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Drug-Induced Hypoglycemia

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1. Introduction

Although it is noted throughout the literature that adverse effects occur, one review of safety reporting determined clinical trials only report adverse effects between 29% (laboratory adverse effects) and 39% (clinical adverse effects) (Ioannidis, et al, 2001). It is important to keep these numbers in mind when looking at the number of drug-induced hypoglycemia cases. Seltzer's review of the literature from 1940 to 1989 reveals 1418 documented cases of drug-induced hypoglycemia. Based on estimates of the lack of adverse effect reporting, it is unlikely that these cases were the only incidents of drug-induced hypoglycemia that occurred during this time (Seltzer, 1989).

It is also reasonable to look at estimates of adverse drug effects (ADEs) in hospitalized patients. Such estimates indicate ADEs may account for between 3 and 5% of all hospital admissions (Pandit et al, 1993). In a 2006 study it was determined approximately 22% of admissions attributed to ADEs were due to hypoglycemia at a university hospital versus 23% at a community hospital (Kilbridge et al, 2006). These admissions were related to an overall admission rate attributed to ADEs of 4.4% at the university hospital and 6.2% at a community hospital (Kilbridge et al, 2006). In addition there are estimates that as many as 30% of hospitalized patients experience an ADE while in the hospital (Pandit et al, 1993). Estimates of 3 – 4.5 billion dollars, which is now outdated, just begin to attribute a cost to treating ADEs. However, the cost is probably grossly underestimated since the actual number of ADEs reported is underestimated (Pandit et al, 1993). Not only is the cost of managing an ADEs a significant issue but the risk of mortality must be considered as well. Mortality has been estimated to occur in as many as 140,000 patients each year (Pandit et al, 1993). One study looking at death due to drug-induced hypoglycemia determined a 1.3% mortality rate (Juurlink et al, 2003).

The incidence and impact of drug-induced hypoglycemia should be contrasted with the incidence and impact of hypoglycemia in patients with diabetes mellitus (DM) – type 1 or type 2. For patients with type 1 DM, it is estimated that hypoglycemia, by the numbers (blood glucose less than 50 – 60 mg/dL), occurs 1 in 10 times when patients check their blood glucose (Cryer et al, 2003). While the number of asymptomatic hypoglycemia episodes is undocumented, it is estimated that patients with type 1 DM experience "an average of 2 symptomatic hypoglycemic episodes per week.and an episode of severe, at least temporarily disabling hypoglycaemia once a year" (Cryer et al, 2003). The incidence of hypoglycemia in patients with type 2 DM is more challenging. When comparing the incidence of severe hypoglycemia in patients with type 1 DM versus patients with type 2 DM being treated with insulin, estimates are anywhere from 10% to equal incidence of hypoglycemia (Cryer et al, 2003). Other studies that have tried to quantify the incidence of

hypoglycemia in type 2 patients have varied from an overall incidence of 20% in patients taking oral agents to 0.5% episodes of severe hypoglycemia in patients using insulin (Jennings AM et al, 1989 & Miller CD et al, 2001). Unfortunately, as with drug-induced hypoglycemia, hypoglycemia may result in death. One estimate of the rate of death from hypoglycemia is 2 to 4% of patients with type 1 DM, but, as with the incidence of hypoglycemia, there is not a reliable estimate of death attributed to hypoglycemia in patients with type 2 DM (Cryer et al, 2003). However, a 1999 review of cases of hypoglycemic coma provides some perspective on potential morbidity and mortality. In this study, out of 102 reported cases, 5 patients died. (Ben-Ami et al, 1999).

These statistics emphasize the importance of recognizing and treating hypoglycemia as well as ADEs when they occur. The numbers also serve as a reminder to all healthcare providers of their responsibility in the prevention of ADEs, especially drug-induced ADEs. However, in order to prevent ADEs, one must know what patients are at risk for development of an ADE. The risk for drug-induced hypoglycemia, the mechanism of potentially causative agents as well as management and prevention are discussed below in effort to make healthcare providers aware of this potential ADE and how to avoid it.

2. Definition of hypoglycemia

Before determining if a patient is experiencing drug-induced hypoglycemia, the definition of hypoglycemia should be established. Since all patients respond to blood glucose concentrations differently, it is challenging to establish a blood glucose at which every patient will experience symptoms. However, it is widely accepted that most patients will begin to experience symptoms when their blood glucose level is less than 3.3 mmol/l (60 mg/dL). The symptoms patients commonly experience are listed in Table 1 below and can be manifestations of the response by the autonomic nervous system as well as the brain's response to being deprived of glucose (Cryer et al, 2003, White, 2007). Physiologic responses with escalating hypoglycemia are shown in Table 2. Severe episodes of hypoglycemia may be characterized by loss of consciousness and/or seizures and, in instances of sustained hypoglycemia, may result in brain damage or death (Cryer et al, 2003). The blood glucose level at which a patient experiences symptoms of hypoglycemia can be influenced by other factors such as: the frequency of hypoglycemic episodes, which may result in hypoglycemic unawareness; frequent hyperglycemia episodes, and increased caffeine intake (Cryer et al, 1999).

