Critical Decisions in Emergency Medicine™

Volume 26 • Number 14

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2012
October

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American College of Emergency Physicians®
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Contributors

Vikramjit Singh Gill, MD, wrote **"Lower Gastrointestinal Bleeding."** Dr. Gill is an attending physician in the Department of Emergency Medicine at Mercy Anderson Medical Center in Cincinnati, Ohio.

Amal Mattu, MD, FACEP, reviewed "Lower Gastrointestinal Bleeding." Dr. Mattu is professor and vice chair, Department of Emergency Medicine, and director of faculty development and emergency cardiology fellowships at the University of Maryland School of Medicine in Baltimore.

Kevin S. Barlotta, MD, FAAEM, FACEP, and **James S. Booth, MD,** wrote **"Oral Hypoglycemic Agents."** Dr. Barlotta is associate professor and assistant residency director in the Department of Emergency Medicine, and medical director of the Department of Critical Care Transport at the University of Alabama at Birmingham Hospital, in Birmingham, Alabama. Dr. Booth is clinical informatics fellow in the Department of Emergency Medicine at the University of Alabama at Birmingham Hospital, Birmingham, Alabama.

George L. Sternbach, MD, FACEP, reviewed "Oral Hypoglycemic Agents." Dr. Sternbach is a clinical professor of surgery at Stanford University Medical Center in Stanford, California, and an emergency physician at Seton Medical Center in Daly City, California.

Frank LoVecchio, DO, MPH, FACEP, reviewed the questions for these lessons. Dr. LoVecchio is research director at the Maricopa Medical Center Emergency Medicine Program and medical director of the Banner Poison Control Center, Phoenix, Arizona, and a professor at Midwestern University/Arizona College of Osteopathic Medicine in Glendale, Arizona.

Louis G. Graff IV, MD, FACEP, is Editor-in-Chief of *Critical Decisions*. Dr. Graff is professor of traumatology and emergency medicine at the University of Connecticut School of Medicine in Farmington, Connecticut.

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Commercial Support. There was no commercial support for this CME activity.

Target Audience. This educational activity has been developed for emergency physicians.

Lesson 27

Lower Gastrointestinal Bleeding

Vikramjit Singh Gill, MD

Objectives

On completion of this lesson, you should be able to:

1. List the most common causes of lower gastrointestinal (GI) bleeding.
2. Describe the approach for resuscitation and the ultimate treatment options for patients who present with lower GI bleeding.
3. Explain the different diagnostic strategies available to find the etiology of lower GI bleeding.
4. Describe when angiography is the most appropriate therapy modality for a patient.
5. Discuss which patients should be admitted to the hospital and which ones can be safely discharged from the emergency department.

From the EM Model

1.0 Signs, Symptoms, and Presentations

1.2 Abdominal

Lower gastrointestinal (GI) bleeding has an annual incidence of approximately 25 cases per 100,000 population. Lower GI bleeding is bleeding that originates distal to the ligament of Treitz. It is a diagnosis that emergency physicians face periodically. The causes of lower GI bleeding include diverticular disease (17% to 40%), angiodysplasia (9% to 21%), colitis (2% to 30%), anorectal disease (4% to 10%), postpolypectomy bleeding (11% to 14%), small bowel bleeding (2% to 9%), and upper GI bleeding (0% to 11%).[1]

The incidence of lower GI bleeding increases with age, with a greater than 200-fold increase seen from the second to eighth decade.[2] The incidence is higher in men than in women, and the mortality rate is approximately 4%, with higher rates seen in the elderly, typically over the age of 60. Patients who need surgery and those who have comorbid conditions have an increased risk of mortality.

Lower GI bleeding can be a simple hemorrhoidal bleed or hemorrhagic shock that can be life-threatening. The astute emergency physician must be ready to recognize the life-threatening lower GI bleed in a timely manner, choose the most appropriate diagnostic study, and concurrently stabilize the patient for the opportunity of definitive therapy.

Case Presentations

Case One

A 63-year-old man with a history of hypertension and type 2 diabetes mellitus presents because he has noticed bright red blood coming from his rectum during bowel movements for the past three days. He states that his past six stools have looked like this. He also has been having left-sided abdominal pain that developed during this time. He denies vomiting, chest pain, shortness of breath, fever, and chills.

Physical examination reveals a diaphoretic man in mild distress. His initial vital signs are blood pressure 76/44, pulse rate 120, respiratory rate 24, and temperature 37°C (98.6°F). Examination of his head and neck reveals pale conjunctivae and tongue, dry mucous membranes, and a patent airway. Pulmonary and heart examinations do not reveal any abnormalities. His abdomen is tender in the left lower quadrant, without rebound; there is no distention. His extremities are cool to touch, and there is decreased capillary refill. His neurologic examination is nonfocal.

The patient is placed on a cardiac monitor, and two large-bore intravenous lines are placed. An ECG reveals no evidence of ischemia. A chest radiograph is unremarkable. He is immediately given a bolus of normal saline and is typed and cross-matched for 2 units of blood. Laboratory studies reveal a WBC count of 14,000 cells/mm^3 and a hemoglobin of 6 g/dL; platelet count and coagulation profile are normal. After the patient receives a fluid bolus and one unit of blood, he has another episode of bright red bloody stool in the emergency department.

Critical Decisions

- How aggressively should ischemic colitis be managed?
- Is the use of a nasogastric tube effective in distinguishing upper GI bleeding from lower GI bleeding?
- For which presentations of lower GI bleeding should angiography be considered?
- When should surgery be considered for a patient who presents with lower GI bleeding?
- Which patients with lower GI bleeding require hospitalization?

■ Case Two

An 82-year-old woman with a history of atrial fibrillation and coronary heart disease presents with severe left-sided abdominal pain that started one day ago. The pain is described as crampy, and onset was sudden. Prior to coming to the emergency department she had developed bloody diarrhea that was bright red. She denies chest pain, shortness of breath, vomiting, fever, and chills. Her current medications are warfarin, metoprolol, and simvastatin.

Physical examination reveals a woman in moderate distress. Her vital signs are blood pressure 100/54, pulse rate 101, respiratory rate 20, and temperature 37°C (98.6°F). Her pulmonary examination is unremarkable. She is in atrial fibrillation without murmur. The abdominal examination reveals left-sided abdominal pain and tenderness to palpation, without rebound. There is some guarding but no distention or rigidity. Rectal examination reveals gross blood.

The patient is placed on a cardiac monitor, and two large-bore intravenous lines are placed. An ECG shows atrial fibrillation but no signs of cardiac ischemia. A chest radiograph is unremarkable, and no free air is present. Laboratory studies reveal a hemoglobin of 9 g/dL and an INR of 2.

■ Case Three

A 29-year-old man presents after noticing some bright red blood in the toilet after several bowel movements. He states that it is not painful for him to have his bowel movements. This has never happened to him before. He denies any chest pain, abdominal pain, shortness of breath, fevers, and chills.

Physical examination reveals a comfortable-appearing young man who does not appear toxic. Vital signs are blood pressure 125/75, pulse rate 90, respiratory rate 16, and temperature 36°C (96.8°F). His head, neck, heart, and pulmonary examinations are unremarkable. The abdominal examination is unremarkable as well, with normal bowel sounds and no tenderness. Rectal examination reveals tenderness and a small amount of bright red blood.

The patient is placed on a cardiac monitor, and an intravenous line is established. His hemoglobin level is 12 g/dL, and the remainder of his laboratory evaluation is unremarkable.

Causes of Lower Gastrointestinal Bleeding

Diverticular Disease

Most diverticular disease in Western countries is located in the sigmoid and left colon. Risk factors include constipation, diets lacking in fiber, and advanced age. Diverticulosis occurs in approximately 30% to 50% of adults in developed countries and is the most common cause of lower GI bleeding. Even though diverticular disease occurs predominantly in the left colon, diverticula in the right colon are responsible for 50% to 90% of all diverticular bleeds when angiography is positive.[2] Approximately 10% to 25% of patients with diverticulosis will go on to develop diverticulitis, although diverticulitis is seldom associated with lower GI bleeding. Most of the diverticula in the colon are acquired, with the incidence increasing with age.[3] Approximately 70% to 80% of diverticular bleeds will resolve spontaneously, but 25% to 30% will be associated with rebleeding.[4]

Angiodysplasia

Angiodysplasia is a type of arteriovenous malformation that can occur anywhere in the GI tract. Lesions develop because of chronic intermittent partial obstruction of submucosal veins from colonic muscle wall contraction. This will lead to dilated and tortuous submucosal veins that are prone to bleeding.[4] These lesions most commonly occur in the cecum and ascending colon and are responsible for approximately 20% to 30% of the acute lower GI bleeding.[2] Angiodysplasias occur with increasing frequency as patients age. The bleeding that is associated with angiodysplasias typically is painless and self-limited.

Colitis

Colitis can be divided in three categories: ischemic, inflammatory, and infectious. Patients who present to the emergency department with colitis typically will have painful bleeding. Ischemic colitis is more common in the elderly population. Ischemic colitis develops usually in the "watershed areas" of the colon, which include the splenic flexure and rectosigmoid junction. These areas are affected the most because of reduced collateral circulation.[5] Risk factors such as cardiac arrhythmias and low-flow states like heart failure, hypovolemia, and sepsis are associated with ischemic colitis. It is important to consider this diagnosis

in elderly patients with lower abdominal pain and bloody diarrhea and with any of the these risk factors. Typically, the bleeding associated with ischemic colitis is not severe. If bleeding is severe, an alternative diagnosis should be sought.[5]

CRITICAL DECISION

How aggressively should ischemic colitis be managed?

