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ANTIBIOTIC-INDUCED HYPOGLYCEMIA: FALL FROM PAN INTO THE FIRE?

Arash Eatemadi*[1], Ali Al Reesi[1], Salim Al Ghaithi[1], Mohammed Abbas Bokhari[1], Reza Eatemadi[2]

[1]General Medicine Department, Suhar Hospital, Suhar, Sultanate of Oman.
[2]Pharmacy Student, College of Pharmacy, National University of Science and Technology, Muscat, Sultanate of Oman.

***Corresponding Author: Dr. Arash Eatemadi**

General Medicine Department, Suhar Hospital, Suhar, Sultanate of Oman.

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ABSTRACT

Antibiotics are widely prescribed in medical practice by various clinicians from different fields. The most prescribers do not know or pay attention to known side effects of antibiotics. This is issue is important when there is concurrent prescription of antibiotics with other drugs which they can potentiate their effects. Hypoglycemia is a well-known side effect of some antibiotics which can happen independently or in co-administration with other drugs, mostly oral hypoglycemic agents. Quinolones and trimethoprim–sulfamethoxazole commonly prescribed and are the most discussed antibiotics regarding hypoglycemic effect.

KEYWORDS: Antibiotics, Side effect, Hypoglycemia, Oral hypoglycemic agents (OHAs)

Drug-induced hypoglycemia is a plasma glucose level <3.9 mmol/L (70 mg/dL) irrespective of hypoglycemia symptoms. There are three categories for Hypoglycemia:
1) Level 1: Blood glucose levels <3.9 mmol/L (70 mg/dL) and ≥3.0 mmol/L (54 mg/dL).
2) Level 2: Blood glucose levels <3.0 mmol/L (54 mg/dL), sufficiently low to indicate serious, clinically important hypoglycemia.
3) Level 3 (defined by symptoms): A severe event presented with decreased level of consciousness and if repeated, can cause cognitive impairment in the long term.

Serum glucose reduction secondary to drugs could happen through several routes including pharmacokinetic/pharmacodynamic drug-drug interactions or additive. Hospitalization due to hypoglycemic event is common in senile patients with diabetes on oral hypoglycemic agents (OHAs), mainly sulfonylureas (SUs). There are several antibiotics with documented or suspected hypoglycemic effect with or without concurrent OHAs use. (Table 1). The mechanisms of their hypoglycemic effect are also different. (Table 2)

Lee et al. conducted a case-control study on 9339 hospitalized adult patients with type 2 diabetes who were diagnosed with hypoglycemia and prescribed SUs for at least 120 days. Exposure to antibiotics in the 30-day period before the first hypoglycemia diagnosis was assessed. An increased risk of hypoglycemia was associated with co-administration of SUs and sulfonamides, fluoroquinolones, macrolides and tetracyclines.[1]

Also, Parekh et al. conducted a retrospective cohort study on patients 66 years or older who were prescribed glipizide or glyburide. They assessed hypoglycemia events in patients prescribed 1 of 7 antimicrobial agents thought to interact with sulfonylureas. They showed the risk of hypoglycemia after certain antibiotics (Quinolones, Clarithromycin, Metronidazole, trimethoprim-Sulfamethoxazole (TMP/SMX) and Fluconazole) and estimated that 13.2% of all hypoglycemic events in patients prescribed sulfonylureas were associated with 1 of 5 interacting antimicrobials.[2]

In addition, Schelleman et al. found that in glipizide users, TMP/SM, clarithromycin, fluconazole, and levofloxacin were associated with 2- to 3-fold higher odds of an episode of severe hypoglycemia compared with patients using cephalexin. In glyburide users, clarithromycin, levofloxacin, sulfamethoxazole-trimethoprim, fluconazole, and ciprofloxacin were associated with 2- to 5-fold higher odds of an episode of severe hypoglycemia.[3]

Recently, Kaitlin et al conducted a study to evaluate the association between hypoglycemia and antibiotics using the US Food and Drug Administration Adverse Event Reporting System (FAERS), while accounting for concomitant sulfonylureas and meglitinides. They found statistically significant hypoglycemia was observed with tigecycline, clarithromycin, ertapenem, moxifloxacin, levofloxacin and linezolid. After adjusting for concomitant sulfonylureas and meglitinides, tigecycline, ertapenem and clarithromycin still were associated with hypoglycemia. Fluoroquinolones were associated with hypoglycemia when they were also taking sulfonylureas

or meglitinides, however, tigecycline, ertapenem, and clarithromycin were associated with hypoglycemia even if not taken with sulfonylureas or meglitinides. The association between ertapenem and hypoglycemia has not been previously reported.[4]

Hypoglycemia related to commonly prescribed antibiotics

1- Fluoroquinolones

Most of the patients who developed hypoglycemia following fluoroquinolone use had risk factors such as old age, diabetes, renal insufficiency, and concomitant use of OHAs, especially sulfonylureas.[9-12]

