DIABETES INSIPIDUS (DRUG TREATMENT AND ANIMAL MODELS): A REVIEW

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Summary

Diabetes insipidus describes the excess production of dilute urine. It is caused by the lack of production or action of the hormone vasopressin, Lack of vasopressin can be treated with synthetic vasopressin analogues.Neurogenic diabetes insipidus has an estimated prevalence of 1/25,000 and affects males and females equally. The prevalence of the other forms is unclear. Most cases present in adults, though familial Neurogenic diabetes insipidus and Nephrogenic diabetes insipidus characteristically present in childhood.In this review we are going to disscuss the most advance drugs used to treat Diabetes insipidus. Some animal models also disscuss in article to makes people understand about the experiment.

Key words: Diabetes insipidus (DI), arginine vasopressin (AVP), antidiuretic hormone (ADH), hydrochlorothiazide (HCTZ), specific gravity (SG).

Introduction

Diabetes Insipidus (DI) is a disorder in which there is an abnormal increase in urine output, fluid intake and often thirst. It causes symptoms such as urinary frequency, nocturia (frequent awakening at night to urinate) or enuresis (involuntary urination during sleep or "bedwetting"). Urine output is increased because it is not concentrated normally. Consequently, instead of being a yellow color, the urine is pale, colorless or watery in appearance and the measured concentration (osmolality or specific gravity) is low[1].

There are several different types of DI, each with a different cause. The most common type is neurogenic DI, caused by a deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH). The second common type of DI is nephrogenic diabetes insipidus, which is caused by an insensitivity of the kidneys to ADH. It can also be an iatrogenic artifact of drug use[2].

Description

The balance of fluid within the body is maintained through a number of mechanisms. One important chemical involved in fluid balance is called antidiuretic hormone (ADH). ADH is produced by the pituitary, a small gland located at the base of the brain. In a healthy person and under normal conditions, ADH is continuously released. ADH influences the amount of fluid that the kidneys reabsorb into the circulatory system and the amount of fluid that the kidneys pass out of the body in the form of urine.

Production of ADH is regulated by the osmolality of the circulating blood. Osmolality refers to the concentration of dissolved chemicals (such as sodium, potassium, and chloride; together called solute) circulating in the fluid base of the blood (plasma). When there is very little fluid compared to the concentration of solute, the pituitary will increase ADH production. This tells the kidneys to retain more water and to decrease the amount of urine produced. As fluid is retained, the concentration of solute will normalize. At other times, when the fluid content of the blood is high in comparison to the concentration of solute, ADH production will decrease. The kidneys are then free to pass an increased amount of fluid out of the body in the urine. Again, this will allow the plasma osmolality to return to normal.

Diabetes insipidus occurs when either the amount of ADH produced by the pituitary is below normal (central DI), or the kidneys' ability to respond to ADH is defective (nephrogenic DI). In either case, a person with DI will pass extraordinarily large quantities of urine, sometimes reaching 10 or more liters each day. At the same time, the patient's blood will be very highly concentrated, with low fluid volume and high concentrations of solute[3].

DI occurs on average when a person is about 24 years old, and occurs more frequently in males than in females[4].

Causes

DI caused by a lack of ADH is called central diabetes insipidus. When DI is caused by a failure of the kidneys to respond to ADH, the condition is called nephrogenic diabetes insipidus.Central diabetes insipidus is caused by damage to the hypothalamus or pituitary gland as a result of:

- Head injury
- Infection
- Surgery
- Tumor

Nephrogenic DI involves a defect in the parts of the kidneys that reabsorb water back into the bloodstream. It occurs less often than central DI. Nephrogenic DI may occur as an inherited disorder in which male children receive the abnormal gene that causes the disease from their mothers.Nephrogenic DI may also be caused by:

- Certain drugs (such as lithium, amphotericin B, and demeclocycline)
- High levels of calcium in the body (hypercalcemia)
- Kidney disease (such as polycystic kidney disease)[5]

Symptoms

The most common signs and symptoms of diabetes insipidus are:

- Extreme thirst
- Excretion of an excessive volume of diluted urine[6]
- weakness, fatigue, fever, low blood pressure, increased heart rate, dizziness, and confusion[4].