Usually, patients with this diagnosis may be managed conservatively with intravenous fluids, bowel rest, and broad-spectrum antibiotics. About 20% of these patients will require surgical intervention because of peritonitis or clinical deterioration.[5]

Inflammatory bowel disease, which includes both Crohn disease and ulcerative colitis, is a common source for lower GI bleeding. It is difficult to differentiate these two disease entities, but these diagnoses should be considered in any patient who presents with diffuse lower abdominal pain and hematochezia. Although the likelihood is low that patients with inflammatory bowel disease will present with life-threatening bleeding, as many as 6% of patients will experience severe lower GI bleeding.[6]

Infectious colitis is another cause of lower GI bleeding. The most common agents to cause lower GI bleeding are *Escherichia coli* O157:H7 and *Salmonella*. In addition to these, *Campylobacter, Shigella,* and *Entamoeba histolytica* are other bacterial causes for lower GI bleeding. A patient infected with any one of these agents may give a history of crampy abdominal pain accompanied by watery diarrhea, which can lead to grossly bloody diarrhea. Patients can have fevers and tenesmus as well.[2]

Neoplasm

Patients with neoplasms rarely present with severe lower GI bleeding, but rather with occult bleeding. Typically, patients with neoplasms are older than 50 years and have recurrent, low-grade bleeding. Patients will sometimes present with nonspecific symptoms such as fatigue or weakness. In addition, they may have iron-deficiency anemia, weight loss, or a change in the frequency or caliber of their stool.[7]

Anorectal Disease

Hemorrhoidal bleeding is typically bright red and may be described as dripping, squirting into, or filling the toilet bowl. Hemorrhoids are classified as either internal (above the dentate line) or external (below the dentate line). Any patient suspected of having hemorrhoids should have a digital rectal examination and anoscopy. Hemorrhoidal disease accounts for approximately 4% to 10% of acute severe hematochezia presentations. One should keep in mind that even if anorectal disease is identified, a more proximal bleeding source could still be causing the GI bleed.[6] It is reasonable to recommend that a patient being discharged with the diagnosis of hemorrhoidal bleeding seek a more complete colonic evaluation as an outpatient.

Postpolypectomy Hemorrhage

Most colonic polyps are currently being treated by endoscopic polypectomy. The incidence of postpolypectomy bleeding cited in the literature varies, but it is increasing. Bleeding at the time of the polypectomy is usually arterial. Delayed bleeding, which will present several days after the procedure, is usually self-limiting and resolves with supportive care in about 70% of cases.[2]

Aortoduodenal Fistula

Lower GI bleeding from an aortoduodenal fistula is a rare but potentially deadly event. There are two types of aortoduodenal fistulas, primary and secondary. Primary aortoduodenal fistulas are not as common and occur in patients with abdominal aortic aneurysm without repair. Secondary aortoduodenal fistulas usually occur in patients who have had an abdominal aortic aneurysm repaired. Patients with these types of fistulas will develop a small herald bleed followed by a massive hemorrhage.[8] If a patient with a known abdominal aortic aneurysm repair comes in with a small or massive bleed, emergent consultation with a vascular surgeon should be arranged because of the possibility of an aortoenteric fistula.[8]

Initial Assessment

A patient who presents with an acute lower GI bleed that involves hemodynamic compromise should be resuscitated immediately while the physician simultaneously obtains a history and performs the physical examination. As with any patient who presents acutely, the patient should be assessed for airway compromise and for unstable vital signs. Patients with acute lower GI bleeding can have decreased oxygen-carrying capacity, which could lead to cardiac ischemia. These patients should be placed on supplemental oxygen. Place patients on a cardiac monitor. Intravenous access should be obtained with large-bore peripheral intravenous lines, and fluids, preferably crystalloid, should be readily available. Blood products (type O negative blood) should be available and considered when patients present with massive hemorrhage. Laboratory values obtained should include a CBC, serum electrolytes (specifically BUN), coagulation profile, and type and screen, with certain cases requiring cross-match. An ECG should be obtained in all patients with moderate to severe GI bleeding to assess for cardiac ischemia, especially in patients with known cardiovascular disease. The emergency physician should consider the use of a nasogastric tube in certain clinical situations to differentiate upper and lower GI bleeding. Finally, a urethral catheter should be placed to adequately monitor urine output as a means of assessing organ perfusion.

While resuscitative measures are ongoing, a thorough history should be obtained. Ask about the frequency, color, consistency, and duration of the bowel movements. Hematochezia

typically is associated with colonic bleeding, while melanotic stools usually represent an upper GI source. Melanotic stools are present in approximately 70% of patients with upper GI bleeding compared to in only 20% to 30% of patients with lower GI bleeding.[9] Lower GI bleeding can present with melena caused by a delayed transit time when the bleeding starts in the small bowel or the ascending colon. It is important to know if the patient is taking aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, or anticoagulants because of their strong association with lower GI bleeding, particularly diverticular bleeding.[2] A history of hypovolemia and lower GI bleeding suggests ischemic colitis. The emergency physician should inquire about previous GI bleeding, a history of diverticulosis, and recent colonoscopy with polypectomy.

The physical examination should focus on whether the patient is in shock or not. This can be determined by the presence of hypotension or tachycardia. The patient's mental status can evaluate cerebral perfusion in the presence of a lower GI bleed. It is important to note whether the patient has decreased pulses and cool, clammy skin, as these are additional signs of poor perfusion. Patients who are taking β-blocker drugs may not exhibit tachycardia in the face of a hypovolemic or hemorrhagic state. A cardiac examination can determine the presence of an arrhythmia, such as atrial fibrillation, or murmur, which should raise suspicion for ischemic colitis. Assess the abdomen for tenderness, masses, and previous abdominal surgeries. An anorectal examination should be performed in all patients presenting with lower GI bleeding. This should include a digital rectal examination and, if the patient is stable, the use of anoscopy. The rectal examination can reveal occult or gross blood in addition to melena or hematochezia. Digital examination will also reveal any polyp or tumor. Anoscopy can identify fissures and fistulas, along with hemorrhoids. Other diagnostic tools such as proctosigmoidoscopy and flexible sigmoidoscopy can be used to evaluate for lower GI bleeding but rarely are used in the emergency department setting.

Diagnostic Strategies

Nasogastric Aspirate and Lavage

At times, the origin of GI bleeding can be elusive. Classically, melanotic stools represent a sign of upper GI bleeding, but bleeding from the small bowel or the right side of the colon with slow transit time can produce this as well. Furthermore, hematochezia is usually thought to be from a lower GI bleeding source, although a brisk upper GI bleed can also produce this.

CRITICAL DECISION

Is the use of a nasogastric tube effective in distinguishing upper GI bleeding from lower GI bleeding?

In cases where the bleeding source cannot be ascertained based on clinical predictors for either upper or lower GI bleeding, a diagnostic nasogastric aspirate can be clinically high yield.[10] Witting et al[10] found three clinical factors that would independently predict an upper GI source for patients with GI bleeding without hematemesis. The three factors are age younger than 50 years, the presence of black-colored stool, and a BUN/creatinine ratio greater than or equal to 30. Only 5% of patients with none of these clinical factors had an upper GI source for their bleeding, while patients with two or more of the factors most likely had an upper GI source. In the latter scenario, an esophagogastroduodenoscopy (EGD) is indicated, and nasogastric aspiration should be discussed with the endoscopist. Witting et al concluded that patients with only one of the factors would be excellent candidates for nasogastric aspiration to determine the source of their bleeding.[10,11] If nasogastric aspiration is positive, the clinician should make arrangements for an upper endoscopy. If the aspirate is negative, the clinician should suspect a bleed distal to the ligament of Trietz, and the evaluation should be tailored towards that.

Colonoscopy

Colonoscopy is the diagnostic procedure of choice in patients with stable lower GI bleeding. It can be done in patients who have been hemodynamically resuscitated. It should be considered for patients with bleeding that is self-limiting or if there is high probability of a localized lesion.[3] Typically, a colonoscopy is not done urgently so that there is time to prepare the colon with a polyethylene glycol solution to best visualize the colon and decrease the risk of bowel perforation. There is data, however, to suggest that performing a colonoscopy urgently can be beneficial. Several recent studies have demonstrated that an urgent rather than a delayed colonoscopy leads to definitive diagnosis and shorter hospital stays.[6,9] In certain cases of patients presenting with severe hematochezia, it may be necessary to perform an EGD to rule out a brisk upper GI bleed. If this study is negative, a colonoscopy should be performed to identify the source of lower GI bleeding. The clinician should consider the radiographic studies below rather than colonoscopy in patients who present with moderate to severe hemorrhage.

Radionuclide Imaging

Technetium scanning using Tc 99m-labeled RBCs is a noninvasive technique that can localize the source of lower GI bleeding (Figure 1). Technetium scanning requires a bleeding rate of at least 0.1 to 0.5 mL per minute to be an effective study. It is less specific than angiography but more sensitive. On average, approximately 45% of tagged RBC nuclear scans will be positive. If a scan is done within 2 hours of erythrocyte injection, the source of the bleed can be identified 95% to 100% of the time. If the scan is done 2 hours after injection, the accuracy drops to between 57% to 67%.[12] If a

scan is positive for a bleeding site, this information is used for direct therapy with either angiography or surgery.

Angiography

CRITICAL DECISION

For which presentations of lower GI bleeding should angiography be considered?

Angiography has the advantage not only of localizing the source of lower GI bleeding, but also of providing treatment once the site is identified. Angiography does require that the rate of bleeding be brisk in order to identify the site of hemorrhage; typically a bleeding rate of 0.5 to 1 mL per minute is required. Angiography is often used in the clinical setting of massive, continuous lower GI bleeding. The overall sensitivity of angiography ranges from 40% to 86%. This diagnostic modality is not without risk, however, and carries a complication rate of approximately 2% to 9%. Some of the complications include contrast reactions, acute renal failure, arterial thrombosis, and dissection.[2,6,9] Once a bleeding source is identified, it is usually treated with either selective arterial infusion of vasopressin or embolization of the bleeding vessel by gel foam or coil springs.[5]

Treatment

As previously mentioned, any acute lower GI bleed that involves hemodynamic compromise requires immediate attention. Assessment for airway compromise and unstable vital signs is paramount. The patient should be placed on cardiac monitoring, and supplemental oxygen should be given. Intravenous access with at least two large-bore peripheral intravenous lines should be established. Blood products (Type O negative blood for patients in need of immediate infusion) should be available and administered early in patients with massive lower GI hemorrhage. An ECG should be obtained to assess for cardiac ischemia, especially in patients with cardiovascular disease.