Neurogenic Symptoms of Hypoglycemia	Neuroglycopenic Symptoms of Hypoglycemia	Physical Signs of Hypoglycemia
Anxiety/arousal	Blurry vision	Increased systolic blood pressure
Hunger	Changes in behavior – irritability is often noted	Pallor
Shaky/trembling	Confusion/difficulty thinking	Sweating
	Difficulty speaking	
Parethesias	Dizziness	
Sweating	Emotional lability	Tachycardia
	Fatigue	
	Loss of consciousness	
	seizures	
	Warmth	
	Weakness	

Adapted from Cryer et al, 2003 and White, 2007

Table 1. Common symptoms of hypoglycemia

Blood glucose level	Classification	Physiologic response
70 mg/dl (3.9 mmol/l)	Hypoglycemia	• Glucagon release • Epinephrine release • Growth hormone release • Cortisol release
54 mg/dl (3 mmol/l)	Symptomatic hypoglycemia	• Autonomic symptoms
36 mg/dl (2 mmol/l)	Hypoglycemia affecting brain function (neuroglucopenia)	• Cognitive decline
18 mg/dl (1 mmol/l)	Severe neuroglucopenia	• Coma • Seizures

Adapted from White, 2007

Table 2. Physiologic response based on blood glucose level

It is important to note that monitoring blood glucose levels is the best way to monitor hypoglycemia since hemoglobin A1C (A1C) does not adequately depict hypoglycemia given that A1C provides a measure of average control of blood glucose over the past 2 to 3 months (American Diabetes Association, 2011).

In one technical review of hypoglycemia in patients with diabetes, it was noted that hypoglycemia resulted in "physical morbidity" as evidenced in the physical symptoms and even neurologic impairment patients may experience as well as "psychological morbidity" which were differences in moods and outlook as a result of experiencing hypoglycemia (Cryer PE et al, 2003). Specific manifestations of physical and psychological morbidity are detailed in Table 3. When thinking of these symptoms of hypoglycemia, it should be recognized that they can make patients feel uncomfortable physically as well as socially since experiencing these symptoms may result in patients receiving unwanted attention. It is important to consider that hypoglycemia affects patients both physically, psychologically, and can have a significant impact on a patient's overall sense of well-being. Although the same evidence does not exist for patients that experience drug-induced hypoglycemia, it could be argued that the toll is equally as hard on these individuals and therefore, emphasizes the importance of avoiding drug-induced hypoglycemia.

Examples of Physical Morbidity Associated with Hypoglycemia	**Examples of Psychological Morbidity Associated with Hypoglycemia**
Physical symptoms – anxiety, hunger, palpitations, sweating, hunger	Fear of experiencing hypoglycemia
Neurologic impairment – changes in behavior, decline in cognitive function, seizures, coma	Guilt related to being fearful of experiencing hypoglycaemia Anxiet overall happiness

Adapted from Cryer PE et al, 2003

Table 3. Physical and psychological morbidity associated with hypoglycemia.

3. Risk factors

Table 4 lists patient characteristics that may increase the risk of drug-induced hypoglycemia. Specific pharmacokinetic and pharmacodynamic drug parameters may affect the level of risk associated with the described patient characteristics.

Risk Factors	Mechanism
Advancing age	Decreased symptoms/decreased awareness, decreased counterregulatory response to low blood glucose
Renal insufficiency	Decreased insulin clearance
Hepatic insufficiency	Decreased gluconeogenesis
Decreased food intake (skipping meals)	Insufficient glucose intake
Excessive alcohol intake	Decreased gluconeogenesis
Polypharmacy	Increased risk of drug interactions resulting in hypoglycemia

Table 4. Risk factors for drug-induced hypoglycemia

It should be noted that the risk factors associated with drug-induced hypoglycemia are similar to the risk factors associated with the development of hypoglycemia in patients with DM. In particular it is known that advanced age, alcohol intake, and polypharmacy are all risk factors for hypoglycemia in patients with type 1 diabetes (Zammitt et al, 2005). As noted above, these are risk factors that may also place patients at risk for drug-induced hypoglycemia. In addition to the risk factors discussed above, risk factors that place patients with type 1 diabetes at risk for hypoglycemia are: caffeine intake; variations in sleep; and physical activity, in particular exercise, in relation to meals and medications (Zammitt et al, 2005). However, it is unknown how these factors affect the risk of hypoglycemia in patients with type 2 diabetes (Zammitt et al, 2005). It is known that patients with type 2 diabetes who have been taking in insulin for more than 10 years are increased risk for experiencing hypoglycemia (Zammitt et al, 2005). Obviously, the greatest concern for the development of drug-induced hypoglycemia becomes when patients have pre-exsiting diabetes and then are placed on a medication that has the potential to cause hypoglycemia.

4. Glucose regulation

Changes in serum glucose levels are a result of the following process: glucose absorption from the gastroinstestinal tract, release of stored glucose through hepatic glycogenolysis, and creation of glucose from non-glucose sources through hepatic gluconeogenesis. Glycogenolysis releases glucose through breakdown of glycogen, the stored form of glucose, and glycogenolysis creates glucose from amino acid and lactate. All three processes affect glucose levels based on proximity to meals. The rate of rise of serum glucose during and after meals is predominantly a result of the rate of gastric emptying. Rate of gastric emptying determines amount of glucose absorbed in gastrointestinal tract. During periods of fasting, glucose levels are regulated by glycogenolysis and gluconeogenesis. Glycogenolysis impacts serum glucose levels in the first 8 to 12 hours of fasting, while gluconeogenesis contributes more to glucose levels after longer periods of fasting (Aronoff et al, 2004).

