International Journal of Diabetes Mellitus 2 (2010) 125–126

Contents lists available at ScienceDirect

International Journal of Diabetes Mellitus

journal homepage: www.elsevier.com/locate/ijdm

Brief Communication

The kidneys as an emerging target for the treatment of diabetes mellitus: What we know, thought we knew and hope to gain

Mohamed H. Ahmed *

Chemical Pathology Department, Southampton University Hospital NHS Trust, Southampton SO16 6YD, UK

ARTICLE INFO

Article history:
Received 6 February 2010
Accepted 10 May 2010

Keywords:
Kidney
Diabetes mellitus
SGLT2

ABSTRACT

Glucose filtered by kidneys is reabsorbed into the proximal tubule through the sodium-coupled glucose co-transporter (SGLT2). This promotes urinary excretion of glucose and results in lowering of plasma glucose level. Administration of agents (e.g. dapagliflozin) that inhibits SGLT2 transporter have shown to be associated with improvement in hyperglycaemia without clinically persistent electrolytes disturbances or change in osmolarity. This may suggest that administration of dapagliflozin is effective and safe as treatment for hyperglycaemia. Ongoing clinical trials will reveal the potential benefit and safety of SGLT2 inhibitors as part of the therapy of type 2 diabetes.

1. Introduction

The kidneys reabsorb 99% of plasma glucose that filters through tubules in normal individuals via mechanisms independent of insulin. It is estimated that the filter load of glucose is 180 mg/day, and only 500 mg of glucose is excreted in urine during the day. In the majority of healthy individuals glucose is not detectable in urine. When the capacity of glucose reabsorption has been exceeded, the surplus glucose is excreted in the urine, and this leads to glucosuria. In normal individuals, the maximum transport rate (Tm) for glucose in kidneys is reached at blood glucose concentration around 200 mg/Dl (11 mmol/L) [1]. Generally speaking, the transport of glucose across cell membranes in different parts of our body is achieved by the facilitative glucose transporters (GLUTS) and sodium–glucose co-transporters (SGLTs – SGLT-1 in the intestine and SGLT-2 in the kidney) [2]. Around 90% of glucose reabsorption in the kidney is achieved by SGLT-2 which is located in the brush border membrane of the first segment of the proximal tubule [2]. Thus, it is not surprising that the Tm of glucose in the kidney is directly under the influence of SGLT-2. There was concern about the safety of agents that inhibit SGLT-2 and this appeared not to be relevant. Familial renal glucosuria is inherited defect in SGLT-2 but individuals with this condition have normal renal function without other complications and is regarded as benign condition [3].

2. Sodium–glucose co-transporters (SGLT-2 inhibitors) and diabetes

Recently, dapagliflozin (due to biochemical structure it can be taken orally in unmodified form an advantage over other SGLT-2 inhibitors) has been shown to be a highly selective inhibitor for SGLT-2. Dapagliflozin is a potent and selective inhibitor of SGLT-2, with 1200-fold greater selectivity for SGLT-2 than SGLT-1 [3]. Administration of SGLT-2 inhibitors in normal and Zuker Diabetic Fatty rats (ZDF) have been shown to be associated with a dose-dependent increase in glucosuria and decrease in fasting and postprandial glucose and a glycated haemoglobin levels. Importantly, the administration of SGLT-2 inhibitors was associated with significant improvements in insulin resistance and, hypertriglyceridaemia without body weight gain in diabetic rats [4–7]. In healthy adult volunteers, maximal inhibition of glucose reabsorption by dapaglifozin has been achieved at a dose of 20 mg, with a terminal half life of around 17 h, with a stable plasma level of over 2 weeks (ideal for once daily administration). Dapaglifozin availability only changes slightly when taken with foods and mainly excreted in urine as glucuronide [8].

The potential anti-diabetic effect of SGLT-2 inhibitors is currently under considerable investigation, and has reached the level of clinical trials. Komoroski et al. administered dapagliflozin to type 2 diabetic individuals for 14 days in a randomized study to four treatment groups receiving daily oral doses of 5-, 25-, or 100-mg doses of dapagliflozin or placebo. Significant reductions in fasting serum glucose were observed on day 2 with 100 mg dapagliflozin (−9.3%, $P < 0.001$), and dose-dependent reductions were observed on day 13 with the 5-mg (−11.7%; $P < 0.05$),

* Present address: Chemical Pathology Department, Mail Point 6 – Level D, South Academic Block, Southampton University Hospitals NHS Trust, Southampton SO16 6YD, UK.
E-mail address: elziber@yahoo.com

1877-5934 © 2010 *International Journal of Diabetes Mellitus*. Published by Elsevier Ltd. Open access under CC BY-NC-ND license.
doi:10.1016/j.ijdm.2010.05.006

