

Oral Agents for the Treatment of Type 2 Diabetes Mellitus: Pharmacology, Toxicity, and Treatment

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Currently available oral agents for the treatment of type 2 diabetes mellitus include a variety of compounds from 5 different pharmacologic classes with differing mechanisms of action, adverse effect profiles, and toxicities. The oral antidiabetic drugs can be classified as either hypoglycemic agents (sulfonylureas and benzoic acid derivatives) or antihyperglycemic agents (biguanides, α -glucosidase inhibitors, and thiazolidinediones). In this review, a brief discussion of the pharmacology of these agents is followed by an examination of the adverse effects, drug-drug interactions, and toxicities. Finally, treatment of sulfonylurea-induced hypoglycemia is described, including general supportive care and the management of pediatric sulfonylurea ingestions. The adjunctive roles of glucagon, diazoxide, and octreotide for refractory hypoglycemia are also discussed.

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INTRODUCTION

The overproduction and underutilization of glucose characterizes type 2 diabetes mellitus (DM).¹⁻³ Diet and exercise remain the cornerstones of treatment, although pharmacologic therapy is frequently necessary.³⁻⁵ Inadequate glycemic control with a single agent should prompt the addition of a second oral agent or bedtime insulin. Persistent unsatisfactory control can lead to (1) continuation of the 2 oral agents with addition of bedtime insulin, (2) conversion to a mixed-split insulin regimen, or (3) addition of a third oral agent.⁶

Current oral treatment options can be subdivided into the hypoglycemic drugs (sulfonylureas and benzoic acid derivatives) and antihyperglycemic drugs (biguanides, α -glucosidase inhibitors, and thiazolidinediones). This review of oral antidiabetic agents focuses on pharmacology, adverse effects, drug interactions, and toxicity. A dis-

cussion of the treatment of hypoglycemia resulting from oral antidiabetic agents follows.

SULFONYLUREAS

All sulfonylureas increase insulin secretion and enhance insulin activity. Second- and third-generation sulfonylureas more readily penetrate cell membranes than do first-generation agents because of enhanced lipid solubility; they also feature a greater selective binding capacity.^{7,8} Sulfonylureas stimulate insulin release from the pancreatic β cells, displaying a more pronounced action in the presence of glucose.⁹ They do so by inhibiting an adenosine triphosphate-dependent potassium channel, which results in cell membrane depolarization and leads to calcium influx and release of stored insulin from secretory granules within the cell.^{3,10} They also decrease hepatic insulin clearance, resulting in increased serum insulin concentrations.¹¹⁻¹⁵ Increased circulating insulin levels then feed back to suppress hepatic glucose production.⁶ In vitro data suggest sulfonylureas indirectly decrease peripheral insulin resistance and enhance its action,¹¹ although the clinical significance of these effects is questionable.¹⁵

In those patients with type 2 DM who do respond to sulfonylureas, secondary treatment failure may ensue. The cause is multifactorial, including patient factors (noncompliance and weight gain), therapy issues (desensitized β cells caused by long-term therapy and other drug effects on insulin homeostasis), and features of the disease itself (escalating insulin resistance and increased insulin deficiency).^{6,16}

Pharmacokinetic data for the sulfonylureas are presented in Table 1.^{6,17-21} The prolonged duration of action,

hepatic metabolism, and renal excretion of active parent compound or metabolite (with selected agents) should be noted. All have implications with regard to sulfonylurea-related hypoglycemia.

The principal toxicity associated with sulfonylureas is hypoglycemia. Overdoses generally occur as intentional attempts or accidental ingestions, and most accidental ingestions involve children. However, there have been several cases of drug-dispensing errors in which nondiabetic patients received sulfonylureas.²² In addition, drug interactions can cause profound hypoglycemia (Table 2).²³⁻³³ Factors that increase the risk of having a hypoglycemic episode include advanced age, poor nutrition, alcohol consumption, renal and hepatic disease, and polypharmacy.^{2,34}

Clinically, time to peak and duration of action are the most important considerations when anticipating hypoglycemia after sulfonylurea overdose (Table 1). Adverse outcomes were rare in case series of pediatric accidental ingestions,³⁵⁻³⁷ and pediatric fatalities from accidental ingestions have not been reported.³⁸ The most recent annual report from the American Association of Poison Control Centers Toxic Surveillance System listed 5,351 reported exposures to oral hypoglycemic agents (not limited to sulfonylureas), resulting in 3,349 cases of treatment in a health care facility and only 9 fatalities.³⁹ However, in a study of 101 intentional ingestions of sulfonylureas in adults, 5 deaths and 5 cases of permanent neurologic deficit occurred.⁴⁰

Of the sulfonylureas, chlorpropamide, glyburide, and the long-acting glipizide (Glucotrol XL) are the most likely to cause prolonged hypoglycemia.^{16,41} The duration of action for all the sulfonylureas will be increased in the