Colonoscopy usually is performed in patients with stable lower GI bleeding. When bleeding is self-limited there is high probability of localizing the culprit lesion. Consultants prefer to perform a colonoscopy on a delayed basis, although recent studies have shown some benefit in performing an urgent colonoscopy. This may lead to definitive diagnosis and a shorter hospital stay.[6,9]

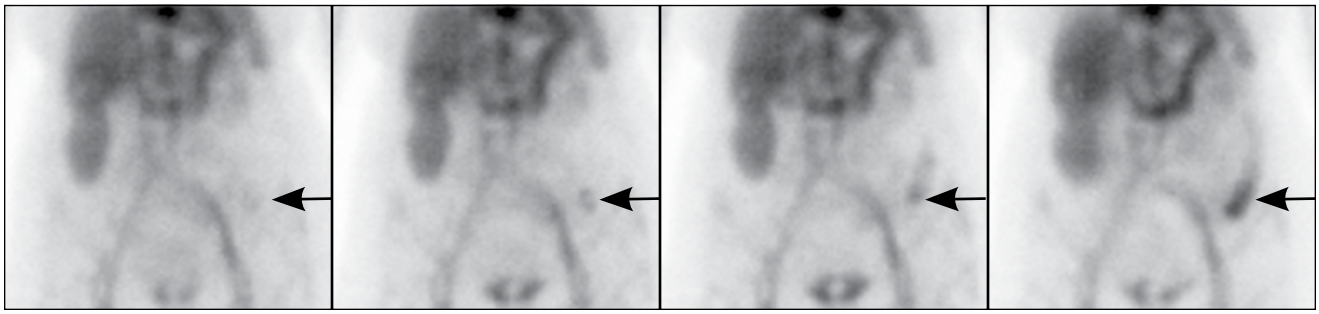
Angiography has both diagnostic and therapeutic capabilities. With this modality, lower GI bleeding can be identified and at the same time be treated. There are several different treatment options available with the use of angiography. Intra-arterial infusion of vasopressin and arterial embolization are two common options. Vasopressin is a vasoconstrictive agent that can reduce blood flow and facilitate hemostasis in a bleeding vessel. Vasopressin infusions are typically more effective when diverticulosis rather than angiodysplasia is the culprit for the bleeding because bleeding in diverticulosis is usually from an arterial source, and bleeding from angiodysplasia is usually from a venous source. Success rates with vasopressin infusions range from 36% to 100%, with recurrent bleeding rates of up to 50% when vasopressin is stopped.[13] Another option, which is used more often, is arterial superselective embolization. This is typically done with the use of either an absorbable gelatin compressed sponge or coil springs to stop the bleeding vessel.[6] If recurrent bleeding occurs with either of these options, operative therapy is usually the next option.

CRITICAL DECISION

When should surgery be considered for a patient who presents with lower GI bleeding?

Surgery should be considered in the acute setting if the treatment modalities are not successful. Typically, surgery becomes an option in continued or rebleeding cases, but in rare cases, when patients present with severe bleeding with active exsanguination, surgery may be the first and only option. Approximately 10% to 25% of patients with acute

Figure 1.
Technetium study of a 67-year-old patient; images shown at 0, 5, 20, and 60 minutes after injection. A focus of increased tracer activity is visible at approximately 5 minutes into the study in the region of the mid to lower left abdomen (arrows), indicating active bleeding in the descending colon. Image courtesy of Joshua S. Broder, MD, FACEP.



lower GI bleeding will need emergent surgery. The indications for surgery in the acute setting typically include transfusion of more than 4 units of packed RBCs in a 24-hour period with active or recurrent bleeding, persistent hemodynamic instability with active bleeding, and persistent, recurrent bleeding.[6] A subtotal colectomy is the surgery of choice, although a specific bleeding site should be identified prior to this. This procedure is associated with low morbidity, low mortality, and low rebleeding rates.[6] A total colectomy can be required if no bleeding site is identified.

Disposition

CRITICAL DECISION

Which patients with lower GI bleeding require hospitalization?

There are few evidence-based criteria or decision algorithms applicable to the disposition of emergency department patients with lower GI bleeding.[7] After the initial assessment and stabilization process, emergency physicians must decide which diagnostic modality should be used to identify the source of the bleeding. Appropriate consultation with a gastroenterologist, interventional radiologist, or surgeon, depending on the clinical situation and potential diagnostic or therapeutic modality, should be done in a timely manner. Patients with hemodynamic compromise, moderate to severe bleeding, or high risk for rebleeding after intervention should be admitted for ICU monitoring. Some physicians will admit to the ICU for patients with ongoing bleeding. Patients with lower GI bleeding who are hemodynamically stable and have no major comorbidities or evidence of ongoing bleeding can safely be admitted to the floor. If the patient is considered to be low risk, with normal vital signs, no significant comorbidities, and direct visual evidence of hemorrhoidal bleeding with anoscopy, then that patient can be safely discharged from the emergency department after several hours of observation.[14]

Pearls

- Involve a gastroenterologist and interventional radiologist early in the management of lower GI bleeding that can be treated without surgery.
- Ischemic colitis may be treated conservatively if it is localized. If it is extensive, get a surgeon on the phone.
- The nasogastric tube can be the best tool in situations in which patients present with hematochezia or melena and the source cannot be localized to the upper or lower GI tract.
- If a patient is bleeding from the rectum and has a known repaired aortic abdominal aneurysm, get a vascular surgeon on the phone quickly.
- Instruct patients to discontinue drugs such as NSAIDs that can worsen lower GI bleeding, especially if used in combination with anticoagulant and antiplatelet drugs.

Pitfalls

- Assuming a patient's hematochezia is from the lower GI tract and not considering a brisk upper GI bleed with the potential to be deadly in a short period of time.
- Forgetting that a potentially more ominous site of bleeding could be hiding more proximally in a patient who presents with rectal bleeding and who is found to have external hemorrhoids,
- Not considering cardiac ischemia in the face of lower GI bleeding. Obtain an ECG and keep ischemia in mind, especially in patients with coronary artery disease; if patients are anemic, have a low threshold for giving them blood.

Case Resolutions

■ Case One

In the case of the man who presented with bright red blood per rectum and who had another episode in the emergency department, he received several liters of fluids along with 3 total units of blood. Gastroenterology and interventional radiology services were called after the patient's hematochezia episode in the emergency department. An angiography suite was prepared immediately. The patient's vital signs had become more stable; blood pressure was 100/55 and pulse rate was 100. In the angiography suite, the active bleeding site was identified and coiled several times. The patient was then transferred to the ICU for further management. He did not have any further episodes of bleeding, and his vital signs improved. He was ultimately found to have extensive diverticular disease.

■ Case Two

In the case of the elderly woman who had sudden onset of abdominal pain with bloody diarrhea afterwards, she received a CT scan of the abdomen and pelvis, which revealed areas of low attenuation consistent with edema and bowel-wall thickening of some areas in the colon. She was started on intravenous fluids and broad-spectrum antibiotics. The patient was admitted to the ICU, where a colonoscopy showed that she had limited areas of ischemia in the sigmoid and descending colon. She continued to receive conservative therapy and broad-spectrum antibiotics. She was discharged from the hospital on hospital day 6 with no further complications.

■ Case Three

In the case of the young man who noticed some bright red blood in the toilet after several bowel movements, an anoscopy was done in the emergency department, which

showed two moderately sized internal hemorrhoids that were not actively bleeding. It was decided that he was at low risk for rebleeding; he was observed for several hours in the emergency department and did well. He received a prescription for stool softeners and was instructed to start a high-fiber diet and do warm sitz baths. Close followup was arranged for him with his primary care physician.

Summary

Lower GI bleeding is a disease process that all emergency physicians will come across during their careers. Any patient with lower GI bleeding could require early and aggressive resuscitation while the physician simultaneously looks for the bleeding source and considers the need for consultants in certain cases. A multidisciplinary team for diagnostic and treatment purposes, consisting of gastroenterology, interventional radiology, and surgery, may be warranted depending on the clinical situation.

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The LLSA Literature Review

"The LLSA Literature Review" summarizes articles from ABEM's "2013 Lifelong Learning and Self-Assessment Reading List." These articles are available online in the ACEP LLSA Resource Center (www.acep.org/llsa) and on the ABEM Web site.

Article 6

Avoiding Circulatory Complications During Endotracheal Intubation and Initiation of Positive Pressure Ventilation

Reviewed by J. Stephen Bohan, MS, MD, FACEP; Harvard Affiliated Emergency Medicine Residency; Brigham and Women's Hospital

Manthous CA. Avoiding circulatory complications during endotracheal intubation and initiation of positive pressure ventilation. *J Emerg Med.* 2010;38(5):622-631.

This review article deals with the interaction between the pathophysiology of respiratory failure and the effects of positive pressure ventilation initiated after endotracheal intubation, noting that the different causes of respiratory failure require different interventions. It does not deal with patients who require intubation simply to maintain airway competence (eg, coma or stroke patients) or apply to patients with congestive heart failure.

Hypoxemic respiratory failure is usually an alveolar disease, whereas hypercarbic respiratory failure represents a mismatch between the need for ventilation and the ability of the individual to produce muscular expiratory force to match the need. Patients, of course, do not always respect our partitioning their problem for our intellectual convenience and often present with an admixture of the two types (eg, emphysema with pneumonia).

Hypotension occurs in as many as a third of patients who, because of intubation and sedation/paralysis, transition from negative pressure (spontaneous) ventilation. This occurs because of insufficient venous return. Recommended preventive measures are: 1) use local anesthesia when possible; 2) use small doses of sedatives frequently versus bolus administration; 3) use volume resuscitation expectantly; 4) use pure vasoconstrictor agents to support vascular tone; 5) begin with a positive end-expiratory pressure (PEEP) of 5 cm water and 8 mL/kg tidal volume; and 6) vary these settings to achieve a constant plateau pressure of 20 to 30 cm water.