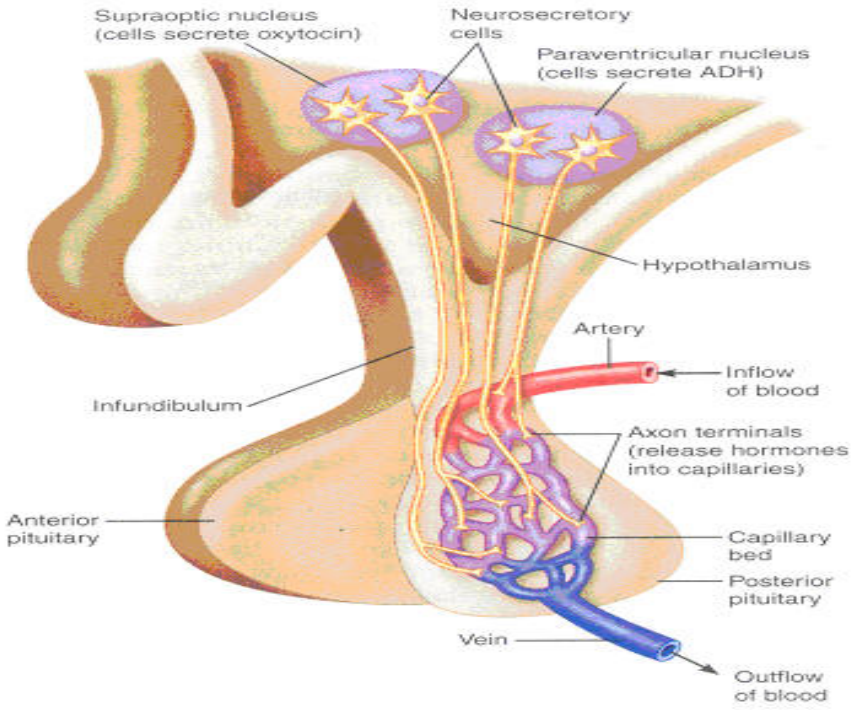
Depending on the severity of the condition, urine output can range from 2.6 quarts (about 2.5 liters) a day if you have mild diabetes insipidus to 16 quarts (about 15 liters) a day if the condition is severe and if you're taking in a lot of fluids. In comparison, the average urine output for a healthy adult is in the range of 1.6 to 2.6 quarts (about 1.5 to 2.5 liters) a day. DI can interfere with appetite, eating, weight gain, and growth as well.[7]Other signs may include needing to get up at night to urinate (nocturia) and bed-wetting.

Infants and young children who have diabetes insipidus may have the following signs and symptoms:

- Unexplained fussiness or inconsolable crying
- Unusually wet diapers
- Fever, vomiting or diarrhea
- Dry skin with cool extremities
- Delayed growth
- Weight loss[6]

Pathophysiology

Electrolyte and volume homeostasis is a complex mechanism that balances the body's requirements for blood pressure and the main electrolytes sodium and potassium. In general, electrolyte regulation precedes volume regulation. When the volume is severely depleted, however, the body will retain water at the expense of deranging electrolyte levels. The regulation of urine production occurs in the hypothalamus, which produces ADH in the supraoptic and paraventricular nuclei. After synthesis, the hormone is transported in neurosecretory granules down the axon of the hypothalamic neuron to the posterior lobe of the pituitary gland where it is stored for later release. In addition, the hypothalamus regulates the sensation of thirst in the ventromedial nucleus by sensing increases in serum osmolarity and relaying this information to the cortex.



The main effector organ for fluid homeostasis is the kidney. ADH acts by increasing water permeability in the collecting ducts and distal convoluted tubule, specifically it acts on proteins called aquaporins which open to allow water into the collecting duct cells. This increase in permeability allows for reabsorption of water into the bloodstream, thus concentrating the urine[8-12].

