Pathophysiology And Pharmacotherapy of Addison’s Disease
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ABSTRACT
Addison’s disease, or primary adrenal insufficiency, results in glucocorticoid and mineralocorticoid deficiency. Orthostatic hypotension, fever, and hypoglycaemia characterize acute adrenal crisis, whereas chronic primary adrenal insufficiency presents with a more insidious history of malaise, anorexia, diarrhoea, weight loss, joint, and back pain. The cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, vermilion border, recent scars, genital skin, and oral mucosa. Measurement of basal plasma cortisol is an insensitive screening test. Synthetic adrenocorticotropin at a dose of 250 μg works well as a dynamic test. Elevated plasma levels of adrenocorticotropin and renin confirm the diagnosis.

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ADDISON’S DISEASE
Addison’s disease (also called adrenal insufficiency (AI) or hypocortisolism) is an endocrine disorder that occurs when the adrenal glands do not produce enough of the hormone cortisol and, in some cases, the hormone aldosterone. Aldosterone belongs to a class of hormones called mineralocorticoids, also produced by the adrenal glands. It helps maintain blood pressure and water and salt balance in the body by helping the kidney retain sodium and excrete potassium. When aldosterone production falls too low, the kidneys are not able to regulate salt and water balance, causing blood volume and blood pressure to drop.

If Addison’s disease isn’t treated, severe abdominal pain profound weakness, extremely low blood pressure, kidney failure, and shock may occur, especially if the body is subjected to stress such as an injury, surgery, or severe infection.
ETIOLOGY

- The most common is destruction of the glands by the body. This process where the body attacks and kills its own tissue is known as 'immune mediated destruction.'
- Other causes can be infections in the gland from granulomatous diseases such as histoplasmosis or blastomycosis, or through other means such as infarcts, tumors, or amyloidosis of the gland.
- Another cause of Addison's can be the failure of the pituitary gland to secrete ACTH, which is a hormone that stimulates the adrenal gland to work. The hypothalamus can also stop producing CRH, which is a hormone that controls the adrenal gland. Failure of the pituitary gland or hypothalamus is usually a result of a tumor, inflammation, or injury.

EPIDEMIOLOGY

The frequency rate of Addison's disease in the human population is sometimes estimated at roughly one in 100,000. Some research and information sites put the number closer to 40-60 cases per million populations. Addison's can afflict persons of any age, gender, or ethnicity, but it typically presents in adults between 30 and 50 years of age. Research has shown no significant predispositions based on ethnicity.

PATHOPHYSIOLOGY

Autoimmune adrenalities, tuberculosis, AIDS and metastatic cancer account for more than 90% of the cases of Addison's disease. Autoimmune adrenalitis is the most common cause of
Addison's disease, contributing to 60-70% of the cases. Autoantibodies to key steroidogenic enzymes are detected in the patients and the antibodies destroy steroid-producing cells. Half of the patients have coexisting autoimmune diseases.

Tuberculosis and fungal infections can cause Addison's disease. While the incidence of tuberculous adrenalitis has decreased with antituberculous therapy, the increase in tuberculous in urban areas, nursing homes, and prisons means it needs to be considered. It is usually associated with active infections in the lungs or GUT. AIDS leaves patient's susceptible to developing adrenal insufficiency from cytomegalovirus and mycobacterium infections.

Metastatic neoplasms are the final of the four major causes of Addison's disease. The adrenals are a common site for metastases in patients with disseminated carcinomas, mostly breast and lung carcinomas. The metastatic growth can destroy sufficient adrenal cortex to produce a degree of adrenal insufficiency.

**SIGNS AND SYMPTOMS**

- Fatigue
- Postural dizziness
- Syncope

Gastrointestinal symptoms

- Nausea
- Vomiting
- Abdominal pain
- Diarrhoea
- Constipation

- Weakness
- Anorexia
- Decreased libido
- Amenorrhea
- Arthralgias
- Myalgias
- Malaise
- Weight loss
- Hyperpigmentation
- Hypotension
- Thinning of axillary and pubic hair
- Vitiligo

**DIAGNOSTIC TEST FOR ADDISON’S DISEASE**

Clinical symptoms suggest possible adrenal insufficiency
Weakness, fatigue, weight loss, hypotension, skin darkening

Blood tests reveal low plasma cortisol and elevated plasma ACTH
Cortisol <5ug/dL, ACTH >200pg/mL

Test plasma cortisol after administration of ACTH
Normal – increase to ≥18-20ug/dL.

Plasma cortisol is elevated
Not Addison’s

Plasma cortisol is low or has not changed
Adrenal insufficiency

Measure plasma aldosterone prior to and after administration of ACTH

Plasma aldosterone is low
Addisons (primary insufficiency)

Plasma aldosterone is normal or increased
Secondary insufficiency

**TREATMENTS AND DRUGS**

All treatment for Addison's disease involves hormone replacement therapy to correct the levels of steroid hormones. Some options for treatment include:

**Oral corticosteroids.**
Fludrocortisone to replace aldosterone. Hydrocortisone, prednisone or cortisone acetate may be used to replace cortisol.

