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**The Role of Oral Carbonic Anhydrase Inhibitors in Glaucoma Management: Indications and Contraindications**

Acetazolamide is an effective treatment for glaucoma, lowering IOP by 30-35%. However, excessive serum accumulations can cause nephropathy, renal stone formation or development of aplastic anemia.

**I. Case History**
- Patient Demographics: 71 year old Caucasian male
- Chief Complaint: None, patient seen with an outside optometrist and sent to the emergency room for elevated intraocular pressures.
- Ocular, medical history:
  - Nephrolithiasis
  - Frank hematuria
  - Chronic osteoarthritis
  - Colonic polyps
- Medications:
  - Multivitamins
- Other salient information:
  - Mother had an unspecified type of glaucoma treated with eye drops

**II. Pertinent Findings**
- Clinical Findings:
  - No corneal edema or keratic precipitates
  - Narrow angles by Van Herick estimation
  - Intraocular pressures (IOPs): 54 mmHg right eye and 46 mmHg left eye
  - Lenticular nuclear sclerosis, density greater in the right eye versus left eye
  - Asymmetric optic nerve cupping larger in the right eye than left with small pupil exam
- Gonioscopy
  - Right eye: posterior trabecular meshwork in one quadrant with no visible structures in the three other quadrants. Peripheral anterior synechiae present at 9:00, 11:00 and 1:00.
  - Left eye: Posterior trabecular meshwork present inferior and nasally and no visible structures in the remaining quadrants with peripheral anterior synechiae present from 11:00-12:00, 7:00-8:00 and 9:00-10:00.
- Ultrasound Biomicroscopy (UBM)
  - Pupillary block mechanism of angle closure and absence of plateau iris configuration.

**III. Differential Diagnosis**
- Primary Diagnosis: **Primary Angle Closure Glaucoma Secondary to Pupillary Block**
• **Primary Angle Closure Glaucoma Secondary to Phacomorphic Mechanism**
  - **Shared findings**: ocular hypertension, narrow angles seen with gonioscopy
  - **Differential characteristics**: Pupillary block typically responds to laser peripheral iridotomy (LPI) with opening of the peripheral iridocorneal angle. Phacomorphic angle closure is not relieved by an LPI and there are clinical and ultrasonographic evidence of an enlarged and anteriorly located lens.

• **Primary Angle Closure Secondary to Plateau Iris**
  - **Shared findings**: ocular hypertension, narrow angles seen with gonioscopy
  - **Differential characteristics**: central anterior chamber depth is normal, iris plane is flat, and double hump signs seen with compression gonioscopy. UBM shows characteristic signs of plateau iris. Anterior chamber remains capable of closure in the presence of a patent iridotomy.

**IV. Diagnosis and discussion**

• **Basic Findings and Testing**
  - Chronic angle closure glaucoma is typically asymptomatic, may have mild symptoms late in the disease.
  - A result of prolonged acute angle-closure glaucoma or multiple episodes of subclinical attacks of acute angle closure resulting in peripheral anterior synechiae (PAS).
  - Elevation of intraocular pressure from a mechanical or physical impairment of aqueous outflow through the trabecular meshwork.
  - Diagnosis made on the basis of optic nerve, visual field changes and gonioscopic evidence of a narrow angle

• **Unique Features**
  - Characteristic finding with gonioscopy of broad bands of PAS in the angle.
  - UBM shows closed angle