Classification

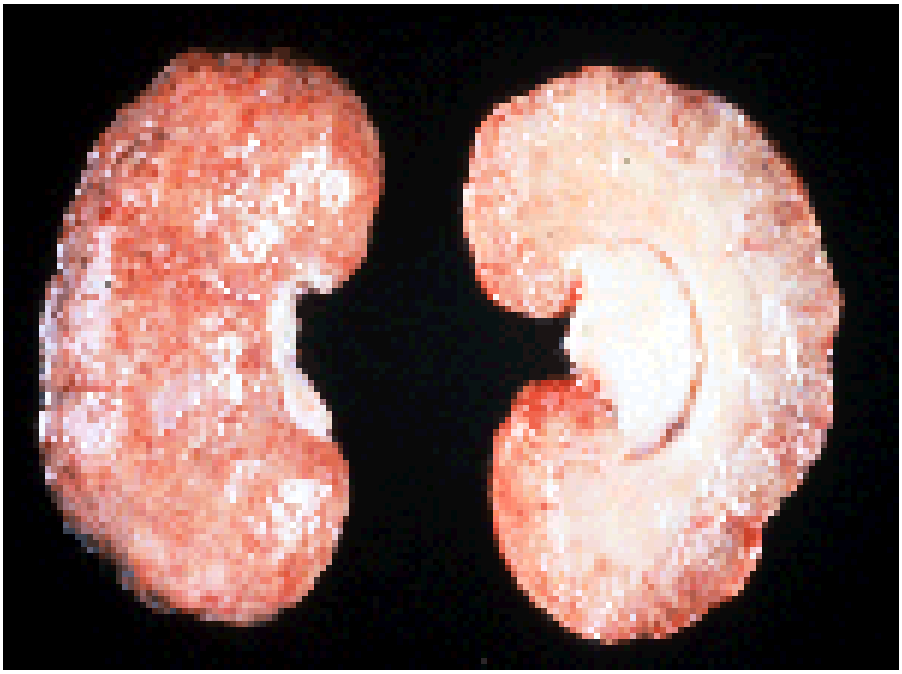
Neurogenic Diabetes insipidus

Central diabetes insipidus is a lack of antidiuretic hormone that causes excessive production of very dilute urine (polyuria).[13] This type of DI is usually due to the destruction of the back or "posterior" part of the pituitary gland where vasopressin is normally produced. Hence, it is commonly called pituitary DI. It is also known as central or neurogenic DI. The posterior pituitary can be destroyed by a variety of underlying diseases including tumors, infections, head injuries, infiltrations, and various inheritable defects. The latter can be recognized by the onset of the DI in early childhood and a family history of parents, siblings or other relatives with the same disorder.

Nearly half the time, however, pituitary DI is "idiopathic" (that is, no cause can be found despite a thorough search including magnetic resonance imaging or MRI of the brain) and the underlying cause(s) is (are) still unknown. Pituitary DI is usually permanent and cannot be cured but the signs and symptoms (i.e. constant thirst, drinking and urination) can be largely or completely eliminated by treatment with various drugs including a modified from of vasopressin known as desmopressin or DDAVP. Because pituitary DI is sometimes associated with abnormalities in other pituitary hormones, tests and sometimes treatments for these other abnormalities are also needed.

Nephrogenic Diabetes insipedus

Nephrogenic diabetes insipidus is due to the inability of the kidney to respond normally to ADH. Nephrogenic DI results when the kidneys are unable to respond to ADH. The kidneys' ability to respond to ADH can be impaired by drugs—like lithium, for example—and by chronic disorders including polycystic kidney disease, sickle cell disease, kidney failure, partial blockage of the ureters, and inherited genetic disorders. Sometimes the cause of nephrogenic DI is never discovered.Desmopressin will not work for this form of DI. Instead, a person with nephrogenic DI may be given hydrochlorothiazide (HCTZ) or indomethacin. HCTZ is sometimes combined with another drug called amiloride. The combination of HCTZ and amiloride is sold under the brand name Moduretic. Again, with this combination of drugs, one should drink fluids only when thirsty and not at other times.



Gestational Diabets insipidus

The lack of vasopressin can develop during pregnancy if the pituitary is slightly damaged and/or the placenta destroys the hormone too rapidly. This type of vasopressin deficiency is called gestagenic or gestational DI and is treatable with DDAVP but, in this case, the deficiency and the DI often disappear 4 to 6 weeks after delivery at which time the DDAVP treatment can usually be stopped. Often, however, the signs and symptoms of DI recur with subsequent pregnancies. Gestational DI occurs only during pregnancy and results when an enzyme made by the placenta destroys ADH in the mother. The placenta is the system of blood vessels and other tissue that develops with the fetus. The placenta allows exchange of nutrients and waste products between mother and fetus.Most cases of gestational DI can be treated with desmopressin. In rare cases, however, an abnormality in the thirst mechanism causes gestational DI, and desmopressin should not be used.

