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VILDAGLIPTIN

Goal

To highlight the role of incretin hormones in the management of type 2 diabetes mellitus with a focus on the pharmacology, pharmacokinetics, efficacy, and safety of vildagliptin, a DPP IV inhibitor.

Objectives

After reviewing this article, the reader should be able to:

1. discuss the importance of incretin hormones in controlling type 2 diabetes;
2. describe how vildagliptin improves glycemic control through inhibition of DPP IV;
3. discuss the role of vildagliptin in the maintenance of glycemic control in patients with type 2 diabetes;
4. select the most common safety concerns with vildagliptin identified in clinical trials.

Test Questions

1. Which of the following statements regarding type 2 diabetes mellitus is true?
 - (a) A small percentage of the total population has diabetes.
 - (b) Sulfonylureas act by improving insulin sensitivity in the body.
 - (c) About 87% of patients have an A1C less than 7.0%.
 - (d) Insulin resistance is an important component.
2. A patient is interested in the most recent research involving incretin hormones in the treatment of diabetes. Information on which of the following hormones would help him become most familiar with incretins?
 - (a) insulin
 - (b) GLP-1

- (c) glucagon
 - (d) amylin
3. Which of the following statements regarding incretin hormones is true?
 - (a) Patients with type 2 diabetes have high levels of GLP-1.
 - (b) GLP-1 has a half-life of 24 hours, making it an attractive therapeutic target.
 - (c) Incretins account for about 50% of the postprandial insulin response in healthy individuals.
 - (d) Patients with diabetes respond well to exogenous injections of GIP.
 4. Incretin hormones have all of the following effects in the body, *except*.
 - (a) glucose-independent stimulation of insulin secretion.
 - (b) delayed gastric emptying.
 - (c) stimulation of glycogen synthesis.
 - (d) induction of β -cell growth.
 5. Which of the following statements regarding DPP IV is true?
 - (a) Exenatide is sensitive to DPP IV degradation.
 - (b) Inhibiting DPP IV may decrease levels of incretin hormones.
 - (c) Vildagliptin is an incretin analog resistant to DPP IV.
 - (d) GLP-1 is rapidly inactivated by DPP IV.
 6. A 65-year-old man with type 2 diabetes is started on vildagliptin therapy. What effects would you expect to see in this patient?
 - (a) decreased DPP IV activity
 - (b) decreased GLP-1 levels
 - (c) increased glucagon release after a meal
 - (d) increased appetite
 7. Regarding the pharmacokinetics of vildagliptin:
 - (a) Significant human data have been published.
 - (b) It has a half-life of 24 hours.
 - (c) It will need to be administered twice daily.

- (d) It is primarily metabolized by hydrolysis.

8. A 52-year-old male was diagnosed with type 2 diabetes about 3 years ago. He had been previously controlled with lifestyle modifications, but his A1C has now risen to 8.0%. Vildagliptin 25 mg twice daily is started. What reduction in A1C would you expect to see based on this therapy?
 - (a) 0.2–0.4%
 - (b) 0.6–1.0%
 - (c) 1.2–1.5%
 - (d) 1.8–2.0%
9. Which of the following is a strength of the available data from clinical trials evaluating vildagliptin?
 - (a) Complete results of all studies have been published.
 - (b) Data are available from both monotherapy and combination therapy trials.
 - (c) Consistent doses were used in all trials.
 - (d) Long-term (>52 wk) efficacy has been shown.
10. Which of the following statements regarding the incidence of hypoglycemia with vildagliptin therapy during clinical trials is true?
 - (a) The incidence of hypoglycemia increased with increasing doses.
 - (b) Frequent discontinuations occurred because of hypoglycemia.
 - (c) Hypoglycemia was usually reported as mild.
 - (d) Significant increases in hypoglycemia were seen with vildagliptin plus metformin compared with metformin monotherapy.
11. When vildagliptin is used in combination with insulin, which of the following appears to be true?
 - (a) Incidence of hypoglycemia is higher compared with vildagliptin plus metformin.
 - (b) Incidence of hypoglycemia is higher compared with insulin monotherapy.
 - (c) Incidence of hypoglycemia is higher compared with both insulin monotherapy and vildagliptin plus metformin.
 - (d) Vildagliptin plus insulin has never been studied.
12. A patient trying to watch her diet to control both her weight and cholesterol level is concerned that vildagliptin may interfere with her efforts. What should you tell her?
 - (a) Vildagliptin may cause some weight gain but has no effect on cholesterol.
 - (b) Vildagliptin does not affect weight, but may increase triglycerides.
 - (c) Vildagliptin tends to increase both weight and total cholesterol.
 - (d) Vildagliptin has limited effects on weight and cholesterol.
13. During each of the clinical trials, vildagliptin was administered:
 - (a) subcutaneously.
 - (b) 30 minutes prior to meals.

