LESSON ASSIGNMENT

SUBCOURSE MD0806  Therapeutics III.

LESSON 8  Diuretic and Antidiuretic Agents.

LESSON ASSIGNMENT  Paragraphs 8-1--8-7.

LESSON OBJECTIVES  After you finish this lesson you should be able to:

8-1. Given a group of statements, select the statement that best defines the term diuretic.

8-2. Given a list of conditions, select the condition(s) that are treated with diuretic therapy.

8-3. Given the name of a type of diuretic and a group of statements describing the mechanisms of action of different types of diuretics, select the mechanism of action for that type of diuretic.

8-4. Given the trade and/or generic name of a diuretic agent or antidiuretic agent and a list of indications, uses, side effects, or precautionary statements, select the indication(s), use(s), side effect(s), or precautionary statements(s) for that particular agent.

8-5. Given a group of trade and/or generic names of various diuretic or antidiuretic agents match each trade or generic name with its corresponding trade or generic name.

8-6. Given the trade or generic name of a diuretic agent and a list of types of diuretic agents select the type of diuretic to which that agent belongs.

SUGGESTION  After studying the assignment, complete the exercises at the end of this lesson. These exercises will help you to achieve the lesson objectives.
LESSON 8
DIURETIC AND ANTIDIURETIC AGENTS

Section I. DIURETIC AGENTS

8-1. INTRODUCTION

In Lesson 3 of this subcourse, congestive heart failure was described as a condition characterized by sodium retention that results in expanded extracellular fluid volume or edema. This same process of increased tubular reabsorption of sodium--resulting in an accumulation of fluid--may accompany cirrhosis of the liver, renal disease, toxemia of pregnancy, the side effects of drugs, and other states of fluid retention. In all of these conditions, treatment of sodium retention is what is desired. REMEMBER: WHERE SODIUM GOES, WATER GOES! Therefore, the treatment as sodium retention by sodium excretion--not just the increase in urine volume--is the desired goal. Diuretic agents increase the amount of sodium excreted from the body.

8-2. DEFINITION OF DIURETIC

A diuretic is any agent that produces diuresis (an increase in the volume of urine output that results in the mobilization of edema fluid). You have heard the term edema before. Edema is the presence of abnormally large amounts of fluid in the body. Many diuretics reduce edema by increasing the amount of sodium removed from the body. Remember, where sodium goes, water goes. Thus, when sodium is removed from the body, there is a corresponding increase in the volume of urine produced.

8-3. USES OF DIURETICS

The general uses of diuretics include the treatment of congestive heart failure, hypertension, glaucoma, ascites, toxemia of pregnancy, and diabetes insipidus. Congestive heart failure has been discussed in Lesson 3 of this subcourse, hypertension has been discussed in Lesson 7 of this subcourse, and glaucoma has been discussed in MD0805, Therapeutics II. Review these materials if you have a need. The other conditions will be explained in this paragraph. Ascites is the accumulation of fluid in the abdominal cavity. Toxemia of pregnancy is a group of pathologic conditions--essentially metabolic disturbances--which sometimes occurs in pregnant women. Toxemia of pregnancy is manifested by preeclampsia (a toxemia of late pregnancy characterized by hypertension, albuminuria, and edema) and fully developed eclampsia (this condition includes convulsions and coma, which might occur in a pregnant woman or in a woman who has just delivered). Hypertension, edema, and/or proteinuria characterize eclampsia. Diabetes insipidus is a metabolic disorder caused by a lack of production of antidiuretic hormone (ADH), which is marked by great thirst and the passage of a large amount of dilute urine with no excess of sugar.
8-4. TYPES OF DIURETICS

There are several types of diuretics. The categories are defined based upon their mechanism of action.

a. Osmotic Diuretics.

(1) General. Osmotic diuretics produce a diuresis of water rather than a diuresis of sodium. The body does not metabolize osmotic diuretics. Instead, the drug molecules are not reabsorbed in the kidney tubules. This greatly affects the tonicity of every part of the kidney tubules through which the glomerular filtrates pass. By the process of osmosis, the drug molecules draw an increased amount of water from the interstitial fluid compartment. The result is that a great volume of urine is produced (water diuresis). Sodium is contained in that urine and is subsequently removed from the body. Thus, the osmotic diuretics indirectly produce a removal of sodium from the body.