Table 1.
Pharmacokinetics of the sulfonylureas.^{6,17-21}

Generation	Generic Name	Trade Name	Time to Peak (h)	Half-life (h)	Duration of Action (h)	Metabolism	Renal Excretion of Active Metabolite
First	Chlorpropamide	Diabinese	2-7	36	60	Hepatic	Yes*
First	Tolbutamide	Orinase	3-4	3-28	6-12	Hepatic	Insignificant
First	Acetohexamide	Dymelor	3	4-6	12-18	Hepatic	Yes
First	Tolazamide	Tolinase	4-6	4-8	12-24	Hepatic	No
Second	Glipizide	Glucotrol	1-3	7	12-24	Hepatic	No
Second	Glipizide	Glucotrol XL	6-12	7	24	Hepatic	No
Second	Glyburide	Micronase, DiaBeta, Glynase	2-6	10	12-24	Hepatic	Yes
Third	Glimepiride	Amaryl	2-3	5-9	16-24	Hepatic	Yes (?)

*Parent drug undergoes prolonged excretion.

presence of hepatic and, in some cases, renal disease and is especially a concern in the elderly.^{2,34,41} The frail elderly, those taking multiple medications, and those frequently hospitalized have been found to be at increased risk for sulfonylurea-related hypoglycemia.⁴² A recent prospective study⁴³ of well patients with type 2 DM subjected to a 23-hour fast while taking glyburide or glipizide found that none of the 58 patients had hypoglycemia during the fast. Laboratory data suggested an enhanced counterregulatory hormonal response was responsible for the prevention of hypoglycemia. It should be noted that severe concurrent medical problems (cardiovascular, gastrointestinal, renal, or hepatic problems), substance abuse, and concurrent medications that interfere with glucose homeostasis were criteria for exclusion, and many of the patients had poorly controlled blood glucose levels at the time of the study.⁴³ Thus, generalization to the emergency department population is limited. A recent retrospective study looking at only patients with end-stage renal disease found glyburide to be the culprit sulfonylurea in all patients who had prolonged sulfonylurea-induced hypoglycemia.⁴⁴ Excretion of active metabolite in the urine makes glyburide a less desirable therapeutic option in patients with severe renal insufficiency. Recently, prolonged hypoglycemia after chlorpropamide ingestion (27 days after suicidal ingestion of 5 to 10 g) was reported,⁴⁵ again illustrating the toxic potential of long-acting sulfonylureas with active metabolites.

Beyond hypoglycemia, several other toxicologic issues should be mentioned with regard to the sulfonylureas.

Chlorpropamide deserves special attention because of its association with symptomatic hyponatremia, regardless of dosage. It has been shown to induce inappropriate antidiuretic hormone secretion, featuring serum hyponatremia and hypo-osmolality with an elevated excretion of urinary sodium.⁴⁶ The incidence of chlorpropamide-induced hyponatremia is increased in elderly patients and in those receiving thiazide diuretics.⁴⁷ There have also been a few reports of hyponatremia associated with tolbutamide.¹⁶ Chlorpropamide can also induce cholestatic jaundice, which can occur at higher doses (>500 mg/d) but resolves rapidly with drug discontinuation. Agranulocytosis, thrombocytopenia, and anemia have all been associated with chlorpropamide use.^{48,49}

Glipizide undergoes some enterohepatic circulation, possibly leading to a prolonged duration of action in patients with liver failure, yet it appears safer than glyburide in renal insufficiency.⁴⁴ Adverse effects include gastrointestinal discomfort and abnormal liver function test results.³ Glyburide has the highest incidence of hypoglycemia of the second- and third-generation sulfonylureas, possibly because of the presence of its active metabolite.^{16,30,41} Hepatic breakdown results in multiple metabolites, one of which is active. All metabolites are renally excreted, leading to potentiation of hypoglycemic effects in patients with kidney dysfunction.^{3,15,44,48,49}

Glimepiride, the newest sulfonylurea, has few clinical differences when compared with earlier sulfonylureas. It is completely metabolized by the liver, and one of its metabolites is active, although the clinical relevance of

Table 2.
Drug-drug interactions: first- and second-generation sulfonylureas.