Dipsogenic Diabetes insipidus

Dipsogenic diabetes insipidus is a syndrome of disordered thirst, in patients without psychiatric disease, which may be confused with partial central diabetes insipidus. Dipsogenic DI occurs when vasopressin is suppressed by excessive intake of fluids. The latter is usually referred to as primary polydipsia and is most often caused by an abnormality in the part of the brain that regulates thirst. This subtype is called dipsogenic DI and is difficult to differentiate from pituitary DI particularly since the two disorders can result from many of the same brain diseases. The only sure way to tell them apart is to measure vasopressin during a stimulus such as fluid deprivation or to observe the effects of DDAVP treatment. In dipsogenic DI, DDAVP also eliminates the excessive urination but, unlike pituitary DI, it does not completely eliminate the increased thirst and fluid intake. Thus, it also results in water intoxication, a condition associated with symptoms such as:

- headache
- loss of appetite
- lethargy
- nausea
- signs such as an abnormally large decrease in the plasma sodium concentration (hyponatremia).

Because of this and the current lack of a way to correct the underlying abnormality in thirst, dipsogenic DI cannot be treated at present, although the most troubling symptoms, nocturia, can be safely relieved by taking small doses of DDAVP at bedtime. The other subtype of primary polydipsia is due not to abnormal thirst but to psychosomatic causes and is often referred to as pyschogenic polydipsia. It cannot be treated at present.[13-19]

Difference between diabetes insipidus and diabetes mellitus[27]:

	Diabetes Insipidus		**Diabetes Mellitus**
	Central DI	**Nephrogenic DI**	
How common is the condition?	Uncommon	Uncommon	Common
What causes the condition?	The pituitary is unable to secrete vasopressin or the hypothalamus is unable to make vasopressin.	The kidneys are unable to respond to the diuretic hormone vasopressin. It is acquired (as in lithium-induced nephrogenic DI) or may be inherited, usually by male children.	Not enough of the hormone insulin is secreted, or the body's cells do not respond to it. Heredity, stress, obesity, pregnancy and drugs can also lead to diabetes mellitus.
What do these hormones do in our bodies?	Vasopressin is a diuretic hormone that controls water metabolism. It is made in the hypothalamus (a part of	It causes the kidney to reabsorb water. Water that is not absorbed is released to the bladder as urine.	Insulin is made in the pancreas, where it controls carbohydrate metabolism. It controls sugar

	the brain) and is stored and secreted by the posterior pituitary gland (also in the brain).		(glucose) levels in the body.
How do I know if I have this condition?	Sudden or gradual urination of large amounts of clear, or almost colorless urine (polyuria), accompanied by excessive thirst (polydipsia). Dehydration can occur if fluid balance is not maintained.	Sudden or gradual urination of large amounts of clear, colorless urine (polyuria), accompanied by excessive thirst (polydipsia). Dehydration can occur if fluid balance is not maintained.	Excessive urination (polyuria), excessive thirst (polydipsia), excessive appetite (polyphagia). You may experience a sudden or gradual change with no symptoms. Other symptoms include tiredness, weight gain or loss, and skin infections that do not heal.
How is the condition diagnosed?	Water deprivation test/vasopressin test. Also, MRI to determine if the post pituitary bright spot is present.	Water deprivation test/vasopressin test.	Fast blood sugar-24hr. post-prandial test. Glucose tolerance test.
How is the condition managed?	Balance fluid intake and urine output. Replace antidiuretic hormone, vasopressin (usually with synthetic hormone: desmopressin), find, if possible, underlying injury to pituitary gland that is causing the condition.	Balance urine output with fluid intake. Treatment with thiazide and potassium-sparing diuretics. Low-sodium diet (500-600 mg/day or less for adults; 300 - 500 mg/day for children).	Correct sugar/insulin intake. Prevent progression of disease. Change the diet. Oral medication

Diagnosis

In order to distinguish DI from other causes of excess urination, blood glucose levels, bicarbonate levels, and calcium levels need to be tested. Measurement of blood electrolytes can reveal a high sodium level (hypernatremia as dehydration develops). Urinalysis demonstrates a dilute urine with a low specific gravity. Urine osmolarity and electrolyte levels are typically low.