- (c) in combination with other antidiabetic medications.
- (d) once daily.

14. What initial dose of vildagliptin would you recommend based on available data from clinical trials?

- (a) 25 mg daily
- (b) 50 mg daily
- (c) 100 mg daily
- (d) 100 mg twice daily

15. The addition of vildagliptin may be *most* beneficial for patients with which of the following diagnoses and current management therapies?

- (a) uncontrolled type 1 diabetes, with insulin pump
- (b) controlled type 2 diabetes, with insulin therapy
- (c) uncontrolled type 2 diabetes (A1C 7.5%), with metformin
- (d) uncontrolled type 2 diabetes (A1C 10.0%), with metformin and glipizide

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BAZEDOXIFENE

Goal

To present clinical studies and other available literature regarding bazedoxifene to assist pharmacists in understanding the drug's pharmacology, pharmacokinetics, pharmacodynamics, dosage/administration, adverse effects, and drug interactions.

Objectives

After reviewing this article, the reader should be able to:

1. distinguish bazedoxifene's key features, including potential uses, from those of other SERMs;
2. given a case study of a patient with osteoporosis, select the proper use of bazedoxifene;
3. given a case study, develop an appropriate drug therapy regimen utilizing bazedoxifene for a patient needing prevention of or treatment for osteoporosis;
4. assess the impact of therapy with bazedoxifene from selected laboratory values and patients' concomitant disease states.

Test Questions

1. A 42-year-old premenopausal female with a family history of osteoporosis wants to know how she can prevent osteoporosis. Dual energy X-ray absorptiometry shows no evidence of osteoporosis or osteopenia based on T-score. Which of the following preventive measures would you recommend to the patient?

- (a) raloxifene 60 mg daily plus adequate calcium intake
- (b) weight-bearing exercise and adequate calcium intake, both dietary and through supplementation

- (c) weight-bearing exercise plus conjugated equine estrogen (CEE) 0.625 mg daily
- (d) tamoxifen 20 mg daily plus adequate calcium intake

2. A postmenopausal woman currently on raloxifene for treatment of osteoporosis presents with complaints of severe hot flashes. What recommendations can be made for this patient?

- (a) initiate lifestyle changes, such as avoiding hot beverages and wearing layers
- (b) change to an estrogen-progestin regimen
- (c) switch therapy to bazedoxifene and initiate lifestyle changes
- (d) initiate CEE to be used with raloxifene

3. A 61-year-old postmenopausal female has been taking CEE for the past 12 months and was recently started on bazedoxifene 10 mg. At her last physician visit, she was noted to have a slight increase in endometrial thickness. What is an appropriate course of action?

- (a) Discontinue both medications.
- (b) Increase the bazedoxifene dose to 40 mg.
- (c) Continue estrogen and discontinue bazedoxifene.
- (d) No action is necessary.

4. What are the primary outcomes of ongoing Phase III trials that will better define bazedoxifene's place in therapy for the treatment of osteoporosis?