Sulfonylurea	Drug	Mechanism	Effect	Reference No.
Chlorpropamide	Warfarin, chloramphenicol	↓ Hepatic metabolism	↑ Hypoglycemia	23, 24
	Probenecid, allopurinol	↓ Renal tubular secretion	↑ Hypoglycemia	25
	Rifampin	↑ Hepatic metabolism	↓ Hypoglycemia	26
Tolbutamide	Digoxin		↑ Digoxin level	27
	Warfarin, chloramphenicol, sulfonamides	↓ Hepatic metabolism	↑ Hypoglycemia	24, 28, 29
Glipizide	Rifampin	↑ Hepatic metabolism	↓ Hypoglycemia	26
	Salicylates, clofibrate	Displace from proteins	↑ Hypoglycemia	30, 31
	Trimethoprim-sulfamethoxazole, miconazole	Inconsistent/unclear	↑ Hypoglycemia	30, 31
	Cholestyramine	↓ Absorption	↓ Hypoglycemia	30, 31
	Rifampin	↑ Hepatic metabolism	↓ Hypoglycemia	30, 31
Glyburide	H ₂ blockers	↓ Hepatic metabolism	↑ Hypoglycemia	30, 31
	H ₂ blockers	↓ Hepatic metabolism	↑ Hypoglycemia	31
	Trimethoprim-sulfamethoxazole	Inconsistent/unclear	↑ Hypoglycemia	31
	Ciprofloxacin	↓ Hepatic metabolism	↑ Hypoglycemia	32
	Rifampin	↑ Hepatic metabolism	↓ Hypoglycemia	31, 33

this is unknown. Metabolites are eliminated in the feces and urine.⁸ Although there are conflicting data, hypoglycemia is either similar to or less than that which is seen with the second-generation agents.⁸ The most common adverse effects are headache and dizziness. Hyponatremia is a rare complication, as are leukopenia, thrombocytopenia, and anemia. Thrombocytopenic purpura associated with glimepiride was recently reported.⁵⁰ Drug interactions are similar to those of the second-generation sulfonylureas; however, cimetidine and ranitidine do not alter the effect of glimepiride. There is evidence that propranolol increases glimepiride concentrations by about 20%.⁸

Other drugs may enhance or attenuate the hypoglycemic effect of the sulfonylureas (Table 2). Enhancement of effect may result from competition for binding sites on plasma proteins, hepatic metabolic inhibition, or impairment of renal excretion.^{30,31} On the other hand, attenuation of the hypoglycemic effect of sulfonylureas may result from drug interactions, leading to a decrease in digestive absorption or induction of liver metabolism.^{30,31}

BIGUANIDES

Three biguanides—metformin, phenformin, and buformin—have historically been used for the treatment of type 2 DM, but only metformin remains in wide use today.¹⁷ Phenformin was taken off the market in the United States and Europe in 1976 because of its association with lactic acidosis⁵¹⁻⁵³; however, it is still rarely encountered in this country today because patients from overseas may still be using this agent.⁵³ Metformin is

indicated either as monotherapy or in combination with a sulfonylurea.^{17,54} Sulfonylureas and metformin cause a similar decrease in fasting blood glucose levels in diabetic subjects, but whereas the sulfonylureas generally cause weight gain, metformin does not.^{54,55}

Metformin decreases hepatic production and intestinal absorption of glucose in addition to decreasing the oxidation of fatty acids. Moreover, it increases insulin sensitivity, thereby decreasing the insulin resistance that is often a problem in patients with type 2 DM.^{17,54,56} It decreases the blood glucose level of diabetic patients but not that of nondiabetic patients.⁵⁷ As such, it is an antihyperglycemic agent and not a hypoglycemic agent, as are the sulfonylureas.^{17,54} Metformin undergoes virtually no hepatic metabolism and is 90% to 100% excreted by the kidneys. The pharmacokinetics (Table 3)^{6,17,54,55,58-65} differ from those of phenformin, which undergoes metabolism by the liver, is excreted in the bile and urine, and features some degree of protein binding and a larger volume of distribution.^{17,51,53,54,56-58}

Lactic acidosis is the most serious adverse effect linked to the biguanides, although the link is much stronger with phenformin than with metformin.^{17,34,51,52,54,56,66,67} Phenformin was found to be associated with lactic acidosis at a rate of approximately 66 cases per 100,000 patient-years, whereas the incidence with metformin is only about 3 per 100,000 patient-years.⁵⁴ The lactic acidosis is characterized as type B (aerobic lactic acidosis), which is attributable to enhanced metabolic production of lactate; this is in contradistinction to type A, which is caused by tissue hypoxia and thus termed anaerobic lactic acidosis.^{51,53} Signs and symptoms are nonspecific, including

Table 3.

Pharmacokinetics of nonsulfonylurea antidiabetic agents: biguanides, α-glucosidase inhibitors, thiazolidinediones, and benzoic acid derivatives.

Generic Name	Trade Name	Time to Peak (h)	Half-life (h)	Duration of Action	Metabolism	Renal Excretion of Active Metabolite	Reference No.
Metformin	Glucophage	2-3	1-5	>3-4 wk	Insignificant hepatic	Yes*	6, 54, 55
Acarbose	Precose	1-2†	2	4 h	Intestinal	Yes‡	6, 17, 58-61
Miglitol	Glyset	2-3†	2	4 h	Intestinal	Yes	17, 61
Rosiglitazone	Avandia	1-2	3-4	>3-4 wk	Hepatic	No	6, 62
Pioglitazone	Actos	1-2	3-7	>3-4 wk	Hepatic	No	6, 63
Repaglinide	Prandin	1	1	4-6 h	Hepatic	No	6, 64, 65

*Parent drug excreted >90% unchanged in the urine.