A fluid deprivation test helps determine whether DI is caused by:

- excessive intake of fluid
- a defect in ADH production
- a defect in the kidneys' response to ADH

Water deprivation test

- Initial samples of blood (plasma) and urine are taken to measure sodium (Na) levels and osmolality, and urine specific gravity (SG). SG is a simple bedside test to track progress. Weight is measured at each sample time. Food and water are withheld for the duration of the test.
- Depending on severity, hourly or second hourly sampling is done until either urine osmolality stabilises at inappropriately dilute levels while plasma osmolality is higher than normal, or if weight declines by 5% or more.
- The test is terminated by the administration of desmopressin, allowing the patient to drink, and measuring the blood and urine again following that.[20-26].
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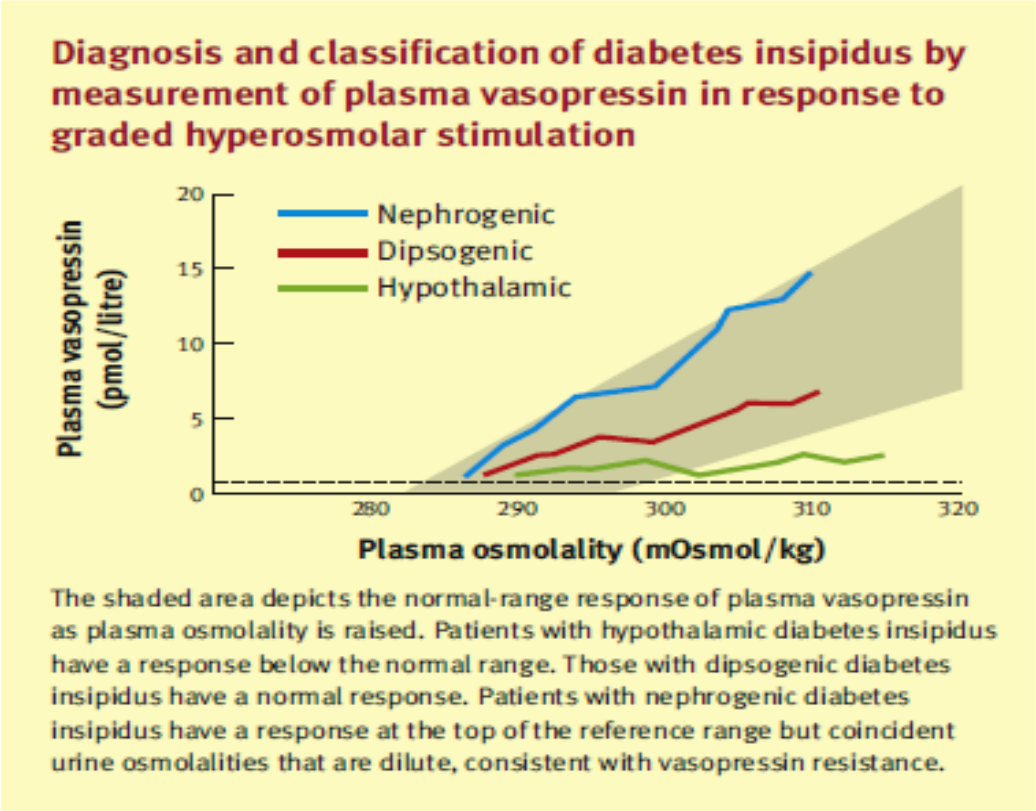

Diabetes insipidus treatment

Medical Care

Treat patients with diabetes insipidus (DI) in an inpatient setting because of the risk of severe dehydration. Destructive or compressive intracranial lesions mandate inpatient stay.

Distinguishing between central and nephrogenic etiology is essential to the treatment modality.

Surgical Care

Demonstration of an intracranial mass necessitates surgical care.

Consultations

Consultation with the following specialists may be appropriate.

- Nephrologist
- Endocrinologist: The presence of central diabetes insipidus should prompt an evaluation of anterior pituitary function.
- Diagnostic radiologist

Diet

Provide affected infants a breast milk diet to decrease solute load. Protein should comprise 6% of caloric intake, and sodium should be reduced to 0.7 mEq/kg/d.

Provide young children 8% of their caloric intake as protein to enable normal growth. Sodium intake must be maintained at 0.7 mEq/kg/d.

Activity

Activities resulting in increased insensible water loss should be moderated in the presence of massive urinary water loss to prevent dehydration.

Heat exposure should be minimized, especially when participating in sport.[28-29]

MEDICATION

Treat diabetes insipidus (DI) with desmopressin and/or nonhormonal drugs. In central diabetes insipidus, the primar problem is a hormone deficiency; therefore, physiologic replacement with desmopressin is usually effective. Use a nonhormonal drug if response is incomplete or desmopressin is too expensive. Nonhormonal drugs usually are more effective in treating nephrogenic diabetes insipidus.

