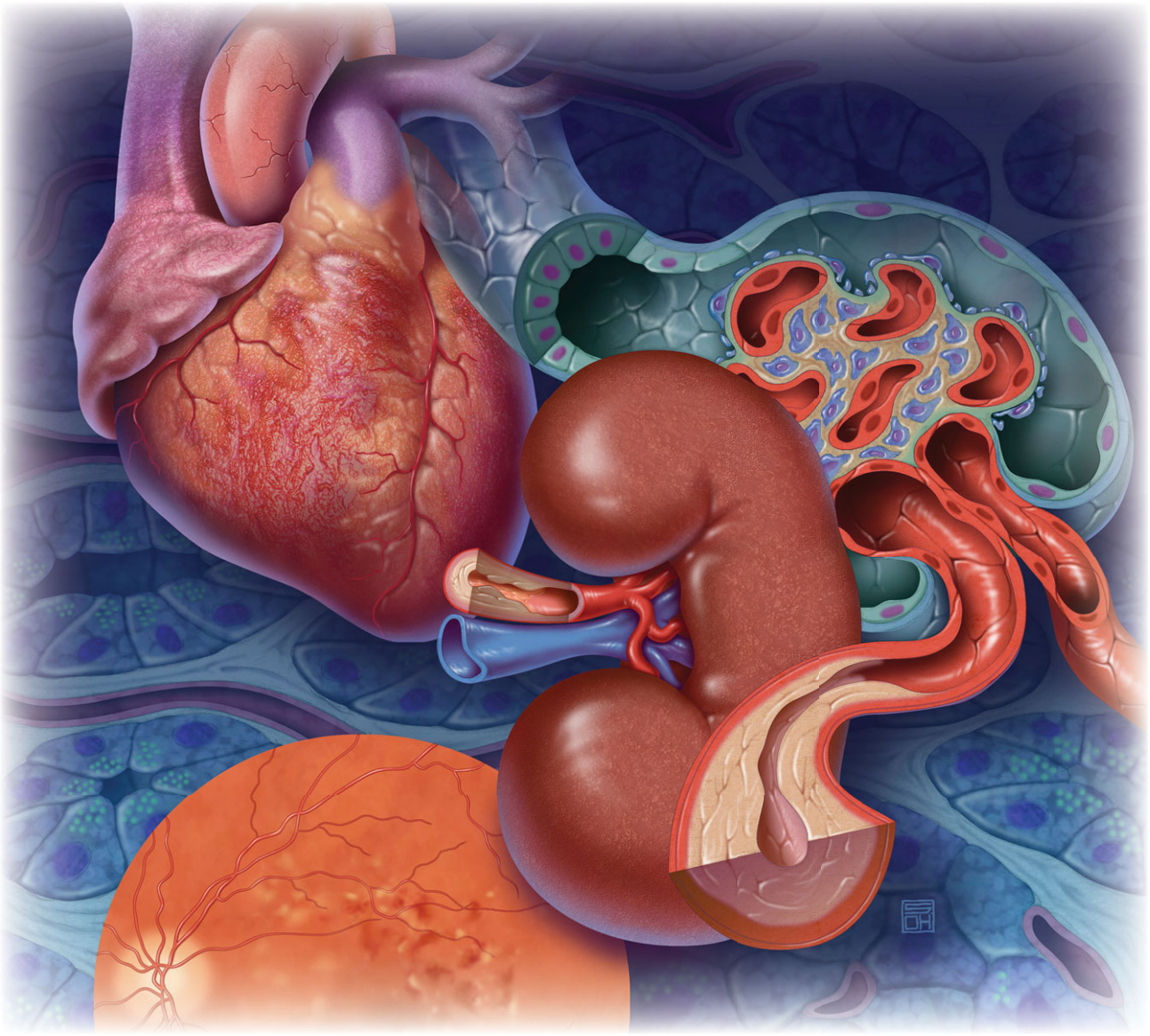

Managing Medication Effects in Type 2 Diabetes

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Using five case examples, the authors highlight a range of isolated symptoms from cognitive impairment to cough that should focus suspicion on the patient's medical regimen if it includes an oral or inhaled agent for glycemic control.

As the prevalence of type 2 diabetes steadily rises, so does the likelihood that on any given day, an urgent care physician will be called on to care for someone experiencing adverse effects or drug-drug interactions from the oral medications that constitute the mainstay of treatment for this disease.[1,2] These medications have diverse mechanisms of action, and, as a result, wide variations in side effects. Furthermore, they are often prescribed in combination, increasing the risk of side effects or complications, especially in the over-65 age-group.

Although most of the life-threatening complications seen in diabetes management occur in patients with insulin-dependent type 1 disease, it is important to recognize the different oral hypoglycemic agents used and the manifestations of their side effects.