†Pharmacologic effect not dependent on systemic absorption.

‡Fraction (2%) of drug absorbed is excreted unchanged in the urine.

nausea, vomiting, diarrhea, somnolence, epigastric pain, anorexia, tachypnea, and lethargy. The pathogenesis of metformin-associated lactic acidosis is incompletely understood. It seems to occur only in certain settings: renal insufficiency, hepatic dysfunction, cardiovascular disease, severe infection, or alcoholism.^{17,54} This has led to the development of certain exclusion criteria for the use of metformin in the management of DM, which include the following: (1) renal insufficiency (plasma creatinine level ≥ 1.5 mg/dL in male subjects or ≥ 1.4 mg/dL in female subjects); (2) cardiac or pulmonary insufficiency likely to result in decreased tissue perfusion or hypoxia; (3) history of lactic acidosis; (4) profound infection that might cause impaired tissue perfusion; (5) liver disease, including alcohol-related liver disease (as evidenced by abnormal liver-function tests); (6) alcohol abuse with binge pattern capable of causing acute liver toxicity; and (7) use of intravenous contrast agents.⁵⁴ A report⁶⁷ of a patient receiving metformin with normal renal function and no other exclusion criteria who had lactic acidosis revealed that, at the time of presentation with the syndrome, he no longer had a creatinine level of less than 1.5 mg/dL. Thus, physicians must be aware that although patients may meet criteria initially, conditions may develop that preclude the safe use of the drug.^{17,67} A recent report has shown that the rate of lactic acidosis in diabetic subjects not taking metformin is equivalent to that of diabetic subjects taking metformin, suggesting the conditions underlying lactic acidosis may be operative in diabetic subjects independent of metformin therapy.⁵⁷ Lactic acidosis in patients taking metformin who have been given radiocontrast media seems to occur principally in those with underlying renal insufficiency, and thus the previously recommended blanket exclusion of intravenous contrast administration to patients taking metformin has been questioned.^{68,69} A recent case series of patients with metformin-associated lactic acidosis demonstrated that arterial lactate levels and plasma metformin levels did not have prognostic significance with regard to mortality; fatal outcome instead seemed to be linked to other concomitant conditions (eg, hypoxia), resulting in elevated lactate levels.⁷⁰

Other adverse effects associated with metformin are largely gastrointestinal. Nausea, vomiting, diarrhea, anorexia, and abdominal discomfort are all well described; they are usually mild, dose related, and transiently seen at the initiation of therapy.^{34,54} Hypoglycemia is said to occur rarely with metformin monotherapy but may be seen with concomitant ethanol abuse.^{53,54,56,66} Malabsorption of vitamin B₁₂ and folate occurs with long-term

treatment, although it usually does not lead to anemia.^{34,54,56} Recently, a case of metformin-induced hemolysis with jaundice was described, which occurred on rechallenge with the drug.⁷¹ No clinically important drug interactions are known to occur,⁵⁶ although cimetidine reduces its renal clearance.⁷² Some authors have cautioned about the concomitant use of nonsteroidal anti-inflammatory drugs in diabetic subjects taking metformin because of the propensity for nonsteroidal anti-inflammatory drugs to reduce the glomerular filtration rate and possibly cause deterioration of renal function, with resultant decreased clearance of metformin.⁷³

More cases of toxicity have been described with the therapeutic use of biguanides than in overdose. The clinical course is generally mild in cases of small ingestions.^{17,74} Gastrointestinal symptoms, as described above, predominate; hypoglycemia may rarely occur in the milieu of prolonged fasting.^{17,53,74} Lactic acidosis may also occur in overdose. The onset may take several hours, and therefore, in cases of serious ingestion, the patient should be observed for approximately 6 to 8 hours.¹⁷ Treatment is supportive and should include standard gastrointestinal decontamination. Metabolic acidosis, should it develop, should be treated with bicarbonate, although this should be done with caution because of the incumbent high sodium load (and issues of volume overload).⁷⁵ The nearly nonexistent protein binding of the drug makes hemodialysis a possible treatment option in cases of massive ingestion, especially if lactic acidosis occurs.⁵⁴ Three cases of metformin overdose have been described recently, 2 of which were fatal.⁷⁵ All 3 featured profound metabolic acidosis caused by lactate; the 2 fatal cases were refractory to treatment with sodium bicarbonate and ultimately venovenous hemofiltration, whereas the other patient responded. In both fatalities, refractory hypotension with low systemic vascular resistance precluded hemodialysis treatment. Both patients were hypothermic and hypoglycemic, the latter condition being without any known coingestion of hypoglycemic agents. Two of the cases featured large ingestions (ie, 50 g [nonfatal] and 35 g [fatal]), and the other fatality involved an indeterminate amount, suggesting that profound acidosis may be associated with massive ingestions.