Many morbid conditions cause acid-base disturbance, which also appears in other conditions because of protracted periods of respiratory failure. This state, if untreated, eventually causes cardiac arrhythmias and arrest. It is important in such states to start ventilation to match the patient's preintubation rate so as to promote carbon dioxide excretion. Additionally, the interventions listed above (to avoid hypotension) are important.

In patients with severe obstructive disease such as severe asthma, initial settings should be particularly attentive to inspiratory and expiratory ratios as failure to manage this correctly can result in "breath stacking," that is, the retention of some of the forced inspiratory air because of inadequate time to expire against obstruction. Attention to tidal volume here is important as smaller volumes can also aid in prevention of breath stacking. As treatment reduces the obstruction, PEEP levels may be reduced and tidal volume carefully increased.

This same attention to the tuning of the PEEP/tidal volume relationship applies in management of acute respiratory distress syndrome. Again, the maintenance of a plateau pressure of less than 30 cm water reflects a good working combination of the two.

Highlights

- Because emergency physicians usually see patients with respiratory failure when they are at their worst, knowledge of the pathophysiology and how assisted ventilation can make the patient both better and worse is important.
- Postintubation hypotension is common and should be managed expectantly.
- As patients' pathology varies so should their treatment; standard "cookbook" interventions can be dangerous.
- Maintenance of a plateau pressure of less than 30 cm of water is a suitable goal across most types of respiratory failure.

Lesson 28

Oral Hypoglycemic Agents

Kevin S. Barlotta, MD, FAAEM, FACEP, and James S. Booth, MD

Objectives

On completion of this lesson, you should be able to:

1. Describe the clinical manifestations of patients presenting with symptomatic hypoglycemia.
2. Discuss the pharmacologic methods of glycemic control associated with oral hypoglycemic agents.
3. List the oral hypoglycemic agents currently used to treat diabetic patients.
4. Describe the major adverse effects stemming from the newer hypoglycemic agents.
5. Discuss the factors that place patients at risk for adverse effects secondary to oral hypoglycemic agents.
6. Describe the management strategies for and disposition of patients with adverse effects related to hypoglycemic agents.

From the EM Model

5.0 Endocrine, Metabolic, and Nutritional Disorders

5.4 Glucose Metabolism

Diabetes mellitus affects over 25 million people (>8%) in the United States. It is the seventh leading cause of death and a major cause of heart disease, stroke, kidney failure, peripheral vascular disease, and acquired blindness.[1] It is estimated that more than 200 million people have diabetes worldwide, with type 2 diabetes making up 90% of the cases.[2]

With such an astounding prevalence, the treatment of diabetes represents a major market for pharmaceutical development and has led to the introduction of several new oral hypoglycemic agents over the past two decades. As physicians and patients look to minimize the long-term effects of diabetes through tighter glycemic control, short-term complications, including medication side effects and hypoglycemic episodes, remain common. Although the number of exposures to oral hypoglycemic agents reported to poison control centers has decreased from approximately 11,000 to 6,000 between the years 2004 and 2010, these numbers are considered a fraction of the true incidence of toxic exposures.[3]

The use of oral hypoglycemic agents in the setting of hypoglycemia has critical implications in the treatment strategies and safe disposition of patients. Emergency physicians are often the first to encounter patients with complications resulting from the treatment of diabetes. Therefore, it is essential that emergency physicians be familiar with these newer hypoglycemic agents and the management and disposition of patients with related adverse effects.

Case Presentations

Case One

A 51-year-old woman with type 2 diabetes mellitus presents via ambulance with a history of altered mental status. EMS providers report finding her minimally responsive at home with a finger-stick glucose of 33 mg/dL. They established intravenous access and administered 1 ampule of dextrose 50% in water. The patient is now alert and oriented and has no complaints. The patient has been taking her prescribed glyburide once daily and reports recently starting a new medication called exenatide.

Her vital signs are blood pressure 130/80, pulse rate 76, respiratory rate 18, oral temperature 36.5°C (97.8°F), and oxygen saturation 98% on room air. The patient is in no distress and follows all commands. Her heart has a regular rhythm without murmur, and her lungs are clear to auscultation bilaterally. Her abdomen is soft, and her neurologic examination is unrevealing. Her repeat finger-stick glucose level in the emergency department is 120 mg/dL.

Case Two

A 37-year-old man with type 1 diabetes is brought in by his wife after he had a concerning episode of hypoglycemia at home He reports weakness 1 hour prior to arrival, at which time his wife checked his blood sugar level, which was found to be 50

Critical Decisions

- What are the signs and symptoms of hypoglycemia?
- What factors place patients at risk for symptomatic hypoglycemia secondary to oral hypoglycemic use?
- How is hypoglycemia related to sulfonylurea use managed in the emergency department?
- What is the appropriate disposition of a patient with hypoglycemia associated with meglitinide use?
- How might α-glucosidase inhibitors affect the treatment strategy for hypoglycemia?
- How is the disposition of a hypoglycemic patient affected by associated glucagon-like peptide 1 (GLP-1) receptor agonist use?
- What clinical implications are associated with the use of dipeptidyl peptidase IV (DPP-4) inhibitors?
- How does amylin analogue use affect the disposition of a hypoglycemic patient?

mg/dL. He ingested several crackers at home, and his weakness was mildly improved. After calling his primary care physician, he was advised to go to the emergency department for further assessment.

Vital signs on arrival are blood pressure 120/70, pulse rate 106, respiratory rate 20, and temperature 36.7°C (98°F). His room air oxygen saturation is 98%. He is alert and oriented and follows all commands appropriately. He complains of mild, generalized weakness. No chest pain, palpitations, shortness of breath, fever, cough, or syncope is reported. His heart rhythm is regular, and lungs are clear. His abdomen is soft and nontender. His neurologic examination is normal. The patient's finger-stick glucose level in the emergency department is 85 mg/dL. His wife reports that he was recently started on pramlintide in addition to his short-acting insulin regimen.

Pathophysiology

Diabetes mellitus is an endocrine disorder characterized by either absolute insulin deficiency (type 1) or relative insulin deficiency in the setting of insulin resistance (type 2). Hyperglycemia results from an increase in gluconeogenesis in the liver and reduced glucose uptake by peripheral tissues. Hyperglycemia can have profound short-term and long-term effects on diabetic patients and is associated with significant morbidity and mortality. Strict glycemic control has been shown to improve the long-term microvascular complications (retinopathy, neuropathy, and nephropathy) but has an associated increased incidence of short-term complications including hypoglycemia.[4,5]

Glucose is derived from intestinal absorption, glycogenolysis (the breakdown of glycogen), and gluconeogenesis (the formation of glucose from lactate, pyruvate, amino acids, and glycerol). Plasma glucose levels are maintained at a relative steady state (typically between 60 and 150 mg/dL) by a complex interaction of insulin and counter-regulatory hormones (glucagon, cortisol, the catecholamines, and growth hormone) that serve to balance dietary glucose intake, endogenous glucose production, and glucose utilization.

Insulin is secreted by the beta cells of the pancreas in response to an elevation in blood glucose levels. It is the main hormone serving to lower glucose levels by increasing utilization and suppressing endogenous glucose production. Typically, insulin has a half-life of 3 to 10 minutes and is rapidly degraded in the liver and kidneys. Counter-regulatory hormones serve to prevent low glucose levels during a fasting state by increasing endogenous glucose production. Glucagon, secreted by the alpha cells of the pancreas, is the main counter-regulatory hormone serving to increase blood glucose. Glucagon enhances glycogenolysis and thus uses glycogen stores in the liver for glucose production. Glucagon also increases hepatic gluconeogenesis and promotes ketogenesis.

Diabetes is diagnosed by any random plasma glucose level higher than 200 mg/dL, a fasting plasma glucose concentration of more than 126 mg/dL, or a 2-hour post-load oral glucose tolerance test. Measurement of glycosylated hemoglobin (HBA_{1c}) is an important means of assessing the level of glucose control in diabetics. In the setting of hyperglycemia, glucose binds progressively and irreversibly to hemoglobin in red blood cells and thus provides an indicator of glycemic control over the preceding 6 to 8 weeks. Normal values typically range from 4% to 6% of total hemoglobin. The American Diabetes Association (ADA) currently recommends a treatment goal of an HBA_{1c} of less than 7%.

Although the mainstay of treatment for type 1 diabetes mellitus is insulin replacement, the therapeutic options for the treatment of type 2 diabetes mellitus include dietary restriction, weight reduction combined with oral hypoglycemic agents, and potential insulin replacement. Oral hypoglycemic agents serve to pharmacologically enhance the innate mechanism of glucose metabolism and utilization to improve overall glycemic control.

Pharmacology

Historically, there are three major mechanisms involved in oral hypoglycemic and antidiabetic therapy (Table 1). Secretagogues increase the amount of insulin released by the pancreas and include sulfonylureas and meglitinides. Sensitizers increase the sensitivity of target organ responsiveness to insulin and include biguanides and thiazolidinediones. α-Glucosidase inhibitors decrease glucose absorption from the gastrointestinal tract. Recently, several newer agents, including glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase IV (DPP-4) inhibitors, and amylin analogues, have been developed. These agents exhibit a combination of effects and use novel mechanisms to aid in tight glycemic control (Table 2).

CRITICAL DECISION

What are the signs and symptoms of hypoglycemia?

The clinical manifestations of hypoglycemia are often associated with a serum glucose level below 50 mg/dL; however, the rate of decline and prior episodes of hypoglycemia can influence the severity of symptoms in individual patients. Common signs and symptoms range from minor tremulousness and diaphoresis to focal neurologic deficit, seizure, and coma (Table 3). Hypoglycemia can be rapidly diagnosed and easily reversed to prevent significant morbidity and mortality; therefore, emergency physicians must be vigilant for symptomatic hypoglycemia.

CRITICAL DECISION

What factors place patients at risk for symptomatic hypoglycemia secondary to oral hypoglycemic use?

