Thinking on your feet

Common side effects of diabetes medications

Kalpa Shah (Meds 2012)
Faculty reviewer: Dr. Terri Paul, Department of Medicine, UWO

In Canada an estimated 3 million individuals are affected by diabetes and the incidence of type 2 diabetes mellitus (T2DM) is expected to continue to rise. As the prevalence of T2DM rises, a larger portion of the population will be using diabetic medications, which underscores the importance of being familiar with the side effects of these therapies. The article will discuss some of the main classes of diabetic medications, their side effects and contraindications to use. The side effects of commonly used diabetic medications will be explored and discussed through a series of vignettes.

Case 1

An 82-year-old woman who lives alone is found by her daughter one morning confused, disoriented and sweating profusely. Her daughter is concerned that she is having a heart attack and calls the ambulance. The paramedics arrive and, on discovering the patient has diabetes, check her blood sugar. It is 2.0 mmol/L. She is given glucose and transported to the ER. As the physician treating her in the ER, you ask her the following:

♦ How long have you had DM? 2 years
♦ What medications are you taking? Metformin and glyburide
♦ Have you been eating appropriate meals? You find out that she has often just been having tea for breakfast but has been routinely taking her diabetes medications. She admits to often feeling “shaky” in the mid morning.

The patient is hypoglycemic which is confirmed by her low blood sugar. Although hypoglycemia is commonly associated with patients using insulin to control their diabetes, it is also a major adverse effect of insulin secretagogues - medications that stimulate the beta cells in the pancreas to produce insulin. There are two classes of insulin secretagogues: sulfonylureas and meglitinides. Sulfonylureas have been a mainstay of oral therapy for T2DM since the 1950s. They exert their effect by binding to the potassium channel in the pancreatic beta cells, which increases the resting potential of the cell. As a result, the cell is more sensitive to depolarization leading to a calcium influx and insulin secretion. Since sulfonylureas cause insulin release their major side effects are hypoglycemia, as seen in this case, and weight gain.

In this case, the patient was more prone to hypoglycemia since she was elderly and ate a very light breakfast when she took her medication. Other situations when hypoglycemia is more likely to occur include:

♦ after exercise or a missed meal
♦ when the drug dose is too high
♦ with the use of longer-acting drugs (such as glyburide)
♦ in patients who are undernourished or abuse alcohol
♦ in patients with impaired renal or cardiac function or gastrointestinal disease

Other side effects associated with the use of sulfonylureas include weight gain, rash (including photosensitivity) and nausea. Contraindications to the use of these drugs are sulfa allergy, pregnancy or lactation, type 1 diabetes mellitus (since there needs to be some functional beta cells in the pancreas for the drug to act on), cardiovascular disease, and impaired liver or renal function.

Case 2

A 65-year-old man has had diabetes for 8 years. He was initially treated with metformin and glyburide but as his control worsened, his glyburide was stopped and he was switched to insulin 30/70 taking 50 units BID along with his metformin. He comes to clinic complaining that he has gained 40 lbs over the past 3 months. His blood sugars before meals at breakfast are in the range of 5-8 mmol/L. He only occasionally checks at supper time but they are often 7 – 10 mmol/L. He says that he feels shaky and sweaty every morning at 10 am and must have a snack. He has been eating a sandwich and cookie as a mid morning snack. The same thing happens after supper, in the early evening when he feels that he must snack throughout the evening.

After asking him to check some blood sugars 2 hours after eating, you discover that he is having a low blood sugars of 2.5 mmol/L.

He is having symptomatic lows that he is over treating by snacking excessively and this is contributing to his weight gain. You could suggest switching to a shorter acting insulin analogue mixture such as Mix25 (humalog and NPH) or Novomix (novorapid and NPH) and adjusting dose. The ultra fast acting insulin will not last as long as the regular insulin 30/70 and he will no longer have the urge for a morning and evening snack. Another alternative is to transfer him to multiple daily injection (MDI), with fast acting insulin before meals and a long-acting insulin at bedtime.
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<table>
<thead>
<tr>
<th>Class</th>
<th>Prototype drugs</th>
<th>Action in the body</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide, glipizide, glimepiride</td>
<td>increases insulin secretion</td>
<td>Hypoglycemia, Weight gain, nausea, rash, GI symptoms, blurred vision</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>repaglinide, nateglinide</td>
<td>increases insulin secretion</td>
<td>Hypoglycemia, upper respiratory infection, headache, diarrhea, weight gain</td>
</tr>
<tr>
<td>Biguanides</td>
<td>metformin</td>
<td>enhances insulin sensitivity</td>
<td>GI symptoms, lactic acidosis</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>rosiglitazone, pioglitazone</td>
<td>enhances insulin sensitivity</td>
<td>Cardiac events, heart failure, edema, weight gain, fractures</td>
</tr>
<tr>
<td>alpha-glucosidase inhibitors</td>
<td>acarbose, miglitol</td>
<td>reduces absorption of glucose from gut</td>
<td>GI symptoms (diarrhea, flatulence cramping)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>sitagliptin</td>
<td>inhibits breakdown of GLP-1 (a gut hormone that enhances insulin secretion)</td>
<td>upper respiratory infection, headache, sore throat</td>
</tr>
</tbody>
</table>

Table 1. Summary of major classes of diabetic medications. Adapted from The Medical Letter.\(^\text{11}\)

He returns in 1 month after starting the new regimen and has lost 5 lbs.