The processes above are all regulated by glucoregulatory hormones. The hormones, their site of origin, and specific gluco-regulatory actions are listed in table 5. In addition to those listed, blood glucose levels are affected by epinephrine, cortisol, and growth hormones (Aronoff et al, 2004).

Hormone	Site of origin/production	Action
Insulin	Beta (β)-cells of the pancreas	Induces uptake of glucose by cells Inhibits glucagon secretion post-prandially Enhances protein and fat synthesis Stimulates glycogenesis in the liver
Glucagon	Alpha (α)-cells of the pancreas	Stimulates hepatic glycogenolysis, hepatic gluconeogenesis, and hepatic ketogenesis
Amylin	B-cells of the pancreas	Slows gastric emptying Inhibits glucagon secretion post-prandially Decreases food intake
Glucagon-like peptide 1 (GLP-1)	L-cells of the intestine	Slows gastric emptying Stimulates glucose-dependent (prandial) insulin secretion Inhibits glucagon secretion post-prandially Decreases food intake
Glucose-dependent insulinotropic peptide (GIP),	L-cells of the intestine	Stimulates glucose-dependent (prandial) insulin secretion Inhibits glucagon secretion post-prandially

Table 5. Gluco-regulatory hormones

Insulin and glucagon play large roles in the overall regulation of blood glucose (Figure 1). Increases in serum blood glucose stimulate insulin release from the pancreas. The amount of insulin released is dependent on the level of blood glucose. Insulin is not released until blood glucose levels reach 3.3 mmol/l (59.4 mg/dl). Insulin acts to both decrease existing glucose in the blood and to decrease production of further glucose. Insulin binds to receptors on fat, muscle, and liver cells to stimulate glucose uptake. Additional serum glucose is converted to glycogen, the storage form of glucose, through hepatic glycogenesis. Insulin decreases production of glucose from gluconeogenesis and glycogenolysis by inhibiting glucagon release from the pancreas. The combination of these actions results in a decrease in serum blood glucose. Glucagon serves as the hormone that balances the glucose lowering effects of insulin. Glucagon controls fasting levels by stimulating gluconeogenesis and glycogenolysis in the liver. Stimulation of these mechanisms results in release of glucose, increasing serum blood glucose levels. Release of glucagon from the pancreas occurs when serum glucose levels fall below approximately 5 mmol/l (90 mg/dl) (Aronoff et al, 2004).