**V. Treatment, Management**

• **Treatment and response to treatment**:
  - Initial lowering of IOP with topical and systemic medications:
    - Apraclonidine (topical alpha agonist)
    - Timolol (topical beta-blocker)
    - Pilocarpine (topical miotic)
    - Dorzolamide (topical carbonic anhydrase inhibitor)
    - Latanoprost (topical prostaglandin analog)
    - Acetazolamide (systemic carbonic anhydrase inhibitor)
  - To prevent recurrence of acute primary angle closure and to reduce risk of chronic rise in IOP.
    - YAG laser peripheral iridotomy
  - If anatomical angle appearance is stable and open after LPI, but elevated IOP
    - Topical IOP lowering drops or systemic medications
- If angles are still not opened after iridotomy or progressive narrowing of angle
  - Argon Laser Peripheral Iridoplasty OR cataract extraction
- If sustained high IOP, progression of PAS or majority of angle closure caused by phacomorphic component
  - Cataract extraction
- The role of oral carbonic anhydrase inhibitors in glaucoma: In which patients should it be used with caution or avoided?
  - Oral carbonic anhydrase inhibitors (oral CAIs) include acetazolamide (Diamox™, Duramed Pharmaceuticals, Inc., Pomona, NY) and methazolamide (Neptazane™, Fera Pharmaceuticals, Locust Valley, NY)
  - Acetazolamide, used for the treatment of acutely elevated IOP and glaucoma that is nonresponsive to topical therapy, has a maximum fall in IOP of 30-35%.
  - Almost twice as efficacious as the topical carbonic anhydrase inhibitor, dorzolamide, in reducing aqueous outflow.
  - Standard doses of acetazolamide do not produce significant systemic acidosis.
  - With the use of acetazolamide, there is a mild metabolic acidosis in all those receiving the drug, which is self-limiting and short in duration in healthy individuals.
  - 68% of adverse reactions occur during the first 6 months of acetazolamide therapy.
  - Certain people, for unknown reasons, while receiving standard doses of acetazolamide, develop higher than needed serum levels.
  - Overtreatment with acetazolamide causes systemic acidosis, which can cause declining mental status, delirium, dyspnea, nephropathy, renal stones, aplastic anemia and others.
  - There is a direct relationship between age and plasma concentration. Individuals over age 80 have two times the plasma concentration of acetazolamide compared to those under the age of 60 given the same dose.
  - In patients with renal insufficiency or failure, there is a longer serum half-life of acetazolamide, 5 to 22 times longer than in normal subjects.
  - Even with a short duration of acetazolamide administration, there can be sulfonamide-like nephropathy that can present as early as 3 days to 5 weeks. More chronic usage is associated with nephrolithiasis, presenting at 2 months to 3 years.
  - IOP spikes seen during dialysis can be normalized using acetazolamide therapy, however this can cause detrimental metabolic acidosis.
  - Those with hepatic encephalopathy treated with 2 grams of acetazolamide demonstrate cerebral metabolic deterioration and decreased cerebral oxygen consumption.
  - It is estimated to be one acetazolamide user in 18,000 will develop aplastic anemia in as little as three months. This level of aplastic anemia is associated with a 50% mortality rate. These reactions are difficult to predict due to their idiosyncratic nature.
Co-administration of hydrochlorothiazide along with acetazolamide can cause clinical hypokalemia, that can be alleviated with potassium supplements\(^3\)

Chronic hyperventilation resulting from acetazolamide induced metabolic acidosis in combination with systemic beta-blockers increases pulmonary vascular resistance, decreases left ventricular function and blocks the protective effect of catecholamine on the failing heart\(^9\)

Use of salicylates with acetazolamide in the absence of renal and hepatic failure can cause serious metabolic acidosis\(^2, 28\)

The combination of phenytoin with chronic acetazolamide can lead to osteomalacia\(^6\)

Recommendations for preventing accumulation of acetazolamide and adverse reactions include measuring serum creatinine for renal function and serum level of acetazolamide to monitor for over accumulation and to adjust dosage accordingly\(^3\)

**VI. Conclusion**

- **Clinical pearls:**
  - Oral CAIs are an effective IOP lowering medication
  - Oral CAI usage should be used with caution in:
    - Elderly patients over the age of 80
    - Renal insufficiency or failure
    - Co-administration with hydrochlorothiazide
    - Beta blockers in conjunction with acetazolamide in cases of chronic hyperventilation
    - Co-administration of acetazolamide and phenytoin
  - Oral CAI usage should be contraindicated in:
    - Patients who are on dialysis
    - Co-administration of acetazolamide and salicylates
    - Doses of acetazolamide 2 grams or more with hepatic encephalopathy
  - If necessary to prescribe an oral CAI in at risk groups, one should monitor for overdose by measuring serum creatinine and serum level of acetazolamide and alter dosage accordingly
BIBLIOGRAPHY:


