

KEY DRUGS

| Subclass | Prototypes | Other Significant Agents |
|--|---------------|-------------------------------------|
| GH analogs | Somatropin | Somatrem |
| IGF-1 analog | Mecasermin | |
| GH antagonists | | |
| Somatostatin analog | Octreotide | |
| Dopamine D ₂ receptor agonists | Bromocriptine | |
| GH receptor antagonist | Pegvisomant | |
| Gonadotropin analogs | | |
| Mixed LH and FSH | Menotropins | |
| FSH | Follitropin | Urofollitropin |
| LH | hCG | Lutropin |
| GnRH analogs | Gonadorelin | |
| | Leuprolide | Goserelin, histrelin, nafarelin |
| GnRH receptor antagonists | Ganirelix | Cetrorelix |
| Prolactin antagonists (dopamine D ₂ receptor agonists) | Bromocriptine | Cabergoline, pergolide, quinagolide |
| Oxytocin agonist | Oxytocin | |
| Oxytocin antagonist | Atosiban | |
| Vasopressin agonist | Desmopressin | |
| Vasopressin antagonist | Conivaptan | Tolvaptan |

Several antagonists of vasopressin receptors (eg, **conivaptan**, **tolvaptan**) have been developed to offset the fluid retention that results from the excessive production of vasopressin associated with hyponatremia or acute heart failure (Chapter 15).

QUESTIONS

- A drug that is purified from the urine of postmenopausal women and used to promote spermatogenesis in infertile men is
 - Desmopressin
 - Gonadorelin
 - Goserelin
 - Somatropin
 - Urofollitropin
- A 29-year-old woman in her 41st week of gestation had been in labor for 12 h. Although her uterine contractions had been strong and regular initially, they had diminished in force during the past hour. To facilitate this woman's labor and delivery, she would be treated with
 - Dopamine
 - Leuprolide
 - Oxytocin
 - Prolactin
 - Vasopressin
- A 3-year-old boy with failure to thrive and metabolic disturbances was found to have an inactivating mutation in the gene that encodes the growth hormone receptor. The drug that is most likely to promote improve his metabolic function and promote his growth is
 - Atosiban
 - Bromocriptine
 - Mecasermin
 - Octreotide
 - Somatropin
- An important difference between leuprolide and ganirelix is that ganirelix
 - Can be administered as an oral formulation
 - Can be used alone to restore fertility to hypogonadal men and women

(C) Immediately
(D) Initially
and FSH
(E) Must be

- A 27-year-old and galactorrhoea successfully rest before being fully questioned problems, which to take the drug patient was pro
 - Bromocriptine
 - Desmopressin
 - Human growth hormone
 - Leuprolide
 - Octreotide

- Who is LEAST likely to have growth deficiency?
 - A 3-year-old child
 - A 4-year-old child
 - A 4-year-old child with growth deficiency
 - A 10-year-old child
 - A 37-year-old syndrome

- A 3-year-old girl with pituitary enlargement, and more consistent with the findings revealed preoperative drug treatment
 - Atosiban
 - Follitropin
 - Leuprolide
 - Octreotide
 - Pegvisomant

- A 47-year-old man with acromegaly. Radiology of a large pituitary tumor was only part of the disease. At this point, the most likely to be used
 - Cosyntropin
 - Desmopressin
 - Leuprolide
 - Octreotide
 - Somatropin

- A 37-year-old woman with obstructed fallopian tubes. After 10 days of preoperative induction of labor, the next step in the procedure is
 - 10–14 days of treatment

- (C) Immediately reduces gonadotropin secretion
 (D) Initially stimulates pituitary production of LH and FSH
 (E) Must be administered in a pulsatile fashion
5. A 27-year-old woman with amenorrhea, infertility, and galactorrhea was treated with a drug that successfully restored ovulation and menstruation. Before being given the drug, the woman was carefully questioned about previous mental health problems, which she did not have. She was advised to take the drug orally. The drug used to treat this patient was probably
 (A) Bromocriptine
 (B) Desmopressin
 (C) Human gonadotropin hormone
 (D) Leuprolide
 (E) Octreotide
6. Who is LEAST likely to be treated with somatropin?
 (A) A 3-year-old cow on a dairy farm
 (B) A 4-year-old girl with an XO genetic genotype
 (C) A 4-year-old boy with chronic renal failure and growth deficiency
 (D) A 10-year-old boy with polydipsia and polyuria
 (E) A 37-year-old patient with AIDS-related wasting syndrome
7. A 3-year-old girl presented with hirsutism, breast enlargement, and a height and bone age that was more consistent with an age of 9. Diagnostic testing revealed precocious puberty. The most appropriate drug treatment is
 (A) Atosiban
 (B) Follitropin
 (C) Leuprolide
 (D) Octreotide
 (E) Pegvisomant
8. A 47-year-old man exhibited signs and symptoms of acromegaly. Radiologic studies showed the presence of a large pituitary tumor. Surgical treatment of the tumor was only partially effective in controlling his disease. At this point, which of the following drugs is most likely to be used as pharmacologic therapy?
 (A) Cosyntropin
 (B) Desmopressin
 (C) Leuprolide
 (D) Octreotide
 (E) Somatropin
9. A 37-year-old woman with infertility due to obstructed fallopian tubes was undergoing ovulation induction in preparation for in vitro fertilization. After 10 days of treatment with leuprolide, the next step in the procedure is most likely to involve 10–14 days of treatment with
 (A) Bromocriptine
 (B) Follitropin
 (C) Gonadorelin
 (D) hCG
 (E) Pergolide
10. A 7-year-old boy underwent successful chemotherapy and cranial radiation for treatment of acute lymphocytic leukemia. One month after the completion of therapy, the patient presented with excessive thirst and urination plus hypernatremia. Laboratory testing revealed pituitary diabetes insipidus. To correct these problems, this patient is likely to be treated with
 (A) Corticotropin
 (B) Desmopressin
 (C) hCG
 (D) Menotropins
 (E) Thyrotropin

ANSWERS

1. Spermatogenesis in males requires the action of FSH and LH. Urofollitropin, which is purified from the urine of postmenopausal women, is used clinically to provide FSH activity. The answer is E.
2. Oxytocin is an effective stimulant of uterine contraction that is routinely used to augment labor. The answer is C.
3. This child's condition is due to the inability of GH to stimulate the production of insulin-like growth factors, the ultimate mediators of GH effects. Mecasermin, a combination of recombinant IGF-1 and the binding protein that protects IGF-1 from immediate destruction, will help correct the IGF deficiency. Because of the inactive GH receptors, somatropin will not be effective. The answer is C.
4. Leuprolide is an agonist of GnRH receptors, whereas ganirelix is an antagonist. Although both drugs can be used to inhibit gonadotropin release, ganirelix does so immediately, whereas leuprolide does so only after about 1 week of sustained activity. The answer is C.
5. Bromocriptine, a dopamine receptor agonist, is used to treat the amenorrhea-galactorrhea syndrome, which is a consequence of hyperprolactinemia. Because of its central dopaminergic effects, the drug should not be used in patients with a history of schizophrenia or other forms of psychotic illness. The answer is A.
6. Somatropin, recombinant human GH, promotes growth in children with Turner's syndrome (an XO genetic genotype) or chronic renal failure. It also helps combat the AIDS-associated wasting syndrome. Bovine GH promotes milk production in cows. GH would not be appropriate for the boy with

- polydipsia and polyuria, which is probably symptomatic of a form of diabetes. The answer is **D**.
7. In precocious puberty, the hypothalamic-pituitary-gonadal axis becomes prematurely active for reasons that are not understood. Treatment involves suppressing gonadotropin secretion with continuous administration of a long-acting GnRH agonist such as leuprolide. The answer is **C**.
8. Octreotide, a somatostatin analog, has some efficacy in reducing the excess GH production that causes acromegaly. The answer is **D**.
9. Once the patient's endogenous gonadotropin production has been inhibited through continuous administration of the GnRH agonist leuprolide, the next step in ovulation induction is the administration of a drug with FSH activity to stimulate follicle maturation. Follitropin is recombinant FSH. The only other drug listed that is used in ovulation induction is hCG, but this is a LH analog. The answer is **B**.
10. Pituitary diabetes insipidus results from deficiency in vasopressin. It is treated with desmopressin, a peptide agonist of vasopressin V_2 receptors. The answer is **B**.