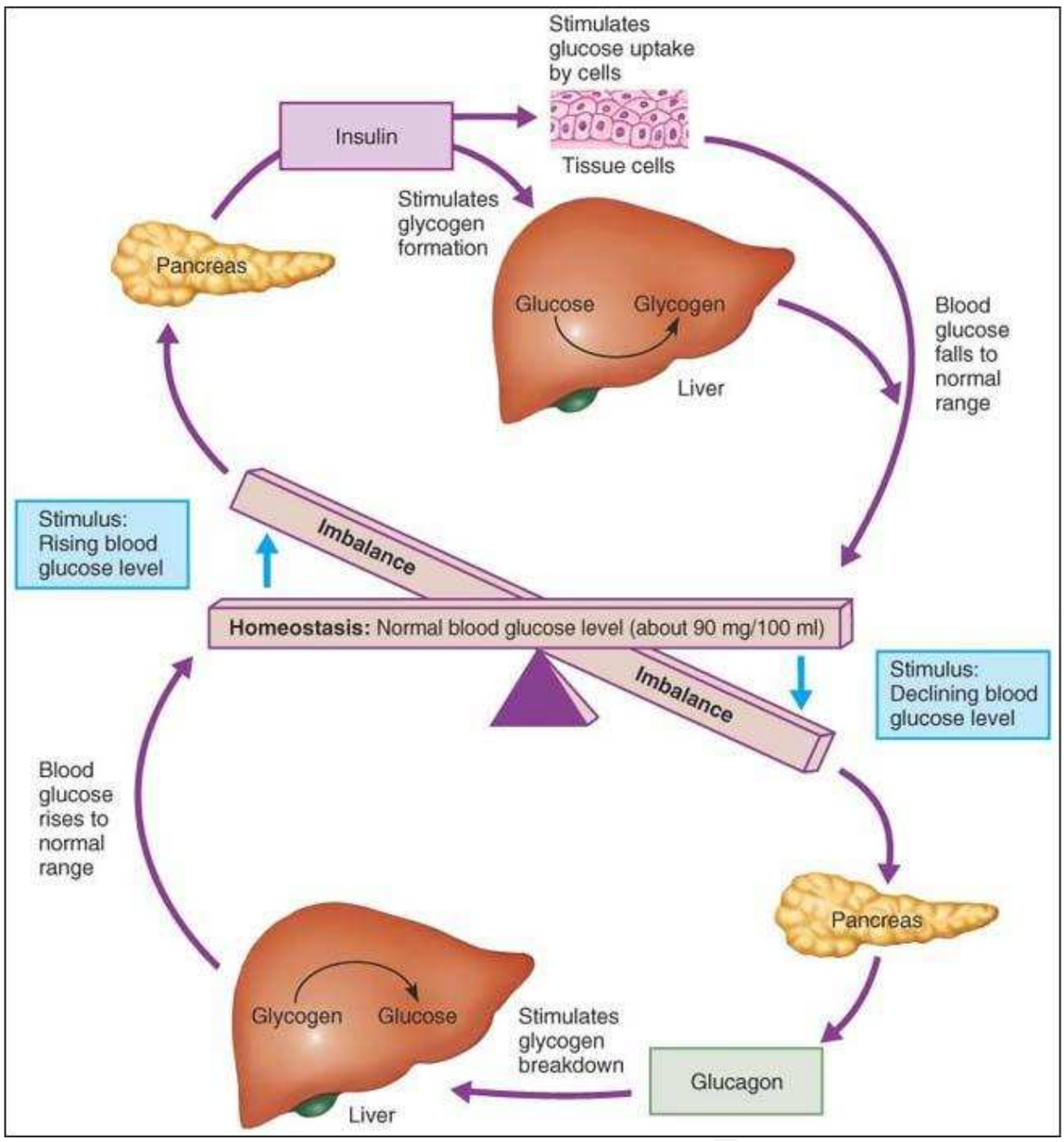

Fig. 1. Glucose regulation (Dugi K, 2009)

5. Causative agents

5.1 There are a number of agents implicated in causing hypoglycemia; however, the level of evidence available varies significantly amongst agents. The most highly documented drug-induced hypoglycemia occurs with medications used to treat hyperglycemia. The specific agents and classes are included in table 6 below.

Anti-diabetic agents
Exenatide
Insulin
Pramlintide
Secratagogues (non-sulfonylurea)
Sitagliptin
Sulfonylureas

Table 6. Anti-diabetic agents with greatest evidence of causing hypoglycaemia

Of potentially greater concern are the agents which are used for indications other than hyperglycemia because the hypoglycemic episodes are often less predictable and/or unexpected. These agents often have very little or no quality evidence to document the frequency and severity of their hypoglycemic effects. This is illustrated in the systematic review of literature through 2007 conducted by The Hypoglycemia Task Force of The Endocrine Society which identified hypoglycemia associated with 164 different medications (Murad et al, 2009). This study found that no individual or class of drugs has high quality evidence supporting its impact on glucose levels, though drugs used to treat hyperglycemia were not included. Table 7 provides a list of the most commonly cited agents in the literature and their level of evidence. Level of evidence was defined by use of the GRADE approach to literature evaluation. Available evidence was evaluated for quality of study design, strength of association of the medication to the reported adverse effects, and quantity of evidence available (Murad et al, 2009).

Moderate Quality Evidence	
Agent/Class	**Mechanism of hypoglycemia**
Fluoroquinolones (gatifloxacin)	Unclear May increase insulin secretion from pancreas
Indomethacin	Increase insulin secretion from pancreas, decrease in insulin clearance, decrease in gluconeogenesis, and increase in glucose uptake in periphery
Pentamadine	Increased insulin secretion from pancreas through cell damage
Quinine	Increased insulin secretion from pancreas
Poor Quality Evidence	
Agent/Class	**Mechanism of hypoglycemia**
Angiotensin Converting Enzyme Inhibitors (ACEIs)	Increase insulin sensitivity
Beta blockers	Mask signs/symptoms of hypoglycemia, increase in glucose uptake in the periphery
Ethanol	Decrease in gluconeogenesis in the liver
Lithium	Unclear
Propoxyphene	Unclear
Sulfamethoxazole	Increase insulin secretion from pancreas

Table 7. Strength of evidence of drug-induced hypoglycemia and proposed mechanisms (Murad, et al, 2009).

Drug-induced hypoglycemia may be a result of direct changes to glucose homeostasis or indirect effects on a patient's ability to recognize onset of hypoglycemia. Changes that affect glucose homeostasis include direct increase in insulin secretion from the pancreas, indirect increase in insulin secretion through decreased degradation of incretin hormones (GLP-1 and GIP), cytotoxic effects on pancreatic cells leading to increase insulin release, decrease in gluconeogenesis, increase in glucose utilization and storage, decrease in glucagon release from the pancreatic α cells, and decreased gastric emptying (Pandit et al, 1993). Many agents affect glucose homeostasis through a combination of these mechanisms. Location of mechanism is exhibited in table 8.

Pancreas	Liver	Periphery	Kidney	Gut
• Pentamidine • Fluoroquinolones • Sulfamethoxazole • Quinine • Indomethacin • Exenatide • Sulfonylureas • Non-sulfonylurea secretagogues • Sitagliptin	• Ethanol • Indomethacin • Exenatide Pramlintide • Sitagliptin	• Beta adrenergic antagonists • Angiotensin converting enzyme (ACE) inhibitors • Indomethacin • Insulin	• Indomethacin	• Pramlintide

Table 8. Location of action of agents implicated in drug-induced hypoglycemia

5.2 Specific agents

Specific agents, including risk factors and frequency of hypoglycemic events, are discussed below.

