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Improving Glycemic Control with Glucokinase Activators
in Geriatric Patients with Type II Diabetes Mellitus

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PERMISSION

Title: Improving Glycemic Control with Glucokinase Activators in Patients with Type II Diabetes Mellitus

Department: Nursing

Degree: Master of Science

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Abstract

Type II Diabetes Mellitus is a growing global health concern that is associated with increased medical costs and negative health outcomes, especially for those over the age of 65. This review offers a case report on an elderly female patient who has failed traditional treatment measures evidenced by an increasing hemoglobin A1c. A major concern in the management of glucose control for the elderly population is to avoid hypoglycemic events and to maintain adequate treatment of other coexisting comorbidities. Some of the more popular diabetic medication options increase adverse outcomes for the elderly diabetic population. Recent antidiabetic medication trials have focused on development of drugs that focus on improving pancreatic beta-cell function and number as well as efficiency of glucose utilization within the liver, both of which are dysfunctional in those patients with Type II diabetes mellitus. Results are promising at providing efficient glycemic control while limiting adverse effects that cause far greater negative health outcomes in geriatric patients.

Background

One of the world's most common chronic diseases is diabetes which affects over 425 million people, and Type 2 diabetes mellitus (T2DM) is the predominant form of the disease (Fujieda, et al., 2018). T2DM has become a destructive disease globally, it impacts health economics with overwhelming costs and every year there is an increasing number of patients who are diagnosed (Chatterjee, Khunti, & Davies, 2017). There are two abnormalities that occur physiologically which can be seen in T2DM; insulin resistance within both muscle and liver tissues, and impaired insulin secretion due to pancreatic beta-cell failure (Dunphy, Winland-Brown, Porter, & Thomas, 2015). The result is a hyperglycemic state which leads to further microvascular and macrovascular damage throughout the body.

For the aging population, T2DM is an important health concern as approximately one-half are considered pre-diabetic and one-quarter of people over the age of 65 have diabetes (American Diabetes Association, 2019). There are multiple reasons that people develop diabetes mellitus (DM) as they age including genetics, as well as age-related reasons such as mental or social issues and nutrition (Yanase, Yanagita, Muta, & Nawata, 2018). As people age, they develop sarcopenia, increase in their visceral fat, as well as lose mitochondria functioning; these are all thought to increase insulin resistance (Yanase et al., 2018). Furthermore, it is well documented that older adults with diabetes will have increased rates of multiple comorbidities, such as hypertension and cardiovascular diseases, as well as increased risk of geriatric syndromes, such as polypharmacy, frequent falls, and cognitive impairment (American Diabetes Association, 2019).

In addition to the increased development of DM, DM itself is considered an independent risk factor for falls and development of hip fractures (Yanase et al., 2018). Management of

diabetes for the older adult should include assessment of medical, functional, psychological, and social areas to determine what is the best treatment approach for each different individual patient (American Diabetes Association, 2019). A significant concern for the geriatric population and diabetes management is to avoid hypoglycemic events, which can lead to adverse outcomes (American Diabetes Association, 2019). For those diagnosed with T2DM, the key to management is glucose control. Once management with diet and exercise fails, the treatment with oral glucose-lowering agents is initiated. The American Diabetes Association recommends that metformin be the preferred initial pharmacological agent for older adults with T2DM (2019). However, with any drug, their effectiveness can decrease over time and this has been shown through research in patients who are treated with metformin, a biguanide and glipizide, a sulfonylurea (UKPDS, 1998). Therefore, continued research is important to develop new pharmacological approaches for the treatment of T2DM.

Glucokinase (GK), a monomeric enzyme, is a major regulator of glucose homeostasis by initiating the conversion of glucose to energy as well as acting as the physiological sensor of glucose (Vella et al., 2019). Research has found glucokinase activators that can directly affect the pancreatic beta-cells, regardless of glucose concentration (Xu et al., 2017a). In consideration of diabetes, targeting glucokinase activators (GKAs) to stimulate insulin secretion and protect Beta-cells from losing function and mass has become a new approach to the treatment of T2DM (Xu et al., 2017a). A newly developed drug, identified as TPP399, is currently in phase II clinical trials and its mechanism of action specifically targets hepatic glucokinase as a hepatoselective glucokinase activator (Vella et al., 2019). Another drug being studied, Dorzagliatin (HMS5552), has a mechanism of action that is considered a dual acting GKA since it targets both pancreatic and hepatic glucokinase (Zhu et al., 2018). Most importantly, in recent

clinical trials these drugs have both shown positive results in reducing hemoglobin A1C levels and sustaining those levels without causing hypoglycemic events, an increase in blood pressure, or affecting changes in both plasma lipids or liver enzymes (Vella et al., 2019; Xu et al., 2017a; Zhu et al., 2018). The case presented here is of an uncontrolled diabetic elderly female patient who failed current treatment with glipizide and requires a reevaluation of her pharmacologic management of diabetes.

