

ACETAZOLAMIDE



"Twilight", Dante and Virgil at the foot of the First Terrace of Purgatory, woodcut print, 1867, Gustave Dore.

*When the game of dice breaks up,
the loser, left dejected,
rehearses every throw and sadly learns,*

*while all the others crowd around the winner.
One goes in front, one grabs him from the back,
and, at his side, another calls himself to mind.*

*The winner does not stop, but listens first to one
and then another. Those to who he gives his hand
then let him be, and so he gets away.*

*Such was I among that pressing throng,
turning my face this way and that,
and through my promises I freed myself of
them....*

*As soon as I was free of all those shades,
whose only prayer it was that others pray
and speed them on to blessedness,*

*I began, "O my light, it seems to me,
that in one passage you expressly contradict
that prayer can bend decrees from heaven,*

*"and yet these people pray for that alone.
Will this their hope, then, be in vain,
or are your words not really clear to me?"*

*He answered: "Plain is my writing
and their hopes not false
if with a sound mind you examine it.*

*"for not demeaned or lessened is high justice
if in one instant love's bright fire achieves
what they who sojourn here must satisfy.*

*"And there, where I affirmed that point
defect was not made good by prayer
because that prayer did not ascend to God.*

*"But do not let these doubts beset you
with high questions before you hear from her
who shall be light between the truth and intellect*

*"I don't know if you understand: I speak of
Beatrice
You shall see her above, upon the summit
of this mountain, smiling and in bliss".*

*Dante Alighieri, Purgatorio,
Canto VI, 1- 48
1306-1317.*

Much to his relief Dante has finally been led out of the terrifying underworld realm of Hell. Suddenly he now finds himself in Ante-Purgatory, a vast plain, that surrounds the immense Mountain of Purgatory proper, wherein are held the souls of the late repentant, the excommunicates, those who did not leave bad lives but who died suddenly and violently, among others. Almost immediately the shades discover Dante is a living being and not dead.

A huge host gathers around him each begging that he pray for them. They inform him that by the prayers of the living their ordeal on the seven Terraces of Purgatory will be lessened. This is in sharp contrast, to the souls in Hell, where prayer is of no use. They are grateful that they will eventually be saved, if they can negotiate the Terraces, but nonetheless the punishments to be endured there will be no less horrific than those suffered in Hell! However, Dante finds himself overwhelmed as if he is a winner of a large fortune in a game of dice and now being rich he is besieged by petitioners on all sides. He only manages to escape the throng by promising to pray for each and every one of them.

Virgil manages to lead him away to a quiet ridge where they can finally sit down in peace. The light is rapidly fading, and Virgil suggests that Dante gets some sleep as tomorrow they must attempt to enter the Gates of Purgatory and new ordeal will begin. As the two of them sit at the foot of the First Terrace, Dante, can't get the image of the frenzied pleas for help by prayer from the souls in Ante-Purgatory. He asks Virgil about the efficacy of prayer. Virgil essentially replies that he thinks prayer can mitigate a harsh fate, but that it cannot alter it. In other words prayer will not get a soul out of Purgatory, but it may lessen the time spent there.