α -GLUCOSIDASE INHIBITORS

There are 3 α -glucosidase inhibitors: acarbose was released first, miglitol has just recently been marketed in the United States, and voglibose is not yet widely available.¹⁷ Although they can be used as monotherapy for type 2 DM,

these antihyperglycemic drugs are frequently used in combination with the sulfonylureas or insulin.^{17,58-60}

These agents competitively and reversibly inhibit α -glucosidase, an intestinal brush border hydrolase enzyme. This leads to a postprandial decrease in carbohydrate absorption because complex dietary polysaccharides are not broken down into absorbable monosaccharides. As a result, there is a decrease in hyperinsulinism and in hepatic triglyceride synthesis. Lactose absorption is not affected because lactase is a β -galactosidase.^{17,58-60} The pills should be taken with the first bite of each meal.⁶⁰ The mechanism of action of the α -glucosidase inhibitors has implications for the treatment of hypoglycemia; should it develop, simple sucrose (table sugar) will not be effective. Glucose should be administered, if oral therapy is used, to raise the serum blood glucose.⁶⁰

Acarbose is poorly absorbed; its mechanism of action is dependent on its local effects, as is its side effect profile.^{17,58,60} Miglitol is rapidly and fully absorbed at low doses. Its antihyperglycemic mechanism of action is similar to that of acarbose; the implications of its systemic absorption are unknown.^{17,61} Hypothetically, because miglitol is cleared by the kidney, its use in patients with significant renal impairment may lead to toxicity (Table 3).^{60,61}

As might be expected, the side effect profile of the α -glucosidase inhibitors is predominantly gastrointestinal because of their limited absorption. The undigested sugars may lead to bloating, flatulence, diarrhea, and abdominal pain. Side effects may decrease in 1 to 2 months, and gradual escalation from low to higher doses may attenuate the adverse effects.^{17,58-60} The gastrointestinal side effects may be additive with those of metformin. General contraindications to α -glucosidase inhibitor therapy include cirrhosis, inflammatory bowel disease, predisposition to bowel obstruction, and malabsorption syndromes.⁶⁰ The α -glucosidase inhibitors are not known to cause hypoglycemia when used as monotherapy.^{17,60} Acarbose appears to inhibit iron absorption, and although the clinical relevance appears to be negligible, mild anemia may occur.^{58,60}

Significant hepatic injury has been reported with chronic acarbose therapy.^{60,76-80} Not detected in clinical trials, the incidence appears to be low, unpredictable, and idiosyncratic, although real because it has occurred with rechallenge.^{59,78,79} Laboratory and histologic data do not reflect a hypersensitivity mechanism.^{78,79} It is recommended that transaminase levels be checked regularly in patients taking acarbose,⁷⁸ and the emergency physician should be aware of the potential for hepatic toxicity in patients taking this agent.

There are no published reports of overdose or severe toxicity with the α -glucosidase inhibitors.^{17,58} Their localized mechanism of action makes systemic toxicity unlikely; it seems reasonable that the abdominal side effects seen in therapeutic use could be expected in overdose. It may be prudent to perform liver function tests in cases of massive acarbose overdose.¹⁷

THIAZOLIDINEDIONES

There are 2 drugs from this class currently on the market in the United States: rosiglitazone and pioglitazone. Troglitazone, the first of the thiazolidinediones on the market, received much recent public and professional scrutiny because of a link with serious, and at times fatal, hepatic dysfunction.⁸¹⁻⁸⁹ It was withdrawn from the market in the United States early in 2000.

The thiazolidinediones enhance the effect of insulin in skeletal muscle, adipose, and hepatic tissues without increasing pancreatic secretion of insulin. They seem to bind to peroxisomal proliferator-activated receptors, changing insulin-dependent gene expression in the liver; the exact mechanism remains elusive. The thiazolidinediones decrease blood glucose levels in diabetic subjects, variably lower triglycerides, and have a mild, clinically insignificant, antihypertensive effect caused by decreasing insulin levels.⁸¹

Rosiglitazone and pioglitazone are rapidly absorbed. Both agents are greater than 99% protein bound. They undergo extensive hepatic metabolism, with metabolites being excreted in the urine and feces (Table 3). They are not recommended for use in patients with hepatic disease but require no dosage adjustment in individuals with renal impairment. Both drugs can be taken without regard to meals.^{62,63}

The thiazolidinediones are generally very well tolerated.^{62,63,81} Both rosiglitazone and pioglitazone may reinstate ovulation in premenopausal women who have not been ovulating. They also should be used with caution in patients with congestive heart failure because of a propensity to increase the circulating plasma volume, which may lead to edema.^{62,63} Ethinyl estradiol/norethindrone plasma levels are reportedly decreased by pioglitazone, leading to a loss of contraceptive effect. Ketoconazole may inhibit the metabolism of pioglitazone, thereby increasing the effect of the latter.⁶³