This article will review the main classes of oral medications for the treatment of type 2 diabetes, introducing each with an illustrative patient presentation and highlighting their major side effects and complications. This information is also summarized for convenience in the Table.[3-6]

CASE #1

A 43-year-old woman is brought in by police for confusion and agitation after being picked up for shoplifting at an upscale department store. She is well groomed and appears well nourished, with no signs of trauma and no obvious focal neurologic deficits. Her blood glucose level, as measured by reagent strip testing, is 34 mg/dL, and after finding glucometer strips in her purse you ascertain that she has a history of diabetes mellitus.

While hypoglycemia is more commonly seen in patients requiring insulin to manage their diabetes, profound hypoglycemia can be a major complication associated with oral medications that increase the availability of endogenous insulin. There are two classes of these insulin secretagogues: the sulfonylureas and the meglitinides.[3,7]

The sulfonylureas, which include glyburide, glipizide, and glimepiride, increase the release of endogenous insulin. At the same time, they reduce hepatic glucose production while also accelerating glucose transport into muscle and fat cells. The most significant side effect of this drug class is hypoglycemia, but others, such as weight gain, rash, and nausea, are more common.[3,7] Contraindications to the use of these agents include sulfa allergy, pregnancy or lactation, type 1 diabetes mellitus, advanced age, debilitated condition, impaired liver function, impaired renal function, and cardiovascular disease.

A second class of insulin secretagogues is the meglitinides, which include repaglinide and nateglinide. Although their site of action differs from that of the sulfonylureas,[7] the end result of increased insulin secretion is the same. Like the sulfonylureas, meglitinides can lead to hypoglycemia, as well as weight gain, and they are contraindicated in type 1 diabetes mellitus, pregnancy or lactation, hemodialysis, diabetic ketoacidosis, advanced age, malnourished state, and hepatic impairment. Nateglinide has a faster onset and a shorter duration than repaglinide and is less likely to cause hypoglycemia.[3]

Treatment of hypoglycemia provoked by an agent from either class includes immediate replacement of glucose with either oral or parenteral glucose. In mild cases, oral carbohydrate replacement therapy is sufficient, provided there is adequate normalization of blood glucose levels on repeat measurements. In patients who cannot tolerate oral therapy or in more severe cases, therapy should include immediate infusion of a 25- to 50-mL bolus of 50% dextrose with repeat glucose measurements every 30 to 60 minutes. In severe, refractory hypoglycemia, a continuous IV infusion of 10% dextrose in water at a rate of 1 to 2 mL/kg/h is recommended.[4,8] In addition, gastric decontamination using charcoal may be indicated in the event of an overdose with hypoglycemic agents, if administered within one hour. Due to these agents' long duration of action, patients with symptomatic hypoglycemia should be admitted for glucose monitoring.

>>FAST TRACK<<

Due to the insulin secretagogues' long duration of action, patients with symptomatic hypoglycemia should be admitted.

CASE #2

A 72 year-old woman is admitted after being found unwell in her home by family members.

TABLE. Key Characteristics of Diabetes Medications by Class

Class	Mechanism of action	Examples	Major side effects	Other side effects
sulfonylureas	increase insulin secretion	glyburide, glipizide, glimepiride	hypoglycemia	weight gain, rash (photosensitivity), GI symptoms, blurred vision
meglitinides	rapid insulin secretagogue with short duration of action	repaglinide, nateglinide	hypoglycemia	upper respiratory infection, headache, arthralgia, diarrhea, nausea and vomiting, weight gain
biguanides	decrease hepatic glucose production; enhance skeletal muscle glucose uptake and utilization	metformin	lactic acidosis	GI symptoms, metallic taste, agitation, diaphoresis, headache
TZDs	enhance insulin sensitivity in peripheral tissues, reduce hepatic glucose formation	rosiglitazone, pioglitazone	ischemic cardiac events, congestive heart failure	edema, elevated lipids, weight gain, mild anemia, long bone fractures
alpha-glucosidase inhibitors	slow digestion and absorption of complex carbohydrates	acarbose, miglitol	lower GI symptoms (diarrhea, flatulence, cramping)	exacerbation of bowel disease, hypoglycemia when used in combination with other oral agents
DPP-4 inhibitors	inhibit degradation of GLP-1, a gut hormone that enhances insulin	sitagliptin	upper respiratory infection, headache, sore throat	may inhibit lymphocyte activity

Data extracted from *The Medical Letter*. 2005[3]; Tomaszewski. 2003[4]; USP DI. 2007[5]; Unger. 2007.[6]
GI = gastrointestinal; TZDs = thiazolidinediones; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide 1

She has a decreased level of consciousness and cannot give any history, but her daughter states that the dosage of one of her diabetes medications was increased 2 weeks ago, and earlier in the week she seemed to be suffering from a "stomach flu." On examination, she is hypotensive, tachycardic, and tachypneic. She responds only to painful stimuli but has no other remarkable findings. You order basic laboratory studies and find an anion gap metabolic acidosis.