(2) Mannitol. Mannitol is used to prevent acute renal (kidney) failure, evaluate kidney functioning, treat glaucoma (by the reduction of intraocular pressure), promote the urinary excretion of toxic substances (diuresis in certain drug intoxications) and reduce intracranial pressure (pressure in the head). The usual dosage of mannitol is from 50 to 200 grams in a 24-hour period by intravenous infusion. Side effects associated with the use of mannitol include pulmonary congestion, fluid and electrolyte imbalance, acidosis, electrolyte loss, and dryness of mouth and dehydration. Since mannitol may crystallize on exposure to low temperatures, you should observe mannitol vials and premixed bags for such crystals. When you observe these crystals, you should warm the vials or bags in a 50ºC water bath in order to dissolve the crystals. The product should be cooled to body temperature before the mannitol solution is administered. Mannitol is available in a 5, 10, 15, 20, and 25 percent injection.

b. Thiazide Diuretics. Thiazide diuretics work by the inhibition of sodium reabsorption in the first portion of the distal tubule. The passive diffusion of the accompanying water and chloride is correspondingly reduced. Thus, the result is an increased excretion of sodium, water, and chloride from the body. When the thiazide acts on the proximal tubule, the carbonic anhydrase activity in the distal tubule is also decreased. This causes increased secretion of potassium. Consequently, the water lost contains sodium, potassium, and chloride. This loss of potassium can present problems to the patient.

(1) Hydrochlorothiazide (Hydrodiuril®). Hydrochlorothiazide is used in the treatment of essential hypertension and edema found in congestive heart failure. The usual dose of this drug is from 12.5 to 100 milligrams per day. Side effects commonly associated with hydrochlorothiazide include hypokalemia, hyperglycemia, and hyperuricemia. This drug should be used in caution in patients suffering from diabetes or gout and in patients who take digitalis.
(2) **Chlorothiazide (Diuril®)**. This drug is used as a diuretic and as an antihypertensive. It is available in both parenteral and oral dosage forms. For side effects, refer to hydrochlorothiazide.

(3) **Chlorthalidone (Hygroton®)**. Although chlorthalidone is not the same chemically as the thiazide diuretics, it has the same effects as these agents. For indications and side effects, you should refer to hydrochlorothiazide.

c. **Potassium-Sparing Diuretics**. This type of diuretic is used when there is a need to maintain normal levels of potassium in the patient along with the diuresis. The specific mechanisms of actions of selected drugs in this category are given below.

(1) **Spironolactone (Aldactone®)**. Spironolactone causes sodium diuresis and potassium retention by acting as an aldosterone competitive antagonist. That is, this drug acts on the distal tubule to block the sodium-potassium exchange mechanism. The net result is sodium loss and potassium retention. Consequently, by antagonizing aldosterone, sodium as well as water diuresis and potassium retention are affected. Spironolactone is used for primary hyperaldosteronism, edema associated with congestive heart failure, cirrhosis of the liver or ascites, essential hypertension, and in hypokalemia when other means are considered inappropriate or inadequate. The usual dose of this drug is from 25 to 400 milligrams per day depending upon the condition of the patient. Although spironolactone is a mild diuretic, it can hasten major side effects such as gastrointestinal symptoms (for example: cramping and diarrhea), lethargy, hyperkalemia, and hyponatremia. Hyperkalemia is a major side effect that occurs in patients who have impaired renal function. Hyperkalemia can cause irregularities that may be fatal. Spirolactone also causes estrogen-like side effects because of its hormone-like structure.