1.Hormones:

These agents prevent complications of DI and reduce morbidity.

Desmopressin (DDAVP)

Synthetic analogue of arginine vasopressin with potent antidiuretic, but no vasopressor, activity.

Dose:
Adult
5-20 mcg intranasal qd/bid
0.05-0.8 mg PO once or more daily
Pediatric
0.05-0.3 mg/d PO
Contraindications:
hypersensitivity
Interactions:
Lithium and demeclocycline diminish ADH effects; chlorpropamide, fludrocortisone, and glucocorticoids enhance ADH response; monitor with pressor agents
Precautions
Pregnancy
B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals.
Precautions
Observe for effects on blood pressure; institute fluid restriction in children to avoid hyponatremia or water intoxication.

Vasopressin (Pitressin)
Has vasopressor and antidiuretic hormone (ADH) activity. Increases water resorption at collecting ducts (ADH effect) and promotes smooth muscle contraction throughout vascular bed of renal tubular epithelium (vasopressor effects). However, vasoconstriction is also increased in splanchnic, portal, coronary, cerebral, peripheral, pulmonary, and intrahepatic vessels. Decreases portal pressure in portal hypertension. A notable undesirable effect is coronary artery constriction that may dispose patients with coronary artery disease to cardiac ischemia. This can beprevented with concurrent use of nitrates.
Dose:
Adult
5-10 U SC q3-6h
Pediatric
2.5-10 U SC bid/qid
Contraindications:
hypersensitivity; coronary artery disease; hypertension; angina
Interactions:
Lithium, demeclocycline, and alcohol diminish ADH effects; chlorpropamide and fludrocortisone or glucocorticoids enhance ADH effects

Precautions:
Pregnancy
B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions
Caution in cardiovascular disease, seizure disorders, nitrogen retention, asthma, or migraine; excessive doses may result in hyponatremia

2.Hypoglycemics
These agents help relieve diuresis

Chlorpropamide (Diabinese)
Promotes renal response to ADH.
Dose:
Adult
125-250 mg PO bid
Pediatric
Not recommended
Contraindications:
hypersensitivity; type I diabetes; severe renal or hepatic impairment; thyroid dysfunction**.**
Interactions:
NSAIDS, salicylates, sulfonamides, Coumadin, MAOIs, and beta-blockers may enhance hypoglycemia
Precautions:
Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Precautions
Hypoglycemia may occur

3.Anticonvulsants:
Certain antiepileptic drugs, such as carbamazepine, have proven helpful in DI.

Carbamazepine (Tegretol)
Amelioration by releasing ADH. Not useful in total DI and generally not a first-line drug.
Dose:
Adult
100-300 mg PO bid
Pediatric
Not recommended

Contraindications:
hypersensitivity; history of bone marrow suppression; MAOI use
Interactions:

Serum levels may increase significantly within 30 d of danazol coadministration (avoid whenever possible); do not coadminister with MAOIs; cimetidine may increase toxicity, especially if taken in first 4 wk of therapy; carbamazepine may decrease primidone and phenobarbital levels (their coadministration may increase carbamazepine levels)

Precautions:

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Do not use to relieve minor aches or pains; caution with increased intraocular pressure; obtain CBCs and serum iron baseline prior to treatment, during first 2 months, and yearly or every other year thereafter; can cause drowsiness, dizziness, and blurred vision; caution while driving or performing other tasks requiring alertness

4.Antilipidmic agents:

Certain antilipidmic drugs, such as clofibrate, may increase the release of ADH in partial DI.

Clofibrate (Atromid-S)

No longer on US market. May release ADH in partial DI.

Pharmacology:

Clofibrate is an antilipidemic agent similar to gemfibrozil. It acts to lower elevated serum lipids by reducing the very low-density lipoprotein fraction (S_f 20-400) rich in triglycerides. Serum cholesterol may be decreased, particularly in those patients whose cholesterol elevation is due to the presence of IDL as a result of Type III hyperlipoproteinemia. Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time. Reduction of triglycerides in some patients treated with clofibrate or certain of its chemically and clinically similar analogs may be associated with an increase in LDL cholesterol. Increase in LDL cholesterol has been observed in patients whose cholesterol is initially normal. Animal studies suggest that clofibrate interrupts cholesterol biosynthesis prior to mevalonate formation.