**SKILL KEEPER ANSWERS:
DRUGS THAT CAUSE
HYPERPROLACTINEMIA
(SEE CHAPTER 29)**

1. *Drugs that block dopamine D_2 receptors cause hyperprolactinemia by blocking the inhibitory effects of endogenous dopamine on the pituitary cells that release prolactin.*
2. *The older antipsychotic drugs (eg, phenothiazines, haloperidol), with their strong dopamine D_2 receptor-blocking activity, are most likely to be the pharmacologic cause of hyperprolactinemia (see Chapter 29). This adverse effect is less likely with the newer antipsychotic drugs (eg, olanzapine). Drugs or drug groups that cause hyperprolactinemia through mechanisms that are not well characterized include methyl dopa (an antihypertensive), amphetamines, tricyclic and other types of antidepressants, and opioids.*

CHECKLIST

When you complete this chapter, you should be able to:

- Diagram the hypothalamic-pituitary endocrine system and indicate the sites of release of and links between the hormones in the system.
- Describe the drugs used as substitutes for the natural pituitary hormones and list their clinical uses.
- List the gonadotropin analogs and GnRH agonists and antagonists and describe their clinical use in treating male and female infertility, endometriosis, and prostate cancer.
- Describe the drugs used for treatment of acromegaly and hyperprolactinemia.

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THYROID HOI

A. SYNTHESIS & TR

The thyroid secret thyroxine (T_4) and necessary for the sy from food or iodide taken up by and h gland, where it is coi roidal peroxidase (. **roglobulin** serves as synthesis. Tyrosine n nated to form monoi sine (DIT). Within t combine to form T_4 , DIT combine to forr liberates the T_4 and thyroid. After release

the size and vascularity of the hyperplastic thyroid gland. Because iodide salts inhibit release as well as synthesis of the hormones, their onset of action occurs rapidly, within 2–7 days. However, the effects are transient; the thyroid gland “escapes” from the iodide block after several weeks of treatment. Iodide salts are used in the management of thyroid storm and to prepare patients for surgical resection of a hyperactive thyroid. The usual forms of this drug are Lugol’s solution (iodine and potassium iodide) and saturated solution of potassium iodide. Adverse effects include rash, drug fever, metallic taste, bleeding disorders and, rarely, anaphylactic reactions.

C. RADIOACTIVE IODINE

Radioactive iodine (^{131}I) is taken up and concentrated in the thyroid gland so avidly that a dose large enough to severely damage the gland can be given without endangering other tissues. Unlike the thioamides and iodide salts, an effective dose of ^{131}I can produce a permanent cure of thyrotoxicosis without surgery. ^{131}I should not be used in pregnant or nursing women.

D. IODINATED RADIOCONTRAST MEDIA

Iodinated radiocontrast media (eg, oral diatrizoate or oral or intravenous iohexol) rapidly suppress the conversion of T_4 to T_3 in the liver, kidney, and other peripheral tissues (Figure 38–1). Inhibition of hormone release from the thyroid may also play a part. Iodinated radiocontrast media are useful for rapidly reducing T_3 concentrations in thyrotoxicosis.

E. OTHER DRUGS

Another class of drugs used in the treatment of thyrotoxicosis is the β -blockers. These agents are particularly useful in controlling the tachycardia and other cardiac abnormalities of severe thyrotoxicosis. **Propranolol** also inhibits the peripheral conversion of T_4 to T_3 .

The iodine-containing antiarrhythmic drug **amiodarone** (Chapter 14) can cause hypothyroidism through

its ability to block the peripheral conversion of T_4 to T_3 . It also can cause hyperthyroidism either through an iodine-induced mechanism in persons with an underlying thyroid disease such as multinodular goiter or through an inflammatory mechanism that causes leakage of thyroid hormone into the circulation. Amiodarone-associated hypothyroidism is treated with thyroid hormone. Iodine-associated hyperthyroidism caused by amiodarone is treated with thioamides, whereas the inflammatory version is best treated with corticosteroids.

QUESTIONS

1–3. A 24-year-old woman was found to have mild hyperthyroidism due to Graves’ disease. She appears to be in good health otherwise.

- In Graves’ disease, the cause of the hyperthyroidism is the production of an antibody that
 - Activates the pituitary thyrotropin-releasing hormone (TRH) receptor and stimulates TSH release
 - Activates the thyroid gland TSH receptor and stimulates thyroid hormone synthesis and release
 - Activates thyroid hormone receptors in peripheral tissues
 - Binds to thyroid gland thyroglobulin and accelerates its proteolysis and the release of its supply of T_4 to T_3
 - Binds to thyroid binding globulin (TBG) and displaces bound T_4 to T_3
- The decision is made to begin treatment with methimazole. Methimazole reduces serum concentration of T_3 primarily by
 - Accelerating the peripheral metabolism of T_3
 - Inhibiting the proteolysis of thyroid-binding globulin
 - Inhibiting the secretion of TSH

- Inhibiting thyroid
- Preventing residues of

- Though rare, a thioamide is
 - Agranulocytosis
 - Lupus erythematosus
 - Myopathy
 - Torsades de pointes
 - Thrombotic

4–5. A 56-year-old woman was admitted to the emergency department with tachycardia and chest pain. She had been on methimazole for the past 2 days and had previously reported that she had been on methimazole 2 weeks earlier. Her serum T_4 value of < 0.01 mIU/L is consistent with a diagnosis of thyroid storm.

- In the treatment of thyroid storm, the use of antithyroid drugs is essential. A rapidly acting agent that inhibits conversion of T_4 to T_3 is
 - Diatrizoate
 - Levothyroxine
 - Propylthiouracil
 - Triiodothyronine
 - Radioactive iodine

- A drug that is used in the treatment of thyroid storm is
 - Amiodarone
 - Betamethasone
 - Epinephrine
 - Propranolol
 - Radioactive iodine

- A symptom that occurs in the event of chronic overproduction of thyroid hormone is
 - Bradycardia
 - Dry, puffy skin
 - Large tongue and protruding lower lip
 - Lethargy, sleepiness
 - Weight loss

- When initiating treatment of thyroid storm with long-standing hyperthyroidism, the first step to begin with small doses of
 - A flare of exophthalmos
 - Acute renal failure
 - Hemolysis
 - Overstimulation
 - Seizures

DIRECTIONS: 8–10. This section consists of a list of

KEY DRUGS

| Subclass | Prototypes | Other Significant Agents |
|-------------------|-------------------------------|-----------------------------------|
| Thyroid hormones | Thyroxine (T_4) | Triiodothyronine (T_3) |
| Antithyroid drugs | Methimazole | Propylthiouracil |
| | Iodide salts ^{131}I | |
| | Diatrizoate | Iohexol |
| Miscellaneous | Propranolol | |

- (D) Inhibiting the uptake of iodide by cells in the thyroid
 - (E) Preventing the addition of iodine to tyrosine residues on thyroglobulin
3. Though rare, a serious toxicity associated with the thioamides is
- (A) Agranulocytosis
 - (B) Lupus erythematosus-like syndrome
 - (C) Myopathy
 - (D) Torsades de pointes arrhythmia
 - (E) Thrombotic thrombocytopenic purpura (TTP)

4-5. A 56-year-old woman presented to the emergency department with tachycardia, shortness of breath, and chest pain. She had had shortness of breath and diarrhea for the past 2 days and was sweating and anxious. A relative reported that the patient had run out of methimazole 2 weeks earlier. A TSH measurement revealed a value of < 0.01 mIU/L (normal 0.4-4.0 mIU/L). The diagnosis of thyroid storm was made.