(2) **Triamterene (Dyrenium)**. While triamterene produces effects similar to those of spironolactone, the effects produced by triamterene are not dependent on the presence of aldosterone. This agent acts directly on the distal tubule where it prevents the passage of sodium across the membrane of the tubule. Thus, by blocking sodium reabsorption, potassium loss is reduced. Triamterene is used for edema associated with congestive heart failure and cirrhosis of the liver. The usual dosage of this drug is from 25 to 200 milligrams per day. The daily dose should not exceed 300 milligrams. Side effects associated with this agent include electrolyte imbalances, hyperkalemia, weakness, and dry mouth. Like spironolactone, hyperkalemia is a major side effect which can occur in patients who have impaired renal function or when the drug is administered alone.
d. **Carbonic Anhydrase Inhibitor Diuretics.**

(1) Carbonic anhydrase inhibitors produce diuresis by inhibiting carbonic anhydrase in the renal tubules. Carbonic anhydrase is an enzyme that catalyzes the following reaction.

\[
\text{CO}_2 + \text{H}_2 \xrightleftharpoons{\text{carbonic anhydrase}} \text{H}_2\text{CO}_3 \xrightleftharpoons{} \text{H}^+ + \text{HCO}_3^-
\]

(2) From the reaction above, it can be deduced that removal of or blocking the enzyme carbonic anhydrase would result in a much slower reaction. Consequently, there would be a greatly reduced production of hydrogen ions and bicarbonate ions. This interferes with the ion exchange mechanism at the distal tubule, where the sodium ion that accompanies the bicarbonate ion is reabsorbed only by exchange for hydrogen or potassium ions secreted into the tubule. Normally the bicarbonate ion that accompanies the sodium ion (provided by the glomerular filtrate) is reabsorbed almost complete at the distal tubule. With reduced production of hydrogen ion due to inhibition of the carbonic anhydrase, the bicarbonate ion, together with the sodium ion will not be reabsorbed. Thus, the sodium will be excreted in an unusually large amount—with a corresponding loss of water (remember, where sodium goes, water goes).

(3) Acetazolamide (Diamox®) is one example of a carbonic anhydrase inhibitor. Although rarely used today, it may be used in the treatment of edema because of congestive heart failure; drug-induced edema; petit mal and unlocalized seizures; and open-angle and secondary glaucoma. The usual dosage of this drug ranges from 250 milligrams to 2 grams—depending on the type of condition being treated. Actually, the dosage recommendations for glaucoma and epilepsy differ considerably from those of congestive heart failure, since the first two conditions are not dependent on carbonic anhydrase inhibition in the kidney which requires intermittent dosage if it is to recover from the inhibitory effect of the therapeutic agent. The side effects of this agent include loss of appetite, transient myopia (nearsightedness), drowsiness, and acidosis. Acetazolamide is available in the injectable form.

e. **Inhibition of Sodium Transport in the Ascending Limb of the Loop of Henle, the Distal Tubule, and the Proximal Sites Diuretics.** Diuretics of this type are extremely potent and rapidly acting. In fact, they are used only after less potent—but safer—diuretics have failed. As the category type states, this type of diuretic acts by inhibiting sodium transport in the ascending limb of the loop of Henle, the distal tubule, and in the proximal sites. Thus, a greater fraction of filtered sodium can escape reabsorption. Thereby, increased sodium and water excretions occur. Diuretics of this type are called "loop diuretics".
(1) **Furosemide (Lasix®).** Furosemide is used in the treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease, pulmonary edema, and hypertension. It is particularly useful when an agent with a greater diuretic potential than that of those commonly used is desired. This agent is also a rapidly acting diuretic. When administered orally it acts within one hour. When administered by injection it acts within 5 to 10 minutes. However, the agent does produce massive changes in electrolyte and water balance in the body. The usual dosage of furosemide is 20 to 80 milligrams given in a single dose—preferably in the morning. Depending on the patient's response, this dose can be repeated, maintained, or reduced. There are numerous adverse effects associated with the use of furosemide. These adverse effects include hypokalemia, hyponatremia, hyperglycemia, electrolyte depletion, and hypovolemia. Reversible and irreversible hearing impairment and loss may occur with any of the loop diuretics. It is often associated with rapid infusion and the use of extremely high doses. The injectable form of the drug must be stored at controlled room temperature and should not be used if the solution is yellow. The oral solution and tablet preparations should be dispensed in light–resistant containers.