The class of agents known as the biguanides includes metformin. These medications reduce both intestinal glucose absorption and hepatic glucose formation while sensitizing tissue to insulin, which increases glucose transport into skeletal muscle and adipose tissue. By interfering with the hepatic metabolism of lactic acid, they may raise the risk of lactic acidosis, particularly when associated with renal insufficiency. Among the side effects of this drug class are gastrointestinal problems related to delayed gastric emptying, metallic taste, agitation, sweating, and headache. The biguanides are contraindicated in pregnancy or lactation, diabetic ketoacidosis, type 1 diabetes mellitus, congestive heart failure, impaired liver function, impaired renal function, and major surgery.[5]

In most cases, patients presenting with lactic acidosis demonstrate signs and symptoms associated with systemic inflammatory response syndrome and sepsis. The early goals of therapy should include airway management, ventilatory support (if needed), fluid resuscitation, and electrolyte replacement. The indications for treatment of lactic acidosis with sodium bicarbonate include severe acidosis (serum bicarbonate level below 4 mEq/L or pH below 7.2) with signs of myocardial instability. Recommended treatment is 0.5 mEq/kg sodium bicarbonate for each mEq/L of increased HCO_3 required to raise it to the target level.[4] In most instances, the patient should be admitted to the intensive care unit for hemodynamic monitoring and ventilatory support.[9,10]

CASE #3

A 55-year-old man arrives after 2 hours of crushing substernal chest pain. He notes a history of type 2 diabetes, for which he was recently started on an oral agent. He reports having normal lipid profiles in the past. On ECG he is found to have an acute anterior myocardial infarction, and he is transferred to a nearby hospital for emergent percutaneous intervention.

The thiazolidinediones (TZDs), which include rosiglitazone and pioglitazone, enhance insulin action in the peripheral tissues, reduce hepatic glucose formation, and increase fat cell proliferation. Their mode of action is dependent on the presence of insulin and involves nuclear transcription. With routine treatment, it is recommended that liver function tests be performed prior to their use. Adverse effects of this drug class include increased risk of ischemic coronary events, pulmonary edema, weight gain, edema, and mild anemia. Rosiglitazone has also been found to increase the risk of long bone fractures. Long term effects are not known. TZDs are contraindicated in pregnancy or lactation, type 1 diabetes mellitus, Killip class III or IV congestive heart failure, and impaired liver function.[11,12]

Patients presenting with acute coronary syndrome in the setting of TZD use should be treated according to American Heart Association/American College of Cardiology guidelines, and the offending agent should be discontinued.[9]

CASE #4

A 52-year-old woman from out of town presents with complaints of abdominal cramping, bloating, and diarrhea. She was started on a new diabetes medication 1 week ago by her primary care doctor. She has had no sick contacts, and she has not been exposed to uncooked foods or unfiltered water. Her examination is normal.

The alpha-glucosidase inhibitors, which include acarbose and miglitol, reduce postprandial glucose levels by slowing the digestion of complex carbohydrates and inhibiting enzymes required for absorption at the brush border. These agents are moderately effective as monotherapy. Exacerbation of preexisting bowel disease can occur, with two-thirds of patients having flatulence, diarrhea, and abdominal pain. Rarely, alpha-glucosidase inhibitors may induce hypoglycemia when used in combination with other oral agents. Under these circumstances, only oral dextrose can be used to reverse the hypoglycemia, as absorption of sucrose is inhibited by the drug.[13]

These medications are contraindicated in pregnancy or lactation, chronic renal failure, cirrhosis, diabetic ketoacidosis, type 1 diabetes mellitus, inflammatory bowel disease, and insulin users. In addition, miglitol should not be used with beta-blockers.[13]

Discontinuation of the offending agent and symptomatic treatment are recommended. In most cases, a complete resolution of symptoms will occur.

CASE #5

A 39-year-old man from Canada presents with a 2-week history of nasal congestion and cough. He denies fever or sputum production. His only medical history consists of diabetes for which he uses an inhaled medication. Your examination reveals normal vital signs; normal head, eye, ear, nose, and throat findings; and clear lung fields. A complete blood count and a chest radiograph are both normal.

>>FAST TRACK<<

Adverse effects of the TZD drug class include increased risk of ischemic coronary events.

The enzyme dipeptidyl-peptidase 4 (DPP-4) rapidly inactivates a class of gastrointestinal hor-

mones called incretins, an example of which is glucagon-like peptide 1. The incretins cause an increase in the amount of insulin released from the beta cells after eating, slow the rate of absorption of nutrients into the blood by reducing gastric emptying, and inhibit glucagon release from alpha cells, thus suppressing hepatic glucose formation. DPP-4 inhibitors prevent the breakdown of incretins in the setting of glucose digestion, resulting in increased insulin production and decreased endogenous glucose production. The DPP-4 inhibitors include sitagliptin. These agents may be used as monotherapy or in combination with biguanides or TZDs. Major side effects include upper respiratory infections, headache, sore throat, and, rarely, inhibition of lymphocyte activity. Contraindications to their use include pregnancy or lactation, type 1 diabetes mellitus, and diabetic ketoacidosis.[14,15,16]

Discontinuation of the offending agent and symptomatic treatment are recommended. In most cases, a complete resolution of symptoms will occur. □

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