoma

Consultation to nephrologist:

Can we, and, if yes, how do we, use diamox ?

# Diamox

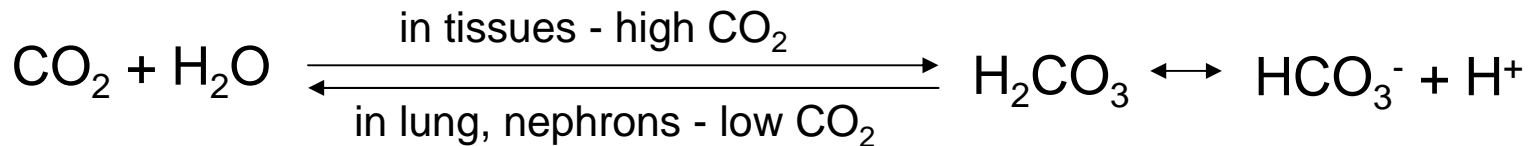
= acetazolamide (carbonic anhydrase inhibitor)



cf. MW of creatinine = 113  
but 98% protein bound

# Carbonic anhydrase: what ?

- an enzyme that assists rapid inter-conversion of carbon dioxide and water into carbonic acid, protons and bicarbonate ions



# There are many iso-enzymes !

- metalloenzymes consisting of a single polypeptide chain (MW ~29,000) complexed to an atom of zinc

<i>Isozyme</i>	<i>Catalytic activity (CO<sub>2</sub> hydration)</i>	<i>Affinity for sulfonamides</i>	<i>Sub-cellular localization</i>
CA I	Low (10% of that of CA II)	Medium	Cytosol
CA II	High	Very high	Cytosol
CA III	Very low (0.3% of that of CA II)	Very low	Cytosol
CA IV	High	High	Membrane-bound
CA V	Moderate-high <sup>a</sup>	High	Mitochondria
CA VI	Moderate	Medium-low	Secreted into saliva
CA VII	High	Very high	Cytosol
CARP VIII	Acatalytic	*	Probably cytosolic
CA IX	High	High	Membrane-bound
CARP X	Acatalytic	*	Unknown
CARP XI	Acatalytic	*	Unknown
CA XII	Active (no quantitative data)	Unknown	Membrane-bound
CA XIII <sup>b</sup>	Probably high	Unknown	Unknown
CA XIV	Low	Unknown	Membrane-bound