(2) **Other loop diuretics.** Other loop diuretics include bumetanide (Bumex®), ethacrynic acid (Edecrin®), and torsemide (Demadex®).

f. **Inhibition of Sodium and Chloride Reabsorption Diuretics.**

(1) **General.** The mechanism of action of this type is very similar to the thiazide diuretics. That is, drugs of this category inhibit sodium and chloride reabsorption that results in the increased excretion of sodium, chloride, and water.

(2) **Chlorthalidone (Hygroton®).** This agent differs from the thiazide diuretics only in chemical structure. Chlorthalidone’s pharmacological action is indistinguishable from the thiazide diuretics. Chlorthalidone is used in the management of hypertension—either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in patients who have the more severe forms of hypertension. It is also used as adjunctive therapy in the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and various forms of renal dysfunctions. Refer to the information on hydrochlorothiazide for side effect information.

g. **Combination Diuretics (Potassium--Sparing and Thiazide Diuretic Combination).** The potassium--sparing and thiazide diuretics have different but complementary mechanisms and sites of action. Therefore, when given together they produce additive diuretic and antihypertensive effects. The thiazide component blocks the reabsorption of sodium and chloride ions and thus increases the quantity of sodium traversing the distal tubule and the volume of water excreted in the urine. This characteristically induces potassium loss. The potassium-sparing component inhibits the reabsorption of sodium in exchange for potassium and hydrogen ions at the distal tubule so that sodium excretion is greatly favored and the excess loss of potassium, as well as hydrogen and chloride ions induced by the thiazide, is reduced.
(1) Aldactazide® (combination of spironolactone and hydrochlorothiazide). This drug is used for the treatment of edema associated with congestive heart failure, cirrhosis of the liver and ascites and for essential hypertension.

(2) Dyazide® (combination of triamterene and hydrochlorothiazide). This agent is used in the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and hypertension. The usual dosage of this product is from 1 to 2 capsules taken twice daily after meals. The patient should take no more than four capsules per day. The side effects associated with this agent include hyperglycemia, hyperuricemia, and gastrointestinal disturbances. Each Dyazide® capsule contains 37.5 milligrams of triamterene and 25 milligrams of hydrochlorothiazide. There are other combinations of these diuretics available as generics or as Maxide® (75/50; 50/25). One must be very careful and double check the active ingredients to ensure that the correct product is dispensed.

Section II. ANTIDIURETIC AGENTS

8-5. INTRODUCTION

The antidiuretic hormone has been discussed in Lesson 8 of this subcourse. As you will remember, it is a hormone secreted by the pituitary gland. The antidiuretic hormone (ADH) acts on the distal tubule and collecting ducts to increase water reabsorption (and thus to decrease urine output). The agents discussed below are those that work in a manner opposite the diuretics. This process is called antidiuresis. Antidiuresis is the suppression of urinary secretion. Consequently, an antidiuretic is an agent that suppresses urine formation as well as the rate of urine formation.

8-6. MECHANISM OF ACTION OF ANTIDIURETICS

Antidiuretics work by increasing the reabsorption of water at the distal tubule and collecting ducts without significantly modifying the rate of glomerular filtration.

8-7. EXAMPLES OF ANTIDIURETIC AGENTS

Two examples of antidiuretic agents are presented below.

a. Vasopressin (Pitressin®). This agent is used for the control or prevention of the symptoms and complications of diabetes insipidus. For vasopressin injection, the dose is 5 to 10 units (0.25 to 0.5 milliliters) by intramuscular or subcutaneous injection as required (usually every 2 to 3 hours as needed). The side effects associated with this product include abdominal cramps, fluid retention, and increased blood pressure. It is dispensed for hospital use only and should never be administered intravenously. This drug is available as a solution containing 20 pressor units per milliliter.
b. **Lypressin (Diapid®)**. This agent is also used for the control or prevention of the symptoms and complications of diabetes insipidus. The usual dosage of this drug is 1 to 2 sprays applied to each nostril four times daily. The side effects associated with lypressin are abdominal cramps, nasal congestion, fluid retention, and increased bowel movements. Lypressin is useful in patients suffering from diabetes insipidus who have become unresponsive to other therapy or who experience allergic or other undesirable reactions to antidiuretic hormone of animal origin. The product has to be kept refrigerated. This product has an expiration date of 36 months. It is available as a nasal spray, 0.185 milligrams of lypressin per milliliter of solution (equivalent to 50 units per milliliter).
EXERCISES, LESSON 8

INSTRUCTIONS. The following exercises are to be answered by marking the lettered response that best answers the question or best completes the incomplete statement.