Case Report

History

A sixty-five-year-old Caucasian female, who is a retired teacher, presents to the clinic for a 6-month follow-up diabetic recheck. She resides at home with her spouse and does not have any in home services. She has adult children as well as grandchildren, who reside in the same community. Her medical history includes; Obesity, Hyperlipidemia, Actinic Keratosis, and Diabetes Mellitus Type II. Her surgical history includes; Cataract, Carpal Tunnel, Colon polyp removal.

She had been diagnosed with T2DM ten years earlier and was able to manage her diabetes with lifestyle modifications up until 6 months ago, which corresponds with her retirement. At that time, she had been prescribed 10 mg glipizide (Glucotrol) daily and a combination pill 50-1000 mg metformin/sitagliptin (Janumet) twice a day to manage her diabetes as her A1C was 8.1% . She reports her at home morning blood glucose checks have been in the 170-220 range and she has not noted any decrease since starting the medications at her last visit.

Her other routine medications include lisinopril, 10 mg daily; metoprolol (Toprol XL) 50 mg daily; simvastatin (Zocor) 20 mg daily; aspirin, 81 mg daily; and a multivitamin daily. She reports compliance with all medications as prescribed. She denies use of nicotine and

recreational drugs, uses alcohol socially on occasion; has no known drug allergies; and is not up to date on immunizations.

She reports overall good health. She reports eating three meals per day with snacks. She does try to “watch what she eats” but it has been challenging. She has retired from teaching within the past year and now states that she has noted an increase in weight of approximately 10 pounds, which she feels is a result of her increased free time and availability of snacking throughout the day.

She reports that she has an upcoming eye exam scheduled and notes vision changes related to her diagnosed cataracts. She currently wears corrective lenses.

She denies fever, chills, fatigue, sore throat, congestion, ear pain, cough, SOB, chest pain, nausea, vomiting, diarrhea, constipation, abdominal pain, hematochezia, dysuria, frequency, urgency, hematuria, numbness, weakness, swelling to feet/ankles, or skin concerns.

Physical Examination

She appears well, pleasant, conversant, and obese but in no apparent distress. A limited physical exam reveals:

- Weight: 122 kg (269 lb); calculated BMI is 36.5
- Temperature: 97.9
- Blood pressure: 146/90
- Pulse: 72 bpm; respirations 18 per minute
- HEENT: head is normocephalic, conjunctiva pink, pupils equal and reactive, no exudate noted, normal bilateral ear canals, TMs, hearing, oropharynx pink, moist, and without lesions.

- Neck: supple, no adenopathy, trachea midline
- Lungs: clear to auscultation bilaterally, no wheeze, rales, or rhonchi
- Cardiac: heartrate regular, no murmur
- Extremities: normal pulses, no edema
 - Diabetic foot exam: bilateral feet warm to touch, pulses palpable, no sores or open areas, monofilament touch test is intact to all aspects bilaterally.
- Neuro: alert and oriented x3
- Psych: normal mood and affect, good eye contact, normal judgement, and insight

Lab Tests

Creatinine Urine	30.00 - 259.00 mg/dL	101.82
Microalbumin mg/L	mg/L	22.17
Microalbumin/Creatinine Ratio	0 - 30 mg/g	22
Cholesterol	0 - 200 mg/dL	133
Triglyceride	30 - 150 mg/dL	167 Abnormally high
HDL	40 - 60 mg/dL	39 Abnormally low
LDL	0 - 129 mg/dL	61
Fasting	Yes, No, Unknown	Yes
CMP:		
Glucose	70 - 100 mg/dL	324 Abnormally high
BUN	7 - 18 mg/dL	16
Creatinine	0.70 - 1.30 mg/dL	0.92
BUN/Creatinine Ratio	15.0 - 20.0	17.4
Sodium	136 - 145 meq/L	139
Potassium	3.5 - 5.1 meq/L	4.3
Chloride	98 - 107 meq/L	102
CO2	21 - 32 meq/L	28
Anion Gap with K	6 - 20 meq/L	13
Calcium	8.5 - 10.1 mg/dL	9.0
Protein Total	6.4 - 8.2 g/dL	7.8
Albumin	3.5 - 5.0 g/dL	4.7
Alkaline Phosphatase	46 - 116 U/L	84
AST - SGOT	15 - 37 U/L	19