**Corticosteroid injections.** If you're ill with vomiting and can't retain oral medications, injections may be needed.
**Androgen replacement therapy:** To treat androgen deficiency in women, dehydroepiandrosterone can be prescribed. Some studies suggest that this therapy may improve overall sense of well-being, libido and sexual satisfaction.

An ample amount of sodium is recommended, especially during heavy exercise, when the weather is hot, or if you have gastrointestinal upsets, such as diarrhoea.

**ALDOSTERONE HORMONE REPLACEMENT THERAPY**

Aldosterone hormone replacement therapy is an element of the treatment for Addison's disease, which causes the adrenal glands to produce too little of two hormones, aldosterone as well as cortisol. Addison's disease is an autoimmune disorder, and is caused by the immune system attacking the adrenal glands. Through aldosterone hormone replacement therapy and the replacement of other affected hormones, the negative effects of Addison's disease are mitigated.

**FUNCTION**

Aldosterone is a hormone of the mineralocorticoid group. According to the National Endocrine and Metabolic Diseases Information Service (NEMDIS), aldosterone participates in maintaining proper blood pressure levels as well as helping the kidneys maintain sodium/potassium balance, which promotes the balance of salt and water within the body.

**EFFECTS**

When the adrenal glands do not produce enough aldosterone, the kidneys lose the ability to maintain a proper balance of sodium and potassium. According to the NEMDIS, this can lead to a decrease in the volume of blood and of blood pressure.

**TREATMENT**

To correct an underproduction of aldosterone caused by Addison's disease, the medication fludrocortisone acetate is administered. This medication is taken orally either once or twice a day, according to the NEMDIS. People who are on aldosterone replacement therapy often need to increase their dietary intake of salt.
<table>
<thead>
<tr>
<th>NAME</th>
<th>GLUCOCORTICOID POTENCY</th>
<th>MINERALOCORTICOID POTENCY</th>
<th>DURATION OF ACTION(t1/2 in hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>(cortisol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>Oral 8, intramuscular 18+</td>
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<tr>
<td>Prednisone</td>
<td>3.5-5</td>
<td>0.8</td>
<td>16-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>16-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5-7.5</td>
<td>0.5</td>
<td>18-40</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25-80</td>
<td>0</td>
<td>36-54</td>
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<tr>
<td>Betamethasone</td>
<td>25-30</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>12-36</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>8 puffs 4 times a day</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>equals 14 mg oral</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>prednisone once a day</td>
<td></td>
<td>-</td>
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<td>Fludrocortisone</td>
<td>15</td>
<td>200</td>
<td>24</td>
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<tr>
<td>acetate</td>
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<td></td>
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<tr>
<td>Deoxycorticosterone</td>
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<td>20</td>
<td>-</td>
</tr>
<tr>
<td>acetate</td>
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</table>
NEWER TREATMENT

A newer option in the treatment of Addison's disease is a drug called DOCP (Deoxycorticosterone pivalate). The injection is long acting and only needs to be given once every 25 days. DOCP has been intensively tested and been shown to provide better electrolyte regulation than Florinef. Some animals on DOCP may also need to be placed on a low maintenance dose of prednisolone. Grapefruit juice and liquorice increase cortisol availability in patients with Addison's disease.

ACE PRODUCTS AND THEIR USES (adrenal cortical extract)

ACE is obtained from the cortex of the adrenal glands of healthy domestic food animals (usually cattle, sheep, or swine). The major active component is the hormone hydrocortisone. For many years, ACE was recommended for treating Addison's disease. It was also labelled for use in preventing surgical shock, treating acute shock, burns, and loss of strength due to Addison's disease. More recently, ACE was offered by its distributors for acute and chronic drug addiction, hypotension, muscular fatigue, and control of hypoglycaemia. The typical marketed product was an injectable formulation containing in each millilitre an amount of extract equivalent to the biological activity of 0.1 to 0.2 mg (milligrams) hydrocortisone.

According to Goodman and Gilman's "Pharmacological Basis of Therapeutics" the preparation of ACE with a reasonable degree of activity was first accomplished by investigators in 1930. Harrison's "Principles of Internal Medicine" states that in 1937 the first natural corticosteroid was synthesized. The synthesis of several other compounds, including cortisone and hydrocortisone, was achieved from 1940 to 1950. Aldosterone, the principal salt-retaining hormone of the adrenal cortex was identified in 1954. Harrison's publication also states that several advances followed, including refinements in the ease and accuracy with which steroids and their metabolic products may be measured.

TREATING THE UNDERLYING CAUSE

In some cases, the underlying causes of Addison’s disease can be treated. For example, tuberculosis (TB) is treated with a course of antituberculous medication over a period of at least six months.
Other infections may be treated with antibiotics or antifungal medication, as necessary. Autoimmune conditions will be treated, although they cannot usually be cured.

**REFERENCE**