5.2.1 Fluoroquinolones

Fluoroquinolones are antibiotics which exhibit their antimicrobial activity through inhibition of DNA gyrase and topoisomerase IV, enzymes involved in bacterial cell division (Product Information: Tequin, 2006). The class includes the following agents: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and rofloxacin. Though there are reports of hypoglycemia with most agents in this class, a majority of the evidence with fluoroquinolone-induced hypoglycemia is with gatifloxacin (Murad et al, 2009). The exact mechanism of this hypoglycemic effect is not clear; however, it is proposed that fluoroquinolones increase insulin secretion from the pancreas and may have a pharmacokinetic or pharmacodynamic interaction with various antidiabetic agents, including sulfonylureas. The adverse effect does not appear dose-related and presents typically within the first three days of therapy for less severe hypoglycemia (Frothingham, 2005; Gajjar, et al, 2000; Park-Wyllie et al, 2006; Product Information: Tequin, 2006). More severe episodes, specifically those requiring hospitalization or prolonged hospitalization, are more common after three days of therapy. Hypoglycemia has been reported with intravenous and oral therapies in both outpatient and inpatient settings, and discontinuation of the medication is often required to resolve the glucose abnormalities (Murad et al, 2009). Though new onset diabetes has been reported, risk factors for patients who are more likely to experience hypoglycemic episodes are: pre-existing diabetes,

concomitant use of hypoglycemic medications, advanced age, and decreased renal function (Frothingham, 2005; Product Information: Tequin, 2006; Yip & Lee, 2006).

5.2.2 Indomethacin

Indomethacin belongs to the class of agents called non-steroidal anti-inflammatory drugs (NSAIDs). Anti-inflammatory agents, including salicylates, are all thought to increase risk of hypoglycemia, with indomethacin having the greatest evidence, likely due to the population being treated. Though often used for osteoarthritis and other inflammatory conditions, indomethacin may also be used to close a patent ductus arteriosis in neonates, often in those born prematurely. Increases in pancreatic insulin secretion, decreases in insulin clearance, increases in glucose utilization in the periphery, and decreases in gluconeogenesis all appear to contribute to the hypoglycemic effects of these drugs. Less than three per cent of neonates exposed to therapeutic levels of intravenous indomethacin for patent ductus arteriosis experience hypoglycemia (Product Information: Indocin, 2010). Whether this effect is dose-related is unclear; however, the risk may be significantly decreased by use of a concomitant infusion of intravenous glucose (Hosono, 1999).

5.2.3 Pentamidine

Pentamidine is an anti-fungal agent which exhibits its effects through inhibition of microbial nuclear metabolism. Direct cytotoxic effects on beta cells of the pancreas results in increased secretion of insulin. This early release of insulin is due to the lytic effects on the cell which result in cell death. This can ultimately result in insulin-dependent diabetes as a result of this cell loss (Pandit et al, 1993). Pentamidine is associated with a 6-40% risk of hypoglycemia in patients receiving intravenous or intramuscular administration. Hypoglycemia is most commonly seen in patients with acquired immune deficiency syndrome (AIDS) treated for *Pneumocystis carinii* (Murad et al, 2009 & Product Information: Pentin, 2008) (Product Information: Pentam, 2008 & Product Information: Nebupent, 2008). The risk of hypoglycemia and resultant pancreatic damage associated with pentamidine is greater with higher doses, higher cumulative doses, and prolonged use (Pandit et al, 1993). There also appears to be increased risk with use of pentamidine mesylate compared to pentamidine isothionate (Waskin, 1996).

5.2.4 Quinine

Quinine is an anti-malarial agent used acutely for systemic and cerebral disease. More than 300 cases of hypoglycemia have been reported with quinine therapy and 30 clinical studies have demonstrated similar findings (Murad et al, 2009). The crux of the hypoglycemic effects of quinine appear to be the result of increased insulin secretion from beta cells. Though this is most common in patients infected with malaria, there are reports of quinine-induced hypoglycemia in patients without malaria. Patients with malaria often exhibit more severe or sustained hypoglycemia since the organism responsible for malaria, *Plasmodium falciparum,* independently lowers glucose levels. There is also an increased risk of hypoglycemia with higher doses of quinine and with infusion times of intravenous doses of less than one hour. Manufacturers recommend intravenous infusions occur over four hours to minimize risk of hypoglycemia (Product Information: Qualaquin, 2010). Quinine-induced hypoglycemia can be resistant to traditional therapy with glucose and glucagon; however, treatment with octreotide has been shown to be beneficial (Pandit et al, 1993).

5.2.5 Beta blockers

Non-selective beta-adrenergic antagonists, also known as beta blockers, are vasodilators which are often used to treat hypertension and cardiac disease. A list of non-selective beta blockers is provided in table 9 below. These agents have been linked with hypoglycemic effects in patients with and without diabetes (Murad et al, 2009). Oral formulations are most commonly the culprit; however, hypoglycemia associated with topical formulations is documented (Pandit et al, 1993). Though there are numerous reports of hypoglycemia associated with beta blockers , the quality of the data is limited. Murad, et al, theorizes that the high numbers of reports are a representation of the frequency of use of these agents more than the frequency of the actual hypoglycemic events (Murad et al, 2009).