The withdrawal of troglitazone as a result of hepatic toxicity is concerning because of the structural similarity among the thiazolidinediones. To date, although there are no reports of serious hepatotoxicity with pioglitazone,

there have been 2 reported cases of hepatotoxicity attributed to rosiglitazone.^{90,91} One case involved hepatocellular injury that rapidly reversed on cessation of the drug,⁹⁰ whereas the other patient manifested liver failure with a period of profound metabolic acidosis and coma, which gradually resolved.⁹¹ Neither patient underwent a liver biopsy. The manufacturers of rosiglitazone vehemently disagreed with the attribution of liver failure to the drug in the latter case, stating that their review of the case suggested ischemic hepatitis to be the culprit.⁹² The manufacturers of both pioglitazone and rosiglitazone recommend monitoring of alanine aminotransferase levels in patients taking these agents, including baseline levels, followed by levels at 2-month intervals for the first year and periodic checks thereafter.^{62,63}

BENZOIC ACID DERIVATIVES

Repaglinide is the first nonsulfonylurea oral hypoglycemic agent on the market in the United States.^{17,64} It is indicated either as monotherapy or in combination with metformin; clinical and toxicologic experience with this agent is limited to date.^{64,65}

Repaglinide binds to the adenosine triphosphate-sensitive potassium channels on pancreatic β cells at a receptor different from that of the sulfonylureas. However, it decreases insulin levels, whereas the sulfonylureas do not, and an extrapancreatic effect leading to increased insulin sensitivity has been postulated.^{64,65} It is rapidly absorbed (within 1 hour) and quickly metabolized by the liver, with an apparent half-life of approximately 1 hour, and then excreted primarily in the bile, with only 6% being excreted by the kidneys (Table 3). Protein binding is greater than 98%. Absorption is not affected by food. Its pharmacokinetics require dosing to be synchronized with meals (within 30 minutes of the meal is optimal), leading to a profound decrease in postprandial hyperglycemia.^{64,65,93}

Comparative clinical trials have shown that mild-to-moderate hypoglycemia occurred in approximately 16% of patients taking repaglinide, as opposed to 20% of those taking glyburide and 19% of those taking glipizide. The pharmacokinetics of the drug should decrease the frequency, severity, and duration of the hypoglycemia, however. Downregulation of the β cells in the pancreas, which leads to secondary drug failure, is also expected to be less of a problem with repaglinide than with the sulfonylureas. Drug interactions have not yet been reported; it is anticipated that CYP3A4 inhibitors (eg, erythromycin) and CYP3A4 inducers (eg, rifampin) may increase and decrease the effects of the drug, respectively. It should be

used cautiously in patients with liver dysfunction but appears to be safe in patients with renal insufficiency on the basis of limited data.^{64,65}

There have been no reports of repaglinide overdose and toxicity. It is expected that hypoglycemia would occur in cases of overdose, as with the sulfonylureas.¹⁷

TREATMENT OF HYPOGLYCEMIA RESULTING FROM ORAL ANTIDIABETIC AGENTS

Hypoglycemia is a well-known occurrence after both accidental and intentional ingestion of sulfonylureas, as well as in patients taking these drugs as prescribed for type 2 DM. It also may arise in patients with DM because of impaired hepatic metabolism or renal excretion, depending on the degree of impairment and the clearance characteristics of the drug (Table 1). Hypoglycemia is not expected to be encountered in patients treated solely with metformin or a thiazolidinedione, but the addition of these antihyperglycemic agents to a regimen that includes sulfonylureas may precipitate hypoglycemia. Repaglinide has the capacity to induce hypoglycemia, yet taken therapeutically, it should not cause prolonged hypoglycemia because of its pharmacokinetics, and hypoglycemia should be avoided altogether if the dose corresponding to a missed meal is omitted.⁹³

Thus, a discussion of the treatment of hypoglycemia caused by oral antidiabetic agents should focus on the treatment of hypoglycemia as a result of sulfonylureas. Several issues will be highlighted below: (1) general supportive treatment; (2) recommendations for periods of observation after sulfonylurea ingestion in the pediatric population; and (3) pharmacotherapeutic adjuncts to the administration of glucose in cases of refractory hypoglycemia.