Many factors can increase the likelihood that diabetic patients will develop symptomatic hypoglycemia. Patients on oral hypoglycemic agents and with renal and hepatic dysfunction, alcohol ingestion, and poor oral intake are at particularly high risk. Other common precipitating factors include increasing physical activity, sepsis, and unintentional overdoses.[6] Elderly patients are at particularly high risk of hypoglycemia due to age and potential for polypharmacy.[6] It is essential to inquire about any new medications because many (sulfonamides, salicylates, azoles, H_2-blockers, β-blockers, warfarin, and tricyclic antidepressants) have been shown to increase the risk of symptomatic hypoglycemia in patients taking oral hypoglycemic agents.

Table 1.
Basic methods of glycemic control

Secretagogues	Increase the amount of endogenous insulin secreted by the pancreas.
Sensitizers	Increase the insulin sensitivity of the target organs.
Glucose absorption inhibitors	Decrease the rate of glucose absorption from the gastrointestinal tract.

Table 2.
Hypoglycemic agents

Drug class	Basic action	Examples	Complications
Sulfonylureas	Secretagogue	Glipizide, glyburide, glimepiride	Hypoglycemia
Meglitinides	Secretagogue	Repaglinide, nateglinide	Hypoglycemia, weight gain
Biguanides	Sensitizer, inhibit hepatic glucose production, inhibit glucose absorption	Metformin	Lactic acidosis
Thiazolidinediones	Sensitizer	Rosiglitazone, pioglitazone	Hepatitis/liver injury, edema
α-Glucosidase inhibitors	Inhibit glucose absorption	Acarbose, miglitol	Bloating, flatulence
GLP-1 receptor agonists	Secretagogue, inhibit glucagon release, promote satiety	Exenatide, liraglutide	Nausea, vomiting, possible pancreatitis
DPP-4 inhibitors	Secretagogue, inhibit glucagon release, delay gastric emptying, promote satiety	Sitagliptin, saxagliptin, linagliptin	Possible nasopharyngitis, upper respiratory tract infections, headaches, urinary tract infections
Amylin analogues	Inhibit glucose absorption, inhibit glucagon release, delay gastric emptying, promote satiety	Pramlintide	Nausea, vomiting

CRITICAL DECISION

How is hypoglycemia related to sulfonylurea use managed in the emergency department?

Sulfonylureas, first developed in the 1940s, remain one of the most widely prescribed classes of oral hypoglycemic agents in the world.[7] Older, first-generation sulfonylureas have largely been replaced by more potent, second-generation agents such as glipizide, glyburide, and glimepiride. Their potential to decrease HBA_{1c} by 1% to 2% and their relatively low cost make sulfonylureas a particularly popular choice for glycemic control.[7]

Sulfonylureas are considered secretagogues and stimulate endogenous pancreatic insulin secretion by inhibiting the potassium-ATP (K_{ATP}) channels on pancreatic beta cells. Their action is dependent on functioning beta cells. Consequently, sulfonylureas are not used for type 1 diabetes. Patients with type 2 diabetes often become insulin-dependent over time, likely from beta-cell failure. As a result, the efficacy of sulfonylureas may diminish over the course of a patient's lifetime.

The most significant adverse effect of sulfonylureas is hypoglycemia. Between 1,712 and 4,148 cases of sulfonylurea overdoses were reported to poison control centers in the United States yearly over the past 6 years.[5,8]

Hypoglycemia associated with sulfonylureas can be prolonged and recurrent. The hypoglycemic effects of second-generation agents typically begin within 1 to 2 hours of dosing and last from 12 to 24 hours.[9,10] As a consequence, a patient's blood glucose level may correct with initial therapy but subsequently drop to dangerous levels again after several hours. Prolonged and severe hypoglycemia from sulfonylureas can lead to permanent neurologic damage, convulsions, or even death. The propensity of sulfonylureas to cause recurrent hypoglycemia necessitates that patients be evaluated and treated beyond the 3- to 4-hour emergency department visit with either outpatient observations services or inpatient admission depending on the physician's judgment of level of care needed.[10,11] Inpatient admission requires physician documentation that the physician judges that the patient has moderate to severe illness (risk of an adverse event if treated as an outpatient) and physician documentation that the physician judges that the patient requires inpatient treatment for more than 24 hours. Without both, outpatient observation (in an emergency department observation unit or an in-hospital observation bed) is the required level of care.

In cases of known or suspected sulfonylurea overdose, hypoglycemia typically presents within 6 to 8 hours of ingestion but can be delayed up to 16 hours. This delayed response can be falsely reassuring if a patient is euglycemic a few hours after ingestion without any intervention. Most cases of hypoglycemia associated with sulfonylureas correct with standard glucose therapy. This can include intravenous boluses of 50% dextrose with water, continuous intravenous infusions of dextrose, and oral carbohydrates once the patient is alert and able. Subcutaneous or intramuscular glucagon may be considered if intravenous access cannot be established in a timely manner, but it should not be considered definitive management.[11] In cases of refractory or recurrent hypoglycemia associated with sulfonylureas, octreotide may be used in addition to glucose administration. Octreotide inhibits insulin secretion and has been shown to be superior to glucose alone in preventing recurrent hypoglycemia.[11] It is commonly administered as 50 to 100 mcg subcutaneously every 6 to 8 hours as needed. In cases of refractory hypoglycemia, emergency physicians should always consider other serious precipitating factors such as renal failure, hepatic failure, sepsis, and adrenal insufficiency.

Table 3.
Presenting symptoms of hypoglycemia

Agitation
Altered mental status
Bradycardia
Coma
Diaphoresis
Focal neurologic deficits
Lethargy
Nausea
Seizure
Tremor

CRITICAL DECISION

What is the appropriate disposition of a patient with hypoglycemia associated with meglitinide use?

Meglitinides are a class of secretagogues similar to sulfonylureas. Like sulfonylureas, they work by inhibiting the K_{ATP} channels on pancreatic beta cells, inducing endogenous insulin release. Unlike sulfonylureas, meglitinides are considered "short-acting" secretagogues. Their onset of action is between 30 and 60 minutes, and their duration of action is approximately 4 hours.[12,13] Typically they are taken 10 to 30 minutes before meals to enhance insulin response and held when meals are skipped. Repaglinide and nateglinide are the two meglitinides available in the United States. Repaglinide, approved by the FDA in 1997, was the first major meglitinide on the market and remains the most commonly prescribed meglitinide today. Nateglinide was approved by the FDA in 2000. Repaglinide is typically dosed as 0.5 to 4 mg before meals, and nateglinide is dosed as 60 to 120 mg before meals.

As with sulfonylureas, the major side effect of meglitinides is hypoglycemia. Weight gain has also been described. Hypoglycemia associated with meglitinides can be life-threatening, but the incidence of this adverse effect is less common than with sulfonylureas. If initiated early, activated charcoal can help

prevent absorption of meglitinides in cases of large overdoses; however, standard glucose therapies resolve most cases. The short half-lives of meglitinides make recurrent hypoglycemia less common than with sulfonylureas. As a result, opinions differ regarding patient disposition. Some sources recommend admission for glucose monitoring as in sulfonylurea overdose, while other sources suggest discharge of asymptomatic patients after 4 hours of glucose monitoring.[11,13] Recurrent hypoglycemia has been shown to occur in cases of intentional, large overdoses up to 6 hours after ingestion.[10] This should lead emergency physicians to err on the side of admitting intentional overdoses.

CRITICAL DECISION

How might α-glucosidase inhibitors affect the treatment strategy for hypoglycemia?

α-Glucosidase inhibitors are a class of antidiabetic agents that blunt the postprandial rise in serum glucose by slowing the digestion and absorption of complex carbohydrates in the gastrointestinal tract. They also stimulate the release of an incretin hormone, GLP-1.

There are currently two α-glucosidase inhibitors available in the United States: acarbose and miglitol. Both medications are taken orally just before main meals and both have similar doses, ranging from 25 to 100 mg per meal. The amount of complex carbohydrates in each meal determines the efficacy of α-glucosidase inhibitors, but in general there is an average decrease of 0.5% to 0.8% in a patient's HBA_{1c} over time. Acarbose is primarily metabolized in the gut, with less than 2% absorbed systemically.[9,14] In contrast, most miglitol is absorbed and undergoes renal clearance, with a half-life of 0.4 to 1.8 hours.

The primary adverse effects of α-glucosidase inhibitors are gastrointestinal-related and include flatulence, abdominal bloating, and diarrhea.[15] Although α-glucosidase inhibitors are popular in some areas around the world, their use is limited in the United States as a result of these side effects. Hypoglycemia has not been shown to result from an isolated α-glucosidase inhibitor ingestion; however, these drugs can enhance the hypoglycemic effects of other medications such as insulin or insulin secretagogues like sulfonylureas.

In the clinical setting, the presence of an α-glucosidase inhibitor can affect the treatment strategy for hypoglycemia. The administration of simple oral glucose may be more effective than ingestion of complex carbohydrates (sandwiches or crackers).[9]

CRITICAL DECISION

How is the disposition of a hypoglycemic patient affected by associated GLP-1 receptor agonist use?

GLP-1 is an incretin, belonging to a class of endogenous peptide hormones that regulate postprandial insulin secretion. It is derived from a preproglucagon precursor that undergoes cleavage to produce glucagon and GLP-1. The effect of endogenous GLP-1 on insulin secretion is directly proportional to serum glucose levels. In the setting of low serum glucose, the GLP-1 effect is limited, preventing hypoglycemia.[9] In early studies involving intravenous administration of exogenous GLP-1, the GLP-1 peptide has been shown to stimulate insulin secretion, delay gastric emptying, and inhibit glucagon release.[9] GLP-1 has also been shown to promote the sensation of satiety, making it a promising target for drug therapy. Endogenous GLP-1 is rapidly metabolized and cleared, with a half-life of 1 to 2 minutes, which makes the peptide impractical for therapeutic use.[9] Instead, GLP-1 receptor agonists have been developed to resist degradation and allow for a longer therapeutic effect. Currently, there are two major GLP-1 receptor agonists available on the US market: exenatide and liraglutide.