There are two proposed mechanisms for this hypoglycemic effect in beta blockers. First, there is a blunting of the signs and symptoms of hypoglycemia (White, 2007). The exception to this blunting effect is sweating, an important educational point for all patients (Product Information: Innopran XL, 2010). The second mechanism is a direct potentiation of the effects of insulin. This heightened insulin effect increases glucose utilization in the periphery and inhibits lipolysis. Further, there is a diminished physiologic response to hypoglycemia in patient receiving beta blockers, specifically a decrease in glycogenolysis and gluconeogenesis (Pandit et al, 1993 & White, 2007). Patients at greatest risk for hypoglycemia with beta blockers include patients with hepatic disease, patients on hemodialysis, neonates, and patients with type 1 diabetes (Product Information: Innopran XL, 2010). Use of selective beta blockers, such as atenolol, metoprolol, and bisoprolol are thought to have a decreased risk of hypoglycaemia and may be a reasonable alternative to patients unable to tolerate non-selective agents (Pandit et al, 1993).

Non-selective beta-adrenergic antagonists
Alprenolol Bucindolol Carteolol Nadolol Penbutolol Pindolol Propranolol Sotalol Timolol
Non-selective beta-adrenergic antagonists with additional alpha antagonism:
Carvedilol Labetalol

Table 9. Non-selective beta-adrenergic antagonists (beta blockers)

5.2.6 ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors are a class of drugs that are typically used for hypertension and cardiovascular disease. Eleven studies document the potential for ACEI inhibitor-associated hypoglycemia, and a majority of these are with the use of

captopril (Murad et al, 2009; Herings et al, 1995). All members of this class are listed in table 10 below. Though the mechanism for this drug-induced hypoglycaemia is not well defined, it is proposed that the increase in bradykinins associated with ACE inhibitor use may cause an increase in insulin sensitivity (Pandit et al, 1993; Vuorinen-Markkola & Yki-Jarvinen, 1995). One study by Pollare, et al, suggests that captopril increases glucose utilization in the periphery compared to use of hydrochlorothiazide (Pollare et al, 1989); however, Wiggam, et al, demonstrates in one study that ACE inhibitors have no impact on hepatic or peripheral insulin sensitivity (Wiggam et al, 1998). Because of the contradicting information available, the actual impact of ACE inhibitors on blood glucose is not clear. ACE inhibitor therapy is a mainstay of hypertension, diabetes, and cardiovascular disease management. To date, there is insufficient evidence available to warrant discontinuation of this therapy in patients at risk for hypoglycemia with these disease states; however, in patients with suspected captopril-induced hypoglycemia, switching to another ACE inhibitor is a reasonable recommendation.

ACE Inhibitors
Benazepril
Captopril
Enalapril
Fosinopril
Lisinopril
Moexipril
Perindopril
Quinapril
Ramipril
Trandolapril

Table 10. Angiotensin Converting Enzyme (ACE) Inhibitors

5.2.7 Ethanol

Despite the poor level of evidence, ethanol has been touted as one of the most common causes of drug-induced hypoglycaemia in the United States (Pandit et al, 1993). The proposed mechanism is a direct suppression of gluconeogenesis in the liver, a process that typically occurs in more long-standing fasting states. Some studies suggest that this hypoglycemic potential is present in both occasional and chronic alcohol consumers and is more common with use of non-carbohydrate laden drinks (Pandit et al, 1993). Because of this, patients at greater risk for hypoglycemia should avoid consuming alcohol.

6. Prevention

One easy way to prevent drug-induced hypoglycemia is to avoid the medication that poses the potential for drug-induced hypoglycemia in patients that are at high risk for drug-induced hypoglycemia. Unfortunately, it may not be practical to avoid certain medications that may cause drug-induced hypoglycemia. As when deciding to use any medication, weigh the benefit of using the medication versus risk, in this case drug-induced hypoglycemia.

If avoiding the agent is not possible, attempt to minimize the risk of hypoglycemia by keeping in mind the following restrictions. Use extended-release/sustained-released products if that is an option for the medication needed (Pandit et al, 1993). Reinforce with patients the need to avoid alcohol intake (Pandit et al, 1993). Minimizing the lenth of time and dose of an offending agent may also be beneficial. Since hypoglycemia awareness is largely reliant on patient perception of the signs and symptoms of hypoglycemia, education is key (Cryer et al, 2003). Therefore, it is important to review the signs and symptoms of hypoglycemia with patients and caregivers. One way to monitor patients for evidence of hypoglycemia is to monitor their blood glucose concentrations, which is especially in important in patients with pre-existing diabetes. Blood glucose should be carefully monitored with initiation, dose changes, or discontinuation of any medication in patients with diabetes. It is usually recommended for patients to regularly check their fasting blood glucose readings during the initiation of a medication that can cause drug-induced hypoglycemia. The healthcare provider can make patient specific recommendations on how often to monitor blood glucose based on the patient's underlying risk for hypoglycemia (e.g. patients already taking 1 or more agents that can cause drug-induced hypoglycemia or those patients with a diagnosis of diabetes) as well as any manufacturer recommendations. In addition to instructing the patient to monitor and record their blood glucose levels at home, it is helpful for a healthcare provider to review the history of the patient's blood glucose levels at every visit and ask about signs and symptoms of hypoglycemia. Tracking the patient's weight and reviewing the trend over the time the patient is taking a potentially offending agent may also provide insight into whether the patient is experiencing asymptomatic hypoglycemia, especially when reviewed with the patient's fasting blood glucose levels. When at all possible, patients should not be taking multiple agents that may cause drug-induced hypoglycemia. Healthcare providers should also be diligent to review a patient's medication profile for drug interactions, pharmacokinetics and pharmacodynamic, with potentially offending hypoglycemic agents. Tables 11 and 12 provide a summary of points to remember when prescribing medications with a potential for drug-induced hypoglycemia.

