Review Article

Management of diabetes in the elderly with canagliflozin: A newer hypoglycemic drug on the horizon

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ABSTRACT

Canagliflozin is the first available oral inhibitor of sodium/glucose cotransporter 2 (SGLT2) in the market. At the outset it sounds excellent for the use in the elderly diabetic population, because of its minimal tendency to cause hypoglycemia. However, the clinician needs to exercise caution as it needs to be dosed renally. The clinician needs to be circumspect about potential drug interactions, especially when there is an underlying chronic kidney disease (CKD) and congestive heart failure (CHF). Also its use is best avoided in people who are predisposed to genital mycotic and urinary tract infections (UTI).

Key words: Chronic kidney disease, congestive heart failure, diabetes mellitus type 2, drug interactions, elderly

INTRODUCTION

With an increase in the longevity of life and an increasingly sedentary lifestyle, there is an increased incidence of diabetes mellitus (DM2) in the elderly, who may get admitted to hospital for symptomatic or operative treatment.[1-3] In the US, seven million Americans are undiagnosed and 25 million are known diabetics, which might double up in the next decade.[3] This is projected to keep increasing and is estimated to cost about 100 billion dollars per year to the tax payers.[4]

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The challenge of treating diabetes in this section of population is to avoid hypoglycemia.[5] With minimal tendency to cause hypoglycemia, canagliflozin sounds appropriate for the geriatric population. However, the drug needs to be used with caution, as it causes a drop in blood pressure and its use in the elderly needs to be closely monitored. Also it needs to be titrated renally. It has a tendency to cause mycotic infections in the genital area and causes recurrent urinary infections, which may cause many unwanted side effects, especially in elderly women.

For our discussion, elderly is defined as people with a chronological age of more than or equal to 65.

Literature search strategies

Articles in various international and national bibliographic indices were extensively searched, with an emphasis on canagliflozin, mycotic infections, and management of diabetes in the elderly. The various search sites included Entrez (including PubMed), NIH.gov, and Medscape.com,

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WebMD.com, MedHelp.org, Searchmedica, MD consult, and google.com.

Elderly and diabetes

As a person ages, the physiology of the body slows down. The body attains the peak body mass around the age of 30 years. Thereafter, there is a slow progressive decline of the Glomerular filtration rate (GFR), even if there is no superimposed pathology. With aging there is an increased prevalence of diabetes and hypertension, which further exacerbates the picture.[6,7]

This also complicates the diagnosis and monitoring of diabetes in the elderly. In the elderly, HbA1c[8] should be interpreted with cynicism, keeping in view the comorbidities of the changing body physiology. In the elderly, it could be a misleading diagnostic tool. In rapid cell turnover states like hemolytic anemia, HbA1c could be falsely low. During treatment with iron, B12 or erythropoietin, as in chronic kidney disease (CKD), there may be rapid red blood cell turnover and falsely low HbA1c.[9] On the other hand, in low cell turnover states, especially iron, B12 or folate deficiency or in the very elderly, when the marrow turnover is low, HbA1c may be falsely high. In CKD, HbA1c may be falsely high or low. When there is high carbamylated hemoglobin it may be falsely high and if erythropoietin is being used it may be falsely low [Figure 1].

Pharmacology of canagliflozin - the new oral hypoglycemic

Canagliflozin is the first oral inhibitor of sodium/glucose cotransporter 2 (SGLT2) in the kidney. SGLT2 is responsible for the reabsorption of a majority of the glucose filtered by the kidneys. It is present predominantly in the proximal convoluted tubules of the nephron. It reabsorbs glucose from the lumen of the nephron. Canagliflozin acts by promoting loss of glucose in the urine, in a dose-dependent manner. The time taken for the drug concentration to peak is one to two hours (time to peak (T_{max})). The area under the curve is increased in a dose-dependent manner. Depending on the dose used, the half-life (T½) of the drug is 10.6 and 13 hours. Its

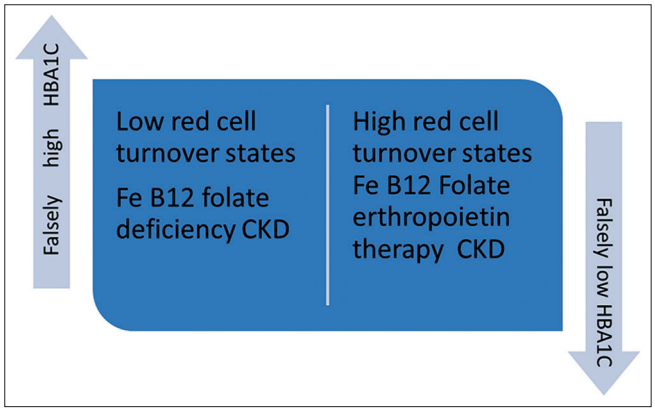

Figure 1: Pitfalls of HBA1C monitoring in the elderly

oral bioavailability is 65% and it is advised to be taken before breakfast. The volume of distribution is 119 L and it is 99% protein-bound. It is metabolized by O-glucuronidation and is metabolized to inactive metabolites by Uridine diphosphate glucose (UDP) glucuronyltransferase (UGT). Two enzymes are predominantly involved, namely, UGT1A9 and UGT2B4. Cytochrome CYH3A4 is minimally involved in the metabolism of canagliflozin.