Exenatide, approved by the FDA in 2005, is a synthetic derivative of a naturally occurring peptide called exendin-4, which is found in the salivary gland venom of the Gila monster. Exendin-4 is a potent GLP-1 receptor agonist, and it has a half-life of 2 to 3 hours, making it more practical for drug therapy. Exenatide is administered twice daily via a self-injecting pen, typically before breakfast and before dinner in 5-mcg or 10-mcg doses. Peak concentrations are reached approximately 2 hours after injection, and clearance is primarily via the renal system. Exenatide alone, or in combination with other hypoglycemic agents, has been shown to decrease HBA_{1c} by 0.5% to 1% and result in up to a 10-pound weight loss with long-term use.[16,17]

Liraglutide, approved by the FDA in 2010, is structurally very similar to endogenous GLP-1. An additional fatty acid side chain allows it to bind serum proteins, increasing its half-life to 12 to 14 hours. This allows for once-daily dosing administered via a self-injecting pen in 0.6-mg, 1.2-mg, or 1.8-mg doses. Peak concentrations are reached 8 to 12 hours after injection. Unlike exenatide, liraglutide undergoes little renal clearance. Liraglutide has been shown to decrease HBA_{1c} 0.6% to 1.5%. In one comparative trial, liraglutide was associated with a 30% greater reduction in HBA_{1c} when compared with exenatide and has been shown to cause an average weight loss of 1 to 6 pounds.[18]

The most common side effects from GLP-1 receptor agonists are gastrointestinal effects. Forty percent of patients report nausea when drug therapy is first initiated.[17] This effect is dose-dependent and thought to be related to the delayed gastric emptying seen with GLP-1.[19] It typically abates over time; however GLP-1 use is contraindicated in patients with gastroparesis. The delayed gastric emptying can adversely affect the absorption of

antibiotics and oral contraceptives requiring patients to take other medications 1 hour before taking exenatide doses.

In the setting of GLP-1 receptor agonist monotherapy, hypoglycemia is uncommon and mild, and patients often do not require admission. Secondary causes of hypoglycemia should be excluded, and patients should be monitored for several hours to ensure they remain euglycemic.

In combination therapy, GLP-1 receptor agonists increase the severity of hypoglycemia associated with sulfonylureas.[19,20] Treatment should be approached similarly to treatment for hypoglycemia associated with sulfonylureas alone; admission for close glucose monitoring is necessary.[13]

Additional, rare side effects include acute renal failure and necrotizing pancreatitis.[17] Clinicians should consider GLP-1 receptor agonists as a cause of a newly elevated creatinine or elevated lipase in patients taking exenatide.

Liraglutide currently has a black box warning for causing C-cell neoplasias and medullary thyroid carcinomas in rodents. The relevance for human application is still unclear. Currently, liraglutide is contraindicated in patients with medullary thyroid carcinoma, those with a family history of thyroid cancer, and those with multiple endocrine neoplasia type 2 (MEN 2).[17]

Several additional GLP-1 receptor agonists are currently in development. In January 2012, an extended-release formulation of exenatide was approved by the FDA for once weekly administration.[21] The treatment of hypoglycemia in the setting of these extended-release formulations has yet to be determined. It is likely that we will see more of these medications entering the market within the next few years.

CRITICAL DECISION

What clinical implications are associated with the use of DPP-4 inhibitors?

DPP-4 is a serine protease responsible for degradation of GLP-1. DPP-4 inhibitors serve to increase GLP-1 activity by inhibiting the natural degradation process of GLP-1. These agents have been shown to decrease DPP-4 activity more than 95%, resulting in more than a two-fold increase in endogenous GLP-1 levels.[9] Unlike GLP-1 receptor agonists, DPP-4 inhibitors are taken orally rather than by injection.

There are currently three DPP-4 inhibitors available in the United States. Sitagliptin and saxagliptin are the two most commonly used DPP-4 inhibitors. Sitagliptin was the first DPP-4 inhibitor approved by the FDA (in 2006) and is administered as a once-daily oral dose of 100 mg. Studies have shown that sitagliptin taken as monotherapy or in combination with other hypoglycemic agents reduces a patient's HBA_{1c} by 0.7%.[17,22] Saxagliptin was approved by the FDA in 2009 and is administered as a 5-mg oral dose, once daily. Saxagliptin taken as monotherapy or in combination with other hypoglycemic agents reduces a patient's HBA_{1c} by 0.6% to 0.9%.[17] Linagliptin, a third DPP-4 inhibitor, was approved by the FDA in 2011. Vildagliptin has been approved by the European Medicines Agency but has not been approved in the United States. DPP-4 inhibitors are generally used as adjuncts to other oral hypoglycemic agents including metformin. Combination tablets including sitagliptin/metformin and saxagliptin/metformin are now available and simplify daily medication regimens.

DPP-4 inhibitors primarily undergo renal excretion, and lower doses are recommended in patients with impaired renal function. Saxagliptin undergoes additional metabolism via the hepatic CYP3A4 system and requires a reduced dose to 2.5 mg daily if the patient is taking known CYP3A4 inhibitors (such as ketoconazole or clarithromycin).

DPP-4 inhibitors are generally considered safe and have few side effects. The incidence of hypoglycemia with DPP-4 inhibitor use was similar to that for placebo in monotherapy.[20] Similarly to GLP-1 receptor agonists, the combination of a DPP-4 inhibitor with a sulfonylurea increases the incidence of hypoglycemia when compared to a sulfonylurea alone.[22,23] Although GLP-1 receptor agonists are linked with weight loss, DPP-4 inhibitors such as sitagliptin do not appear to have any significant effect on weight.[22] An increased incidence of nasopharyngitis, upper respiratory tract infections, and urinary tract infections has been reported; however recent studies have called these side effects into question.[22,23] Nausea is less commonly reported than with GLP-1 receptor agonists; however, pancreatitis has been reported in patients taking sitagliptin. Since its FDA approval, sitagliptin has been associated with several rare but serious allergic reactions including anaphylaxis, angioedema, and Stevens-Johnson syndrome. Recently a relationship between DPP-4 inhibitors and cancer has been proposed. Endogenous DPP-4 has demonstrated suppressive effects on the growth of certain tumors (including non-small cell lung cancer and transitional cell carcinoma of the bladder), and the use of DPP-4 inhibitors theoretically increases the risk of tumor growth.

CRITICAL DECISION

How does amylin analogue use affect the disposition of a hypoglycemic patient?

Amylin (or islet amyloid polypeptide, IAPP) is a small peptide hormone released into the bloodstream with insulin by the beta cells of the pancreas. Amylin serves to blunt the postprandial rise in blood glucose levels by slowing gastric emptying and the release of digestive enzymes in the gastrointestinal tract, inhibiting the release of glucagon

and promoting satiety. Patients with type 1 diabetes are deficient in both insulin and amylin, which contributes to poor glycemic control.

Pramlintide is a synthetic analogue of amylin that was approved by the FDA in 2005. It is unique in that it is approved for use in both type 1 and type 2 diabetes. Pramlintide is administered as an injection before meals and has a half-life of 50 minutes. It undergoes metabolism and clearance by the kidney. The dosing of pramlintide ranges from 15 to 60 mcg for patients with type 1 diabetes and from 60 to 120 mcg for patients with type 2 diabetes. It has been shown to reduce HBA_{1c} by 0.4% to 0.6% and has been associated with a weight loss of 2 to 5 pounds.[17,24,25]

Pramlintide is typically administered in combination with other hypoglycemic agents (including insulin). In monotherapy, pramlintide is not associated with hypoglycemia; however, when combined with insulin, the incidence and severity of hypoglycemia has led to a black box warning. Onset of hypoglycemia is typically within 3 hours because of the relatively short half-life of pramlintide. Nausea is reported in 30% to 50% of patients, and like GLP-1 receptor agonists, improves over time.[25] Pramlintide slows gastric emptying and may delay absorption of ingested substances. It is contraindicated in patients with gastroparesis and may delay correction of hypoglycemia treated with oral carbohydrates. Emergency physicians should anticipate that oral carbohydrates may not be as effective in restoring serum glucose levels. To avoid hypoglycemia, it is recommended that patients with insulin-dependent diabetes reduce their insulin regimen by 30% to 50% during the initiation of pramlintide therapy.

Hypoglycemia from pramlintide alone does not necessitate prolonged glucose monitoring, and admission is typically dependent on the hypoglycemic agent that was co-administered (ie, sulfonylurea or long-acting insulin). For hypoglycemia from pramlintide in combination with a short-acting insulin, patients can be safely discharged after several hours of glucose monitoring.

Pearls

- Clinical manifestations of hypoglycemia are varied and include seizure, altered mental status, and focal neurologic deficits, making rapid assessment of serum glucose essential.
- Advanced age, renal dysfunction, alcohol ingestion/abuse, and hepatic failure are risk factors for developing hypoglycemia.
- Hypoglycemia associated with sulfonylurea ingestions can recur over 24 hours and requires in-hospital evaluation and treatment beyond the 3- to 4-hour emergency department visit. Depending on the physician's judgment of the patient's risk and estimate of required treatment, this should be provided as an outpatient hospital observation level of care or as an inpatient admission.
- Octreotide is a potential rescue therapy for prolonged and recurrent hypoglycemia associated with sulfonylurea ingestion.
- Exenatide and pramlintide are newer agents that have been shown to increase the risk and severity of hypoglycemia when prescribed as adjuncts to other hypoglycemic agents.
- Pramlintide slows gastric emptying and is contraindicated in patients with gastroparesis because of an even higher risk of hypoglycemic events.

Pitfalls

- Failure to rapidly assess serum glucose in patients presenting with altered mental status, acute focal neurologic deficit, and seizure.
- Failure to recognize the potential for recurrent and prolonged hypoglycemia associated with sulfonylurea ingestion.
- Failure to realize that β-blockers may blunt the manifestations of hypoglycemia.
- Failure to investigate recent changes or additions in a patient's medications (or dose).
- Failure to recognize that a delayed onset of hypoglycemia can occur depending on the agent used and the route of administration.
- Failure to lower the dose of a DPP-4 inhibitor when a patient has impaired renal function.