4. In the treatment of thyroid storm, it is important to use antithyroid drugs with a rapid onset of activity. A rapidly acting antithyroid drug that blocks the conversion of T_4 to T_3 is
- (A) Diatrizoate
 - (B) Levothyroxine
 - (C) Propylthiouracil
 - (D) Triiodothyronine
 - (E) Radioactive iodine
5. A drug that is a useful adjuvant in the treatment of thyroid storm is
- (A) Amiodarone
 - (B) Betamethasone
 - (C) Epinephrine
 - (D) Propranolol
 - (E) Radioactive iodine
6. A symptom that would be expected to occur in the event of chronic overdose with exogenous T_4 is
- (A) Bradycardia
 - (B) Dry, puffy skin
 - (C) Large tongue and drooping of the eyelids
 - (D) Lethargy, sleepiness
 - (E) Weight loss
7. When initiating T_4 therapy for an elderly patient with long-standing hypothyroidism, it is important to begin with small doses to avoid
- (A) A flare of exophthalmos
 - (B) Acute renal failure
 - (C) Hemolysis
 - (D) Overstimulation of the heart
 - (E) Seizures

DIRECTIONS: 8-10. The matching questions in this section consist of a list of 5 lettered options followed by

several numbered items. For each numbered item, select the ONE lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

- (A) ^{131}I
 - (B) Diatrizoate
 - (C) Propranolol
 - (D) Propylthiouracil
 - (E) T_3
8. Produced in the peripheral tissues when T_4 is administered
9. Radiocontrast medium that is also useful in thyrotoxicosis
10. Produces a permanent reduction in thyroid activity

ANSWERS

1. The antibodies produced in Graves' disease activate thyroid gland TSH receptors. Their effects mimic those of TSH. The answer is **B**.
2. The thioamides (methimazole and propylthiouracil) primarily act in thyroid cells to prevent conversion of tyrosine residues in thyroglobulin to MIT or DIT. The answer is **E**.
3. Rarely, the thioamides cause severe adverse reactions that include agranulocytosis, vasculitis, hepatic damage, and hypoprothrombinemia. The answer is **A**.
4. Diatrizoate, an iodinated radiocontrast medium, has a rapid onset of antithyroid activity resulting from inhibition of the peripheral conversion of T_4 to T_3 . The answer is **A**.
5. In thyroid storm, β -blockers such as propranolol are useful in controlling the tachycardia and other cardiac abnormalities, and propranolol also inhibits peripheral conversion of T_4 to T_3 . The answer is **D**.
6. In hyperthyroidism, the metabolic rate increases and even though there is increased appetite, weight loss often occurs. The other choices are symptoms seen in hypothyroidism. The answer is **E**.
7. Patients with long-standing hypothyroidism, especially those who are elderly, are highly sensitive to the stimulatory effects of T_4 on cardiac function. Administration of regular doses can cause overstimulation of the heart and cardiac collapse. The answer is **D**.
8. T_4 is converted into T_3 in the periphery. The answer is **E**.
9. Diatrizoate is a radiocontrast agent. The answer is **B**.
10. Radioactive iodine is the only medical therapy that produces a permanent reduction of thyroid activity. The answer is **A**.

B. SYNTHESIS INHIBITORS

Several drugs are used in the treatment of adrenal cancer when surgical therapy is impractical or unsuccessful because of metastases. The most important of these drugs are **aminoglutethimide**, **metyrapone**, and **ketoconazole**.

Ketoconazole (an antifungal drug) inhibits the cytochrome P450 enzymes necessary for the synthesis of all steroids and is used in a number of conditions in which reduced steroid levels are desirable (eg, adrenal carcinoma, hirsutism, breast and prostate cancer). Aminoglutethimide blocks the conversion of cholesterol to pregnenolone and also inhibits synthesis of all hormonally active steroids. It can be used in conjunction with other drugs for treatment of steroid-producing adrenocortical cancer. Metyrapone inhibits the normal synthesis of cortisol but not that of cortisol precursors; the drug can be used in diagnostic tests of adrenal function.

QUESTIONS

- Pharmacologic effects of exogenous glucocorticoids include
 - Increased muscle mass
 - Hypoglycemia
 - Inhibition of leukotriene synthesis
 - Improved wound healing
 - Increased excretion of salt and water
 - Toxic effects of long-term administration of a glucocorticoid include
 - A "lupus-like" syndrome
 - Adrenal gland neoplasm
 - Hepatotoxicity
 - Osteoporosis
 - Precocious puberty in children
 - A 46-year-old male patient has Cushing's syndrome that is due to the presence of an adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of this man's disease?
 - Betamethasone
 - Cortisol
 - Fludrocortisone
 - Ketoconazole
 - Triamcinolone
 - In the treatment of congenital adrenal hyperplasia in which there is excess production of cortisol precursors because of a lack of 21 β -hydroxylase activity, the purpose of the administration of a synthetic glucocorticoid is
 - Inhibition of aldosterone synthesis
 - Normalization of renal function
 - Prevention of hypoglycemia
 - Recovery of normal immune function
 - Suppression of ACTH secretion
 - A glucocorticoid response element is
 - A protein regulator that controls the interaction between an activated steroid receptor and DNA
 - A short DNA sequence that binds tightly to RNA polymerase
 - A small protein that binds to an unoccupied steroid receptor protein and prevents it from becoming denatured
 - A specific nucleotide sequence that is recognized by a steroid hormone receptor-hormone complex
 - The portion of the steroid receptor that binds to DNA
 - Glucocorticoids have proved useful in the treatment of
 - Chemotherapy-induced vomiting
 - Chronic obstructive pulmonary disease
 - Hyperprolactinemia
 - Parkinson's disease
 - Type II diabetes
 - For patients who have been on long-term therapy with a glucocorticoid and who now wish to discontinue the drug, gradual tapering of the glucocorticoid is needed to allow recovery of
 - Depressed release of insulin from pancreatic B cells
 - Hematopoiesis in the bone marrow
 - Normal osteoblast function
 - The control by vasopressin of water excretion
 - The hypothalamic-pituitary-adrenal system
- 8-9. A 54-year-old man with advanced tuberculosis has developed signs of severe acute adrenal insufficiency.
- This patient is likely to exhibit
 - A moon face
 - Dehydration
 - Hyperglycemia
 - Hypertension
 - Hyperthermia
 - The patient should be treated immediately. Which of the following combinations is most rational?
 - Aldosterone and fludrocortisone
 - Cortisol and fludrocortisone
 - Dexamethasone and metyrapone
 - Fludrocortisone and metyrapone
 - Triamcinolone and dexamethasone

10. A drug that blocks the glucocorticoid receptor is
 (A) Aminoglutethimide
 (B) Beclomethasone
 (C) Ketoconazole
 (D) Mifepristone
 (E) Spironolactone