- (a) new vertebral and hip fractures
- (b) reduction of vertebral and hip fractures
- (c) bone mineral density at the lumbar spine and new vertebral fractures
- (d) bone mineral density of the hip and lumbar spine

5. Which of the following are examples of endpoints being evaluated in trials combining bazedoxifene with CEE?

- (a) bone mineral densities of the hip and spine
- (b) vasomotor symptoms and vaginal atrophy
- (c) breast pain and vaginal atrophy
- (d) clinical fractures of the hip and wrist

6. A frail 78-year-old female weighing 54 kg is prescribed bazedoxifene 40 mg daily for osteoporosis due to intolerable adverse effects experienced with alendronate 70 mg weekly. Laboratory studies reveal serum creatinine 1.0 mg/dL, blood urea nitrogen 23 mg/dL, sodium 135 mEq/L, potassium 3.2 mEq/L, aspartate aminotransferase (AST) 40 U/L, and alanine aminotransferase (ALT) 38 U/L. What should be done regarding the patient's bazedoxifene dose?

- (a) The AST/ALT levels are close to the upper limit of normal; therefore, the dose should be reduced by 75%.
- (b) The dose should be reduced by 50% because she is frail and elderly.

- (c) No dosage adjustment is necessary.
- (d) No dosage adjustment is necessary until the creatinine clearance is less than 20 mL/min.

7. A 58-year-old female has been taking bazedoxifene in combination with CEE for the past 6 months. She is admitted to the hospital with a diagnosis of pulmonary embolism. What is the *best* course of action?

- (a) Discontinue CEE.
- (b) Discontinue bazedoxifene.
- (c) Discontinue both CEE and bazedoxifene.
- (d) Discontinue both CEE and bazedoxifene only until the patient is stabilized and taking a therapeutic dose of warfarin.

8. SERMs are most noted for their role in:

- (a) cardiovascular functions.
- (b) lipid metabolism.
- (c) skeletal remodeling.
- (d) thyroid dysfunction.

9. Which of the following statements *best* describes why bazedoxifene is being studied in combination with CEE?

- (a) The combination is being studied as a medroxyprogesterone-sparing regimen for women with an intact uterus.
- (b) The addition of bazedoxifene to CEE decreases the dose of estrogen needed to treat menopausal symptoms.
- (c) The combination of bazedoxifene and CEE will be more efficacious than the bisphosphonates at decreasing bone turnover.
- (d) Using bazedoxifene with CEE decreases the risk of thromboembolism associated with traditional hormone replacement therapy.

10. Bazedoxifene is metabolized through which of the following pathways?

- (a) CYP3A4 isoenzyme system
- (b) glucuronidation
- (c) bazedoxifene is renally cleared, unchanged
- (d) CYP2C9 isoenzyme system

11. A pharmaceutical company has decided to develop a new SERM for use in the treatment and prevention of postmenopausal osteoporosis. Which of the following *most* accurately describes the optimal SERM for this indication?

- (a) agonist activity at the bone, uterine, vaginal, and breast tissues
- (b) antagonist activity at the bone and uterine tissues, with agonist activity at the vaginal and breast tissues
- (c) agonist activity at the bone and vaginal tissues, with antagonist activity at the uterine and breast tissues
- (d) antagonist activity at the bone, uterine, vaginal, and breast tissues

12. With which of the following medications does bazedoxifene interact?

- (a) CEE
- (b) ibuprofen
- (c) alendronate
- (d) None has been identified.

13. In which of the following patients would bazedoxifene possibly be a better treatment choice than a bisphosphonate for the treatment of osteoporosis?

- (a) premenopausal patient with diabetes and depression
- (b) postmenopausal patient with hypertension, diabetes, and history of multiple venous thromboemboli
- (c) premenopausal patient with long-standing corticosteroid use due to Crohn's disease
- (d) postmenopausal patient with severe hot flashes and gastroesophageal reflux disease

14. A pharmaceutical company is developing a Phase III head-to-head clinical trial to evaluate bazedoxifene versus the bisphosphonate risedronate for the treatment of osteoporosis in postmenopausal women. Which of the following would be the *best* primary outcome data to collect?