The prescribing information for ciprofloxacin mention hypoglycemia as a side effect in patients with diabetes, due to drug-drug interaction[13-15] or hyperinsulinemia.[16] on July 10, 2018, the U.S. Food and Drug Administration (FDA), in its review of post-market pharmacovigilance data, communicated a safety alert on fluoroquinolones and risk of hypoglycemia.[17]

The postulated mechanism of quinolones-induced hypoglycemia is increased insulin release via blockade of ATP-sensitive potassium channels in the beta-cells of the pancreas and stimulation of insulin release from these cells which enhances insulin release in a dose-dependent manner. (table 2)[18-19] Hypoglycemic events also have been reported in individuals without a history of diabetes.[17,20,21]

2- Trimethoprim–sulfamethoxazole (TMP/SMX)

In patients taking TMP/SMX, the most common reason for hypoglycemia is the concomitant receiving of sulfonylureas[24,25] or repaglinide.[26] The effect of glyburide and glipizide may be altered by drugs that inhibit CYP2C9, a cytochrome P450 enzyme involved in their hepatic metabolism and TMP/SMX is an inhibitor of CYP2C9.

Juurlink et al. reported that use of TMP/SMX was associated with a sixfold greater risk of hospitalization for hypoglycemia among older patients taking glyburide, compared with those using amoxicillin.[24] Similarly, Schelleman et al. reported that use of TMP/SMX was associated with 3 times higher odds of hospitalization due to hypoglycemia among patients who took glipizide, using cephalexin as the reference.[3] TMP/SMX should be avoided in diabetic patients taking glyburide or glipizide.[27] The study by Alai Tan et al. showed that many senile diabetic patients on sulfonylureas were exposed to one well-described drug interaction. They estimated that 32.1% of older patients with diabetes were on glyburide or glipizide. Among these glyburide or glipizide users, 16.6% also had a co-trimoxazole prescription over a 3-year period.[25]

Hypoglycemia related to rarely used antibiotics

1- Pentamidine

Pentamidine is used as alternative treatment of Pneumocystis pneumonia. Hypoglycemia is the most common metabolic abnormality observed within 5–14 days of initiating therapy and occurs in about 6–40% of patients.[28,29] Intravenous glucose before starting pentamidine administration is often advised. The postulated mechanism of hypoglycemia is cytolytic release of insulin.[30] Gradually, insulin deficiency becomes progressive due to destruction of the pancreas tissue leading in hyperglycemic events which finally led to of new-onset diabetes.[28,29]

2- Quinine

Recent evidence from clinical and laboratory studies has indicated that quinine is a potent stimulant to the release of insulin from the pancreatic beta cells, so can cause hypoglycemia.[31-36]

quinine can simulate the action of glucose on potassium permeability of the beta cell membrane, with subsequent calcium influx.[37,38] However, clinically apparent hypoglycemia is rarely reported.[39,40] close monitoring of blood glucose level during the 1st hour of quinine infusion in patients with severe falciparum malaria is highly advised[41], because they are vulnerable to hypoglycemia due to high parasite load as well.

Miscellaneous antibiotics

There are also scattered, even conflicting reports about hypoglycemic effect of Metronidazole[42-44], Linezolid[45], Clarithromycin[46-49], Doxycycline[50-53], Tigecycline[54,55], Azoles[56-58] in medical literature.

In conclusion, knowledge of common side effects and interactions of widely prescribed antibiotics is necessary for all clinicians. Antibiotic-induced hypoglycemia could be a life-threatening matter, particularly in senile patients on concurrent use of OHAs.

Table 1: Antibiotics with documented or suspected hypoglycemic effect.

Group 1: Antibiotics with potent evidences or clear mechanism of hypoglycemic effect	Group 2: Antibiotics less evidences or no clear mechanism of hypoglycemic effect
Quinolones Clarithromycin TMP/SMX Metronidazole Fluconazole Pentamidine Quinine	Piperacillin- tazobactam Cephalexin Cefuroxime Azithromycin Linezolid Doxycycline Tigecycline Ertapenem

Table 2: The mechanism of hypoglycemic effect of commonly prescribed antibiotics.

Antibiotic	*Mechanism*
Ciprofloxacin	*Inhibits ATP K+ channels in pancreatic B-cells initiating insulin secretion[5,6] *Enhances glucose-induced insulin secretion[5,6]
Levofloxacin	*Inhibits ATP-sensitive K+ channels affecting insulin release[5,6] *May serve as P-glycoprotein inhibitor, which can increase concentrations of sulfonylureas[7,8]
Moxifloxacin	*Enhances glucose-induced insulin secretion[5]
TMP/SMX	*CYP2C9 inhibitor, interfering with sulfonylurea metabolism[22,23]
Clarithromycin	*May increase sulfonylurea level by inhibiting P-glycoprotein in the intestinal wall[46,47]
Metronidazole	*CYP2C9 inhibitor interfering with sulfonylurea metabolism[42,43]
Fluconazole	*CYP2C9 inhibitor interfering with sulfonylurea metabolism[56]
Pentamidine	*Increase in insulin secretion via a cytolytic response in the pancreas[30]
Quinine	*Stimulant to the release of insulin from the pancreatic beta cells[31-34]

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