ALT - SGPT	12 - 78 U/L	30
Bilirubin Total	0.2 - 1.0 mg/dL	1.1 Abnormally high

Recent Hgb A1C – 9.5 6 months ago – 8.1

Diagnosis

Uncontrolled type 2 diabetes mellitus without complication

Hyperlipidemia

Obesity

Treatment/Plan

Diabetes Mellitus, type 2 uncontrolled – Discontinue glipizide. Continue to take Janumet twice a day. Initiation of 15 units glargine (Lantus) insulin every morning. Referrals placed and appointments scheduled for patient to see diabetic educator and dietitian for insulin teaching, further evaluation, and treatment. Return to clinic in 6-8 weeks with repeat of fasting lipid panel, CMP, and urine. Counseled patient to keep written log of home blood glucose levels and to bring that in to her next appointment.

Hyperlipidemia – will continue simvastatin (Zocor) as prescribed. Will monitor labs. Patient may have further benefit from appointment with dietitian.

Obesity – Referrals placed, and appointments scheduled for patient to see diabetic educator and dietitian for further evaluation and treatment. Encouraged her to increase activity.

Health Promotion – Referral and schedule appointment for colonoscopy. Vaccinations provided today included: Prevnar 13, Tetanus, and Shingrix.

Literature Review

Glucose homeostasis loss in T2DM is caused by a combination of defects that involves both insulin secretion and insulin resistance (American Diabetes Association, 2019; Chatterjee, Khunti, & Davies, 2017; DeFonzo et al., 2013). Throughout the literature multiple authors note that achieving an optimal glucose control in patients with T2DM is a challenge. Specifically, patients treated with both metformin and sulfonylurea were shown to experience a progressive decline in their hemoglobin A1c (HgbA1c) as demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS, 1998). Furthermore, DeFonzo et al., reports a continued rise of HgbA1c in those patients treated with both metformin and sulfonylurea, so that more than 50% of those diabetic patients would require an additional drug to achieve a HgbA1c <7% (2013). To further complicate this issue of medication ineffectiveness in providing satisfactory glycemic control over time, it is especially concerning for those elderly patients over the age of 65. It is extremely important to find a balance between glycemic control and the management of their additional comorbidities, which is often more difficult due to age-related physical and mental deficits (Chatterjee, Khunti, & Davies, 2017). When patients fail to reduce their HgbA1c levels with oral medications, the introduction of basal insulin is often the next step. Of course, use of insulin to manage glycemic levels is the most effect treatment form, but there is frequently poor adherence to this method due to difficulties with self-injection, fears of weight gain, lifestyle restrictions, and general refusal (Chatterjee et al., 2017). However, insulin is also associated with hypoglycemic events, especially in the elderly population (Chatterjee et al., 2017). Furthermore, it would require the patient to have good vision and motor skills as well as cognitive capabilities to safely administer insulin on their own (ADA, 2019). The need to better manage T2DM patients, including populations with unique needs like the elderly, has led to

multiple attempts to create and identify drugs that can not only stimulate insulin secretion, regardless of plasma glucose levels, but would also protect pancreatic beta-cells from their continued loss of function and mass.

Since the 1990s one area of research has been focused on the use of glucokinase activators as a potential new oral antidiabetic drug class. There have been some difficulties pursuing this approach to treatment as early testing was riddled with adverse events, such as increased risk of hypoglycemia, hypertriglyceridemia, hypertension, and liver steatosis (Nakamura & Terauchi, 2015). These adverse events would be especially harmful for the geriatric population, who can experience far greater detrimental outcomes such as injury or death. Specifically, when we look at the geriatric population and their special considerations with regards to medication and disease management, especially for T2DM, one of the greatest concerns is related to hypoglycemic events. As cited by Yanase et al. the maintenance of an appropriate HgbA1c level is thought to also reduce the risk for frailty in elderly T2DM patients; they further theorize, that the risk of dementia, stroke, falls, and increased mortality can be impacted by both low and high HgbA1c levels (2018).

