Oral Antihyperglycemic Agents and Renal Disease: New Agents, New Concepts

Jean-François Yale
Metabolic Day Centre, Royal Victoria Hospital, Montreal, Quebec, Canada

The results of the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study trials in type 1 and type 2 diabetes, respectively, have proved the importance of intensive glucose management in the prevention of microvascular complications (retinopathy, nephropathy, and neuropathy). Both trials showed encouraging trends for a decrease in macrovascular complications, and this is being pursued in new studies. These findings have led to more strict goals for glucose control. As glucose levels are aimed to be closer to the normal range, the risk for hypoglycemia also increases dramatically. The choice of the agent therefore is more influenced currently by the risk for hypoglycemia. There are presently four classes of oral antihyperglycemic agents. These agents differ greatly in terms of mechanisms of action, efficacy, side effect profiles, and cost. Except for Acarbose, all classes decrease the glycosylated hemoglobin by a similar magnitude: 1.0 to 1.5%. In chronic renal failure, the oral agents that can be used therefore include the insulin secretagogues repaglinide and nateglinide and the thiazolidinediones (rosiglitazone and pioglitazone) with caution. Insulin also can be used safely in renal failure.

Type 2 diabetes occurs as a result of a complex interplay among multiple genetic and environmental factors that lead to both increased insulin resistance and impaired pancreatic insulin secretion. Epidemiologic studies have shown a relationship between increasing levels of glucose and increased risk for both micro- and macrovascular complications. The threshold for increased cardiovascular risk occurs in the “nondiabetic” range, and even minimal elevations of glucose are associated with increased cardiovascular risk (1). There is much less randomized controlled trial evidence on the value of glucose control in preventing macrovascular disease. In the UK Prospective Diabetes Study, intensive treatment of individuals with newly diagnosed type 2 diabetes reduced the risk for myocardial infarction by 16% ($P = 0.052$), amputation or death from peripheral vascular disease by 35% ($P = 0.15$), fatal myocardial infarction by 6% ($P = 0.63$), nonfatal myocardial infarction by 21% ($P = 0.057$), fatal sudden death by 46% ($P = 0.047$), and amputation by 39% ($P = 0.099$). Every 1% reduction in glycosylated hemoglobin ($\text{HbA}_1$) was associated with reductions in risk of 21% for any end point related to diabetes, 21% for diabetes-related deaths, 14% for myocardial infarction, and 37% for microvascular complications (all $P < 0.0001$). No threshold of risk was observed for any end point; however, the lowest risk was in individuals with an $\text{HbA}_1$ in the normal range (<6%). In the obese subset, metformin therapy was associated with a lower risk for diabetes-related end points ($P = 0.0034$) and all-cause mortality ($P = 0.021$) compared with the other intensive therapies (4).

Therapy
The diagnosis of type 2 diabetes is often delayed, and 20 to 50% present with microvascular or macrovascular complications at the time of diagnosis of type 2 diabetes. The management regimens of patients with type 2 diabetes should be tailored to the individual patient, aiming for glycemic targets as close to normal as possible ($\text{A1c} < 6\%$ when agents that do not cause hypoglycemia are used) and, in most people, as early as possible (5).

It is known that both weight loss and increased physical activity can improve insulin resistance and thus improve hyperglycemia (6). It is recommended that lifestyle modification strategies be used in all patients with type 2 diabetes, whether medication is used or not (5).

Mechanisms of Action of Oral Antihyperglycemic Agents
The antihyperglycemic agents that are available include the insulin secretagogues (sulfonylureas and meglitinides), metformin, $\alpha$-glucosidase inhibitors, and the thiazolidinediones. These agents differ greatly in terms of mechanisms of action, efficacy, side effect profiles, and cost (Table 1).

Sulfonylureas and meglitinides increase insulin secretion by pancreatic $\beta$ cells. Metformin decreases hepatic glucose production. $\alpha$-Glucosidase inhibitors delay the absorption of glucose from starch and sucrose, attenuating postprandial glucose increases. Thiazolidinediones are potent, highly selective agonists for peroxisome proliferator-activated receptor-$\gamma$. Thiazolidinediones decrease insulin resistance, enhance peripheral disposal of glucose, and have some effect on hepatic production of glucose.