ANSWERS

1. Glucocorticoids inhibit the production of both leukotrienes and prostaglandins. This is a key component of their anti-inflammatory action. The answer is **C**.
2. One of the metabolic effects of long-term glucocorticoid therapy is a net loss of bone, which can result in osteoporosis. The answer is **D**.
3. Ketoconazole inhibits many types of cytochrome P450 enzymes. It can be used to reduce the unregulated overproduction of corticosteroids by adrenal tumors. The answer is **D**.
4. A 21 β -hydroxylase deficiency prevents normal synthesis of cortisol and causes accumulation of cortisol precursors. The hypothalamic-pituitary system responds to the abnormally low levels of cortisol by increasing ACTH release. High levels of ACTH induce adrenal hyperplasia and excess production of steroids, which are diverted to the androgen pathway to cause virilization of females and prepubertal males. A high dose of glucocorticoid is administered to suppress release of ACTH. The answer is **E**.
5. Activated steroid hormone receptors mediate their effects on gene expression by binding to hormone response elements, which are short sequences of DNA located near steroid-regulated genes. The answer is **D**.
6. Glucocorticoids are used in combination with other antiemetics to prevent chemotherapy-induced nausea and vomiting, which are commonly associated with anticancer drugs. The answer is **A**.
7. Exogenous glucocorticoids act at the hypothalamus and pituitary to suppress the production of CRF and ACTH. As a result, adrenal production of endogenous corticosteroids is suppressed. On discontinuance, the recovery of normal hypothalamic-pituitary-adrenal function occurs slowly. Glucocorticoid doses must be tapered slowly, over several months, to prevent adrenal insufficiency. The answer is **E**.
8. In acute adrenal insufficiency, there is loss of salt and water that is primarily due to reduced production of aldosterone. The loss of salt and water can lead to dehydration. The answer is **B**.
9. A rational combination of drugs should include agents with complementary effects (ie, a glucocorticoid and a mineralocorticoid). The combination with these characteristics is cortisol and fludrocortisone. (Note that although fludrocortisone may have sufficient glucocorticoid activity for a patient with mild disease, a patient in severe acute adrenal insufficiency needs a full glucocorticoid such as cortisol.) The answer is **B**.
10. Mifepristone is a competitive antagonist of glucocorticoid and progesterin receptors. Ketoconazole and aminoglutethimide also antagonize corticosteroids; however, they act by inhibiting steroid hormone synthesis. The answer is **D**.



SKILL KEEPER ANSWERS: ALDOSTERONE ANTAGONISTS AND CONGESTIVE HEART FAILURE (CHAPTERS 13 AND 15)

1. *The reduction in cardiac output associated with heart failure decreases the effective arterial blood volume and renal blood flow. Decreased pressure in renal arterioles and increased sympathetic neural activity both stimulate renin release, which increases production of angiotensin II. Angiotensin II is a powerful stimulus of aldosterone secretion.*
2. *Acting through nuclear receptors in the epithelial cells that line renal collecting tubules, aldosterone promotes renal uptake of salt and water. This retention of salt and water exacerbates the peripheral and pulmonary edema that is associated with congestive heart failure, and it further overloads the weakened heart. In addition to these renal effects, aldosterone is also implicated in myocardial and vascular fibrosis and baroreceptor dysfunction.*
3. *The aldosterone antagonists are also known as "potassium-sparing diuretics" because, unlike other diuretics, they do not promote renal excretion of potassium. Because the excretion of potassium in the renal tubule is linked to the reuptake of sodium, the reduction in sodium uptake caused by spironolactone and eplerenone results in potassium retention and an increase in serum potassium.*

CHECKLIST

- When you complete this chapter, you should be able to:
- Describe the mechanism of action of glucocorticoids.
 - List several synthetic glucocorticoids.
 - Describe the mechanism of action of mineralocorticoids.
 - List the indications for the use of mineralocorticoids.
 - Name 3 drugs that act as mineralocorticoid antagonists and describe their mechanism of action.

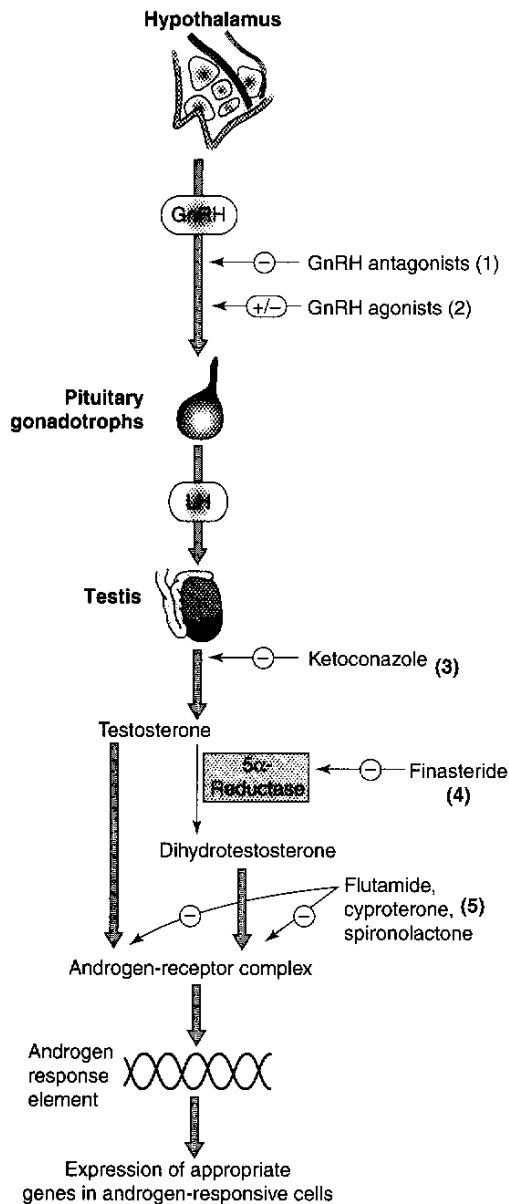


Figure 40-2. Control of androgen secretion and activity and some sites of action of antiandrogens: (1) competitive inhibition of GnRH receptors (see Chapter 37); (2) stimulation (+) or inhibition (-) by GnRH agonists; (3) inhibition of testosterone synthesis by ketoconazole; (4) inhibition of dihydrotestosterone production by finasteride; (5) inhibition of androgen binding at its receptor by flutamide and other drugs. (Modified and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 10th ed. McGraw-Hill, 2007.)

C. GONADOTROPIN-RELEASING HORMONE ANALOGS

Suppression of gonadotropin secretion, especially LH, reduces the production of testosterone. This can be effectively accomplished with long-acting depot preparations of **leuprolide** or similar gonadotropin-releasing hormone (GnRH) agonists (Chapter 37). These analogs are used in prostatic carcinoma. During the first week of therapy, an androgen receptor antagonist (eg, flutamide) is added to prevent the tumor flare that can result from the surge in testosterone synthesis caused by the initial agonistic action of the GnRH agonist. Within several weeks, testosterone production falls to low levels.

D. COMBINED HORMONAL CONTRACEPTIVES

Combined hormonal contraceptives are used in women with hirsutism. The estrogen in the contraceptive acts in the liver to increase the production of SHBG, which in turn reduces the concentration of the free androgen in the blood that is causing the male-pattern hair growth characteristic of hirsutism.

E. INHIBITORS OF STEROID SYNTHESIS

Ketoconazole, an antifungal drug (Chapter 48), inhibits gonadal and adrenal steroid synthesis. The drug has been used to suppress adrenal steroid synthesis in patients with steroid-responsive metastatic prostate cancer.

QUESTIONS

- The estrogen that is used in most combined hormonal contraceptives is
 - Clomiphene
 - Ethinyl estradiol
 - Estrone
 - DES
 - Norgestrel
- A 23-year-old woman desires a combined oral contraceptive for pregnancy protection. A factor that would lead a health professional to recommend an alternative form of contraception is that the woman
 - Has evidence of hirsutism
 - Has a history of gastroesophageal reflux disease and is currently taking omeprazole
 - Has a history of pelvic inflammatory disease
 - Has a history of migraine headache that is well controlled by sumatriptan
 - Plans to use this contraceptive for about 1 year and will then attempt to become pregnant
- Men who use large doses of anabolic steroids are at increased risk of
 - Anemia
 - Cholestatic jaundice and elevation of aspartate transaminase levels in the blood
 - Hirsutism

Subclass

Estrogens

Progestins

Antiestrogens
and antiestrogens
SERMs
Aromatase inhibitors
Synthesis inhibitors
Antiprogestin
GnRH agonist

Androgens

Anabolic steroids

Antiandrogens

Receptor antagonist
5 α -Reductase inhibitors
Synthesis inhibitors
Other

(D) Hyperprolactinemia
(E) Testicular enlargement

- A 50-year-old woman undergoes lumpectomy. Biochemically, the presence of estrogens. After this procedure, she is prescribed a progestin.
 - Danazol
 - Flutamide
 - Leuprolide
 - Mifepristone
 - Tamoxifen
- A 60-year-old man is found to have an elevated prostate-specific antigen (PSA) level and an enlarged prostate. Magnetic resonance imaging (MRI) of the pelvis reveals an enlarged lymph node. This patient is prescribed a progestin.
 - Anastrozole
 - Desogestrel
 - Flutamide
 - Methyltestosterone
 - Oxandrolone
- A young woman complains of irregularity in the timing of menstruation.