Prescribing Considerations
Use extended or sustained release products when possible
Avoid alcohol intake
Minimize the length of time on an offending agent
Utilize the lowest effective dose of the offending agent
Avoid having multiple medications in the patient's profile that can cause hypoglycemia
Screen the patient's medication profile for drug interactions – pharmacokinetic and pharmacodynamic

Table 11. Specific Prescribing Considerations When Prescribing Medications with a Potential to Cause Drug-Induced Hypoglycemia

Prescriber Considerations	Patient Education Points
Monitor blood glucose levels at clinic visits	Demonstration of self-monitoring of blood glucose Discussion of timing of blood glucose monitoring and target levels
Inquire about experiences with hypoglycemia, including specific signs/symptoms	Monitor for signs/symptoms of hypoglycemia Review appropriate treatment of hypoglycemia
Weigh the patient at clinic visits and review the trend	

Table 12. Monitoring Points When Patients Are Taking Medications with a Potential to Cause Drug-Induced Hypoglycemia

7. Management

When measures to prevent drug-induced hypoglycemia do not work or when appropriate prevention measures were not able to be undertaken, hypoglycemia, especially symptomatic hypoglycemia, must be treated. Specific, evidence-based recommendations for management of drug-induced hypoglycemia are not readily available. In the absence of guidelines for drug-induced hypoglycemia, patients who experience this should be treated according to readily accepted guidelines for managing hypoglycemia in patients with diabetes (Cryer et al, 2009, American Diabetes Association, 2011).

7.1 Signs and symptoms of hypoglycemia

As described in the section "Defining Hypoglycemia," patients may experience a variety of nonspecific symptoms (neurogenic symptoms and neuroglycopenic symptoms) as well as physical signs than can be attributed to hypoglycemia. Since there are not clear distinctions in hypoglycemic symptoms that occur regardless of the source of the symptom – drug-induced, diabetes mellitus, or another disease state, it is important that patients and caregivers be knowledgeable of the signs and symptoms of hypoglycemia. Sometimes friends and family members are the ones that recognize the patient is experiencing symptoms that can be attributed to hypoglycemia (Cryer et al, 2003). In particular they may notice changes in the patient's behavior, mood, speech, or train of thought as the patient is trying to communicate with them.

7.2 Differential diagnosis

When hypoglycemia is suspected it is important to recognize that the signs and symptoms a patient may complain of or present with are nonspecific and often other causes of the signs and symptoms must be ruled out. In 2009 the Endocrine Society released a clinical practice guideline specifying a workup strategy for patients who experience hypoglycemia in the absence of DM (Cryer, et al, 2009). The guidelines instruct the healthcare provider to review the patient's past medical history, physical exam, review of systems, laboratory data, and medications – current and past. These guidelines detail additional workup to undertake if

the cause of hypoglycemia is not apparent (Cryer, et al, 2009). However, the guidelines are very specific in stating that patients should be confirmed to have Whipple's triad-documented by signs and/or symptoms of hypoglycemia along with a low blood glucose concentration and recovery of the patient/resolution of the hypoglycemic signs/symptoms when the patient's blood glucose is raised – before the additional workup is pursued (Cryer, et al, 2009).

7.3 Treatment of hypoglycemia

While it is important to determine the cause of a patient's hypoglycemia, once signs and symptoms of hypoglycemia are recognized it is imperative to quickly treat the patient's hypoglycemia. Since there are no guidelines that are specific to managing drug-induced hypoglycemia, the current recommendations for managing hypoglycemia in patients with DM should be followed. Regardless of the cause of hypoglycemia, patients that are conscious should be given 15 – 20 g of glucose or any carbohydrate that contains glucose (American Diabetes Association, 2011). See Table 13 for specific examples of 15 – 20 g carbohydrate sources (National Diabetes Information Clearinghouse, 2008). The patient's blood glucose should be monitored in 15 minutes and they should continue to receive 15 – 20 g of glucose until their blood glucose level is greater than 70 mg/dl (3.9 mmol/l). Once the patient's blood glucose is above 70 mg/dl (3.9 mmol/l), the patient should eat something more substantial (a meal or snack) to maintain their blood glucose in a normal range, usually 70 -130 mg/dl (3.9 – 7.2 mmol/l) (American Diabetes Association, 2011).

Product	**1 serving = 15 g carbohydrates**
Glucose Products	3 – 4 tablets
	1 serving of glucose gel
Beverages	4 oz. = ½ cup of fruit juice
	4 oz = ½ cup of non-diet soft drink
	8 oz = 1 cup of milk
Hard Candy	5 – 6 pieces
Sugar or honey	1 tablespoon

Adapted from National Diabetes Information Clearinghouse, 2008.