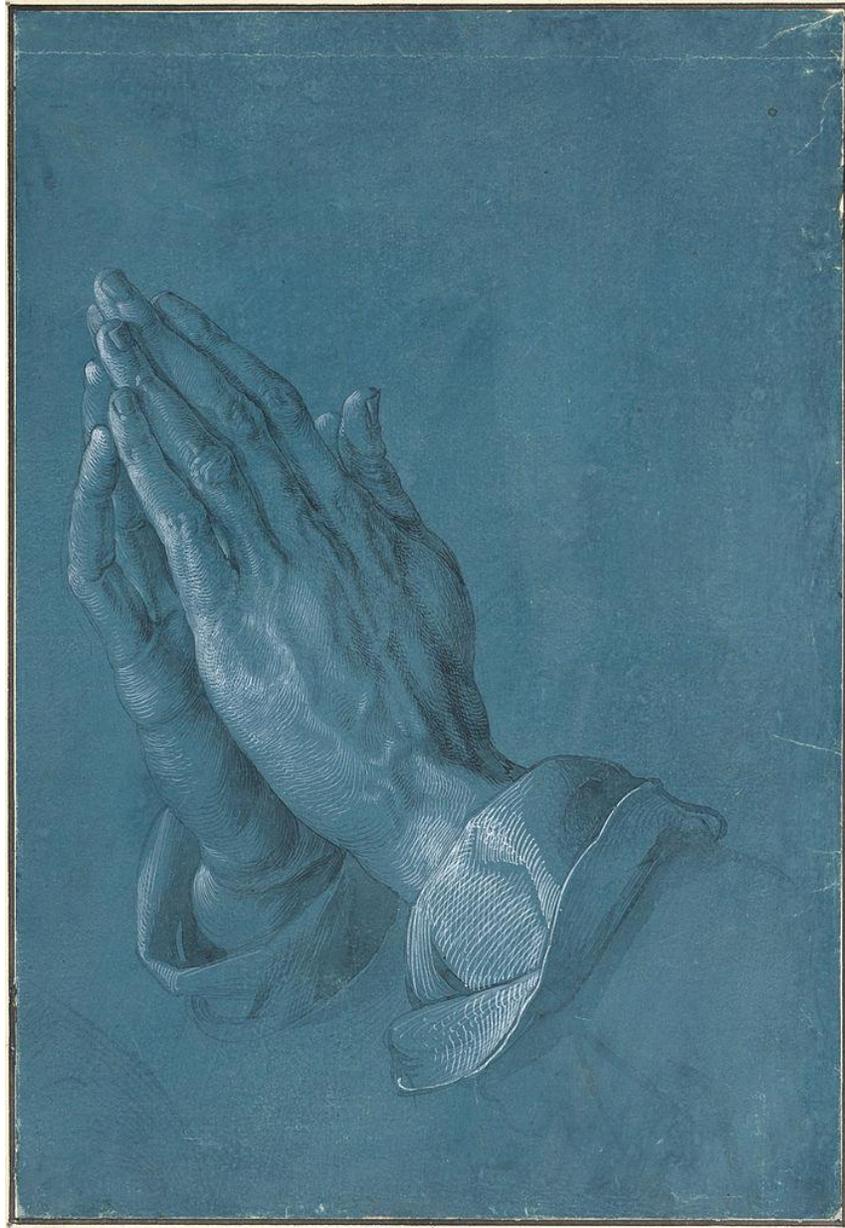
Dante then suddenly remembers a story from the Aeneid, which was written by his guide, literary master and hero, Virgil. In book six, (373-376), Aeneas witnesses the shade of a drowned sailor begging Sibyl to grant him passage across the river Styx. Sibyl tells him to stop dreaming, his body remains unburied and that his prayers cannot alter the will of the Gods. He points out to Virgil that in the Aeneid he contradicts the Christian belief that prayer can alter the will of God, i.e a soul's allotted time in Purgatory can be ameliorated by prayer. Virgil knows all the answers in Hell, but now in Purgatory, he finds, as a pagan, that he is entering into regions where he does not have answers. A little curtly he quips back to Dante, "Plain is my writing!" If Dante was to examine it more closely he would understand, that there is no contradiction.

He explains that part of the debt a soul owes to Purgatory can be paid for by prayer, in lieu of time on the Terraces, and so God is not changing his mind at all. Dante seems a little sceptical with this. Virgil then tries to follow up with the statement that in any case prayers in the Aeneid were not being made to the true God - as this was before the time of Christ. Prayers to pagan deities in other words, are useless. At this point Virgil himself becomes a little embarrassed at his own "special pleading". He finally admits to Dante, that the finer points of Christian theology are beyond him, and that he should wait to discuss these with someone far more qualified than he, the lady, Beatrice, (who is destined to take over from Virgil as guide), once they reach the realm of Paradise, a realm which Virgil, as a pagan is not allowed to enter - "But do not let these doubts beset you with high questions before you hear from her who shall be light between the truth and intellect. I don't know if you understand: I speak of Beatrice".

Dante struggled with the concept of an all knowing God who knows the past, the present and the future - if this was so then all of future time is already predetermined - and so there really is no such thing as free will. Dante justified his belief in free will, with the clever, and quite intriguing Augustinian argument, that God was a being who inhabited all points in time at the same time - and so he knows the future not because he preordained it, but simply because he is already there, as well as the present (and the past)!

*So people do have free will after all, God lets people choose with a free will, he just happens to **know** what they are going to choose! One wonders what St Augustine would have made of Twentieth century Quantum Mechanics, a theory not only compatible with free will, but also one that seems to state that every possible outcome could exist in some dimension at the same time. One gets to wonder then, does God also inhabit not only every time, but also every time-line of every possible "Alternate Universe" as well ? This brings to quite another level the concept of "all knowing and all powerful"!*

Our patients with acute on chronic respiratory failure frequently face long trials of agonizing Purgatory. They are condemned to suffer the protracted torments of mechanical ventilation and iatrogenic complication, before their final salvation. And so we constantly strive to find ways to relieve their long period of suffering. In a scientific age we make use of all manner of marvellous mechanical devices and right wondrous magical potions. One such potion currently employed is acetazolamide, by whose agency we hope to reduce our patients' time on the "Terraces". Sadly however, at this stage of proceedings, acetazolamide appears to be rather less efficacious than prayer!



