An Eye Opening Experience

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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

\[ \text{CO}_2 + \text{H}_2\text{O} \quad \text{in tissues - high CO}_2 \quad \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \quad \text{in lung, nephrons - low CO}_2 \]
There are many iso-enzymes!

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

<table>
<thead>
<tr>
<th>Isozyme</th>
<th>Catalytic activity (CO₂ hydration)</th>
<th>Affinity for sulfonamides</th>
<th>Sub-cellular localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA I</td>
<td>Low (10% of that of CA II)</td>
<td>Medium</td>
<td>Cytosol</td>
</tr>
<tr>
<td>CA II</td>
<td>High</td>
<td>Very high</td>
<td>Cytosol</td>
</tr>
<tr>
<td>CA III</td>
<td>Very low (0.3% of that of CA II)</td>
<td>Very low</td>
<td>Cytosol</td>
</tr>
<tr>
<td>CA IV</td>
<td>High</td>
<td>High</td>
<td>Membrane-bound</td>
</tr>
<tr>
<td>CA V</td>
<td>Moderate-high⁹</td>
<td>High</td>
<td>Mitochondria</td>
</tr>
<tr>
<td>CA VI</td>
<td>Moderate</td>
<td>Medium-low</td>
<td>Secreted into saliva</td>
</tr>
<tr>
<td>CA VII</td>
<td>High</td>
<td>Very high</td>
<td>Cytosol</td>
</tr>
<tr>
<td>CARP VIII</td>
<td>Acatalytic</td>
<td></td>
<td>Probably cytosolic</td>
</tr>
<tr>
<td>CA IX</td>
<td>High</td>
<td>High</td>
<td>Membrane-bound</td>
</tr>
<tr>
<td>CARP X</td>
<td>Acatalytic</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>CARP XI</td>
<td>Acatalytic</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>CA XII</td>
<td>Active (no quantitative data)</td>
<td>Unknown</td>
<td>Membrane-bound</td>
</tr>
<tr>
<td>CA XIII</td>
<td>Probably high</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>CA XIV</td>
<td>Low</td>
<td>Unknown</td>
<td>Membrane-bound</td>
</tr>
</tbody>
</table>

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
  – HCO$_3^-$ reabsorption
  – secretion of H$^+$

• parietal cells (stomach): secretion of acid (i.e. H$^+$)
• pancreatic duct cells: secretion of HCO$_3^-$
• CO$_2$ expiration: RBCs convert CO$_2$ to HCO$_3^-$ for transport, then back to CO$_2$ to be exhaled from lungs

• others
  – 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/HCO3 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...

\[ \text{acetazolamide} \]

\[ \text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{CA-IV}} \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+ \]

↓ aqueous humour
↓ intra-ocular pressure

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
  

- 2 patients; acetazolamide 250 mg q.i.d.
- fatigue, lethargy, and confusion; resolved several days after discontinuing acetazolamide
  
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 unchange 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