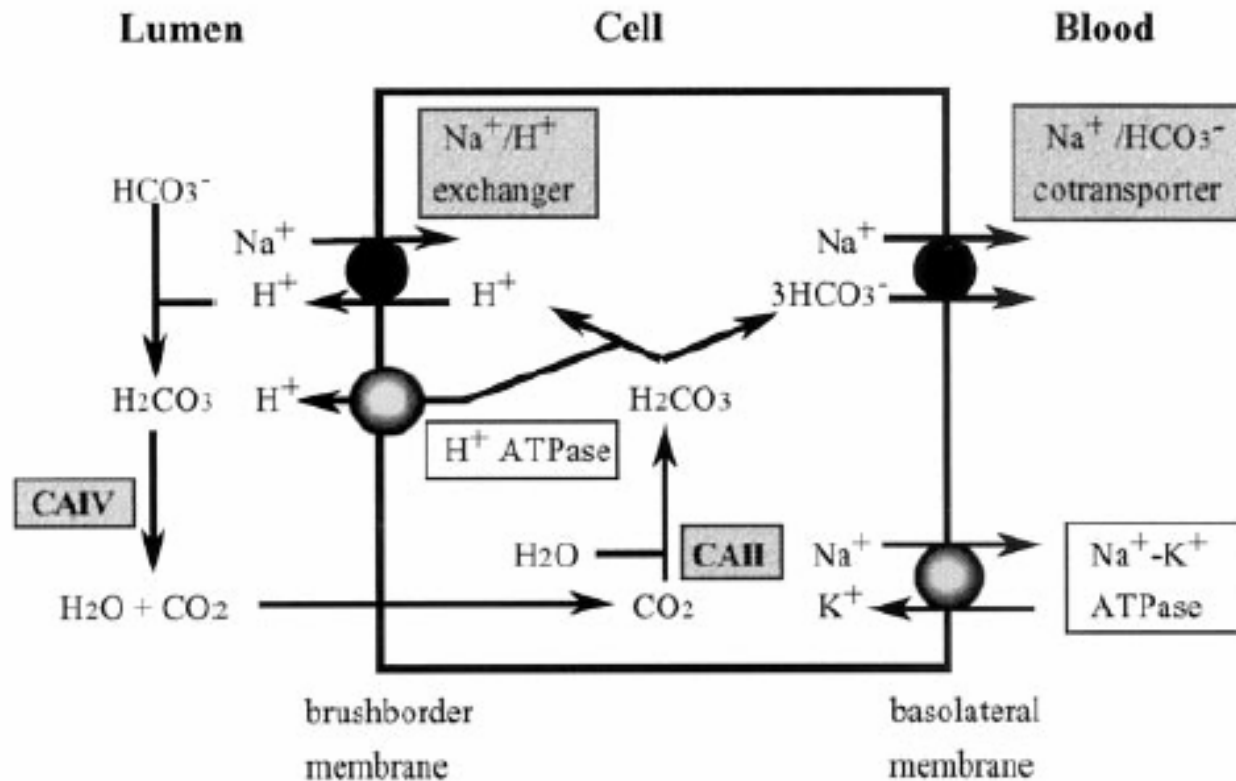
# Families and isoforms

- at least 5 distinct CA families ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  and  $\varepsilon$ ).
- mammals:  $\alpha$ -CA
- 4 broad subgroups, 14 isoforms:
  - cytosolic (CA-I, CA-II, CA-III, CA-VII and CA XIII)
  - mitochondrial (CA-VA and CA-VB)
  - secreted (CA-VI)
  - membrane-associated (CA-IV, CA-IX, CA-XII, CA-XIV)
- kidney: CA-II (cytosol) and CA-IV (luminal membrane)
- eye: CA-IV

# Function by organ-system

- renal tubules
  - $\text{HCO}_3^-$  reabsorption
  - secretion of  $\text{H}^+$
- parietal cells (stomach): secretion of acid (i.e.  $\text{H}^+$ )
- pancreatic duct cells: secretion of  $\text{HCO}_3^-$
- $\text{CO}_2$  expiration: RBCs convert  $\text{CO}_2$  to  $\text{HCO}_3^-$  for transport, then back to  $\text{CO}_2$  to be exhaled from lungs
- others
  - $\text{NH}_3$  transport, bone resorption, muscle contraction, gluconeogenesis, biosynthetic reactions, calcification, tumorigenicity, controls signal transfer through the neural network, signal processing and memory storage