After you have completed all the exercises, turn to “Solutions to Exercises” at the end of the lesson and check your answers with the solutions. For each exercise answered incorrectly, reread the material referenced after the solution.

1. Which of these conditions is treated with diuretics?
   a. Asthma.
   b. Congestive heart failure.
   c. Diabetes mellitus.
   d. Gallstones.

2. Which of the following statements best describes the mechanism of action for the thiazide diuretics?
   a. Thiazide diuretics cause sodium diuresis and potassium retention by acting as an aldosterone competitive antagonist.
   b. Thiazide diuretics produce a diuresis of water by drawing water from the cells in the body and thus by increasing the glomerular filtrate.
   c. Thiazide diuretics work by the inhibition of sodium reabsorption in the first portion of the distal tubule.
   d. Thiazide diuretics inhibit sodium transport--and thus sodium excretion--in the ascending limb of the Loop of Henle, the distal tubule, and in the proximal tubule.
3. Mannitol is used to:
   a. Prevent or treat acute liver failure.
   b. Treat dehydration and electrolyte imbalance.
   c. Promote the excretion of toxic substances in the urine.
   d. Treat epilepsy.

4. Hydrochlorothiazide is used to treat:
   a. Essential hypertension.
   b. Diabetes mellitus.
   c. Hyperglycemia.
   d. Cramping and diarrhea.

5. Vasopressin is used:
   a. For the control or prevention of the symptoms and complications of diabetes insipidus.
   b. To treat hypovolemia.
   c. To treat nasal congestion.
   d. To prevent hyperkalemia.

6. Which of the following is a side effect associated with Dyazide®?
   a. Hypouricemia.
   b. Hyperglycemia.
   c. Hyernatremia.
   d. Fluid retention.
7. Diamox® is used in the treatment of:
   a. Edema because of congestive heart failure.
   b. Drug-induced edema.
   c. Open-angle glaucoma and secondary edema.
   d. All the above.

8. Match the drug name in Column A with its corresponding trade or generic name listed in Column B.

<table>
<thead>
<tr>
<th>Column A</th>
<th>Column B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldactazide®</td>
<td>a. Chlorothiazide.</td>
</tr>
<tr>
<td>Spironolactone.</td>
<td>b. Aldactone.</td>
</tr>
<tr>
<td>Furosemide.</td>
<td>c. Combination of spironolactone and</td>
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<td></td>
<td>hydrochlorothiazide.</td>
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<tr>
<td>Diapid®</td>
<td>d. Lypressin.</td>
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<tr>
<td>Diuril®.</td>
<td>e. Lasix®</td>
</tr>
<tr>
<td>Dyrenium®.</td>
<td>f. Triamterene.</td>
</tr>
</tbody>
</table>

Check Your Answers on Next Page
SOLUTIONS TO EXERCISES, LESSON 8

1. b (para 8-3)
2. c (para 8-4b)
3. c (para 8-4a(2))
4. a (para 8-4b(1))
5. a (para 8-7a)
6. b (para 8-4g(2))
7. d (para 8-4d(3))
8. c Aldactazide® (para 8-4b(2))
   b Spironolactone. (para 8-4c(1))
   e Furosemide. (para 8-4g(2))
   d Diapid®. (para 8-7b)
   a Diuril®. (para 8-4e)
   f Dyrenium®. (para 8-4c(2))

   a. Chlorothiazide.
   b. Aldactone.
   c. Combination of spironolactone and hydrochlorothiazide.
   d. Lypressin.
   e. Lasix®.
   f. Triamterene

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