

# The Contribution of Medications to Hypoglycemia Unawareness

John R. White, Jr., PA, PharmD

Hypoglycemia unawareness is defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms.<sup>1</sup> It is difficult to study in its natural form because of its paroxysmal and unpredictable nature; therefore, well-controlled trials are limited. However, much is known regarding risk factors, biochemical causes, and populations at greatest risk for the development of hypoglycemia unawareness. Less is known regarding the impact of medications on the development or recognition of this condition in patients with diabetes. Several medications are thought to worsen or promote hypoglycemia unawareness, whereas others may have an attenuating effect on the problem. This article will review hypoglycemia unawareness and summarize the effects of medications that may influence it.

## Hypoglycemic Counterregulation

In individuals without diabetes, a predictable, organized response occurs when blood glucose declines to hypoglycemic levels (Figure 1). First, insulin secretion is suppressed as glucose falls to  $< 81$  mg/dl.<sup>1</sup> The suppression of insulin secretion has two effects: peripheral glucose utilization is reduced and hepatic glucose output is induced. This action typically terminates the episode. However, if glucose decline continues to  $< 68$  mg/dl, glucagon secretion from  $\alpha$ -cells and epinephrine secretion from the adrenals are stimulated.<sup>1</sup> These actions promote hepatic glucose production via gluconeogenesis and glycogenolysis. Growth hormone and cortisol are released as glucose levels decline even further (to  $\sim 63$  mg/dl) but are proba-

bly best characterized as responders to prolonged hypoglycemia rather than acute responders. The central nervous system triggers autonomic symptoms of hypoglycemia at plasma glucose levels between 54 and 90 mg/dl (Table 1). These symptoms are aimed at encouraging consumption of calories and are the harbinger of impending neuroglycopenia. If unchecked, the hypoglycemia will cause neuroglycopenic symptoms (Table 1) and eventually seizures and coma.

The glycemic threshold at which this counterregulatory response occurs is predictable in people without diabetes and can be reset to higher or lower glucose levels with chronic hyperglycemia or repeated hypoglycemia, respectively.<sup>2-5</sup> The intensity of the counterregulatory response diminishes with increasing age in people without diabetes.<sup>6</sup> Sex and degree of physical activity also play a role in determining the magnitude of the counterregulatory response. Females have a reduced counterregulatory response to hypoglycemia compared to men but have less blunting of their response by antecedent hypoglycemia. Exercise has been linked to a blunting of the counterregulatory response.

Alterations in the counterregulatory response to hypoglycemia in patients with type 1 or type 2 diabetes have been described in detail elsewhere.<sup>1,7,8</sup> Patients with type 1 diabetes of  $> 5$  years' duration lose their  $\alpha$ -cell-mediated glucagon response to hypoglycemia. Therefore, the thrust of the acute counterregulatory response is carried by epinephrine. Unfortunately, the counterregulatory response is blunted in many patients because of insulin-induced hypoglycemia.

Frequent hypoglycemia reduces the counterregulatory response to hypoglycemia by  $> 50\%$ .<sup>7</sup> Davis et al.<sup>6</sup> have shown that the magnitude of the blunting of the counterregulatory response is proportional to the antecedent hypoglycemia. In addition to a reduction in epinephrine secretion, a reduction in peripheral sensitivity to epinephrine has also been reported. Therefore, with the development of hypoglycemia unawareness, a causal nexus is established in which hypoglycemia causes hypoglycemia unawareness, which in turn results in worsening hypoglycemia.

Patients with type 2 diabetes may also experience hypoglycemia unawareness. Patients early in the course of their disease probably retain most of their  $\alpha$ -cell response (glucagon) to hypoglycemia, whereas patients with advanced type 2 disease have virtually no  $\alpha$ -cell response to hypoglycemia.<sup>9</sup> Patients with type 2 diabetes, like those with type 1 diabetes, also develop a blunting of their epinephrine response that is proportional to antecedent hypoglycemia.