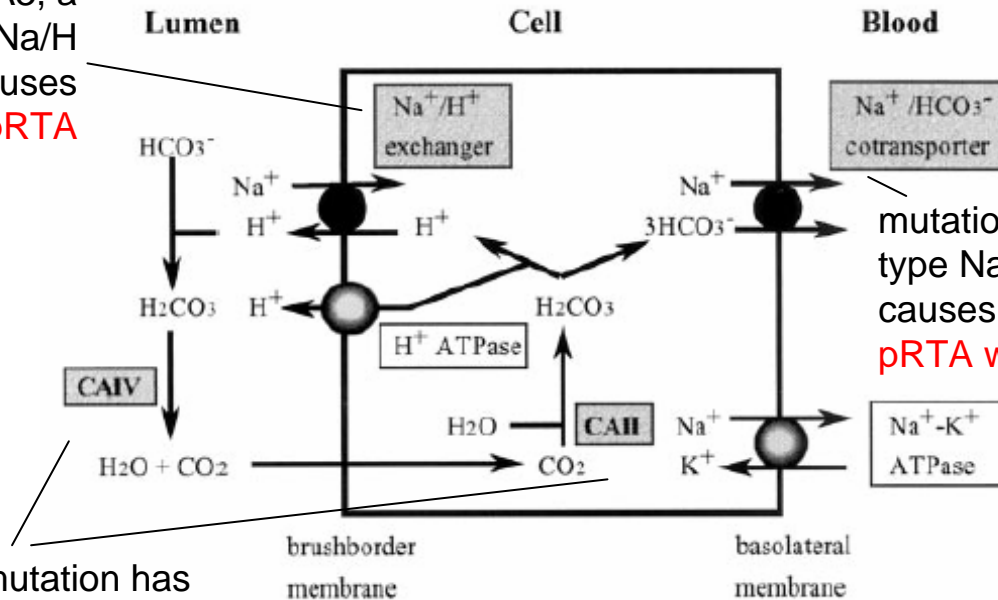
# Carbonic anhydrase: renal action



# CA-IV and proximal RTA ?

- 3 categories of isolated proximal RTA identified

mutation of SLC9A3, a component of Na/H exchanger (NHE3), causes **autosomal dominant pRTA**



mutation of SLC4A4, kidney type Na/HCO<sub>3</sub> cotransporter, causes **autosomal recessive pRTA with ocular abnormalities**

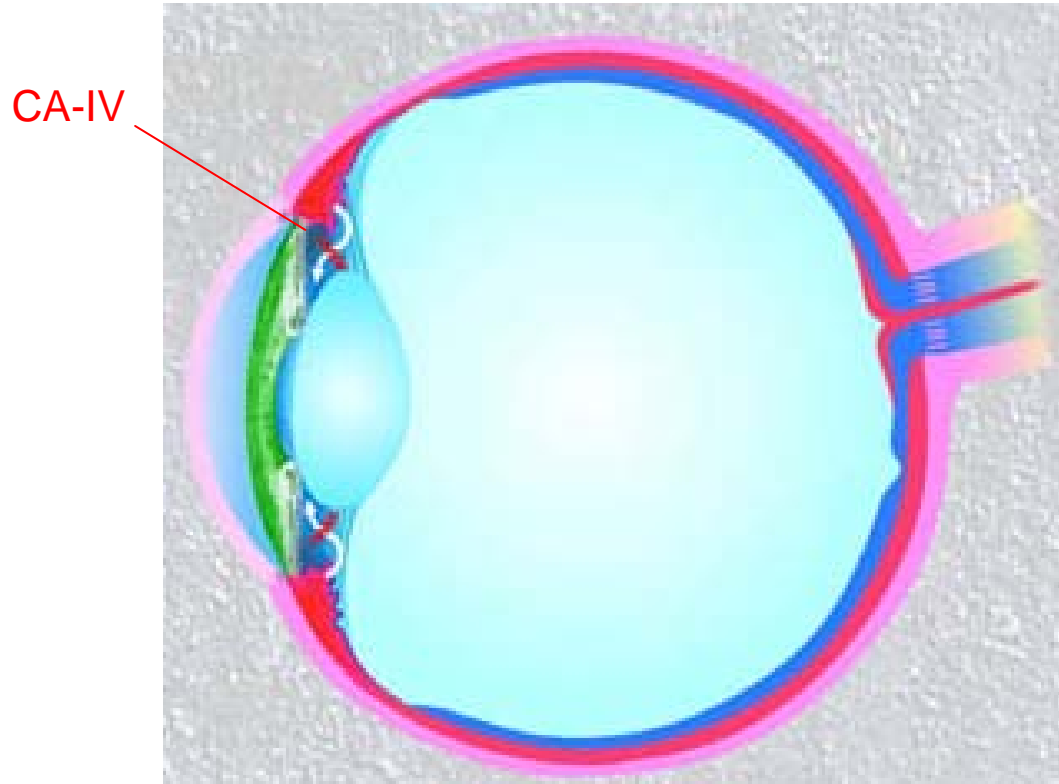
CA-IV or CA-II mutation has **not been reported** (possibly incompatible with life, given its wide tissue distribution)