Canagliflozin is 50% excreted by the hepatobiliary system and 33% renally. It cannot be removed by hemodialysis, owing to a large volume of distribution and high protein binding. The drug dose does not have to be adapted to hepatic dysfunction, but its use is not indicated in Child-Pugh C liver dysfunction. The effect of age, body mass index (BMI), gender, and race is clinically insignificant. There is no data on pregnancy, pediatric population, and nursing mothers, but it definitely causes weight loss.[10,11]

The most common side effects, especially in women, were recurrent urinary tract infection (UTI), *Candida* genital infections, and decreased blood pressure.[11] These side effects are seen in about 10% of the subjects.[12]

There was a concern of carcinogenicity with canagliflozin, especially with respect to the renal tubules, adrenals, and leydig cells of the testis in rats. However, the FDA concluded that these nongenotoxic effects were related to carbohydrate malabsorption and calcium imbalance. Canagliflozin[13] reduces the renal threshold to excrete glucose in a dose-dependent manner.[14] It has been used successfully in older patients with uncontrolled diabetes, in a multicenter, double-blind study by Bode *et al*.[15] In a trial by Cefalu *et al.,* canagliflozin bettered glimepiride in both the doses. The rate of recurrent UTI and genital *Candida* infections was higher than in the control group. The effect was related to the dose of the drug.[16]

Its pharmacokinetic and pharmacodynamic profile favors once daily dosing.[10] SGLT2 is located in the proximal tubules of the kidney and is related to reabsorption of glucose from the proximal tubules.[14] This leads to loss of glucose and thereby causes weight loss and improved glycemic control in an insulin-independent manner.

Canagliflozin also prevents a rise in postprandial glucose due to intestinal SGLT1 inhibition and an increase in the renal excretion of glucose.[17]

Candida genital infections

Candida genital infections are common in women with diabetes.[12,18] Vulvo vaginal candidiasis affects 75% of the women, at least once in their life time.[12,18] High glucose in the tissue promotes *Candida* attachment and growth. This is exaggerated in elderly women who use canagliflozin. Risk

factors include employed woman, diabetes mellitus, use of an intrauterine device or spermicidal jelly for contraception and oral sex.[18,19] The most common species is *Candida albicans*. However, there is a rise in the incidence of *Candida glabrata,* especially in diabetic patients with recurrent vulvo vaginal candidiasis.[20] *Candida glabrata* is less virulent and less susceptible to common antifungals.[21] Increased incidence of *Candida* balanitis is also seen in diabetic uncircumcised men. Balanitis and belanoposthitis might be seen more so in diabetic Indian men, as a majority of Hindu men are not circumcised.[21]

Canagliflozin in the elderly uncontrolled diabetics

In May 2013, FDA approved canagliflozin for use in people with noninsulin-dependent diabetes mellitus (NIDDM) as a monotherapy or in combination with other drugs. A fixed drug combination therapy with metformin has so far not been approved by the FDA. Canagliflozin is still seeking to carve a niche for itself in the management of diabetes in the elderly.

Elderly diabetics often have cognitive dysfunction, and may have difficulty with self-management and may follow complicated treatment regimens.[22] They are less functional compared to the non-diabetic elderly. They are predisposed to frequent episodes of hypoglycemia or deterioration of glycemic control.[22] The unawareness of hypoglycemia is a major complicating factor in the management of elderly diabetics.[23] Canagliflozin with its favorable pharmacokinetic profile and tendency for minimal hypoglycemia may aptly favor its use in the elderly.[23]

Hospitalization is a big stressor, more so for the elderly. The clinician might encounter stress hyperglycemia, especially in perioperative settings.[24] Stress hyperglycemia has complications similar to infection and poor wound healing. This is due to the release of counter regulatory hormones and cytokines.[25] A standard approach of long-acting insulin at meal time and correctional insulin remains the standard even in the treatment of stress hyperglycemia. However, often there may be a wide fluctuation in glycemic control, which is more detrimental than sustained hyperglycemia.[26] Canagliflozin may come in handy in these clinical scenarios when insulin cannot be used for some reason.