In all cases (eg, overdose, unexpected hypoglycemia in adults with DM, and symptomatic pediatric ingestions), the airway should be secured and hemodynamic stability verified while a rapid bedside estimate of serum glucose is obtained. If the patient is hypoglycemic, glucose should be administered. Activated charcoal is expected to bind sulfonylureas and can be reasonably administered in suspected cases of toxicity, although the efficacy of this therapy specific to sulfonylurea overdose is unclear. Randomized controlled trials exist that demonstrate substantial reduction in the absorption of chlorpropamide and glipizide by activated charcoal administered to human volunteers.⁹⁴ A dose of 1 to 2 g/kg is recommended, with maximal efficacy if administered within 1 hour of ingestion.^{17,94,95} Emesis should not be induced because of the

expectation of development of a depressed level of consciousness in the hypoglycemic state.^{17,95}

In general, patients with potentially toxic sulfonylurea overdose or adults with hypoglycemia in the milieu of unintentional therapeutic error, polypharmacy, hepatic insufficiency, or impaired renal clearance are probably best served by admission for observation, even if they are euglycemic on presentation. Long duration of effect and delayed clearance of active drug or metabolites (Table 1) in these situations are well described.⁹⁵ Sulfonylureas are not listed among those drugs that commonly form concretions or bezoars,⁹⁶ but the possibility of a bezoar should be considered in cases of prolonged and profound hypoglycemia. Management may include removal under direct visualization.

There has been some debate in the literature regarding the optimal period of observation in the asymptomatic pediatric patient with an accidental sulfonylurea ingestion. Relevant to this debate are the contrasting issues of onset of action versus duration of effect of these agents.⁹⁵ All sulfonylureas demonstrate a time-to-peak effect of less than 8 hours, with the possible exception of the extended-release formulation of glipizide (Table 1). Thus, onset of hypoglycemia can reasonably be expected during this time,⁹⁵ a finding that has been demonstrated in a recent prospective case series.³⁵ In this study, 53 of 54 patients available for medical evaluation within the 8-hour post-ingestion period had hypoglycemia (defined as blood glucose level of ≤ 60 mg/dL) during that time; the one patient who did not had a value near the threshold (62 mg/dL) at 3 hours after ingestion, which prompted continuous infusion of intravenous dextrose, with a nadir occurring at 16 hours after ingestion. The authors argue persuasively, as do others,⁹⁷ that this lone case represents not the delayed onset of hypoglycemia but the masking of earlier onset hypoglycemia by the administration of intravenous glucose. A retrospective study³⁶ had insufficient data to demonstrate this 8-hour recommendation (ie, a lack of documented frequent blood glucose determinations) but showed that the majority of patients (79%) became chemically hypoglycemic within 4 hours of ingestion, a finding similar to that in the prospective series described above (74% chemically hypoglycemic within 4 hours).³⁵ Others^{98,99} have published cases of "delayed-onset" hypoglycemia (ie, >8 hours) after sulfonylurea ingestion in children, yet these cases appear to demonstrate merely a delayed blood glucose nadir (caused by the administration of intravenous glucose during observation) rather than a truly delayed onset. Thus, the following recommendation seems prudent with regard to observation

duration in cases of asymptomatic pediatric patients with a history of sulfonylurea ingestion. Perform serial fingerstick glucose determinations (every 1-2 hours) while the child is given free access to food (and no intravenous glucose) for 8 hours. If hypoglycemia (blood glucose ≤ 60 mg/dL) develops, admission is warranted. If the child remains euglycemic, she or he can be safely discharged.^{35,95,97} No milligram per kilogram body weight threshold has been established for use in management decisions; all ingestions, even if limited to only one tablet, should be observed.³⁵

Still others advocate a more liberal approach, recommending home management of asymptomatic children with frequent feedings by knowledgeable parents; this center reports successful home management of 206 (54%) of 380 patients without any adverse outcomes.^{37,100}

Three agents deserve discussion as adjuncts to glucose in cases of refractory hypoglycemia caused by sulfonylurea poisoning: octreotide, diazoxide, and glucagon. Refractory hypoglycemia may arise in cases of massive overdose, impaired hepatic function, or impaired renal clearance (in cases wherein the parent compound, metabolites, or both are cleared by the kidney; Table 1). Unintentional ingestions in the pediatric population generally do not require anything more than intravenous glucose supplementation.^{35,36} More complicated are the cases that do not respond to glucose administration or those wherein the hypertonicity of the dextrose (generally $>10\%$ dextrose in children) necessitates central venous access to avoid the associated phlebitis seen with administration of these agents through peripheral lines in children.⁹⁵ In such cases, the addition of an agent that combats the hyperinsulinism associated with sulfonylurea overdose may be effective in reversing persistent hypoglycemia.

Octreotide, a somatostatin analog, is known to suppress the secretion of numerous hormones, including gastrin, vasoactive intestinal peptide, glucagon, and, most importantly here, insulin. There are experimental and clinical data supporting its consideration in selected cases of sulfonylurea-induced hypoglycemia. Boyle et al¹⁰¹ compared octreotide with diazoxide and glucose alone in an 8-patient, simulated, subtoxic overdose study with glipizide, with the patients as their own control subjects. Octreotide outperformed the other 2 arms, with 4 of 8 patients not needing any glucose supplementation; the patients in the octreotide arm also needed significantly less glucose supplementation than the patients in the diazoxide and glucose arms.¹⁰¹ Case reports on the clinical use of octreotide in overdose demonstrate its efficacy and