**sporadic isolated pRTA:**  
mutation not yet identified

## CA inhibitors: renal effects

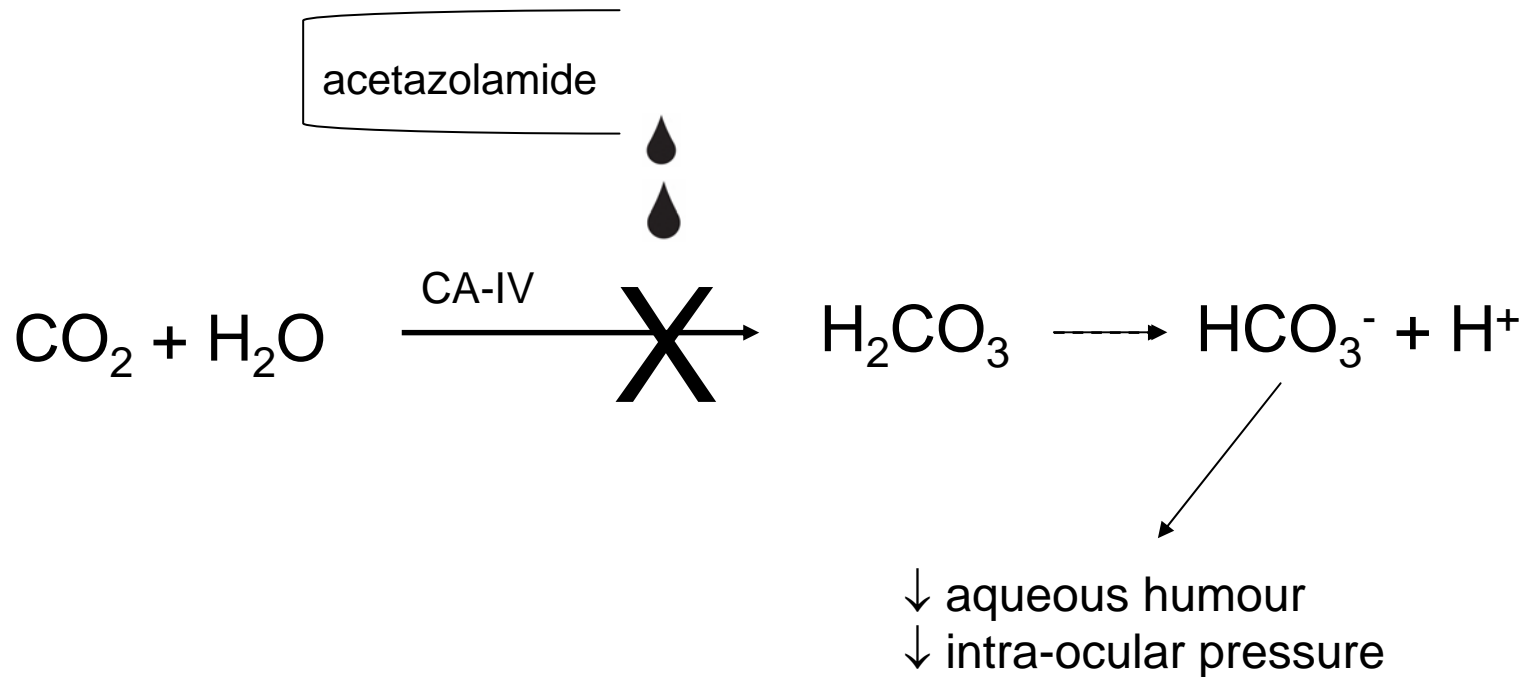
- impaired reabsorption of  $\text{HCO}_3^-$  from tubular fluid
- $\text{Na}^+$  and water lost with  $\text{HCO}_3^-$
- some  $\text{Na}^+$  will be reabsorbed with  $\text{Cl}^-$  instead
- tubular fluid is negatively charged  $\rightarrow$  enhance  $\text{K}^+$  loss
  
- summary
  - $\downarrow$  bicarbonate reabsorption
  - $\uparrow$  chloride reabsorption
  - $\uparrow$  sodium and potassium loss
  
- end result:  
hyperchloremic acidosis + hypokalemia + dehydration

# Carbonic anhydrase in the eye



∴ still useful in advanced renal failure

In the eye...