KEY DRUGS

| Subclass | Prototype | Other Significant Agents |
|-------------------------------------|---|---|
| Estrogens | Ethinyl estradiol | Conjugated estrogens, estrone, estriol, mestranol |
| Progestins | Norgestrel, medroxyprogesterone | Progesterone, norgestimate, norethindrone |
| Antiestrogens and antiprogestins | | |
| SERMs | Tamoxifen, raloxifene | Clomiphene |
| Aromatase inhibitors | Anastrozole | Letrozole |
| Synthesis inhibitor | Danazol | |
| Antiprogestin | Mifepristone (RU 486) | |
| GnRH agonist | Leuprolide | |
| Androgens | Testosterone | Methyltestosterone, fluoxymesterone |
| Anabolic steroids | Oxandrolone | Stanozolol |
| Antiandrogens | | |
| Receptor antagonist | Flutamide | Bicalutamide |
| 5 α -Reductase inhibitor | Finasteride | |
| Synthesis inhibitor | Ketoconazole | |
| Other | GnRH analogs, combined oral contraceptives | |

- (D) Hyperprolactinemia
(E) Testicular enlargement
4. A 50-year-old woman with a positive mammogram undergoes lumpectomy and a small carcinoma is removed. Biochemical analysis of the cancer reveals the presence of estrogen and progesterone receptors. After this procedure, she will probably receive
- Danazol
 - Flutamide
 - Leuprolide
 - Mifepristone
 - Tamoxifen
5. A 60-year-old man is found to have a prostate lump and an elevated prostate-specific antigen (PSA) blood test. Magnetic resonance imaging suggests several enlarged lymph nodes in the lower abdomen, and x-ray film reveals 2 radiolucent lesions in the bony pelvis. This patient is likely to be treated with
- Anastrozole
 - Desogestrel
 - Flutamide
 - Methyltestosterone
 - Oxandrolone
6. A young woman complains of abdominal pain at the time of menstruation. Careful evaluation indicates
- the presence of significant endometrial deposits on the pelvic peritoneum. The most appropriate therapy for this patient is
- Flutamide, orally
 - Medroxyprogesterone acetate by intramuscular injection
 - Norgestrel as an IUD
 - Oxandrolone by intramuscular injection
 - Raloxifene orally
7. Diethylstilbestrol (DES) should never be used in pregnant women because it is associated with
- Deep vein thrombosis
 - Feminization of the external genitalia of male offspring
 - Infertility and development of vaginal cancer in female offspring
 - Miscarriages
 - Virilization of the external genitalia of female offspring
8. The unique property of SERMs is that they
- Act as agonists in some tissues and antagonists in other tissues
 - Activate a unique plasma membrane-bound receptor
 - Have both estrogenic and progestational agonist activity

- (D) Inhibit the aromatase enzyme required for estrogen synthesis
 (E) Produce estrogenic effects without binding to estrogen receptors
9. Finasteride has efficacy in the prevention of male-pattern baldness by virtue of its ability to
 (A) Competitively antagonize androgen receptors
 (B) Decrease the release of gonadotropins
 (C) Increase the serum concentration of SHBG
 (D) Inhibit the synthesis of testosterone
 (E) Reduce the production of DHT
10. A 52-year-old postmenopausal patient has evidence of low bone mineral density. She and her physician are considering therapy with raloxifene or a combination of conjugated estrogens and medroxyprogesterone acetate. Which of the following patient characteristics is MOST likely to lead them to select raloxifene?
 (A) Previous hysterectomy
 (B) Recurrent vaginitis
 (C) Rheumatoid arthritis
 (D) Strong family history of breast cancer
 (E) Troublesome hot flashes

ANSWERS

- Ethinyl estradiol, a synthetic estrogen with good bioavailability, is the estrogenic component of most combined oral contraceptives, the transdermal contraceptive, and the vaginal ring contraceptive. The answer is **B**.
- Estrogen-containing hormonal contraceptives increase the risk of episodes of migraine headache. The answer is **D**.
- In men, large doses of anabolic steroids are associated with liver impairment, including cholestasis and elevation of serum concentrations of transaminases. The answer is **B**.
- Tamoxifen has proved useful in adjunctive therapy of breast cancer; the drug decreases the rate of recurrence of cancer. The answer is **E**.
- Antiandrogen drugs are used to treat metastatic prostate cancer because they have efficacy, whereas conventional cytotoxic drugs do not. Flutamide is a competitive antagonist of the androgen receptor that is used in combination with a GnRH agonist in the treatment of men with prostate cancer. The answer is **C**.
- In endometriosis, suppression of ovarian function and production of gonadal steroids are useful. Intramuscular injection of relatively large doses of medroxyprogesterone provides 3 mo of an ovarian

suppressive effect because of inhibition of pituitary production of gonadotropins. The answer is **B**.

7. DES is a nonsteroidal estrogen agonist. Several decades ago, misguided use of the drug in pregnant women appears to have resulted in fetal damage that predisposed female offspring to infertility and a rare form of vaginal cancer. For this reason, the drug should be avoided in pregnant women. Other estrogenic drugs do not appear to have these same effects. Although estrogens do increase the risk of deep vein thrombosis, this is not the reason why DES should be avoided. The answer is **C**.
8. SERMs such as tamoxifen and raloxifene exhibit tissue-specific estrogenic and antiestrogenic effects. The answer is **A**.
9. Finasteride inhibits 5 α -reductase, the enzyme that converts testosterone to DHT, the principal androgen in androgen-sensitive hair follicles. The answer is **E**.
10. Conjugated estrogens and raloxifene both improve bone mineral density and protect against osteoporosis. The 2 advantages of raloxifene over full estrogen

receptor agonists are effects in breast tissue and endometrium. If a surgery, the difference is moot. In patients

CHECKLIST

When you complete this

- Describe the hormonal effects of estrogens
- Name 3 estrogens and their uses
- List the benefits and risks of oral contraceptives
- List the benefits and risks of transdermal and vaginal ring contraceptives
- Describe the use of progestins
- List or describe the uses of SERMs
- Name 2 SERMs and their uses



SKILL KEEPER ANSWERS: CYTOCHROME P450 AND HORMONAL CONTRACEPTIVES (SEE CHAPTERS 4 AND 61)

- Gonadal steroids and their derivatives are metabolized primarily by the cytochrome P450 3A4 (CYP3A4) family of enzymes. Inducers of CYP3A4 include barbiturates, carbamazepine, corticosteroids, griseofulvin, nelfinavir, phenytoin, pioglitazone, rifampin, and rifabutin. The potential reduction in contraceptive efficacy of hormonal contraceptives by carbamazepine and phenytoin are of particular importance because these drugs are known teratogens. St. John's wort, an unregulated herbal product, contains an ingredient that induces CYP3A4 enzymes and can reduce the efficacy of hormonal contraceptives.*
- To prevent an unwanted pregnancy, it would be advisable to use a combined hormonal contraceptive pill with a higher dose of estrogen (eg, a formulation containing 50 mcg of ethinyl estradiol). Alternatively, or additionally, women may use a barrier form of contraception or switch to an IUD.*

receptor agonists are that raloxifene has antagonist effects in breast tissue and lacks an agonistic effect in endometrium. If a patient's uterus was removed by surgery, the difference in the endometrial effect is moot. In patients with a strong family history of

breast cancer, raloxifene may be a better choice than a full estrogen agonist because it will not further increase the woman's risk of breast cancer and may even lower her risk. The answer is D.