Case Resolutions

■ Case One

The woman presenting with hypoglycemia related to sulfonylurea and exenatide ingestion was treated in the emergency department with a sandwich and juice. Her serum glucose level was 88 mg/dL after 1 hour despite an oral carbohydrate load. Recalling the risk of recurrent hypoglycemia associated with sulfonylureas and the additive effect of exenatide, the emergency physician decided that the patient needed further evaluation and treatment for glucose monitoring and medication adjustment. The patient was placed in observation in the emergency department observation unit, but over the evening and next morning she continued to suffer hypoglycemic episodes requiring multiple doses of intravenous dextrose and medication adjustment. With failure of the

outpatient observation treatment and evaluation plan, her physician judged she was at high risk of an adverse event if treated as an outpatient and she was admitted to the inpatient service that next day. She improved by day three with her blood sugar well in control, and she was safely discharged home with a new treatment plan, including a reduction in her glyburide dose.

■ Case Two

The man with type 1 diabetes who was recently placed on pramlintide in addition to his standing short-acting insulin regimen was treated initially with half an ampule of dextrose 50% in water as well as a sandwich and juice. His repeat finger-stick glucose level was 145 mg/dL. He reported feeling much better, and his weakness resolved. His repeat glucose at 3 hours was 140 mg/dL. The emergency physician discussed his presentation with the patient's primary care physician and discharged him with followup in 24 hours. He was instructed to discontinue the pramlintide until his primary physician could adjust his insulin regimen and to begin regular monitoring of his glucose at home.

Summary

Diabetes mellitus is one of the most common endocrine disorders. Tight glycemic control in diabetic patients has been linked to prevention of long-term complications and an overall reduction in patient mortality. Oral hypoglycemic agents are effective when taken in a monitored setting; however, they pose a significant risk of adverse events including hypoglycemia. Management and disposition of patients presenting with complications (side effects) associated with oral hypoglycemic agents vary considerably depending on the agent(s) used. It is essential for emergency physicians to be familiar with these agents and the effects that specific agents have on management and disposition of patients.

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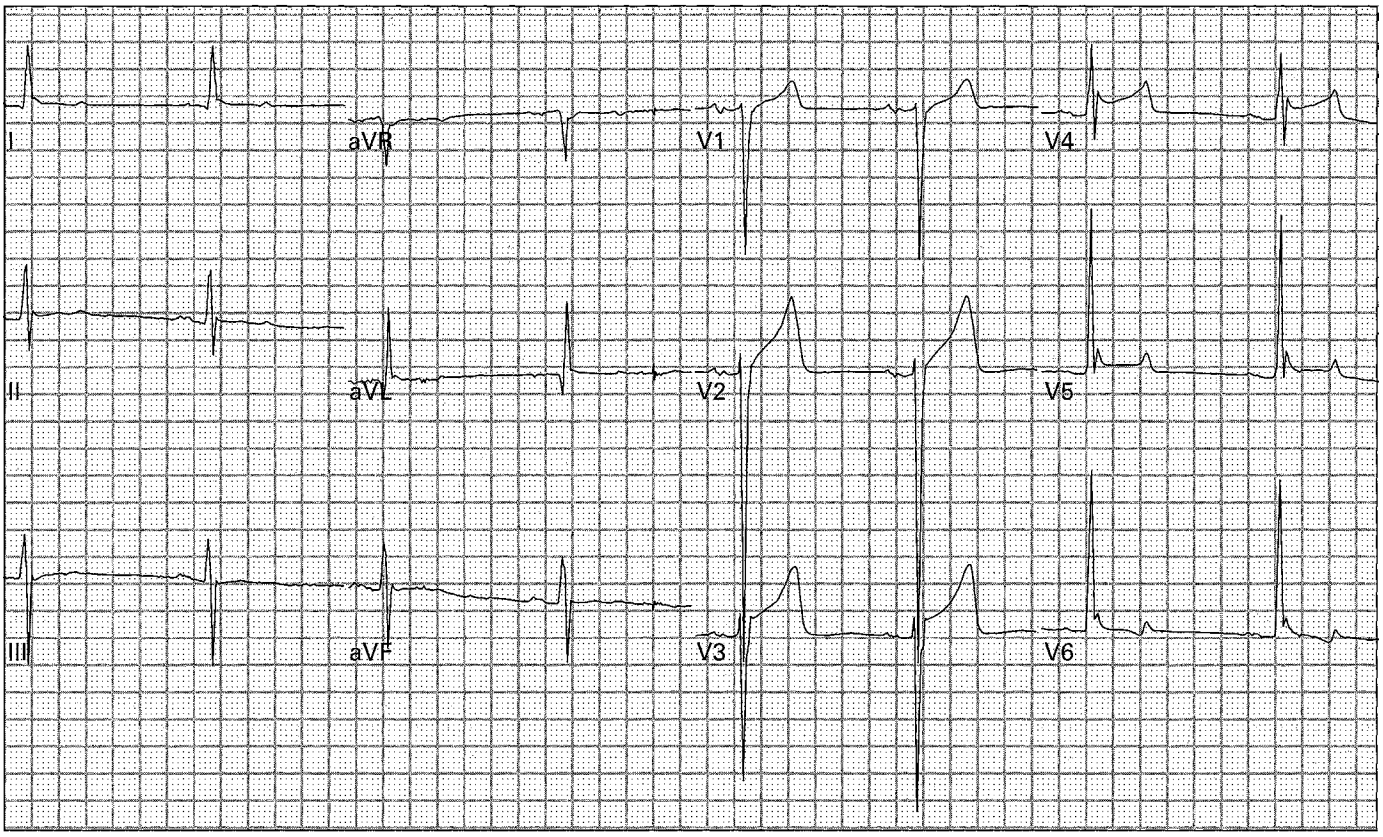
The Critical ECG

A 71-year-old man was sent to the emergency department from a nursing home because of lethargy.

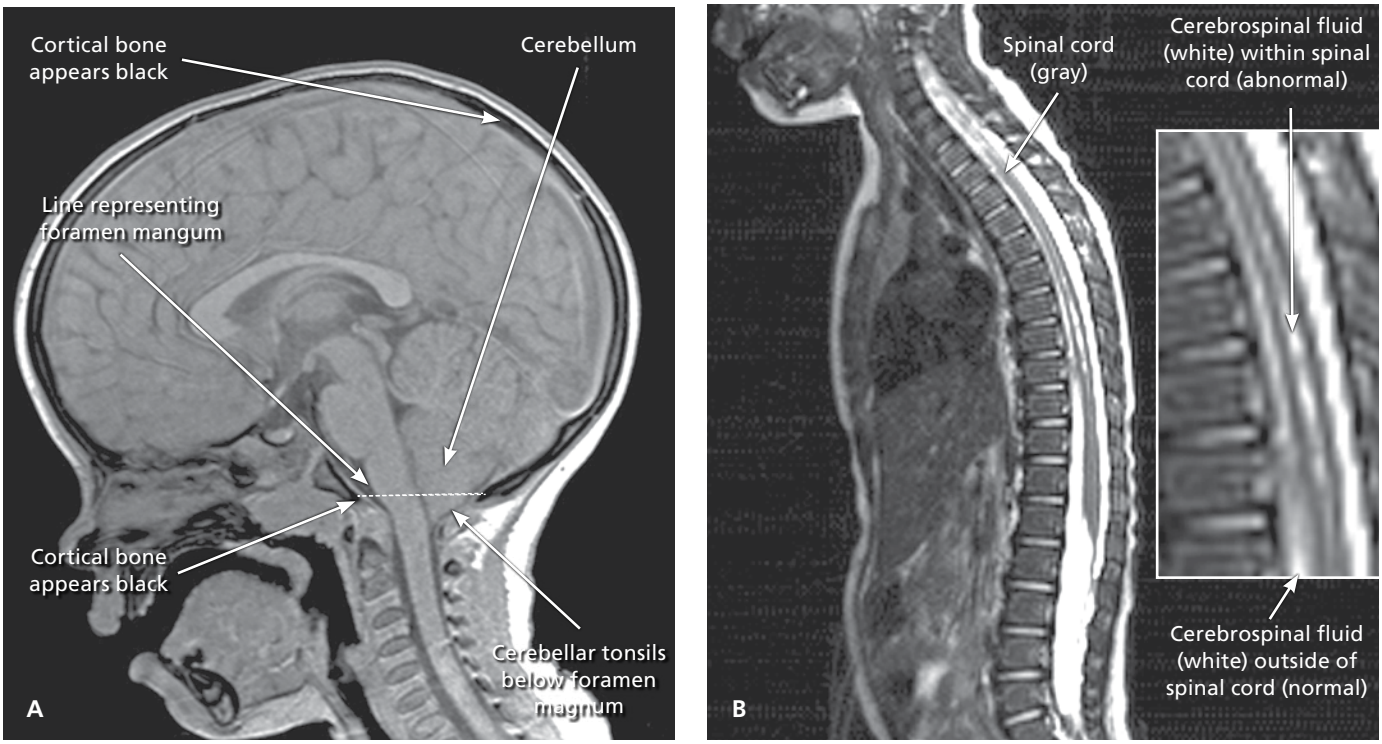


Sinus bradycardia, rate 46, left ventricular hypertrophy, J waves suggestive of hypothermia. This patient had sepsis with acute adrenal insufficiency, hypoglycemia, and hypothermia. His rectal temperature was 30.9°C (87.6°F). J ("Osborne") waves are noted in the lateral precordial leads and produce the appearance of ST-segment elevation. Sinus bradycardia is common in mild to moderate hypothermia.

Feature Editor: Amal Mattu, MD, FACEP. From: Mattu A, Brady W. *ECGs for the Emergency Physician*. London: BMJ Publishing; 2003:120,148. Available at www.acep.org/bookstore. Reprinted with permission.

The Critical Image

A 2½-year-old girl with a history of seizure presenting with headaches awakening her from sleep. Vital signs were temperature 36.4°C (97.5°F), pulse rate 131, blood pressure 118/63, and pulse oximetry 96% on room air. Examination was normal. Brain CT was performed, and an abnormality was noted, prompting brain and spine MRI.