Data regarding the use of canagliflozin for control of hyperglycemia in the elderly is minimal. Its biggest advantage for use in the elderly is its minimal tendency to cause hypoglycemia, which could lead to increased morbidity and mortality.[27] If a patient has a risk for genital and urinary infections, these drugs must be avoided, especially in elderly females.

Unintended hypotension may lead to increased cardiovascular events. Further clinical trials are needed to define the safety profile and refine the indications further.[10] In general, treatment needs to be individualized in this age group, keeping in mind the comorbidities and the benefit to risk ratio.[10,28]

The elderly frequently have ongoing metabolic derangements secondary to multiple comorbidities. This may be worsened secondary to diuretic-like action in the renal tubules, with osmotic diuresis. It is important to continue to monitor for hyperkalemia, hypermagnesemia, hyperphosphatemia, and increase in low-density lipoprotein (LDL).

The elderly are frequently on polypharmacy, which opens the door for potential drug interactions.[29] Uridine diphosphate glucuronosyltransferase (UGT) enzyme inducers like rifampin, phenytoin, phenobarbitone, and protease inhibitors could potentially make canagliflozin subtherapeutic [Table 1]. Rifampin is a non-selective inducer of UGT enzymes - UGT 1A9, UGT2B4. The area under the curve (AUC) is decreased for canagliflozin when used concomitantly with rifampin.

With use of digoxin, which is a UGT enzyme inhibitor, the AUC may increase by 20% for digoxin [Table 1]. Also there is an epidemic of congestive heart failure (CHF) and digoxin is often used in this clinical setting. It could potentially become supratherapeutic. Serum levels of digoxin may need to be monitored when initiating canagliflozin, especially in women, given its narrow therapeutic index. Also patients with CHF would likely be on loop diuretics, which could potentially worsen the metabolic derangements associated with canagliflozin.

Canagliflozin is a weak inhibitor of cytochromes CYH 2B6, CYH2C8, and CYH3A4. Also it is a weak inhibitor of the P-glycoprotein (P-gp) transport system. However, it is not a substrate or inducer for the CYH or the P-gp system.

Use in renal insufficiency

Most of the oral hypoglycemics need to be adjusted as per the changing renal function. Renal insufficiency is one of the common clinical scenarios where severe hypoglycemia is seen, especially during the perioperative period and in critically ill patients.[30] The physician should carefully monitor the renal function in the elderly, especially if there is nephropathy. The dose of canagliflozin needs to be carefully titrated with underlying renal insufficiency [Table 2]. Dose reduction is recommended if the glomerular filtration rate (GFR) <60 ml/minute/1.73 m.[31] It has been used safely in stage 3 CKD.[31] The maximum dose for GFR <60 ml/minute/1.73 m^2 is 100 mg daily. Use is not indicated for a GFR <45 ml/minute/1.73 m^2. Renal insufficiency is a dynamic variable and careful monitoring of the renal function is mandated if canagliflozin is used for renal insufficiency. There is potential for increased side effects in renal insufficiency secondary to volume depletion. The dosing

Table 1: Potential drug interactions of canagliflozin in the elderly

Medications	Adverse effects	Risk category
ACE Inhibitors/ARBS	Increased hyperkalemia and hypotension	C
Eplerenone	Increased hyperkalemia and hypotension	C
Fosphenytoin, Phenytoin, phenobarbitone, Rifampin, Protease inhibitors	Decreased AUC for canagliflozin	D
Heparin, LMWH	Increased hyperkalemia	C
Loop diuretics	Decreased hypoglycemic effect	C
Potassium sparing diuretics	Increased hyperglycemia	C
SSRIs/Digoxin	Increased AUC for digoxin/canagliflozin	C

ACE=Angiotensin converting enzyme inhibitors, ARB=Angiotensin receptor blockers, LMWH=Low molecular weight heparin, SSRIs=Selective serotonin reuptake inhibitors, AUC=Area under the curve. Risk category C, needs monitoring, Risk category D, needs therapy modification

Table 2: Variable renal dosing of canagliflozin

GFR	>60	300 mg/day
GFR	<60 and >45	100 mg/day
GFR	<45	Not indicated

GFR=Glomerular filtration rate

principles should include both evidence-based practices as well as logical empiricism, based on the experience of clinicians.[32] A continuous need is felt to treat diabetes in a wider horizon, keeping in view the various social and behavioral aspects associated with it.[33] However, such practices need time and more evidence-based studies, especially in critically ill and elderly diabetic surgical patients.

CONCLUSION

Canagliflozin could accentuate side effect profile, if its dose is not adjusted to renal function. Also given the tendency of canagliflozin to decrease blood pressure, it might be prudent to avoid its use in patients with CHF, until further clinical trials are available to refine the indications further. Given the high incidence of genital mycotic infection it might be prudent to avoid the use of canagliflozin in the elderly, who have a tendency for recurrent UTI or genital mycotic infections.

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