- (a) decrease in bone turnover markers for bazedoxifene versus risedronate
- (b) bone mineral density at the lumbar spine and hip for bazedoxifene versus risedronate
- (c) incidence of vertebral and wrist fracture for bazedoxifene versus risedronate
- (d) increase in bone turnover markers for bazedoxifene versus risedronate

15. What effect has bazedoxifene exhibited on bone metabolism in Phase II trials?

- (a) Bone metabolism indices were not significantly changed.
- (b) Dose-dependent reduction occurred in bone turnover markers.
- (c) Decreases in bone metabolism indices were less than those that occurred with raloxifene.
- (d) Changes in bone turnover markers were greatest at lower doses.

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HYPONATREMIA

Goal

To review the physiology, pathophysiology, classification, risk factors, conventional therapeutic management, and role of AVP receptor antagonists in the treatment of hyponatremia.

Objectives

After reviewing this article, the reader should be able to:

1. discuss the normal physiology of water balance;

2. discuss the mechanism of AVP release;
3. identify the classification of hyponatremia;
4. recognize common causes of hyponatremia in hospitalized patients;
5. based on case studies, select appropriate conventional treatment options;
6. based on case studies, select appropriate monitoring parameters to achieve desired therapeutic outcomes;
7. discuss the role of conivaptan HCl for the management of hyponatremic disorders;
8. identify the role of other AVP receptor antagonists in hyponatremia disorders.

Test Questions

1. Total body water:

- (a) is composed of transcellular and intracellular fluid.
- (b) is composed of extracellular and intracellular fluid.
- (c) accounts for 60% of total body weight in men.
- (d) accounts for 50% of total body weight in women.

2. Which of the following statements about aquaporins in renal water regulation is *true*?

- (a) Aquaporins are family of water channel carbohydrates necessary for osmotic balance.
- (b) Aquaporins inhibit vasopressin-mediated actions.
- (c) Aquaporins allow for passing of water across a biological membrane to achieve osmotic balance.
- (d) Aquaporins allow additional water excretion.

3. A patient involved in a motor vehicle accident has lost approximately 15% of his total blood volume based on a blood pressure reading of 85/55 mm Hg. Which of the following physiological mechanisms would be involved in restoring the patient's blood volume and pressure?

- (a) Baroreceptors detect volume depletion and trigger a decrease in arginine vasopressin release.
- (b) Baroreceptors detect volume depletion and trigger the release of arginine vasopressin.
- (c) Low plasma osmolality inhibits arginine vasopressin release.
- (d) High plasma osmolality triggers arginine vasopressin release.

4. A 64-year-old male with a history of Addison's disease presents with loss of appetite, nausea, lethargy, and delayed reflexes including positive Babinski sign. The following vital signs and laboratory results (reference) are determined on admission: blood pressure 128/85 mm Hg (120/80), serum sodium 108 mEq/L (135–146), plasma osmolality 260 mOsmol/kg (278–305), urine sodium 36 mEq/L (>20), and urine osmolality 324 mOsmol/kg (50–1200). Which of the following is the *most*

accurate classification of hyponatremia in this patient?

- (a) hypovolemic
- (b) hypervolemic
- (c) euvolemic
- (d) pseudohyponatremia

5. Based on the data reported by Coenraad et al.,⁴⁷ which of the following statements is *true*?

- (a) The major etiologies associated with the development of hyponatremia included abdominal hysterectomy and exploratory laparotomy.
- (b) Hyponatremia may have developed in response to SIADH following mild head injury.
- (c) The most common causes of hyponatremia included vomiting, diarrhea, hepatic cirrhosis, drug-induced disorders, and SIADH.
- (d) Hyponatremia induced by salt-wasting syndrome occurred most frequently after elective surgical procedures including transluminal dilation of the right coronary artery.

6. A patient requires immediate fluid resuscitation using intravenous NaCl 0.9%. Based on current evidence to limit potential neurologic injury from osmotic demyelination syndrome, which of the following rates of sodium correction is *correct*?