"Praying Hands of an Apostle", 1508, Albrecht Durer

ACETAZOLAMIDE

Introduction

Acetazolamide (trade name in Australia, “**Diamox**”) is a **carbonic anhydrase inhibitor** and a mild diuretic agent.

In the past it was used as a mild diuretic in patients with heart failure.

Today its use is limited to:

1. Glaucoma.
2. Altitude sickness:
 - Prophylaxis
 - Treatment (adjunctive in HACE)
3. Acute on chronic respiratory failure with persisting metabolic alkalosis.

History

When the sulfonamide antibacterial **sulfanilamide** (or **sulphanilamide**) was introduced to clinical practice it was noticed that patients developed a mild **metabolic acidosis**. Further study showed that sulfanilamide was acting as a carbonic anhydrase inhibitor.

Subsequently a large number of sulfonamides were synthesized and tested for their ability to inhibit carbonic anhydrase.

Acetazolamide was found to be the most effective.

Chemistry

Acetazolamide is a derivative of the sulfonamide antibiotics.

Preparation

Tablets:

- 250 mg.

Ampoules:

- 500 mg (as powder for reconstitution).

Mechanism of Action

Carbonic anhydrase is an enzyme found primarily in:

- Red blood cells
- Proximal tubules of the kidney.

It catalyzes the rapid interconversion of carbon dioxide and water to bicarbonate and hydrogen ions (or vice versa):

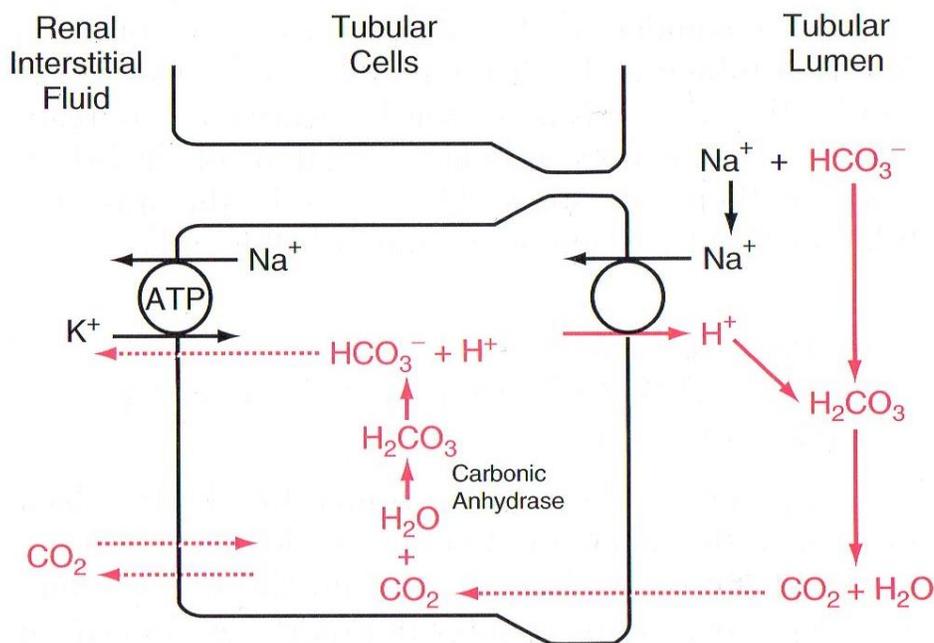


Diagram showing how H^+ ion secretion and HCO_3^- resorption are coupled to Na^+ reabsorption. The overall net result is that carbonic anhydrase inhibitors, inhibit Na^+ and HCO_3^- reabsorption from the tubular lumen, and so are lost in the urine.

Within the tubular cells carbonic anhydrase inhibits the production of $\text{HCO}_3^- + \text{H}^+$

This means that:

- Less H^+ is available for exchange with tubular lumen H^+ ions and so more HCO_3^- is lost in the urine.
- Na^+ is also lost in the tubules; and hence water with it - and hence a diuresis occurs.

- Less HCO_3^- is reabsorbed from the tubule cells back into the interstitial fluid (and so back into the blood stream) - and a metabolic **acidosis develops**.

Note that HCO_3^- does not cross the tubular lumen membrane, but can cross the interstitial fluid membrane.

Use in Chronic Metabolic Alkalosis:

Patients with acute on chronic respiratory failure will usually be acidotic, however in certain settings they may have a mixed picture of chronic metabolic alkalosis and chronic respiratory failure, where the alkalosis predominates.

Alkalosis can depress respiration in its own right (i.e. over and above the depression of respiration that occurs in COPD patients who have lost responsiveness to hypercapnia).

Acetazolamide in these situations can reduce HCO_3^- and pH values back towards normal.