CHECKLIST

When you complete this chapter, you should be able to:

- Describe the hormonal changes that occur during the menstrual cycle.
- Name 3 estrogens and 4 progestins. Describe their pharmacologic effects, clinical uses, and toxicity.
- List the benefits and hazards of hormonal contraceptives.
- List the benefits and hazards of postmenopausal estrogen therapy.
- Describe the use of gonadal hormones and their antagonists in the treatment of cancer in women and men.
- List or describe the toxic effects of anabolic steroids used to build muscle mass.
- Name 2 SERMs and describe their unique properties.

KEY DRUGS

| Subclass | Prototypes | Other Significant Agents |
|----------------------------------|-----------------------------------|-----------------------------------|
| Insulins | | |
| Rapid-acting | Insulin lispro | Insulin aspart, insulin glulisine |
| Short-acting | Regular insulin | |
| Intermediate-acting | NPH insulin | Insulin detemir |
| Long-acting | Insulin glargine | |
| Insulin secretagogues | | |
| Sulfonylureas | Glipizide, glimepiride, glyburide | Chlorpropamide, tolbutamide |
| Meglitinide | Repaglinide | |
| D-Phenylalanine derivative | Nateglinide | |
| Biguanides | Metformin | |
| Thiazolidinediones | Pioglitazone, rosiglitazone | |
| α -Glucosidase inhibitors | Acarbose | Miglitol |
| Amylin analog | Pramlintide | |
| Incretin modifiers | | |
| GLP-1 analog | Exenatide | |
| DPP-4 inhibitor | Sitagliptin | |

HYPERGLYCEMIC DRUGS: GLUCAGON

A. GLUCAGON

1. Chemistry, mechanism, and effects—Glucagon is a protein hormone secreted by the A cells of the endocrine pancreas. Acting through G protein-coupled receptors in heart, smooth muscle, and liver, glucagon increases heart rate and force of contraction, increases hepatic glycogenolysis and gluconeogenesis, and relaxes smooth muscle. The smooth muscle effect is particularly marked in the gut.

2. Clinical uses—Glucagon is used to treat severe hypoglycemia in diabetics, but its hyperglycemic action requires intact hepatic glycogen stores. The drug is given intramuscularly or intravenously. In the management of severe β -blocker overdose, glucagon may be the most effective method for stimulating the depressed heart because it increases cardiac cAMP without requiring access to β receptors (Chapter 59).

QUESTIONS

1–2. A 13-year-old boy with type 1 diabetes is brought to the hospital complaining of dizziness. Laboratory findings include severe hyperglycemia, ketoacidosis, and a blood pH of 7.15.

- To achieve rapid control of the severe ketoacidosis in this diabetic boy, the appropriate antidiabetic agent to use is
 - Crystalline zinc insulin
 - Glyburide
 - Insulin glargine
 - NPH insulin
 - Tobutamide
- The most likely complication of insulin therapy in this patient is
 - Dilutional hyponatremia
 - Hypoglycemia
 - Increased bleeding tendency
 - Pancreatitis
 - Severe hypertension
- A 24-year-old woman with type 1 diabetes wishes to try tight control of her diabetes to improve her long-term prognosis. Which of the following regimens is MOST appropriate?
 - Morning injections of mixed insulin lispro and insulin aspart
 - Evening injections of mixed regular insulin and insulin glargine
 - Morning and evening injections of regular insulin, supplemented by small amounts of NPH insulin at mealtimes
 - Morning mented t mealtime
 - Morning injection
- Which one of the following is the most appropriate agent for the release of endogenous insulin?
 - Acarbose
 - Glipizide
 - Metformin
 - Miglitol
 - Pioglitazone
- An important effect of thiazolidinediones is
 - Increased cardiac output
 - Increased glucose utilization
 - Increased glucose production
 - Inhibition of lipolysis
 - Stimulation of lipolysis
- A 54-year-old man with type 2 diabetes and a history of liver disease is prescribed metformin. Which of the following is the most likely side effect?
 - A disulfiram reaction
 - Excessive weight gain
 - Hypoglycemia
 - Lactic acidosis
 - Serious hepatotoxicity
- Which of the following is the most appropriate agent for the first part of a meal?
 - Acarbose
 - Exenatide
 - Glipizide
 - Pioglitazone
 - Repaglinide
- The PPAR- γ receptor is a nuclear receptor. Which of the following is the most likely effect of PPAR- γ activation?
 - Activating adipocyte lipolysis
 - Inactivating adipocyte lipolysis
 - Inhibiting adipocyte lipolysis
 - Regulating transcription of glucose utilization genes
 - Stimulating transcription of glucose utilization genes
- Which of the following is the most appropriate agent for the treatment of type 2 diabetes?
 - Acarbose
 - Glyburide

- (D) Morning injections of insulin glargine, supplemented by small amounts of insulin lispro at mealtimes
 (E) Morning injection of NPH insulin and evening injection of regular insulin
4. Which one of the following drugs promotes the release of endogenous insulin?
 (A) Acarbose
 (B) Glipizide
 (C) Metformin
 (D) Miglitol
 (E) Pioglitazone
5. An important effect of insulin is
 (A) Increased conversion of amino acids into glucose
 (B) Increased gluconeogenesis
 (C) Increased glucose transport into cells
 (D) Inhibition of lipoprotein lipase
 (E) Stimulation of glycogenolysis
6. A 54-year-old obese patient with type 2 diabetes and a history of alcoholism probably should not receive metformin because it can increase the risk of
 (A) A disulfiram-like reaction
 (B) Excessive weight gain
 (C) Hypoglycemia
 (D) Lactic acidosis
 (E) Serious hepatotoxicity
7. Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?
 (A) Acarbose
 (B) Exenatide
 (C) Glipizide
 (D) Pioglitazone
 (E) Repaglinide
8. The PPAR- γ receptor that is activated by thiazolidinediones increases tissue sensitivity to insulin by
 (A) Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
 (B) Inactivating a cellular inhibitor of the GLUT2 glucose transporter
 (C) Inhibiting acid glucosidase, a key enzyme in glycogen breakdown pathways
 (D) Regulating transcription of genes involved in glucose utilization
 (E) Stimulating the activity of a tyrosine kinase that phosphorylates the insulin receptor
9. Which of the following drugs is MOST likely to cause hypoglycemia when used as monotherapy in the treatment of type 2 diabetes?
 (A) Acarbose
 (B) Glyburide
 (C) Metformin
 (D) Miglitol
 (E) Rosiglitazone
10. Which of the following patients is MOST likely to be treated with intravenous glucagon?
 (A) An 18-year-old woman who took an overdose of cocaine and now has a blood pressure of 190/110
 (B) A 27-year-old woman with severe diarrhea caused by a flare in her inflammatory bowel disease
 (C) A 57-year-old woman with type 2 diabetes who has not taken her glyburide for the past 3 days
 (D) A 62-year-old man with severe bradycardia and hypotension resulting from ingestion of an overdose of atenolol
 (E) A 74-year-old man with lactic acidosis as a complication of severe infection and shock

ANSWERS

1. Oral antidiabetic agents are inappropriate in this patient because he has insulin-dependent diabetes. He needs a rapid-acting insulin preparation that can be given intravenously (see Table 41-1). The answer is **A**.
2. Because of the risk of brain damage, the most important complication of insulin therapy is hypoglycemia. The other choices are not common effects of insulin. The answer is **B**.
3. Insulin regimens for close control usually take the form of establishing a basal level of insulin with a small amount of a long-acting preparation (eg, insulin glargine) and supplementing the insulin levels, when called for by food intake, with short-acting insulin lispro. Less tight control may be achieved with 2 injections of intermediate-acting insulin per day. Because intake of glucose is mainly during the day, long-acting insulins are usually given in the morning, not at night. The answer is **D**.
4. Glipizide is a second-generation sulfonylurea that promotes insulin release by closing potassium channels in pancreatic B cells. The answer is **B**.
5. Insulin lowers serum glucose concentration in part by driving glucose into cells, particularly into muscle cells. The answer is **C**.
6. Biguanides, especially the older drug phenformin, have been associated with lactic acidosis. Thus, metformin should be avoided in patients with conditions that increase the risk of lactic acidosis, including alcoholism. The answer is **D**.
7. To be absorbed, carbohydrates must be converted into monosaccharides by the action of α -glucosidase

enzymes in the gastrointestinal tract. Acarbose inhibits α -glucosidase and, when present during digestion, delays the uptake of carbohydrates. The answer is **A**.