Mechanism of Action:

Clofibrate increases the activity of extrahepatic lipoprotein lipase (LL), thereby increasing lipoprotein triglyceride lipolysis. Chylomicrons are degraded, VLDLs are converted to LDLs, and LDLs are converted to HDL. This is accompanied by a slight increase in secretion of lipids into the bile and ultimately the intestine. Clofibrate also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for VLDL.

Dose:

Adult

100-300 mg PO bid

Pediatric
Not recommended
Contraindications:
hypersensitivity; hepatic or renal insufficiency; biliary cirrhosis
Interactions:
Rifampin decreases serum level and effect; warfarin may increase PT; chlorpropamide may increase hypoglycemia; probenecid increases serum level and effect
Precautions:
Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Precautions
Consider tumorigenicity; caution in breastfeeding, cardiac disease, and hypothyroidism.

5.Hypoglycemics:
These agents help relieve diuresis

Hydrochlorothiazide (Esidrix, HydroDIURIL, Microzide)
Thiazide diuretic that decreases urinary volume in absence of ADH. May induce mild volume depletion and cause proximal salt and water retention, thereby reducing flow to the ADH-sensitive distal nephron. Effects are additive to other agents.
Dose:
Adult
25-50 mg PO qd or divided bid
Pediatric
Not recommended
Contraindications:
hypersensitivity; renal dysfunction
Interactions:
Alcohol, antihypertensive drugs, and other diuretics increase diuretic effect; corticosteroids and other diuretics increase hypokalemic effect; decreases hypoglycemic effect of insulin and oral agents; increases lithium serum levels; NSAIDs decrease diuretic and antihypertensive effects.
Precautions:
Pregnancy
B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals
Precautions
Considered pregnancy risk factor D by some experts; observe for changes in fluids and electrolytes.

6.Nonsteroidal Anti-inflammatory Agents (NSAIDs):
Their mechanism of action is not known, but they may act by inhibiting prostaglandin synthesis.

Ibuprofen (Ibuprin, Advil, Motrin)

Inhibition of prostaglandin synthesis reduces delivery of solute to distal tubules, reducing urine volume and increasing urine osmolality. Usually used in nephrogenic DI.

Dose:

Adult

600-800 mg PO tid

Pediatric

Not recommended

Controindications:

hypersensitivity; advanced renal disease; GI bleeding or risk of bleeding

Interactions:

Aspirin decreases serum levels; increases serum levels of digoxin, methotrexate, lithium; increases effect of anticoagulants; decreases hypotensive effects of ACE inhibitors and furosemide.

Precautions:

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Fluid retention, platelet effects, and renal disease may occur

Indomethacin (Indocin)

Inhibition of prostaglandin synthesis reduces delivery of solute to distal tubules,reducing urine volume and increasing urine osmolality. Usually used in nephrogenic DI.

Dose:

Adult

25-50 mg PO bid/tid

75 mg SR PO bid; not to exceed 200 mg/d

Pediatric

Not established

Contraindications:

hypersensitivity; GI bleeding or renal insufficiency

Interactions:

Coadministration with aspirin increases risk of inducing serious NSAID-related side effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT when taking anticoagulants (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; phenytoin levels may be increased when administered concurrently.

Precautions:

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Acute renal insufficiency, hyperkalemia, hyponatremia, interstitial nephritis, and renal papillary necrosis may occur; increases risk of acute renal failure in patients with preexisting renal disease or compromised renal perfusion; reversible leukopenia may occur (discontinue if there is persistent leukopenia, granulocytopenia, or thrombocytopenia.[30-33]

Animal models

Hereditary Diabetes Insipidus in the Brattleboro Strain of Rat

Biological features

The Brattleboro rat was discovered in 1961.[34-36] It is born with hypothalamic diabetes insipidus, which is inherited as an autosomal semirecessive trait at a single gene locus.[37] One can therefore distinguish three genotypes: a) Brattleboro homozygotes (also often referred to as DI rats); b) Brattleboro heterozygotes; and (c) normal rats of the Long-Evans hooded strain, from which Brattleboro rats were

