Drugs that Affect the Endocrine System

2.1.7

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2.1.7 Drugs that affect the endocrine system
2.1.7.1 Antidiabetic drugs
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2.1.7.5 Sex hormones, growth hormones, anabolic steroids
2.1.7.6 Thyroid drugs
2.1.7.7 Vasopressin and somatostatin analogues

Antidiabetic Drugs

2.1.7.1
Insulin

- Released from pancreas, binds to receptors on cell surface of insulin-sensitive tissue
- Hepatocytes, myocytes, adipocytes

Sulfonylureas

- Stimulate pancreatic insulin release
- Bind to receptors that result in closure of the $K_{ATP}$ channels
- Results in multistep process that increases insulin release

Meglitinides

- Structurally different from sulfonylureas
- Bind to same receptors that result in closure of the $K_{ATP}$ channels
- Results in multistep process that increases insulin release
**Biguanides**

- Inhibits gluconeogenesis, decreasing hepatic glucose output
- Also enhances peripheral glucose uptake

**Thiazolidinediones**

- Decrease insulin resistance by potentiating insulin sensitivity in the liver, adipose, and skeletal muscle
- Also reduce hepatic glucose production

**Glucosidase Inhibitors**

- Acarbose, miglitol
- Oligosaccharides that inhibit alpha-glucosidase enzymes in small intestine
- Blunts postprandial blood glucose concentration
Pharmacokinetics

- Many sulfonylureas have long durations of action

Clinical Manifestations

- Insulin, sulfonylureas, meglitinides
- All cause hypoglycemia
- CNS effects predominate with hypoglycemia
- Brain uses glucose almost exclusively as energy source (ketones in starvation)

Management

- Supportive care
- Reversal of hypoglycemia
- Insulin
  - Titrate dextrose infusion as needed
Management

- Sulfonylureas
- Feed patient when appropriate,
- Octreotide
  - Somatostatin analogue, blocks insulin release from pancreas

Special Consideration

- Metformin associated lactic acidosis (MALA)
- Metformin inhibits hepatic lactate update and conversion of lactate to glucose
- 2 entities

Special Consideration

- MALA
  - Lactic acidosis associated with underlying medical disease (especially renal insufficiency)
  - Metformin overdose
Bone Active Drugs

2.1.7.2

Calcitonin & bisphosphonates

Calcitonin

- Inhibits osteoclast activity, reduces bone reabsorption
- Used to treat hypercalcemia
- Can cause hypocalcemia

• Inhibits osteoclast activity, reduces bone reabsorption
• Used to treat hypercalcemia
• Can cause hypocalcemia
Bisphosphonates

- Inhibits osteoclast activity, reduces bone reabsorption
- Can be used to treat hypercalcemia, osteoporosis
- Associated with osteonecrosis of the jaw

Electrolytes & Minerals

2.1.7.3

Calcium

- Ca++ homeostasis is regulated by the endocrine system
- Interaction between vitamin D, parathyroid hormone, and calcitonin
- Ca++ essential in maintaining function of heart, vascular smooth muscle, skeletal muscle and nervous system
Calcium

- Hypocalcemia
- Paresthesias, muscle cramps, carpopedal spasm, tetany, seizures, prolonged QTc
- Hypercalcemia
- Lethargy, muscle weakness, nausea, vomiting, constipation, altered mental status, dysrhythmias

Glucocorticoids

2.1.7.4

- Class of steroid hormones that bind to the glucocorticoid receptor (present in nearly all vertebrate animal cells)
- Both metabolic and immunologic effects
Adverse Effects

- Immunosuppression
- Hyperglycemia
- Skin fragility
- Osteoporosis
- Weight gain
- Adrenal insufficiency
- Anovulation

Sex Hormones, Growth Hormones, and Anabolic steroids

2.1.7.5

Anabolic Steroids

- Androgenic anabolic steroids (AAS)
- Increase muscle mass, lean body weight, cause nitrogen retention
- Responsible for secondary sex characteristics (hair, voice, etc)
- Testosterone is the prototype
Anabolic Steroids

- 1990 Anabolic Steroid Control Act
- Amended the Substance Control Act
- Made AAS schedule III
- 2004 Anabolic Steroid Control Act
- Added certain precursors (like androstenedione) to the list of substances

Anabolic Steroids

- Testosterone is rapidly degraded in the liver
- For clinical usefulness:
  - Esterify the 17-hydroxy position to form a hydrophobic compound suitable for injection
  - Alkylate the 17-hydroxy position for an oral preparation

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<td>Testosterone enol</td>
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Goldfrank’s Toxicologic Emergencies, 8th ed
Terminology

- Cycling
  - AAS use intervals (2 months on/2 off)
- Stacking
  - Combining several AAS at one time
- Plateauing
  - Developing tolerance

Terminology

- Pyramiding
  - Start with low dose, increase, then decrease
- Bridging
  - Changing to short acting agents just prior to drug testing
Endocrine

Clinical Manifestations

• Musculoskeletal
  • Increase muscle mass and size
• Hepatic
  • Hepatic subcapsular hematoma, peliosis hepatis

Clinical Manifestations

• Infectious
  • Local complications from injecting
• Dermatologic
  • Keloids, sebaceous cysts, comedones, seborrheic furunculosis, folliculitis, striae

Clinical Manifestations

• Endocrine
  • Gynecomastia, testicular atrophy, reduced spermatogenesis, breast atrophy in women
Clinical Manifestations

- Cardiovascular
  - Acute MI, sudden cardiac death, biventricular hypertrophy, myocardial fibrosis, contraction band necrosis
- Psychiatric
  - Depression, mania, delirium, insomnia, aggression

Clenbuterol

- Beta-2 agonist with anabolic properties
- Overdose will have beta-2 agonist characteristics

Human Growth Hormone

- Anabolic peptide hormone
- Stimulates protein synthesis
- Adverse effects
  - Myalgias, arthralgias, carpel tunnel syndrome, edema, acromegaly, hyperglycemia
Thyroid Drugs

2.1.7.6

Thyroid Function

• Influenced by hypothalamus, pituitary gland, thyroid gland, and target organs

Thyroid Function

• Hypothalamus releases thyrotropin releasing hormone (TRH)
• TRH causes pituitary gland to release thyroid stimulating hormone (TSH)
• TSH causes thyroid to release T3 and T4
• T3 and T4 affect end organs (metabolic consequences)
Thyroid Function

- 95% of circulating hormone is T4
- T3 has 3x hormonal activity
- T4 is de-iodinated intracellularly to T3

Pharmacology

- Desiccated thyroid
  - Animal derived, contains T3 and T4
- Levothyroxine
  - Synthetic T4
  - Most widely used for hypothyroidism

Toxicity

- 7-10 day delay
- Most remain asymptomatic or only mildly symptomatic
- Treatment
  - Supportive care, beta-blockers
Thioamides
- PTU and methimazole
- Used to treat hyperthyroidism
- Both inhibit T3/T4 release
- PTU also blocks peripheral deiodination of T4 to T3
- Little data on overdose

Iodides
- Iodide salts were used before Thioamides were available
- Inhibit T3/T4 release

Iodism
- Rash, laryngitis, bronchitis, esophagitis, conjunctivitis, drug fever, metallic taste, salivation, headache, bleeding diathesis