Current treatment trends for T2DM, includes oral medications that work to off-set hyperglycemia by inhibiting the appearance of glucose in the blood or by increasing the rate that glucose is cleared from the blood (Laight, 2014). Metformin is the initial pharmacological choice for treatment of T2DM in elderly patients, unless it is specifically contraindicated, and is often used in combination therapy with a sulfonylurea (ADA, 2019; Chatterjee et al., 2017). While metformin reduces glucose output from the liver, it also works to enhance glucose uptake by both muscle and adipose tissue, as well as stimulating glucagon-like peptide-1 (GLP-1) receptors (ADA, 2019; Chatterjee et al., 2017; Laight, 2014). Alternatively, sulfonylureas work

by stimulating pancreatic beta-cells to increase insulin secretion (Chatterjee et al., 2017).

Sulfonylureas have been noted to carry an increased risk of hypoglycemic events, especially in elderly patients, with 11-18% of users noting hypoglycemic complications. (ADA, 2019; Chatterjee et al., 2017; Lapan, et al, 2015; Laight, 2014). A challenge that faces drug research is to identify an approach to treatment of T2DM through alternate mechanisms of action that also limits the number of adverse events (Grimsby et al., 2003). Approaching a treatment alternative towards the glucokinase enzyme may be the future direction of management of T2DM (Grimsby et al., 2003).

Glucokinase (GK) is an enzyme that has an essential role in glucose homeostasis (Fujieda et al., 2018, Grimsby et al., 2003, & Zhu et al., 2018). It acts as both a glucose sensor in the pancreas, which aids in the insulin and glucagon secretion, and when in the liver, it processes glucose by converting it into glycogen (Zhu et al., 2018). Patients with T2DM have been identified as having an impaired glucokinase function and expression (Haeusler et al., 2015). Researchers have found that pharmacological or environmental glucokinase activators can influence both the impaired pancreatic glucose sensing and the conversion of glucose within the liver into action (Perreault, Faerch, Kerege, Bacon, & Bergman, 2014). Grimsby et al. first studied the effects of an identified compound that increased the enzymatic activity of GK and lead them to the synthesis of RO-28-0450 as a lead glucokinase activator (2003). This compound was further synthesized and the subsequent R- and S-enantiomers were tested which resulted in the R enantiomer, RO-28-1675 as a potent GKA (Grimsby et al., 2003). They found that RO-28-1675 had a dual mechanism of action, one which enhanced insulin release from the pancreas as well as the stimulation of glucose usage in the liver (Grimsby et al., 2003). This has led the

direction of research further into the use of GKAs as a possible safe and effective monotherapy treatment option for T2DM.

Glucokinase activators (GKAs) have become an ideal target in the development of new T2DM drugs (Fujieda et al., 2018; Grimsby et al., 2003, & Xu et al., 2017b). GKAs ability to function in the capacity to impact both the insulin release and the metabolism of glucose in the liver make them an ideal future monotherapy treatment option, especially with their improved glycemic control results (Grimsby et al., 2003). There are 7 different GKAs which can be classified into two groups: dual-acting GKAs, which targets both pancreatic and hepatic GK, and liver-selective GKAs, which only targets hepatic GK (Zhu, et al., 2018b). The dual-acting GKAs are further separated into two subgroups based on their effects on the GK kinetic properties; full GKAs, which increases the maximum velocity of GK or partial GKAs, which reduces the maximum velocity (Zhu et al., 2018b). These GKAs that have been included in multiple phase II studies (Xu et al., 2017a, Xu et al., 2017b, Zhu et al., 2018b).

Investigation of the use of GKAs that work primarily on influencing the glucose uptake in the liver is focused on the interaction between glucokinase and glucokinase regulatory protein (GKRP). The GKRP is an endogenous inhibitor that affects the hepatic glucokinase activity (Nakamura & Terauchi, 2015). At times of low glucose concentrations, GKRP and GK are together as an inactive complex which is localized in the nucleus (Nakamura & Terauchi, 2015). When glucose concentrations rise, the GK/GKRP complex is disassociated and translocates into the cytoplasm, which then signals glucose disposal (Nakamura & Terauchi, 2015). Studies have been able to use GKAs to stimulate glycolysis and glycogen synthesis, which leads to that disassociation between GK/GKRP complex within hepatocytes (Nakamura & Terauchi, 2015).

