Oral Hypoglycemic Agents: The Risk of Hypoglycemia

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Recently attention has been drawn to the risk of hypoglycemia in patients receiving oral hypoglycemic drugs. In a study of patients taking glyburide, the investigators found a 6.6-fold increase in the risk of hypoglycemia in those who had received co-trimoxazole (eg, Bactrim, Septra) in the week prior to admission for hypoglycemia.[1] These patients were compared with patients who had received glyburide and amoxicillin. The increased risk of hypoglycemia was likely caused by sulfamethoxazole-induced inhibition of glyburide metabolism.

Table 1 lists the current oral hypoglycemic agents and their pathways of elimination. Notice that all of the agents, except metformin, are metabolized by the cytochrome P-450 system. The majority of the agents are substrates for CYP2C9, with CYP3A4 or CYP2C8 metabolizing the remaining agents. Multiple pathways are responsible for the metabolism of several of the newer oral hypoglycemic agents.

Table 2 lists common drugs that are known CYP2C9, CYP3A4, or CYP2C8 inhibitors. The combination of an oral hypoglycemic drug with a drug known to inhibit its metabolism is likely to result in a drug interaction. The plasma concentration of the hypoglycemic agent will increase, leading to an enhanced hypoglycemic response. The magnitude of each interaction and the ultimate effect on the patient's blood glucose concentrations will be difficult to predict.

A number of studies and case reports have described clinically important drug interactions with oral hypoglycemics. As noted above, several antibiotics can reduce the metabolism of oral hypoglycemics. Diabetic patients frequently develop urinary tract, systemic bacterial, or topical fungal infections. It is common to see blood sugar concentrations change during an infectious episode. The infection itself may cause elevations of blood glucose, whereas reduced food intake during an acute illness would tend to lower glucose concentrations. These disease-induced alterations in blood glucose will occur in addition to any changes caused by the presence of an interacting drug. The presence of several blood glucose modifiers mandates careful monitoring of the patient's blood sugar, especially during concurrent therapy with drugs known to inhibit the metabolism of oral hypoglycemics.

Some oral hypoglycemic drugs have multiple metabolic pathways. For example, repaglinide is metabolized primarily by CYP2C8 and to a lesser extent by CYP3A4. When gemfibrozil was coadministered with repaglinide, the area under the plasma concentration time curve (AUC) was increased an average of 8-fold.2 During the coadministration of itraconazole and repaglinide, the mean plasma repaglinide AUC was elevated 1.4-fold. The difference in the magnitude of the effect for the 2 inhibitors on repaglinide plasma concentrations reflects the relative dependence of repaglinide on CYP2C8 and CYP3A4 for its metabolism. When both gemfibrozil and itraconazole were coadministered with repaglinide, the AUC of repaglinide was increased more than 20-fold. This study gives an excellent example of an interaction involving a drug with 2 metabolic pathways. An inhibitor of 1 pathway may produce a significant increase in the plasma concentration of the drug, but when

Table 1

Elimination Pathways for Oral Hypoglycemic Agents

Oral Hypoglycemic Agent	Substrate of CYP-450 Enzymes
Chlorpropamide (Diabinese)	2C9
Glipizide (Glucotrol)	2C9
Glimepiride (Amaryl)	2C9
Glyburide (DiaBeta)	2C9
Metformin (Glucophage)	Renal elimination
Nateglinide (Starlix)	2C9 / 3A4
Pioglitazone (Actos)	3A4 / 2C8
Repaglinide (Prandin)	3A4 / 2C8
Rosiglitazone (Avandia)	2C8 / 2C9
Tolbutamide (Orinase)	2C9

Adapted from Hansten PD, Horn JR. *The Top 100 Drug Interactions: A Guide to Patient Management.* Edmonds, WA: H&H Publications; 2004:157-169.

inhibitors of both pathways are administered, the magnitude of the interaction is likely to become very large.

Patients with diabetes who are taking oral hypoglycemic agents should be counseled to closely monitor their blood sugar whenever a drug that may reduce the metabolism of the hypoglycemic agent is initiated, changed in dose, or discontinued from therapy. Very few of the potential interactions with oral hypoglycemic agents have been studied. Pharmacists should be especially alert for the concomitant administration of drugs or drug combinations that can inhibit both metabolic pathways of oral hypoglycemic agents that undergo dual metabolism. PT

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. D. Ryan, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: dryan@mwc.com.

Table 2

Common Inhibitors of CYP2C8, CYP2C9, and CYP3A4

Drug	CYP-450 Enzymes Inhibited
Atazanavir (Reyataz)	3A4, 2C9
Clarithromycin (Biaxin)	3A4
Erythromycin	3A4
Fluconazole (Diflucan)	2C9, 3A4
Fluoxetine (Prozac)	2C9
Fluvastatin (Lescol)	2C9
Fluvoxamine (Luvox)	2C9, 3A4
Gemfibrozil (Lopid)	2C8
Grapefruit (large doses)	3A4
Indinavir (Crixivan)	3A4
Isoniazid (INH)	2C9
Itraconazole (Sporanox)	3A4
Ketoconazole (Nizoral)	3A4
Metronidazole (Flagyl)	2C9
Ritonavir (Norvir)	3A4
Sulfamethoxazole	2C9
Voriconazole (Vfend)	3A4, 2C9

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