highlight its ability to suppress endogenous insulin despite levels elevated because of the action of toxic amounts of sulfonylureas.¹⁰²⁻¹⁰⁷ These cases involve severe refractory hypoglycemia in adults from a variety of agents—tolbutamide,¹⁰² gliclazide,¹⁰³ glipizide,¹⁰⁴ chlorpropamide,¹⁰⁵ and glyburide¹⁰⁷—and in one pediatric case, from glipizide.¹⁰⁶ Dextrose is itself an insulin secretagogue and thus treats the low blood glucose yet paradoxically contributes to rebound hypoglycemia through stimulation of insulin release. Octreotide counters the hyperinsulinism resulting from both the sulfonylurea and the dextrose therapy.⁹⁵ Each of these cases¹⁰²⁻¹⁰⁷ demonstrated a reduced need for further glucose supplementation and a return to euglycemia once octreotide therapy was instituted. A recent retrospective case series¹⁰⁸ of 9 adult patients with sulfonylurea poisoning who were treated with octreotide showed a reduction in mean hypoglycemic events before (3.2) and after (0.2) octreotide ($P=.008$) and a similarly strong reduction in the number of ampules of 50% dextrose used per patient before and after octreotide (2.9 versus 0.2, respectively; $P=.004$). The risk of recurrent hypoglycemia before octreotide was 27 times that of the risk after octreotide in this study. No adverse effects attributable to octreotide therapy for sulfonylurea-induced hypoglycemia have been reported.¹⁰²⁻¹⁰⁸

Optimal dosing guidelines for octreotide in sulfonylurea poisoning have yet to be established. Clinical experience is with subcutaneous or intravenous administration, and it has been given successfully as a continuous infusion.^{107,108} Dosing thus far in adults has ranged from 40 to 100 μg per dose;^{102-105,107,108} intravenous infusions have been administered up to 100 to 125 $\mu\text{g}/\text{h}$.^{107,108} One pediatric case involved a dose of 25 μg subcutaneously in a 5-year-old weighing 20 kg.¹⁰⁶ Octreotide doses of 1 to 10 $\mu\text{g}/\text{kg}$ have been well tolerated in other pediatric scenarios.⁹⁵ The drug has a rapid onset of action, with a distribution half-life of 12 minutes and an elimination half-life of 1.5 hours.⁹⁵

Diazoxide, a nondiuretic vasodilator most commonly associated with the treatment of hypertensive emergencies, also is efficacious in the treatment of hypoglycemia. It has been used successfully in the treatment of sulfonylurea-induced hypoglycemia¹⁰⁹ without the anticipated adverse reactions, which most notably include hypotension and reflex tachycardia. Head-to-head comparison of octreotide and diazoxide has demonstrated greater efficacy with the former,¹⁰¹ yet this trial was a subtoxic overdose simulation in volunteers and thus may not extrapolate to the clinical poisoning scenario. Octreotide suppressed insulin levels, whereas diazoxide and

glucose did not;¹⁰¹ thus, diazoxide is mechanistically less appealing than octreotide. However, diazoxide has been successfully used for more than 20 years in the treatment of sulfonylurea-induced hypoglycemia⁹⁵ and thus is a viable alternative in cases of refractory hypoglycemia. Dosing recommendations in adults are based on clinical experience and include boluses of 300 mg intravenously over 1 hour and 1 to 3 mg/kg in children.^{17,95}

Glucagon, a naturally occurring hormone, works by recruiting hepatic glycogen stores and inducing gluconeogenesis, although its success is partially dependent on the adequacy of glycogen stores.^{17,95,110} Because one physiologic effect of glucagon is the stimulation of insulin release, there is at least a theoretic concern about administering it in cases of sulfonylurea overdose because of the hyperinsulinemic state that is induced by the toxin.⁹⁵ Glucagon has been compared with dextrose in the ED^{111,112} and out-of-hospital¹¹³ treatment of hypoglycemia. Intravenous dextrose resulted in a significantly faster return of normal sensorium,^{111,112} especially when the glucagon was administered intramuscularly (9 [glucagon] versus 3 [dextrose] minutes, $P<.01$).¹¹² Although the out-of-hospital study had a small sample size, it showed that intravenous dextrose outperformed intramuscular glucagon in time to return of normal level of consciousness, even allowing for the time it took to establish intravenous access.¹¹³ Glucagon failures were reported in each study, necessitating rescue glucose administration.¹¹¹⁻¹¹³ Nonetheless, glucagon should be reserved for temporizing treatment in those patients in whom intravenous access cannot be rapidly established for the administration of dextrose. Dosing (subcutaneously or intramuscularly) is as follows: 1 mg in adults, 0.5 mg in children, and 50 $\mu\text{g}/\text{kg}$ in neonates or infants.¹¹⁰

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ORAL AGENTS FOR TYPE 2 DIABETES MELLITUS

Harrigan, Nathan & Beattie

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