25 mg (−13.3%; $P < 0.05$), and 100 mg (−21.8%; $P < 0.0001$) doses as compared with the placebo. Significant improvements in oral glucose tolerance test were observed with all doses on days 2 and 13 ($P < 0.001$ as compared with the placebo). On day 14, urine glucose values were 36.6, 70.1, and 69.9 g/day for the 5-, 25-, and 100-mg doses (as compared with no change for placebo), which were slightly lower than those on day 1. This was attributed to the decrease in filtered glucose load following improved glycemic control [9]. Interestingly the administration of dapaglifozin on a chronic basis is also associated with a favourable metabolic outcome. List et al. showed that administration of dapaglifozin for 12 weeks in type 2 diabetic individuals was associated with induced moderate glucosuria (52–85 g urinary glucose/day) and significant glycemic improvements versus placebo (A1C −0.55 to −0.90% and fasting plasma glucose −16 to −31 mg/dl). Weight loss change versus placebo was −1.3 to −2.0 kg. The authors concluded that dapagliflozin improved hyperglycaemia, and facilitates weight loss in type 2 diabetic patients by inducing controlled glucosuria, with a urinary loss of approximately 200–300 kcal/day without alteration in renal function [10]. Importantly, Wilding et al. showed that SGLT-2 inhibition can improve glycaemic control and weight in individuals with diabetes that is poorly controlled with high insulin doses and oral insulin sensitizer therapy, despite a 50% insulin dose reduction [11].

In summary, the administration of SLGT-2 inhibitors appears to induce glucosuria and significantly improves glycaemic control in patients with type 2 diabetes without risk of severe hypoglycaemia. Hypertension is known to be very common among diabetic individuals and may be diagnosed many years before diabetes. It was postulated that SGLT-2 inhibitors may have a diuretic-like action. In addition to treating hypertension SGLT-2 inhibitors may be favourable option with administration of glitazones which are known to cause fluid retention. Weight reduction achieved with an administration of SGLT-2 for 12 weeks may raise hopes in horizon but not before establishing whether administration of such agents may increase the risk of genital fungal infections. One potential benefit we all hope to gain from SGLT-2 inhibitors in addition to improving glycaemic control is whether they will protect against diabetic nephropathy. Currently, we probably all agree that it is too early to discuss how SGLT-2 inhibitors may modulate cardiovascular disease. Importantly, the intensive glycaemia control intervention used in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was associated with increased mortality and increased rates of severe hypoglycaemia. The ACCORD trial demonstrated that patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control [12]. The main concern with fasting Ramadan and the use of insulin and antidiabetic medication is an association with high risk of hypoglycaemia [13]. The population based Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study conducted in 13 Islamic countries showed that 43% of type1 diabetes and 79% of type 2 fast during Ramadan [14]. In view of the absence of risk of hypoglycaemia with SGLT-2 inhibitors, it is very tempting to postulate that these agents may provide a promising new approach in treating diabetes during the fasting month of Ramadan. Importantly, administration of dapagliflozin for 12 weeks has shown improvement in hyperglycaemia without clinically persistent electrolytes disturbances or change in osmolarity [10].

3. Conclusion

In summary administration of SLGT-2 inhibitors appears to induce glucosuria and significantly improves glycaemic control in patients with type 2 diabetes without significant risk of severe hypoglycaemia, changes in renal function or plasma electrolytes disturbances. Taken together, this may suggest that SGLT-2 inhibitors may emerge as potential anti-diabetic agents during Ramadan. It is not yet established whether administration of such agents may increase the risk of genital fungal infections. Therefore, it is possible to suggest that a clinical trial designed to investigate the potential of SGLT-2 inhibitors for optimizing glycaemic control in diabetic population during Ramadan is now warranted. Perhaps this could be an important gain from this new anti-diabetic medication.

References

[1] Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. Diabetes Care 2001;24(2):382–91.
[2] Wood IS, Trayhurn P. Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. Br J Nutr 2003;89(1):3–9.
[3] Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. J Am Soc Nephrol 2003;14(11):2873–82.
[4] Han S, Hagan DL, Taylor JR, Xin L, Meng W, Biller SA, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes 2008;57(6):1723–9.
[5] Fujimori Y, Katsuno K, Ojima K, Nakashima I, Nakano S, Ishikawa-Takemura Y, et al. Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats. Eur J Pharmacol 2009;609(1–3):148–54.
[6] Fujimori Y, Katsuno K, Nakashima I, Ishikawa-Takemura Y, Fujikura H, Isaji M. Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. J Pharmacol Exp Ther 2008;327(1):268–76.
[7] Oku A, Ueta K, Nawano M, Arakawa K, Kano-Ishihara T, Matsumoto M, et al. Antidiabetic effect of T-1095, an inhibitor of Na(+)-glucose cotransporter, in neonatally streptozotocin-treated rats. Eur J Pharmacol 2000;391(1–2):183–92.
[8] Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther 2009;85(5):520–6.
[9] Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther 2009;85(5):513–9.
[10] List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium–glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32(4):650–7.
[11] Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009;32(9):1656–62.
[12] Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909.
[13] Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, et al. Recommendations for management of diabetes during Ramadan. Diabetes Care 2005;28(9):2305–11.
[14] Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004;27(10):2306–11.