8. The PPAR- γ receptor belongs to a family of nuclear receptors. When activated, these receptors translocate to the nucleus, where they regulate the transcription of genes encoding proteins involved in the metabolism of carbohydrate and lipids. The answer is **D**.
9. The insulin secretagogues, including the sulfonylurea glyburide, can cause hypoglycemia as a result of their ability to increase serum insulin levels. The biguanides, thiazolidinediones, and α -glucosidase inhibitors are euglycemics that are unlikely to cause hypoglycemia when used alone. The answer is **B**.
10. Glucagon acts through cardiac glucagon receptors to stimulate the rate and force of contraction of the heart. Because this bypasses cardiac β adrenoceptors, glucagon is useful in the treatment of β -blocker-induced cardiac depression. The answer is **D**.



SKILL KEEPER ANSWERS: DIABETES AND HYPERTENSION (CHAPTER 11)

1. *The major antihypertensive drug groups are (a) β adrenoceptor blockers; (b) α_1 selective adrenoceptor blockers (eg, prazosin); (c) centrally acting sympathoplegics (eg, clonidine or methyl dopa); (d) calcium channel blockers (eg, diltiazem, nifedipine, verapamil); (e) angiotensin-converting enzyme (ACE) inhibitors (eg, captopril); (f) angiotensin receptor antagonists (eg, losartan); and (g) thiazide diuretics.*
2. *ACE inhibitors slow the progression of diabetic nephropathy and help stabilize renal function. Angiotensin receptor antagonists may have similar protective effects in diabetic patients. Beta adrenoceptor blockers can mask the symptoms of hypoglycemia in diabetic patients. However, many patients with diabetes and cardiovascular disease are successfully treated with these drugs. A large clinical trial showed that control of hypertension decreases diabetes-associated microvascular disease. This trial included many patients being maintained on β adrenoceptor blockers. Thiazide diuretics impair the release of insulin and tissue utilization of glucose, so they are not drugs of first choice for patients with diabetes.*

CHECKLIST

When you complete this chapter, you should be able to:

- Describe the effects of insulin on hepatocytes, muscle, and adipose tissue.
- List the types of insulin preparations and their durations of action.
- Describe the major hazards of insulin therapy.
- List the prototypes and describe the mechanisms of action, key pharmacokinetic features, and toxicities of the major classes of agents used to treat type 2 diabetes.
- Give 3 examples of rational drug combinations for treatment of type 2 diabetes mellitus.
- Describe the clinical uses of glucagon.

Drug Mine

Calcium and strength of the complex require Parathyroid hormones, and its actions are used in Paget's disease

PTH

HORMONAL RE- MINERAL HOME

A. PTH

PTH, an 84-amino-acid protein-coupled receptor, acts on renal tubular cells. In the presence of PTH, it promotes ph

treat hypercalcemia have been associated with renal impairment and osteonecrosis of the jaw.

B. CALCIMIMETICS

Cinacalcet lowers PTH by activating the calcium-sensing receptor in the parathyroid gland. It is used for oral treatment of secondary hyperparathyroidism in chronic kidney disease and for the treatment of hypercalcemia in patients with parathyroid carcinoma. Its toxicities include hypocalcemia and adynamic bone disease, a condition of profoundly decreased bone cell activity.

C. FLUORIDE

Appropriate concentrations of fluoride ion in drinking water or as an additive in toothpaste have a well-documented ability to reduce dental caries. Chronic exposure to the ion, especially in high concentrations, may increase new bone synthesis. It is not clear, however, whether this new bone is normal in strength. Clinical trials of fluoride in patients with osteoporosis have not demonstrated a reduction in fractures. Acute toxicity of fluoride (usually caused by ingestion of rat poison) is manifested by gastrointestinal and neurologic symptoms.

D. OTHER DRUGS WITH EFFECTS ON SERUM CALCIUM AND PHOSPHATE

Gallium nitrate is effective in managing the hypercalcemia associated with some malignancies and possibly Paget's disease. It acts by inhibiting bone resorption. To prevent nephrotoxicity, patients need to be well

hydrated and to have good renal output. The antibiotic **plicamycin (mithramycin)** has been used to reduce serum calcium and bone resorption in Paget's disease and hypercalcemia. Because of the risk of serious toxicity (eg, thrombocytopenia, hemorrhage, hepatic and renal damage), plicamycin is mainly restricted to short-term treatment of serious hypercalcemia. Several diuretics, most notably **thiazide diuretics** and **furosemide**, can affect serum and urinary calcium levels (see this chapter's Skill Keeper). The phosphate-binding gel **sevelamer** is used in combination with calcium supplements and dietary phosphate restriction to treat hyperphosphatemia, a common complication of renal failure, hyperparathyroidism, and vitamin D intoxication.

QUESTIONS

1. A drug that is routinely added to calcium supplements and milk for the purpose of preventing rickets in children and osteomalacia in adults is
 - (A) Cholecalciferol
 - (B) Calcitriol
 - (C) Gallium nitrate
 - (D) Sevelamer
 - (E) Plicamycin
2. A drug that is useful for the treatment of hypercalcemia in Paget's disease is
 - (A) Fluoride
 - (B) Hydrochlorothiazide

KEY DRUGS

| Subclass | Prototypes | Other Significant Agents |
|---|---|--------------------------------------|
| PTH analog | Teriparatide | |
| Vitamin D, metabolites and analogs | | |
| Vitamin D | Cholecalciferol | Ergocalciferol |
| Vitamin D metabolites | Calcitriol | Doxercalciferol |
| Vitamin D analogs | Paricalcitol | Calcipotriene |
| Calcitonin | Calcitonin | |
| Estrogens | Raloxifene | |
| Bisphosphonates | Alendronate | Pamidronate, risedronate, and others |
| Calcimimetics | Cinacalcet | |
| Miscellaneous agents for treating hypercalcemia, hypercalciuria, or hyperphosphatemia | Glucocorticoids Gallium nitrate Plicamycin Furosemide Thiazide diuretics Sevelamer | |

- (C) Pamidronate
(D) Raloxifene
(E) Teriparatide
3. The active metabolites of vitamin D act through a nuclear receptor to
(A) Decrease the absorption of calcium from bone
(B) Increase PTH formation
(C) Increase renal production of erythropoietin
(D) Increase the absorption of calcium from the gastrointestinal tract
(E) Lower the serum phosphate concentration
4. Which of the following conditions is an indication for the use of raloxifene?
(A) Chronic kidney failure
(B) Hypoparathyroidism
(C) Intestinal osteodystrophy
(D) Postmenopausal osteoporosis
(E) Rickets
- 5-7. A 58-year-old postmenopausal woman was sent for dual-energy x-ray absorptiometry to evaluate the bone mineral density of her lumbar spine, femoral neck, and total hip. The test results revealed significantly low bone mineral density in all sites.
5. Chronic use of which of the following medications is MOST likely to have contributed to this woman's osteoporosis?
(A) Lovastatin
(B) Metformin
(C) Prednisone
(D) Propranolol
(E) Thiazide diuretic
6. If this patient began oral therapy with alendronate, she would be advised to drink large quantities of water with the tablets and remain in an upright position for at least 30 min and until eating the first meal of the day. These instructions would be given to decrease the risk of
(A) Cholelithiasis
(B) Diarrhea
(C) Constipation
(D) Erosive esophagitis
(E) Pernicious anemia
7. The patient's condition was not sufficiently controlled with alendronate, so she began therapy with a nasal spray containing a protein that inhibits bone resorption. The drug contained in the nasal spray was
(A) Calcitonin
(B) Calcitriol
(C) Cinacalcet
(D) Cortisol
(E) Teriparatide

8-10. A 67-year-old man with chronic kidney disease was found to have an elevated serum PTH concentration and a low serum concentration of 25-hydroxyvitamin D, the metabolite of vitamin D formed in the liver. He was successfully treated with ergocalciferol. Unfortunately, his kidney disease progressed so that he required dialysis and his serum PTH concentration became markedly elevated.