## Insulin

A discussion of the effects of medications on hypoglycemia unawareness would be incomplete without the mention of insulin. As previously noted, insulin-induced antecedent hypoglycemia is a strong predictor of subsequent hypoglycemia unawareness. In addition, ever since human insulin was introduced as a pharmacological agent, there has been concern that it might be associated with a higher incidence of hypoglycemia unawareness than insulin from animal sources. One of the early double-blind, randomized,

| Classification                             |    | Counterregulatory response or physical consequence |
|--|----|--|
| Lower boundary of physiological euglycemia | 90 |  |
| Hypoglycemia                               |    | Endogenous insulin                                 |
|  | 72 | Release of glucagon and adrenaline                 |
|  |    | Release of growth hormone                          |
|  |    | Release of cortisol                                |
| Symptomatic hypoglycemia                   |    | Onset of autonomic symptoms                        |
| Neuroglycopenia                            | 54 |  |
|  |    | Cognitive deterioration                            |
| Severe neuroglycopenia                     | 36 |  |
|  |    | Coma, seizures                                     |
|  | 18 |  |
| Plasma glucose level (mg/dl)               |    |  |

Figure 1. Glycemic threshold values for counterregulatory response to and physical consequences of insulin-induced hypoglycemia. Adapted from Ref. 1.

**Table 1. Symptoms of Hypoglycemia**

| Autonomic                | Neuroglycopenia        |
|--------------------------|------------------------|
| Anxiety                  | Irritability           |
| Palpitations             | Drowsiness             |
| Sweating                 | Dizziness              |
| Tingling                 | Blurred vision         |
| Trembling                | Difficulty with speech |
| Hypoglycemic unawareness | Confusion              |
|                          | Feeling faint          |

Adapted from Ref. 1.

crossover trials comparing porcine to human insulin reported that the initial symptoms of hypoglycemia with human insulin were more often neuroglycopenic, whereas the symptoms associated with porcine insulin were more often adrenergic.<sup>10</sup>

Another study<sup>11</sup> reported that some (36%) patients who switched to treatment with human insulin experienced more frequent hypoglycemia, impaired recognition of hypoglycemia, and altered symptoms of hypoglycemia than they did when previously treated

with insulin from an animal source. However, the study did not compare these findings to patients who had continued on animal-source insulin. The fraction of patients reporting altered symptoms of hypoglycemia was consistent with the fraction of all long-term patients reporting these changes.<sup>12</sup>

One study<sup>13</sup> evaluating patients who reported that they had developed hypoglycemia unawareness after being switched to human insulin reported no differences in symptomatic or hormonal responses to hypoglycemia.

A recent review of 45 randomized controlled studies comparing animal to human insulin concluded that most of the published studies were poorly designed.<sup>14</sup> The authors also concluded that there were no clinically relevant differences between the two insulin types.

**β-Adrenergic Antagonists**

Theoretically, almost any medication that alters the effects of epinephrine could have potential effects on glucose homeostasis and the hypoglycemic counterregulatory system. Concerns have been raised for years regarding potential and reported adverse

glycemic effects of the β-adrenergic antagonists (β-blockers).<sup>14</sup> These agents have been reported to increase the incidence of hypoglycemia in some individuals.<sup>14</sup> Labetolol administered during a caesarean delivery was reported to cause hypoglycemia in the twins postdelivery. Even ophthalmic dosage forms of β-adrenergic antagonists have been reported to cause hypoglycemia in a patient with type 1 diabetes. Hypoglycemia may be a possible sequela of the use of β-adrenergic antagonists, but if it is, it is probably rare.

The more troubling concern regarding β-blockers is their potential effect on hypoglycemia unawareness and blunting of the return to euglycemic levels after hypoglycemia has occurred. β-Blockers theoretically could suppress or even obviate all of the adrenergically mediated symptoms of hypoglycemia. A study<sup>15</sup> that evaluated this possibility in patients with type 1 diabetes (without hypoglycemia unawareness) reported that adrenergic symptoms did occur at lower glucose levels when patients were treated with β-blockers. However, this deficit was offset by higher hypoglycemia symp-

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tom scores, which resulted from an increased perception of cholinergically mediated diaphoresis.