- (a) no more than 1 mEq/L/h and no more than 16 mEq/L per 24 hours
- (b) no more than 1 mEq/L/h and no more than 18 mEq/L per 24 hours
- (c) no more than 2 mEq/L/h and no more than 18 mEq/L over the first 48 hours
- (d) no more than 2 mEq/L/h and no more than 24 mEq/L over the first 48 hours

7. Which of the following monitoring parameters are *most* appropriate for the management of hyponatremia?

- (a) serum sodium, serum potassium, and hemodynamics
- (b) serum sodium, serum bicarbonate, hemodynamics, and creatine kinase
- (c) serum sodium, hemodynamics, urine and serum osmolality, and arginine vasopressin levels
- (d) serum sodium, hemodynamics, urine and serum osmolality, urine output, and weight

8. A 47-year-old female was hospitalized approximately 48 hours ago for an acute change in mental status. The following laboratory parameters (reference range) are determined: blood pressure 137/82 mm Hg (120/80), serum sodium 100 mEq/L (135–146), plasma osmolality 257 mOsmol/kg (278–305), urine sodium 45 mEq/24 h (40–220), and urine osmolality 455 mOsmol/kg (50–1200). Which of the following is the *most* appropriate treatment option for acute symptomatic hyponatremia?

- (a) fluid restriction 500–1000 mL/day
- (b) NaCl 3% infusion with or without furosemide

- (c) demeclocycline
(d) urea
9. A patient with a recent history of peripheral leg edema was prescribed a loop diuretic (furosemide) 20 mg once daily, but the patient has been taking it 3 times daily for the past week. Laboratory results (reference) include: blood pressure 82/44 mm Hg (120/80), serum sodium 112 mEq/L (135–146), plasma osmolality 272 mOsmol/kg (278–305), and urine sodium 56 mEq/L (>20). Based on subjective and objective data, which of the following is the *most* accurate treatment at this time?
- Increase the furosemide dose to 40 mg 3 times daily and administer conivaptan HCl.
 - Increase the furosemide dose to 40 mg 3 times daily and administer demeclocycline.
 - Discontinue furosemide and administer NaCl 0.9% by intravenous infusion.
 - Discontinue furosemide and initiate fluid restriction of 500 mL/day.
10. Which of the following statements about chronic asymptomatic hyponatremia is *true*?
- Demeclocycline is the preferred treatment due to its potential to limit nephrotoxicity.
 - Lithium increases the antidiuretic action of AVP by increasing V₂-receptor-mediated stimulation of adenylate cyclase.
 - Fluid restriction of 500–1000 mL/day for an adult is the preferred method to correct the electrolyte disturbance.
 - Urea can be used safely in patients with impaired renal function, intracranial bleeding, and liver failure.
11. Which of the following initial dosing strategies utilizing conivaptan HCl by the intravenous route for the treatment of euvolemic hyponatremia is *true*?
- loading dose of 20 mg administered over 30 minutes, followed by 20 mg administered in a continuous intravenous infusion over 24 hours
 - loading dose of 20 mg administered over 30 minutes, followed by 20 mg administered in a continuous intravenous infusion over 48 hours
 - loading dose of 40 mg administered over 30 minutes, followed by 40 mg administered in a continuous intravenous infusion over 24 hours
 - loading dose of 40 mg administered over 30 minutes, followed by 40 mg administered in a continuous intravenous infusion over 48 hours
12. Concurrent administration of conivaptan and simvastatin may result in which of the following effects on the AUC of simvastatin?
- twofold increase
 - threefold increase
 - twofold decrease
 - threefold decrease
13. Based on current evidence, which of the following adverse events has been identified to occur the most often with intravenous conivaptan?
- thirst
 - hypokalemia
 - headache
 - phlebitis
14. The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial was conducted to evaluate:
- tolvaptan in a dose ranging study.
 - lixivapan in a pharmacokinetic study.
 - tolvaptan versus fluid restriction on serum sodium concentrations.
 - lixivaptan effect on free water clearance.
15. Based on current evidence from published clinical trials, lixivaptan has been evaluated in which of the following patient populations?
- head injury and SIADH
 - head injury, renal failure, and liver failure
 - CHF, renal failure, and diabetes insipidus
 - CHF, cirrhosis with ascites, and SIADH