Glucose-Lowering Efficacy of Antihyperglycemic Agents
A large number of clinical trials comparing the efficacy of the oral antihyperglycemic agents have been completed. The com-
Table 1. Summary of oral antihyperglycemic agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>HbA1c Drop</th>
<th>Hypoglycemia</th>
<th>Weight Gain</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
<th>Cost per Month</th>
<th>Use in Renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>1.0–1.5</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Contraindicated when creatinine clearance is &lt;60 ml/min because of the risk for lactic acidosis</td>
</tr>
<tr>
<td>metformin</td>
<td>1.0–1.5</td>
<td>No</td>
<td></td>
<td>250 mg twice daily</td>
<td>850 mg three times a day</td>
<td>$20</td>
<td>Metabolism not affected in renal failure, but fluid retention may be a problem, with heightened risk for congestive heart failure</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1.0–1.5</td>
<td>Yes</td>
<td></td>
<td>4 mg/d</td>
<td>8 mg/d or 4 mg twice daily</td>
<td>$50</td>
<td></td>
</tr>
<tr>
<td>gliclazide</td>
<td>1.0–1.5</td>
<td>Yes</td>
<td></td>
<td>2.5–5 mg/d</td>
<td>10 mg twice daily</td>
<td>$35</td>
<td>The metabolism of all sulfonylureas is affected by renal failure; this will initially require decreases in dosages, and eventually avoidance of these agents</td>
</tr>
<tr>
<td>glibizide</td>
<td></td>
<td></td>
<td></td>
<td>40–80 mg twice daily</td>
<td>160 mg twice daily</td>
<td>$40</td>
<td></td>
</tr>
<tr>
<td>glimepiride</td>
<td></td>
<td></td>
<td></td>
<td>1 mg/d</td>
<td>8 mg/d</td>
<td>$50</td>
<td></td>
</tr>
<tr>
<td>glipizide</td>
<td></td>
<td></td>
<td></td>
<td>5 mg/d or XL 5 mg/d</td>
<td>20 mg twice daily or XL 20 mg/d</td>
<td>$30</td>
<td></td>
</tr>
<tr>
<td>tolbutamidine</td>
<td></td>
<td></td>
<td></td>
<td>500 mg twice daily</td>
<td>500 mg four times a day</td>
<td>$15</td>
<td></td>
</tr>
<tr>
<td>chlorpropamide</td>
<td></td>
<td></td>
<td></td>
<td>100 mg/d</td>
<td>500 mg/d</td>
<td>$10</td>
<td></td>
</tr>
<tr>
<td>acetohexamide</td>
<td></td>
<td></td>
<td></td>
<td>250 mg/d</td>
<td>500 mg three times a day</td>
<td>$10</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>1.0–1.5</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Can be used in the presence of renal failure as the pharmacokinetics are unaffected</td>
</tr>
<tr>
<td>repaglinide</td>
<td>0.5–1.0</td>
<td>No</td>
<td>No</td>
<td>0.5 mg three times a day</td>
<td>4 mg three times a day</td>
<td>$0</td>
<td>Contraindicated in renal failure</td>
</tr>
<tr>
<td>nateglinide</td>
<td></td>
<td></td>
<td></td>
<td>120 mg three times a day</td>
<td>180 mg three times a day</td>
<td>$0</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5–1.0</td>
<td>No</td>
<td>No</td>
<td>25 mg three times a day</td>
<td>100 mg three times a day</td>
<td>$40</td>
<td></td>
</tr>
<tr>
<td>miglitol</td>
<td></td>
<td></td>
<td></td>
<td>25 mg three times a day</td>
<td>100 mg three times a day</td>
<td>$60</td>
<td></td>
</tr>
</tbody>
</table>
parative glycemic effect of some of these agents are well known when used as monotherapy and in combination with other oral antihyperglycemic agents or insulin (Table 1). In general, metformin, the thiazolidinediones, and the insulin secretagogues (sulfonylureas and repaglinide) have approximately equivalent efficacy (reductions in HbA1c of 1.0 to 1.5% compared with placebo) (7–11). Higher reductions are generally seen in treatment-naïve patients and those with higher baseline glycemic values (9,11). Treatment with acarbose seems somewhat less effective with reductions in HbA1c of 0.5 to 1% compared with placebo in previously untreated patients (12–14).

Most of the oral antihyperglycemic agents can be combined with each other and insulin therapy with additive effects. The initial use of combinations of submaximal doses of oral antihyperglycemic agents produces more rapid and improved glycemic control compared with monotherapy with the maximal dose of one agent, without a significant increase in side effects (15).

Therapy with exogenous insulin is recommended when individuals have not achieved glucose targets with oral agents either alone or in combination (5). Oral agents may be continued or added on to insulin therapy as necessary.