Cardioselective agents reportedly cause less alteration in the perception of hypoglycemia symptoms than do the noncardioselective agents.<sup>14</sup> Additionally, cardioselective  $\beta$ -blockers may have less of an effect on correction of hypoglycemia than do their noncardioselective counterparts, probably because gluconeogenesis and glycogenolysis are mediated via  $\beta_2$  receptors in the liver and are relatively unaffected by antagonism of  $\beta_1$  receptors.  $\beta$ -Adrenergic antagonists have been used successfully in several large-scale studies in patients with diabetes with no significant adverse effects reported. These agents, and particularly the cardioselective ones, should not be avoided in patients with diabetes but should be used with the same caution as when any new medication is added to a patient's therapeutic regimen.

#### $\beta$ -Adrenergic Agonists

Several studies have evaluated the effects of  $\beta$ -adrenergic agonists on hypoglycemia and hypoglycemia unawareness. The nocturnal glycemic effects of the  $\beta_2$ -agonist terbutaline were compared to the amino acid alanine (alanine plus glucose), a standard snack, and control (no snack or medication) in 15 insulin-treated type 1 patients.<sup>16</sup> Terbutaline was associated with statistically significant higher glucose levels compared to 1) control subjects during the first half of the night and 2) control subjects during the second half of the night. Glucose levels were also higher during the second half of the night in patients taking terbutaline versus those treated with snack or alanine (statistics not reported). Nocturnal hypoglycemia was treated on 23 occasions in patients in the control and snack arms versus only one incident in the alanine and terbutaline arm. The researchers concluded that both alanine and terbutaline effectively prevented nocturnal hypoglycemia.

One of the concerns about using  $\beta_2$ -agonists for the treatment of hypoglycemia unawareness was associated with reduced  $\beta_2$  sensitivity observed in vitro. Recently, a three-way comparison trial<sup>17</sup> evaluated  $\beta_2$ -adrenergic sen-

sitivity in subjects with type 1 diabetes, those with type 1 diabetes and hypoglycemia unawareness, and nondiabetic subjects.  $\beta_2$ -Adrenergic sensitivity was evaluated via forearm vasodilatory response to escalating doses of an intra-arterial infusion of salbutamol. Forearm blood flow (FBF) was measured bilaterally by venous occlusion plethysmography. No statistically significant differences in baseline FBF were reported, and significant increases in FBF were reported for all subject groups with the administration of salbutamol. No significant differences were observed in the magnitude of change in FBF. The authors concluded that  $\beta_2$ -sensitivity is preserved in patients with type 1 diabetes who have hypoglycemia unawareness.

No long-term clinical trials evaluating the usefulness of  $\beta_2$ -agonists in the prevention of nocturnal hypoglycemia or hypoglycemia unawareness have been reported. However, this option seems worthy of further study.

#### Methylxanthines

Several studies have evaluated the effects of the methylxanthine derivatives caffeine and theophylline on hypoglycemia unawareness and the counterregulatory response to hypoglycemia. Both have been shown to magnify the counterregulatory hormone (i.e., epinephrine, norepinephrine, and cortisol) response to hypoglycemia, as well as recovery from and perception of hypoglycemia in patients with type 1 diabetes both with and without hypoglycemia unawareness.<sup>1</sup>

One study<sup>18</sup> evaluating the impact of theophylline on the response to hypoglycemia compared 15 patients with type 1 diabetes who had a history of hypoglycemia unawareness to 15 matched healthy control subjects. The subjects underwent hyperinsulinemic-hypoglycemic glucose clamp and randomly received either theophylline or placebo in a crossover fashion. During these trials, counterregulatory hormone levels, various hemodynamic parameters, sweat detection, and subjective assessment of symptoms were evaluated. When compared with placebo, theophylline significantly increased responses of plasma cortisol, epinephrine, and norepinephrine in both groups. Symptoms scores increased

with theophylline administration, and scores of the patients with diabetes approached those of the nondiabetic control subjects. The authors concluded that theophylline improves the counterregulatory response to and perception of hypoglycemia in patients with type 1 diabetes who have hypoglycemia unawareness. This was a small trial and evaluated this phenomenon acutely.