Pharmacodynamics

Therapeutic actions include:

1. Mild diuresis:
 - Also alkalinizes the urine.
2. Reduction of aqueous humor:
 - Acetazolamide inhibits carbonic anhydrase and therefore bicarbonate synthesis; in the eye this reduces aqueous humour secretion and thereby intraocular pressure.
3. Hyperventilation:
 - Metabolic acidosis induces a mild hyperventilation which increases oxygenation, which is thought to be of benefit in cases of altitude illness.
4. Normalization of blood gas parameters in cases of a persisting metabolic alkalosis

Pharmacokinetics

Absorption:

- Acetazolamide can be given orally or IV.

It is well absorbed orally.

IM injection is painful and *not* recommended.

Distribution:

- Protein binding is 70-90 %

Metabolism and excretion:

- Acetazolamide is not metabolized

It undergoes renal elimination by tubular secretion.

Indications

Principle indications include:

1. Glaucoma:
 - Chronic
 - Acute.
2. Altitude sickness:
 - Prophylaxis
 - Treatment:
 - ♥ Adjunctive (to oxygen and descent) in HACE.
3. Acute on chronic respiratory failure with persisting metabolic alkalosis.

There is some evidence that acetazolamide may be useful in patients with acute on chronic respiratory failure with persisting co-existent **metabolic alkalosis** (pH > 7.45), due to:

- Frequent dosing of **furosemide**.

Or

- Compensatory metabolic alkalosis in patients who have been on prolonged NIV or mechanical (invasive) ventilation

Acetazolamide can certainly reduce HCO_3^- and pH values back towards normal, however at present there is *no good evidence* to indicate that it reduces the need for intubation or the duration of mechanical ventilation or the period of weaning.

Contra-indications/precautions

These include:

1. Known allergy
2. Hepatic impairment:
 - Contraindicated in hepatic impairment or cirrhosis due to the risk of hepatic encephalopathy.
3. Renal impairment: ²
 - Contraindicated when Cr Cl <10 mL/minute (increased risk of profound acidosis); reduce dose if CrCl 10 - 30 mL/minute.
 - Acetazolamide increases risk of recurrence of urolithiasis.
4. Conditions of metabolic acidosis:
 - Adrenal failure
 - Respiratory failure (with acidosis).
 - Other causes of metabolic acidosis in general, such as hyperchloraemic acidosis.

Contraindicated (increased risk of profound acidosis).
5. Sodium or potassium depletion:
 - Contraindicated (will worsen depletion).
6. Elderly:
 - Increased risk of adverse effects, e.g. metabolic acidosis.
7. Gout:
 - May worsen.

Pregnancy

Acetazolamide is a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans

Breast feeding:

Safe in breast feeding.

Adverse Effects

1. Allergic reactions:
 - There cross-reactivity with sulfonamide allergies.
2. Parasthesiae:
 - Hands/ feet/ perioral
3. GIT upset.
4. Metabolic acidosis.
5. Dermatological hypersensitivity reactions:
 - As acetazolamide is a sulfonamide derivative, dermatological hypersensitivity cross reactions may occur.

Occasionally these can be severe reactions in the form of Stevens Johnson Syndrome or Toxic Epidermal Necrolysis.

6. Electrolyte disturbances:
 - Hyponatremia
 - Hypokalemia

Dosing

Glaucoma:

Acute closed angle glaucoma:

- **Acetazolamide** 500 mg IV stat followed by 250 mg orally 6 hourly.

Chronic open angle glaucoma:¹

- *Adult*, oral, initially 125 mg twice daily, increase to a maximum of 250 mg 4 times daily.
- *Child*, oral 5-10 mg/kg (up to 250 mg) every 6 hours has been used (specialist supervision).

Attitude illness:

Prophylaxis: ¹

There is no substitute for a sensible ascent profile.

However, if unavoidable, prophylactic acetazolamide should be considered in moderate- to high-risk situations.

Use:

- Acetazolamide 125 mg (child: 2.5 mg/kg up to 125 mg) orally, 12-hourly commencing the day before ascent.

Treatment: ¹

Descent and oxygen are the definitive treatments.

For patients with **HACE** who can take oral medications, consider adding acetazolamide to dexamethasone.

Use:

- Acetazolamide 250 mg (child: 2.5 mg/kg up to 125 mg) orally, 12-hourly

Metabolic Alkalosis in Respiratory Failure:

There is no “standard” regimen for this, but one commonly used is as follows, (*personal communication Dr Graeme Duke, September 2016*):

Dose: 250 - 500 mg IV (or oral) 12 hourly.

Duration 48-72 hours; after this there is rarely any further improvement in pH.

Cessation of frusemide therapy.

References

1. eTG - March 2016
2. Acetazolamide in Australian Medicines Handbook, Website Access July 2015.
3. Acetazolamide in MIMs, 1 June 2005.
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