Table 13. Quick Sources of Glucose

Hypoglycemia is defined as **severe** when a patient cannot treat their hypoglycemia on their own due to loss of consciousness. In cases of severe hypoglycemia, caregivers should administer glucagon (American Diabetes Association, 2011). It should be noted that glucagon is a prescription medication, available as a glucagon kit, whereas the glucose products routinely used for mild to moderate hypoglycemia are available without a prescription. Caregivers should be trained on glucagon administration since it requires preparation of the dose and intramuscular administration (Lilly, 2005). It is also important for patient and caregivers to routinely check the expiration date on the glucagon kit to ensure it is still in date (American Diabetes Association, 2011). Although there are numbers indicating the occurrence of hypoglycemia, it is unclear how often drug-induced hypoglycemia is severe. Therefore, it will be up to the healthcare provider to determine the

patient's risk for severe hypoglycemia. If a patient is taking multiple agents that can alter their blood glucose or if they have multiple risk factors for hypoglycemia then it would be reasonable for the patient to be provided with a prescription for a glucagon kit and for their caregiver(s) to receive appropriate training. If the patient's hypoglycemia is severe enough to warrant attention of emergency personnel, then additional measures to raise their blood glucose may include the administration of intravenous dextrose sources.

In addition to quickly trying to reverse the patient's hypoglycemia once it has occurred, a plan should be developed to prevent future episodes of hypoglycemia. As discussed in the "Prevention" section in Table 12, prescribing of the medication suspected to be causing hypoglycemia should be continued under close supervision. Providers should recognize that if offending drugs must be continued that there may need to be decreases in the dose, duration, or timing of administration. Once an episode of hypoglycemia has occurred, afterwards is an appropriate time to re-visit how the situation was managed and to make sure there is an action plan for any future episodes. A summary of general principles of the management of drug-induced hypoglycemic episodes are found below in Table 14.

Initial Treatment of Hypoglycemia
Recognition of signs and symptoms of hypoglycemia – differentiation between mild – moderate versus severe
Appropriate treatment of hypoglycemia – patient-treated with a quick acting glucose source versus caregiver assisted with glucagon or healthcare provider treatment with dextrose
Plan for Prevention of Future Episodes of Hypoglycemia
Evaluation of offending medication for adjustment in dosage and length of therapy
Consider of timing of administration of medication with meals
Consistent intake of meals/snacks
Institute blood glucose monitoring

Table 14. General Management of Drug-Induced Hypoglycemia

7.4 Resolution of hypoglycemia

Once a patient has experienced a hypoglycemic episode, the patient and healthcare providers will be anxious for it be resolved. Since the mechanism by which each offending medication causes hypoglycemia is different, the time to resolution of hypoglycaemia will vary accounting for both pharmacokinetic and pharmacodynamic properties of the offending medication as well as any other interfering medications. The mechanism by which hypoglycemia occurs will also determine whether the effects are reversible. In the case of pentamidine, the beta cell loss that may occur is not reversible (Pandit et al, 1993).

8. Discussion

When evaluating drug-induced hypoglycemia in comparison to what is reported in the literature, it is important to remember that the cases reported in the literature could be a result of publication bias. Many of the cases denoted patients with hospitalization and morbidity indicating patients were experiencing severe hypoglycemia (Murad et al, 2009).

Mild cases of hypoglycemia, even potentially asymptomatic cases, have not necessarily been documented in the literature, reinforcing the under-reporting of drug-induced hypoglycemia (Murad et al, 2009). In the most recent systematic review conducted, the reviewers noted that cases in the literature were patients who were taking medications at their recommended doses; however, the patients still experienced severe, symptomatic hypoglycemic episodes (Murad et al, 2009). This systematic review did reinforce the risk factors for drug-induced hypoglycemia that had been reported in earlier literature. Cases identified for the review were often patients of advanced age and who were experiencing renal and/or hepatic insufficiency. However, one additional patient risk factor that was identified was severe systemic disease (Murad et al, 2009). The drugs most often implicated in the reported cases were anti-diabetic agents, specifically insulin and sulfonylureas, as denoted in Table 6 (Murad et al, 2009).

9. Conclusion

Hypoglycemia is a potentially common and underreported complication of medication use which can result in significant morbidity and mortality. Patients must be educated on common signs and symptoms of hypoglycemia, especially when specific symptoms may be masked by medications. Specific characteristics, including renal insufficiency, hepatic insufficiency, and advancing age, may predispose patients to development of drug-induced hypoglycemia. Patient evaluation may help the clinician identify patients at greatest risk and avoid complications associated with the more commonly associated drugs. Preventative strategies include drug avoidance, minimizing time or dose of offending agents, using controlled-release formulations where available, limiting use of the medication or multiple medications which may cause hypoglycemia, and frequent, proactive blood glucose monitoring. Though these strategies may not prevent all occurrences, they may limit the number or severity of those that do happen. In the case of a hypoglyemic episode, management strategies should include those used in managing hypoglycemia of non-drug-induced origin.

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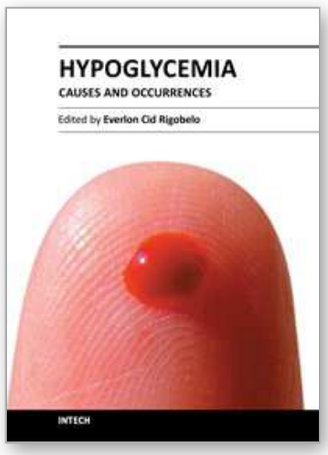

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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