Another trial in "free living" type 1 diabetic patients evaluated the impact of caffeine on the frequency and perception of hypoglycemia over a period of 3 months.<sup>19</sup> After a lead-in phase during which patients adhered to a low-caffeine diet, 34 patients with type 1 diabetes were randomized to twice-daily capsules of either 200 mg of caffeine or matched placebo. Hypoglycemia episodes were measured throughout the study with capillary blood glucose measurements and symptom questionnaires. No changes in glycemic control or lipid profiles were observed. Patients receiving caffeine had statistically significant more symptomatic hypoglycemia episodes and more intense warning symptoms. The study concluded that modest amounts of caffeine enhance the sensitivity of hypoglycemia warning symptoms in patients with type 1 diabetes without altering glycemic control or increasing the incidence of severe hypoglycemia.

Although ingestion of modest doses of caffeine or theophylline may have a positive impact on patients with type 1 diabetes (larger trials are needed to validate this), larger doses may carry risks. A case study of one patient with type 1 diabetes who drank five cups of instant coffee per day reported significantly higher glucose levels at all time points measured compared to levels after consumption of a noncaffeinated beverage (180, 216, 254, and 360 mg/dl vs. 144 mg/dl).<sup>20</sup> Although this is only a case study, it illustrates that more research is needed in this area to determine efficacy, toxicity, and dose-response curves. However, low-dose theophylline (levels were about 8 mg/l in the above-referenced trial) or low-dose caffeine may be effective at reducing hypoglycemia unawareness in patients with type 1 diabetes at a low cost and without significant toxicity.

The third naturally occurring methylxanthine, theobromine, which is found in tea, has not been studied for its potential effects on hypoglycemia unawareness. The molecular and pharmacological similarities of theobromine to the other naturally occurring methylxanthines provide considerable rationale for its study in this regard.

### Selective Serotonin Reuptake Inhibitors

Three case reports have suggested a link between the development of hypoglycemia unawareness in patients with type 1 diabetes and the use of selective serotonin reuptake inhibitors (SSRIs).<sup>21</sup> In all three cases, different SSRIs (fluoxetine, sertraline, paroxetine) were administered to young patients (17–21 years of age) with type 1 diabetes and depression who were previously able to recognize and treat hypoglycemia symptoms. Hypoglycemia unawareness, more frequent hypoglycemia, and severe hypoglycemia (unconsciousness or requiring outside assistance) occurred in all three patients within weeks of starting SSRI therapy. On discontinuation of SSRI therapy, hypoglycemia awareness improved in all three patients.

Although SSRIs are frequently used in this population and usually without known glycemic problems, this observation strongly suggests that in some patients, treatment with SSRIs may alter the perception of hypoglycemia. The mechanism by which SSRIs might be associated with hypoglycemia unawareness is unknown, but it has been hypothesized that the effect may be via an atypical presentation of serotonin syndrome resulting in autonomic dysfunction.<sup>21</sup>

### Conclusions

Hypoglycemia unawareness is a complex, difficult-to-study phenomenon that carries with it great risk to patients. Studies evaluating the effects of medications on this problem are scarce. The choice of the source of insulin (human vs. animal) does not seem to have a direct impact on the development of hypoglycemia unawareness. Conversely, insulin-induced (or probably any drug-induced) antecedent hypoglycemia

clearly promotes subsequent hypoglycemia unawareness.

$\beta$ -Blockers (particularly noncardioselective agents) may have a slight moderating effect on adrenergic symptoms of hypoglycemia and the hepatic counterregulatory response to hypoglycemia. However,  $\beta$ -blockers have been shown to be reasonable choices for the management of hypertension and for their cardioprotective effects in patients with diabetes. Therefore, the use of cardioselective  $\beta$ -blockers should not be discouraged.  $\beta$ -Adrenergic agonists, methylxanthines, and even the amino acid alanine may cause an upregulation of hypoglycemia awareness and should be studied further. SSRIs should be used in patients with diabetes when the risk-benefit considerations include the possibility of reduction in hypoglycemia awareness.

Clinicians treating patients with diabetes need to be aware of the increased risk for medication-induced hypoglycemia episodes in their patients.

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*John R. White, Jr., PA, PharmD, is a professor in the Department of Pharmacotherapy, College of Pharmacy at Washington State University in Spokane.*