NB. still useful in renal failure !

# Acetazolamide: adverse effects

- general: headache, malaise, flushing, nausea and vomiting, growth retardation (children)
- acidosis, electrolyte imbalance, hypoglycemia
- increased risk of renal stone, renal failure
- neurological: drowsiness, paraesthesia confusion
- skin allergy, including Stevens-Johnson syndrome
- blood dyscrasias
- cholestatic jaundice, hepatic insufficiency

## When would we encounter this drug ?

- glaucoma (esp. chronic open angle type)
- enhance urine alkalization
  - urate nephropathy
  - salicylate poisoning
- diuretics (obsolete)
- childhood (centrencephalic) epilepsy
- mountain sickness

# Can we use it ?

- normal dosage: 125 to 500 mg tds
- renal excretion: 90%
- dosage adjustment
  - GFR > 50: no need to reduce dose
  - GFR 10 to 50: half dose
  - GFR < 10: avoid
- dialysis
  - HD: no data
  - PD: no data
  - CVVH: avoid

# Special risks in renal failure subjects

- may potentiate acidosis
- ineffective diuretic in ESRD
- may alter diabetic control
- may cause neurologic side effects in dialysis patients
  - paraesthesia
  - confusion

## Report on the use in HD patients

- acetazolamide 250 mg q.i.d.
- reversible neurological side effects associated with very high plasma concentrations  
[Roy LF, et al. Am J Kidney Dis 1992]
- 2 patients; acetazolamide 250 mg q.i.d.
- fatigue, lethargy, and confusion; resolved several days after discontinuing acetazolamide  
[Schwenk MH, et al. Pharmacotherapy 1995]

## Report in PD patients

- patient was very lethargic during therapy, a possible manifestation of acetazolamide toxicity
- pharmacokinetic study
  - elimination half-life was 28.5 hr  
cf. 5-10 hr in normal renal function
  - CAPD removes only 6.8% of dose
- marked reduction in dosage (~125 mg/day) would be required to prevent drug accumulation and toxicity

# Ask the eye people to use another treatment !?

- medications

- beta blocker
- prostaglandin analogues
- parasympathomimetic agents
- topical carbonic anhydrase inhibitors

but oral CA inhibitor is still often regarded as the most powerful medication for reducing intra-ocular pressure

- laser

- surgery

## Other oral CA inhibitors to choose ?

methazolamide is the only other available on market

- MW 236
- 55% protein bound (concentrated in RBC)
- half life = 14 hours
- 25% excreted unchanged in urine
- but
  - no data on renal failure / dialysis subjects
  - not available in Hong Kong

Many others, with specificities to various isoenzymes,  
are under development !

# How about CA inhibitor eye drops ?

- types
  - brinzolamide
  - dorzolamide
- both have substantial systemic absorption
- gradually accumulate with plasma level plateau after 7 to 10 days of use
- contraindicated in advance renal failure (same side effects as oral acetazolamide)

## What happened to our patient ?

- maintain on temporary HD
- put on “low” dose diamox (250 mg bd) while awaiting definitive surgery
- some dullness and confusion a few days later

# Outcome

- urgent CT brain: new lacunar infarct
- ? neurologic disturbance contributed by acetazolamide
- eye surgery cancelled
- withhold acetazolamide
- put on rehabilitation program

# Summary

- carbonic anhydrase has wide tissue distribution and many isoforms
- both systemic and topical CA inhibitors should be avoided in advanced renal failure
- if deemed necessary, a very low dose of oral acetazolamide (125 mg daily) may be possible
- need careful monitoring of neurologic disturbance