One interesting drug in clinical trial currently is known as TTP399 and is a liver-selective GKA (Xu et al., 2017a; Xu et al., 2017b). The authors hypothesize that by limiting the GKA to hepatocytes, blood glucose levels not only would decrease but it would limit or eliminate hypoglycemic events (Xu et al., 2017a). The thought is that GK mediated glucose in hepatocytes play a key role in increasing hepatic glucose uptake and metabolism, so it would decrease hepatic glucose output (Xu et al., 2017b). In addition, the authors further hypothesize that by targeting pancreatic beta-cells with GKA, there would be a greater increase of sub-euglycemic levels (Xu et al., 2017a). In the completed Phase IIa clinical trial, TTP399 normalized the HgbA1c levels to <7.5% in 40% of patients receiving TTP399, while none of those patients receiving the placebo reached HgbA1c normalization (Buse et al., 2018).

In comparison, the concentration of glucose is directly related to the phosphorylation of glucose within the pancreatic beta-cells (Nakamura & Terauchi, 2015). The rate-limiting step of insulin secretion is due to this phosphorylation of glucose by glucokinase (Nakamura & Terauchi, 2015). Everything occurs based on the glucokinase control of both the glycolytic and oxidative adenosine triphosphate production, so that as the ratio of adenosine triphosphate to adenosine diphosphate increases it closes the potassium (K) channel, which leads to cell depolarization (Nakamura & Terauchi, 2015). As the membrane potential threshold is reached and the L-type calcium (Ca) channel opens, insulin is then released (Nakamura & Terauchi, 2014). Using GKAs to stimulate pancreatic beta-cells to release insulin has been effective and results in improved functioning of those beta-cells (Nakamura & Terauchi, 2015).

The other aspect that has also been studied with consideration to pancreatic beta-cells, is the impact that GKAs have on their proliferation (Nakamura & Terauchi, 2015). Initial research using GKA *in vivo* was found to have shown to induce beta-cell proliferation (Nakamura &

Terauchi, 2015). Those studies further examined the combined and independent effects of the beta-cell-specific glucokinase versus the insulin receptor substrate-2 to determine that GKA does in fact impact insulin secretion in pancreatic beta-cells and improves glucose utilization in the liver, it also induces beta-cell proliferation (Nakamura & Terauchi, 2015).

In consideration of influencing pancreatic beta-cells, another drug that is in clinical trial, Dorzagliatin (HMS5552), is a dual-acting GKA that targets both the pancreatic and hepatic GKs (Zhu et al., 2018a). The effectiveness of this drug in a multiple-ascending dose study, found that the most effective minimum dose was the group receiving 75mg twice daily (Zhu et al., 2018a). This group was well-controlled in their HgbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG) after 12 weeks of treatment with a reduction in HgbA1c occurring after 4 weeks (Zhu et al., 2018a). Furthermore, this group had no increased risk of hypoglycemia and dyslipidemia (Zhu et al., 2018a).

While the development of TTP399, a hepatic selective GKA, does demonstrate its effectiveness at lowering HgbA1c during clinical studies, it may not be the most ideal future treatment option for those patients with T2DM. Since there is a dual failure that occurs within the body, that happens within both hepatic and pancreatic cells, perhaps the most logical approach would be to direct treatment at improving those specific deficits. The use of a dual action GKA, such as Dorzagliatin (HMS5552), that improves insulin secretion, increases the number of pancreatic beta-cells, and also improves glucose utilization within hepatic cells, could lead to better glycemic control. In fact, not only would it result in lowering HgbA1c levels, but because of the improvements at the cellular level, this treatment could stave off the typical medication burn-out that is seen too often after several years when additional medications are being required to help reduce blood glucose levels. In addition, the success that clinical trial has

shown with limiting hypoglycemic events, again is a benefit to minimize those adverse events, which can be so detrimental with elderly patients.

Learning Points

- Optimal glucose control for Type II Diabetes is challenging, especially with disease progression.
- Current diabetic treatment trends can lead to hypoglycemic events or be difficult to manage for geriatric patients
- Future treatment options that focus on both pancreatic beta-cell and hepatic cell function may offer better glycemic control while limiting adverse effects
- Glucokinase activators are showing improvements in reduced HgbA1c with dual action focus on the pancreas and liver
- For diabetic geriatric patients, limiting medication adverse effects and ease of use can improve their health-related quality of life

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