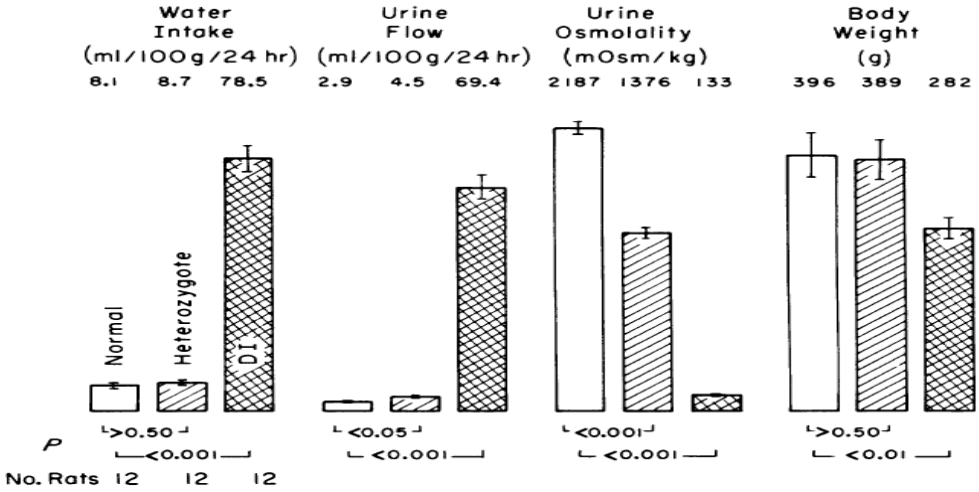

Figure Phenotypic characteristics of normal rats of the Long-Evans hooded strain, of Brattleboro heterozygotes, and of Brattleboro homozygotes (DI). Bars represent means and brackets indicate ±1 SEM. From Valtin etal.5 by permission of the publishers.

derived. The salient phenotypic features are shown in Figure.[38] The average daily output of urine in Brattleboro homozygotes is equivalent to about 70% of the body weight, and the urine has a mean osmolality of about 133 mOsmol/kg H20; water intake is correspondingly high. In contrast, normal rats of the Long-Evans hooded strain have a urine flow that averages about 3%c of the bodv weight per day, and their urine osmolality is about 2200 mOsmol/kg H20. The characteristics of water turnover in Brattleboro heterozygotes are intermediate between those of DI and normal rats. Homozygotes are smaller than normal and heterozygous rats, possibly because of a deficiency in growth hormone.[39]

Applicabiity of the Model

Brattleboro homozx-gotes and heterozygotes have proved useful in thefollowing areas of investigation: renal, fluid, and electrolyte physiology and disease; membrane physiology and morphology; endocrinology and neuroendocrinology; neurophysiology and behavior; and biochemistry.These animals are potentially useful in any study where a discrete absence of vasopressin is required or in which any of the multiple actions of this hormone are to be assessed.

Avalability

Breeding stock of Brattleboro homozvgotes and heterozygotes can be obtained from: Dr. Carl. T. Hansen, National Institutes of Health, Building 14A, Room A102, Bethesda, MD 20014.[40]

The occurrence of nephrogenic diabetes insipidus in domestic fowl

In the present investigation an apparent case of NDI was studied in a strain of White Leghorn domestic fowl. In this strain, water intake of the males equaled 24.0% (controls 5.4%) of their body mass (BM) per day while that of the females equaled 51.4% (controls 11.7%) of their BM per day. Plasma osmolality (mosmol/kgH2O) of the NDI birds was significantly higher than that of controls (males 319 +/- 1.7 vs. 311 +/- 1.2; females 323 +/- 1.5 vs. 310 +/- 2.2). Urine osmolality of NDI birds was substantially lower than that of controls (males 90 +/- 6.2 vs. 524 +/-4.0; females 70 +/- 4.7 vs. no value). In response to water deprivation, plasma osmolality of the NDI birds increased more markedly than that of the control animals (males 357 +/- 2.5 vs. 331 +/- 1.2; females 375 +/- 6.0 vs. 348 +/- 1.4 at 48 h of water deprivation). Basal plasma antidiuretic hormone (plasma arginine vasotocin, PAVT) levels in male NDI birds (9.9 +/- 0.7 microU/ml) and in female NDI birds (7.0 +/- 0.5 microU/ml) were nearly sixfold or nearly threefold higher, respectively, than in control birds. In response to water deprivation, PAVT of both NDI and control birds increased to similar levels, although the absolute increases in PAVT levels were substantially less in NDI birds.[41]

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