**Side Effects of Antihyperglycemic Agents**

**Hypoglycemia**

Within the oral antihyperglycemic agents, insulin secretagogues are associated with the highest occurrence of hypoglycemic episodes, ranging from 10 to 35% (4,7,10). However, severe episodes that require intervention are relatively rare (0 to 1.3%). Metformin, thiazolidinediones, and α-glucosidase inhibitors do not usually cause hypoglycemia when used alone but can potentiate the hypoglycemic potency of insulin secretagogues (4,7,9,12,14). Repaglinide and nateglinide are particular in having a rapid onset and short duration of action and can be given at mealtimes. They have been shown to decrease hypoglycemia when given to patients with irregular mealtimes. Insulin therapy in patients with type 2 diabetes is associated with the highest frequency of hypoglycemia (16 to 34%) (4,7,12), although this frequency is much lower than that seen with insulin therapy of patients with type 2 diabetes.

Although α-glucosidase inhibitors do not cause hypoglycemia, they may prevent sucrose or starch from being absorbed in a timely manner for the treatment of hypoglycemia caused by other treatments. Patients who take α-glucosidase inhibitors therefore must use glucose (dextrose tablets), grape juice, or honey to treat hypoglycemia.

**Body Weight**

Insulin secretagogues, both sulfonylureas and repaglinide, are associated with an increase in body weight compared with placebo of up to approximately 4.5 kg over 3 yr (7). The use of rosiglitazone and pioglitazone in the treatment of type 2 diabetes has been associated with weight gain of 1 to 3 kg. α-Glucosidase inhibitors demonstrate neutral effects on weight, whereas metformin is usually associated with no weight gain and occasionally weight loss.

**Other Side Effects**

Metformin is associated with a high frequency of nausea and diarrhea. This side effect can be reduced by taking the pills in the middle of the meal. Acarbose, by inhibiting proximal absorption of starch and sucrose, can cause flatulence. This side effect is present in >70% of patients in the first months, but some adaptation occurs and the magnitude of this side effect decreases over subsequent months. The major risk of metformin is lactic acidosis. It is a rare side effect, occurring particularly in the presence of renal failure, hepatic dysfunction, or tissue ischemia.

The thiazolidinediones rosiglitazone and pioglitazone have been associated with small decreases in hemoglobin in patients with type 2 diabetes, likely explained by a modest increase in plasma volume. Edema was noted with greater frequency in patients who were treated with pioglitazone or rosiglitazone compared with those who were treated with placebo in clinical trials. A recent American Diabetes Association/American Heart Association position statement recommended avoiding the use of thiazolidinediones in the presence of class III or IV NYHA congestive heart failure (CHF) and to use with caution in those who have less severe CHF or are at risk for CHF (history of heart failure, previous myocardial infarction or angina, hypertension, left ventricular hypertrophy, significant aortic or mitral valve disease, age >70 yr, diabetes duration >10 yr, preexisting edema or treatment with loop diuretics, development of edema or weight gain on thiazolidinediones, insulin co-administration, and chronic renal failure) (16).

**Use of Antihyperglycemic Agents in Patients with Renal Failure**

Metformin is contraindicated in renal failure because of the associated risk for lactic acidosis. It can be used at low dosages up to a creatinine clearance of 30 to 60 ml/min and should be avoided with clearances <30 (17). Although the metabolism of thiazolidinediones is unaffected by renal failure, they must be used with caution in this context because of their volume-retaining effect with a risk for heart failure (18).

The sulfonylureas (glyburide, gliclazide, glipizide, glibenclamide, tolbutamide, and chlorpropamide) have increased potency as the renal function decreases and are contraindicated in severe renal failure (19). The nonsulfonylurea insulin secretagogues repaglinide and nateglinide can be used in renal failure without dose adjustments (20). α-Glucosidase inhibitors (acarbose and miglitol) are contraindicated in renal failure.

**Conclusion**

In the absence of contraindications, metformin should be preferred over other agents for a number of reasons. Compared with insulin secretagogues in general, metformin has equal potency and a low risk for hypoglycemia and causes less weight gain. In obese patients, there is strong clinical evidence of reduced microvascular and macrovascular outcomes.

In the presence of contraindications or intolerance to metformin or when metformin alone does not result in optimal control, thiazolidinediones should be used. They should be favored over insulin secretagogues because they are not asso-
citated with hypoglycemia. Compared with acarbose, thiazolidinediones have more potent antihyperglycemic effects. Sulfonylureas and other insulin secretagogues should be reserved for combination therapy because of the risk for hypoglycemia.

In chronic renal failure, the oral agents that can be used therefore include the insulin secretagogues repaglinide and nateglinide and the thiazolidinediones (rosiglitazone and pioglitazone) with caution. Insulin also can be used safely in renal failure.

References

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