A. Sagittal T1-weighted MRI of the brain. This demonstrates cerebellar tonsils projecting 5 mm below the foramen magnum, consistent with Chiari I malformation. Cortical bone appears black on all MR sequences.

B. Sagittal T2-weighted MRI of the patient's spine, demonstrating an abnormal region of cerebrospinal fluid (CSF) within the patient's central spinal cord around the T6-T12 level, consistent with syrinx. On T2-weighted images, CSF appears white, while the spinal cord appears an intermediate gray.

Chiari I malformation, the most common Chiari malformation, is defined by the presence of cerebellar tonsils 3 to 5 mm or more below the foramen magnum, measured on sagittal CT or MRI obtained with the neck in a neutral position.[1]

Chiari I malformation can result in compression of the brainstem and spinal cord. Symptoms include occipital headaches, Valsalva maneuver–induced headaches, back pain, dysphagia, dysarthria, truncal ataxia, nystagmus, lower cranial nerve dysfunction, motor or sensory deficit in the upper or lower extremities, and abnormal reflexes. Asymptomatic Chiari malformation (sometimes called asymptomatic tonsillar ectopia) can also occur.[2]

Chiari I malformation can cause abnormal cerebrospinal fluid dynamics, resulting in hydrocephalus or syrinx (syringomyelia) formation. Syrinx can result in muscle atrophy and progressive weakness and numbness.

In cases with equivocal clinical symptoms, phase contrast MR flow images may be obtained to assess the effect of cerebellar tonsil position on CSF flow. Normal flow suggests asymptomatic tonsillar ectopia.[1]

Treatment of symptomatic Chiari I malformation is suboccipital craniectomy.

Given the presence of syrinx, this patient underwent suboccipital craniectomy.

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Feature Editor: Joshua S. Broder, MD, FACEP. See also *Diagnostic Imaging for the Emergency Physician* (winner of the 2011 Prose Award in Clinical Medicine, the American Publishers Award for Professional and Scholarly Excellence) by Dr. Broder, available from the ACEP Bookstore, www.acep.org/bookstore.

CME Questions

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1. Which of the following is considered the most common cause of lower gastrointestinal (GI) bleeding in adults?
   A. angiodysplasia
   B. colitis
   C. diverticulosis
   D. postpolypectomy bleeding

2. A 66-year-old man presents after having a massive episode of bright red blood from his rectum this morning. The past medical history is significant for an aortic graft replacement approximately 4 years ago. His vital signs after fluid administration were blood pressure 90/60, pulse rate 110, respiratory rate 16, temperature 37.2°C (99°F), and oxygen saturation 99% on room air. His abdomen is tender. What is the most appropriate next step?
   A. abdominal CT scan
   B. abdominal radiographs
   C. abdominal ultrasonography
   D. emergent laparotomy

3. What is the minimum bleeding rate necessary in order for technetium scanning to be an effective study?
   A. 0.05 mL/min
   B. 0.05 to 0.1 mL/min
   C. 0.1 to 0.5 mL/min
   D. 1.5 to 2.75 mL/min

4. Where are angiodysplasia lesions usually found?
   A. ascending and transverse colon
   B. cecum and ascending colon
   C. cecum and small bowel
   D. cecum and transverse colon

5. Which of the following is an indication for surgery in the acute setting in a patient with lower GI bleeding?
   A. hemodynamic stability
   B. improving vital signs after fluid resuscitation
   C. recurrent bleeding after intervention
   D. requirement for transfusion of 2 units of packed RBCs in a 24-hour period

6. What is the minimum bleeding rate necessary in order for angiography to be an effective study?
   A. 0.4 to 0.5 mL/min
   B. 0.5 to 1 mL/min
   C. 1.1 to 2 mL/min
   D. 2.6 to 3.75 mL/min

7. Which of the following is considered a significant risk factor in patients presenting with lower GI bleeding?
   A. age less than 60 years of age
   B. INR level less than 1.2
   C. known anticoagulant use
   D. no active bleeding at presentation

8. Which of the following causes of lower GI bleeding, while rare, can cause death most rapidly?
   A. angiodysplasia
   B. anorectal disease
   C. aortoduodenal fistula
   D. cancer

9. What percentage of patients with diverticulosis will go on to develop diverticulitis?
   A. 5% to 20%
   B. 10% to 15%
   C. 10% to 25%
   D. 20% to 50%

10. Which of the following patients can be safely discharged home from the emergency department?
    A. 26-year-old man with stable vital signs found to have internal hemorrhoids
    B. 40-year-old with lower GI bleeding and altered mental status
    C. 59-year-old man with diverticulosis presenting with massive lower GI bleeding
    D. 76-year-old woman found to have ischemic colitis

11. Onset of hypoglycemia after ingestion of a sulfonylurea typically occurs in:
    A. 1-2 hours
    B. 3-5 hours
    C. 6-8 hours
    D. 18-24 hours

12. Which of the following is associated with an increased risk of hypoglycemia in a patient taking a sulfonylurea?
    A. a history of inguinal hernia repair
    B. prolonged sunlight exposure
    C. renal insufficiency
    D. use of a topical corticosteroid

13. A physician prescribing clarithromycin (a known inhibitor of the CYP3A4 enzyme) should reassess the dosing of which of the following oral hypoglycemic agents?
    A. glyburide
    B. metformin
    C. repaglinide
    D. saxagliptin

14. Symptoms of hypoglycemia may be masked by concomitant use of which of the following medications?
    A. acarbose
    B. atenolol
    C. hydrochlorothiazide
    D. lisinopril

15. A 50-year-old woman presents 3 hours after a witnessed ingestion of 10 glyburide tablets. After EMS administered one ampule of D50W, she is alert, and a finger-stick glucose is 98 mg/DL. What is the appropriate disposition for this patient?
    A. admit to medical service with close glucose monitoring and inpatient psychiatry evaluation
    B. admit to psychiatry for intentional overdose
    C. provide a meal of simple carbohydrates and recheck finger-stick glucose in 4 hours; if >100 mg/dL, discharge home with close followup
    D. repeat finger-stick glucose in 2 hours and discharge if >100 mg/dL

16. Lactic acidosis is a known adverse effect of which of the following oral hypoglycemic agents?
    A. acarbose
    B. glyburide
    C. metformin
    D. repaglinide

17. In cases of recurrent hypoglycemia secondary to sulfonylurea ingestion, what additional medication may be considered to help prevent recurrence?
    A. calcium gluconate
    B. hydrocortisone
    C. octreotide
    D. pramlintide

18. A 69-year-old man with type 2 diabetes mellitus presents with altered mental status and right-sided weakness. Of the following options, which is the most useful initial test?
    A. basic metabolic panel
    B. CBC with differential
    C. ECG
    D. finger-stick glucose

19. A 45-year-old woman with type 2 diabetes has been diagnosed with an uncomplicated urinary tract infection. She is currently taking metformin and exenatide. What instructions should the patient be given regarding her medications regimen while taking the prescribed antibiotic?
    A. decrease the dose of exenatide by half while taking the antibiotics
    B. double the dose of exenatide while taking the antibiotics
    C. take the antibiotics at least 1 hour before taking a dose of exenatide
    D. take the antibiotics concurrently with exenatide

20. A woman with type 2 diabetes presents with hypoglycemia. She is currently taking acarbose in addition to her sulfonylurea. How might this affect her treatment plan?
    A. acarbose does not cause hypoglycemia and therefore would not affect her treatment plan
    B. acarbose inhibits the effects of glucagon
    C. any hypoglycemic episode necessitates admission for glucose monitoring in patients taking acarbose
    D. oral complex carbohydrates may be less effective at restoring and maintaining euglycemia

Answer key for September 2012, Volume 26, Number 13

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A	A	D	D	C	D	A	C	C	D	A	B	C	D	D	B	C	D	B	D

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The Drug Box

Lacosamide

Kseniya Orlik, MD; Akron General Medical Center

Lacosamide is a relatively new anticonvulsant medication currently indicated for use in conjunction with other anticonvulsant medications for the treatment of partial seizures. In some short-term and long-term clinical trials lacosamide has also been successful in the treatment of diabetic neuropathic pain. Emergency physicians will likely encounter an increasing number of patients who are maintained on this medication for their seizure conditions.

Mechanism of action	Lacosamide exhibits selective enhancement of inactivation of slow voltage-gated sodium channels.
Indications	Adjunct to other anticonvulsant medications in treatment of partial seizures in adults with epilepsy who are at least 17 years old. May be used in its intravenous form on a short-term basis in patients who are unable to take medication by mouth.
Adult dosing (only approved for patients older than 17 years)	Oral: Initially 50 mg twice daily; may increase at weekly intervals by 100 mg/day. Maintenance dose is 200 to 400 mg/day. Short-term intravenous dose: total daily dose and frequency are the same as patients' oral daily dose. Administer over 30 to 60 minutes for up to 5 days. Renal impairment: In severe renal impairment (creatinine clearance <30 mL/minute), maximum dose is 300 mg/day. Discontinuation: Lacosamide should be discontinued gradually as abruptly stopping can result in increased seizure frequency.
Side effects	Serious side effects: arrhythmias, PR prolongation; multiorgan hypersensitivity reactions may occur, as well as suicidal ideation. Common side effects: dizziness, headache, diplopia, and nausea. Less common side effects include fatigue, ataxia, pruritus, syncope, and confusion.
Contraindications/ precautions	Not recommended for those with severe hepatic impairment. Use with caution in those with prolonged PR interval or who are taking other medications that may prolong PR interval and in those with renal and hepatic impairment. Patients should be cautioned not to operate heavy machinery or drive until they know how the drug affects them. Pregnancy category C

Feature Editors: Michael S. Beeson, MD, MBA, FACEP; Steven Warrington, MD

Critical Decisions in Emergency Medicine™

October 2012 • Volume 26 • Number 14

Critical Decisions in Emergency Medicine is the official CME publication of the American College of Emergency Physicians. Additional volumes are available to keep emergency medicine professionals up-to-date on relevant clinical issues.

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