Case 3

A 45-year-old woman presents with newly diagnosed diabetes and is started on metformin 500 mg TID. She returns 1 week later saying she cannot tolerate the medication due to upset stomach and diarrhea.

There are two classes of insulin sensitizers - medications that improve insulin action in the body: biguanides (which include metformin) and thiazolidinediones. Metformin is a first line oral hypoglycemic agent and some of the mechanisms through which it exerts its effects are: 1) decreasing hepatic glucose output 2) increasing insulin-mediated glucose utilization in muscle and liver 3) lowering serum free fatty acid concentrations thus reducing substrate availability for gluconeogenesis. It is believed that these effects are mediated through the activation of AMP-activated protein kinase.\(^5\)

The most common side effects of metformin are gastrointestinal (GI) and include a metallic taste in the mouth, diarrhea, abdominal discomfort, nausea and mild anorexia. These effects are reversible upon stopping the drug or reducing the dosage.\(^5\) Metformin should be started slowly and with food to minimize side effect of GI upset as is illustrated in Case 3. Patients should be started with one pill or half a pill at mealtime once per day and this dose should be increased slowly as the patient tolerates it. The patient can titrate their dose themselves every 5-7 days up to a maximum of 4-5 tablets daily.

Another rare but serious side effect of metformin is lactic acidosis. As a result the following are contraindications to starting metformin therapy: impaired renal function, liver disease, alcohol abuse, heart failure, past history of lactic acidosis, decreased tissue perfusion or hemodynamic instability.\(^5\)

Case 4

A 50-year-old man with newly diagnosed type 2 diabetes mellitus has blood sugars in range of 8-12 mmol/L. He is started on Metformin and pioglitazone as initial therapy. He returns to your clinic in 3 months for follow up and his blood sugars are under much better control with fasting blood sugar of 5-7 mmol/L. However, he complains of a weight gain of 10-11 lbs (5 kg) and says his ankles and legs are puffy. You examine him and discover he has significant pedal edema that extends up his calves. He is not short of breath and has no signs of heart failure.

Pioglitazone has been associated with fluid retention, weight gain, heart failure, loss of bone mineral density and fractures.\(^6,7,8\) This patient is experiencing side effects of
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weight gain and edema from his pioglitazone therapy. His
weight gain is due in part to fluid retention; the rest may be
due to the proliferation of new adipocytes.

Pioglitazone belongs to the thiazolidinedione class of
drugs. Thiazolidinediones are insulin sensitizers that
increase the action of insulin by acting on adipose, muscle
and liver to increase glucose utilization and reduce glucose
production. It is believed that the thiazolidinediones exert
their effect by binding to peroxisome proliferator-activated
receptors (PPARs), which regulate gene expression. Fluid
retention is caused by the binding of PPAR receptors in the
nephron, which causes reabsorption of sodium and resul-
tant fluid retention. This fluid retention often manifests as
peripheral edema and may also precipitate heart failure in
susceptible patients. PPAR receptors are also found in
skeletal muscle, adipose tissue, pancreatic beta cells, liver,
heart, and kidneys, which accounts for the varied effects of
thiazolidinedione therapy.

References

1. Canadian Diabetes Association. “The prevalence and
cost of diabetes”. December 2009. Available at:
http://www.diabetes.ca/about-diabetes/what/
prevalence/
Cloning the β cell high-affinity sulfonylurea receptor:
a regulator of insulin secretion. Science 1995;
268:243.
3. McCulloch DK. Sulfonylureas and meglitinides in the
treatment of diabetes mellitus. In: UpToDate, Basow,
DS (Ed), UpToDate, Waltham, MA, 2009.
4. Alexander J. Managing Medication Effects in Type 2
5. Bailey CJ. Biguanides and NIDDM. Diabetes Care
6. Bogacka I, Xie H, Bray GA, Smith SR. The effect of
pioglitazone on peroxisome proliferator-activated
receptor-gamma target genes related to lipid storage
7. Yki-Jarvinen H. Drug Therapy: Thiazolidinediones. N.
thiazolidinediones and fracture risk. Arch. Intern.
Peroxisome proliferator-activated receptor gene
expression in human tissues. Effects of obesity,
weight loss, and regulation by insulin and glucocorti-
expand body fluid through PPARgamma stimulation
of ENaC-mediated renal salt absorption. Nat. Med
11. Drugs for diabetes—treatment guidelines. The

Acknowledgements

We wish to thank Dr. Terri Paul, Division of Endocrinology
and Metabolism, University of Western Ontario for provid-
ing the cases.