8. The drug that is MOST likely to lower this patient's serum PTH concentration is
(A) Calcitriol
(B) Cholecalciferol
(C) Furosemide
(D) Gallium nitrate
(E) Risedronate
9. Although the drug therapy was effective at lowering serum PTH concentrations, the patient experienced several episodes of hypercalcemia. He was switched to a vitamin D analog that suppresses PTH with less risk of hypercalcemia. The drug MOST likely used was
(A) Calcitriol
(B) Cholecalciferol
(C) Furosemide
(D) Paricalcitol
(E) Risedronate
10. In the treatment of patients like this with secondary hyperparathyroidism due to chronic kidney disease, cinacalcet is an alternative to vitamin D-based drugs. Cinacalcet lowers PTH by
(A) Activating a steroid receptor that inhibits expression of the PTH gene
(B) Activating the calcium-sensing receptor in parathyroid cells
(C) Activating transporters in the GI tract that are involved in calcium absorption
(D) Inducing the liver enzyme that converts vitamin D₃ to 25-hydroxyvitamin D₃
(E) Inhibiting the farnesyl pyrophosphate synthase found in osteoclasts

ANSWERS

1. The 2 forms of vitamin D—cholecalciferol and ergocalciferol—are commonly added to calcium supplements and dairy products. Calcitriol, the active 1,25-dihydroxyvitamin D₃ metabolite, would prevent vitamin D deficiency and is available as an oral formulation. However, because it is not subject to the complex mechanisms that regulate endogenous production of active vitamin D metabolites, it is not suitable for widespread use. The answer is **A**.
2. Paget's disease is characterized by excessive bone resorption, poorly organized bone formation, and

hypercalcemia
first-line treat
phosphonate
cemia. The an

3. The active met
calcium and p
phosphate upt
increasing bon
excretion of bc
than stimulate,
4. Raloxifene, a S
menopausal wo
is **D**.
5. Long-term the
prednisone is a
mineral density
The other drug
effects on bone
6. Oral bisphosph
tate the esophag
toxicity is redu
remaining in an
taking the medic
7. Calcitonin is a pr
resorption. Salm
spray or a parent
is **A**.
8. In patients with c
dialysis, the impa
D metabolites α
phosphate due to
ondary hyperpara
active vitamin D
on the parathyro
Cholecalciferol, a
tive in patients w
cannot form adequ
metabolites. The a
9. Paricalcitol is an ar
(calcitriol) that lo
only rarely precipi
lar basis of this sele
but is of value in th
roidism and psoria
10. Cinacalcet is a men
activate the calcium
cells. When this rec
free ionized calcium
that suppresses PT
answer is **B**.

hypercalcemia. Bisphosphonates and calcitonin are first-line treatments. Pamidronate is a powerful bisphosphonate used parenterally to treat hypercalcemia. The answer is **C**.

3. The active metabolites of vitamin D increase serum calcium and phosphate by promoting calcium and phosphate uptake from the gastrointestinal tract, increasing bone resorption, and decreasing renal excretion of both electrolytes. They inhibit, rather than stimulate, PTH formation. The answer is **D**.
4. Raloxifene, a SERM, is approved for use in postmenopausal women with osteoporosis. The answer is **D**.
5. Long-term therapy with glucocorticoids such as prednisone is associated with a reduction in bone mineral density and an increased risk of fractures. The other drugs are not known to have significant effects on bone or serum calcium. The answer is **C**.
6. Oral bisphosphonates such as alendronate can irritate the esophagus and stomach. The risk of this toxicity is reduced by drinking water and by remaining in an upright position for 30 min after taking the medication. The answer is **D**.
7. Calcitonin is a peptide hormone that prevents bone resorption. Salmon calcitonin is available as a nasal spray or a parenteral form for injection. The answer is **A**.
8. In patients with chronic kidney disease that requires dialysis, the impaired production of active vitamin D metabolites compounded with elevated serum phosphate due to renal impairment leads to secondary hyperparathyroidism. Administration of the active vitamin D metabolite calcitriol acts directly on the parathyroid to inhibit PTH production. Cholecalciferol, a form of vitamin D, is not effective in patients with advanced renal disease who cannot form adequate amounts of active vitamin D metabolites. The answer is **A**.
9. Paricalcitol is an analog of 1,25-dihydroxyvitamin D₃ (calcitriol) that lowers serum PTH at doses that only rarely precipitate hypercalcemia. The molecular basis of this selective action is poorly understood but is of value in the management of hyperparathyroidism and psoriasis. The answer is **D**.
10. Cinacalcet is a member of a novel class of drugs that activate the calcium-sensing receptor in parathyroid cells. When this receptor is activated by cinacalcet or free ionized calcium, it activates a signaling pathway that suppresses PTH synthesis and release. The answer is **B**.



**SKILL KEEPER ANSWERS:
DIURETICS AND CALCIUM
(SEE CHAPTER 15)**

1. *Loop diuretics (eg, furosemide) and thiazide diuretics have opposite effects on urine calcium concentrations; loop diuretics increase urine concentrations of calcium, whereas the thiazides decrease urine calcium.*
2. *Loop diuretics inhibit the Na⁻/K⁺/2Cl⁻ cotransporter in apical membranes of the thick ascending limb of the loop of Henle (see Figure 15-3). By disrupting the positive lumen-positive potential that normally serves as the driving force for resorption of Mg²⁺ and Ca²⁺, loop diuretics inhibit Mg²⁺ and Ca²⁺ resorption, leaving more Mg²⁺ and Ca²⁺ in the urine and less in the blood. In the distal convoluted tubule where thiazides act, Ca²⁺ is actively resorbed through the concerted action of an apical Ca²⁺ channel and a basolateral Na⁺/Ca²⁺ exchanger (see Figure 15-4). The system is under control of the PTH. When thiazides inhibit the Na⁻/Cl⁻ transporter in cells that line the distal convoluted tubule, they lower the intracellular concentration of sodium and thereby enhance the Na⁺/Ca²⁺ exchange that occurs on the basolateral surface. This, in turn, creates a greater driving force for passage of Ca²⁺ through the apical membrane calcium channels. The net effect is enhanced resorption of calcium.*
3. *In patients with hypercalcemia, treatment with a loop diuretic plus saline promotes calcium excretion and lowers serum calcium. In patients with intact regulatory function, increases in calcium resorption promoted by thiazides have minor impact on serum calcium because of buffering in bone and gut. However, thiazides can unmask hypercalcemia in patients with diseases that disrupt normal calcium regulation (eg, hyperparathyroidism, sarcoidosis, carcinoma). Thiazide diuretics are also used for treatment of individuals who are prone to kidney stone formation as a result of idiopathic hypercalciuria. In such individuals, it is crucial that primary hyperparathyroidism is ruled out before thiazide treatment is initiated.*