2.1.7 Drugs that affect the endocrine system
2.1.7.1 Antidiabetic drugs
2.1.7.1.1 Insulin
2.1.7.1.2 Oral hypoglycemics
2.1.7.1.2 Others
2.1.7.2 Bone active drugs
2.1.7.3 Electrolytes and minerals
2.1.7.4 Glucocorticoids
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

- Insulin
- Sulfonylureas
- Meglitinides
- Biguanides
- Thiazolidinediones
- Glucosidase inhibitors

Like insulin, HYPOGLYCEMIC AGENTS

ANTHYPERGLYCEMICS

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

Mechanisms of glucose homeostasis

Mechanisms of glucose homeostasis
Mechanisms of glucose homeostasis

Meglitinides

- Structurally different from sulfonylureas
- Bind to same receptors that result in closure of the K\textsuperscript{+}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

---

### Insulin Preparation

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultra Rapid Acting</strong></td>
<td>0.2-0.5 hours</td>
<td>0.5-2 hours</td>
</tr>
<tr>
<td>Regular (Humulin R/Novolin R)</td>
<td>0.5-1 hour</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>NPH (Humulin N/Novolin N), Insulin detemir (Levemir)</td>
<td>NPH: 1-4 hours, Insulin detemir: 1-3 hours</td>
<td>NPH: 4-10h, Insulin detemir: 9-unknown</td>
</tr>
<tr>
<td>Long Acting</td>
<td>1-3 hours</td>
<td>No peak</td>
</tr>
</tbody>
</table>

---

**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 uptake 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

- Calcitonin & bisphosphonates
Calcitonin
- 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
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

- 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
- Irregular menses
- Growth retardation
- CNS excitation
- Cataracts
- Many others

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

Illicit Steroid Chemistry 101

Testosterone is rapidly degraded in the liver
17-hydroxy position → oil that can be injected IM for depot
17-hydroxy position → compounds resistant to hepatic metabolism and suitable
Illicit Steroids

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boldenone</td>
<td>Equipoise</td>
</tr>
<tr>
<td>Ethylnorandrosterone</td>
<td>Maxbolin</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>Halotestin</td>
</tr>
<tr>
<td>Methandriol</td>
<td></td>
</tr>
<tr>
<td>Methandrosteronol</td>
<td>Dianabol</td>
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<tr>
<td>Nandrolone decanoate</td>
<td>Durabol or</td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>Anavar</td>
</tr>
<tr>
<td>Oxymetholone</td>
<td>Anadrol</td>
</tr>
<tr>
<td>Stanazolol</td>
<td>Winstrol</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Testoviron or</td>
</tr>
<tr>
<td>Testosterone propionate</td>
<td>Testolt</td>
</tr>
<tr>
<td>Trenbolone</td>
<td>Finaster</td>
</tr>
</tbody>
</table>

Adapted from www.usdoj.gov/dea

AAS co-abuse

DHEA

Metabolic pathways of dehydroepiandrosterone (DHEA).
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

Clinical Manifestations of AAS

Psychiatric:
- ↑ aggression, insomnia, depression or mania

Musculoskeletal:
- Increased muscle mass, tendon / ligament rupture

Gastrointestinal:
- Peliosis hepatis - hepatic hemorrhage (Alkyl > ester)

Dermatologic:
- Acne vulgaris, striae

Cardiovascular:
- Biventricular hypertrophy, ↓ HDL (alkyl)

Endocrine:
- Testicular atrophy, ↓ spermatogenesis, gynecomastia
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

Testing

- Chromatography/MS
- Urinary ratio of testosterone to its endogenous epimer, epitestosterone: Normally, the ratio is less than 6 to 1.
- Athletes taking exogenous testosterone (suppresses the production of both testosterone and epitestosterone) have higher ratios

Clenbuterol

- Beta-2 agonist with anabolic properties
- ↑ glycolytic capacity of muscle, ↑ fast-twitch muscle growth
- Overdose will have beta-2 agonist characteristics

\[\text{Clenbuterol} \]
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
Thyroid Exposure

**Acute**
- 7-10 day delay
- Most remain asymptomatic or only mildly symptomatic
- Treatment: Supportive care, beta-blockers
- Tachycardia disproportionate to fever
- Neurologic = anxiety, agitation, seizure
- Death in up to 20% with thyroid storm

**Chronic**
- Thyrotoxicosis factitia (healthcare workers)
- Hamburger thyrotoxicosis
- Meat from neck of animals
- Accelerated osteoporosis
- Manifestations
  - Dyshrhythmias (a. flut/fib, tachy, CHF)

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
- Block thyroid uptake of radioactive iodine
Iodism

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