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Clinical Evaluation of Dapagliflozin in Patients with Poor Glycaemic Control in the Routine Clinical Setting

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Abstract

Background: Published clinical trials of SGLT2 inhibitors have typically recruited participants with modest elevations of HbA1c. Our aim was to evaluate the efficacy of dapagliflozin in patients with uncontrolled glycaemia in a routine clinic setting where patients are taking a range of other therapies.

Methods: A prospective observational evaluation over six months. Dapagliflozin was added to concomitant medications including insulin and glucagon like peptide-1 (GLP-1) agonists. Clinical outcomes were examined in patients with a baseline HbA1c ≥ 9.5% (80 mmol/mol) and an HbA1c<9.5% (80 mmol/mol).

Results: Data was available on 166 patients (65 HbA1c<9.5%; 101 HbA1c ≥ 9.5%). All showed significant reductions in HbA1c, body weight, blood pressure and insulin dose. Those with an HbA1c ≥ 9.5% showed greater reduction in HbA1c (10.8% to 9.3% [94.8 to 78.3 mmol/mol]) than those with an HbA1c<9.5% (8.6 to 8.1% [70.6 to 65.1 mmol/mol]), P<0.001. Those with HbA1c<9.5% had a greater mean weight reduction (104.0 to 100.3 kg v 104.3 to 102.5 kg, P<0.001), which was associated with greater reduction in insulin dose (102 to 83 U/day v 91 to 84 U/day, P<0.001). Reductions in all concomitant medications occurred.

Conclusion: Within our routine practice, dapagliflozin was associated with a greater reduction in HbA1c in patients with worse glycaemic control.

Keywords: Dapagliflozin; HBA1c; Poor glycaemic control

Introduction

The sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral anti-diabetic medication, which inhibit renal glucose reabsorption. In a healthy individual, approximately 180 g of glucose is filtered and reabsorbed by the kidney each day. Approximately 90% of glucose reabsorption is mediated by SGLT2, located in the proximal tubule of the kidney and the remaining 10% by the sodium-glucose co-transporter 1 (SGLT1) [1]. In a person with poorly controlled diabetes, SGLT2 is up-regulated, leading to increased renal glucose reabsorption which contributes to chronic hyperglycaemia [2,3]. SGLT2 inhibitors lead to increased urinary glucose excretion with resulting lower blood glucose concentration and net calorie loss [4]. This effect is dependent on glomerular filtration rate and plasma glucose concentration but is independent of insulin [4]. Dapagliflozin, the first selective SGLT2 inhibitor, gained approval by the European Medicines Agency in November 2012. In the UK, dapagliflozin is recommended by the National Institute of Heath and Clinical Excellence (NICE) as monotherapy or in combination with other anti-diabetic medications including insulin in Type 2 diabetes [5]. Pre-registration randomised control trials have demonstrated that dapagliflozin improves glycaemic control and reduces body weight and blood pressure when used as monotherapy [6], with other oral hypoglycaemic agents [7-10] or insulin [11]. Clinical trial protocols have typically recruited participants with a modest elevation of HbA1c such that the mean baseline HbA1c is in the range of 7.7%-8.57% [6,8-11]. These trial participants do not reflect the full range of glycaemic control seen in the diabetes population. There is little published experience relating to the effectiveness of dapagliflozin in poorly controlled patients. A preliminary analysis using subgroup data from five phase 3 trials (n=139) suggests that dapagliflozin is associated with greater glucose reduction in participants with baseline HbA1c ≥ 9% [12]. The greatest effect was seen in treatment naïve patients with a short duration of diabetes. Our aim was to investigate the efficacy of dapagliflozin in patients with the worst glycaemic control in a routine clinical setting.

Methods

Subjects

We conducted a prospective observational audit in two secondary care hospital diabetes clinics. Dapagliflozin was added to concomitant diabetes medications including insulin and glucagon like peptide-1 (GLP-1) receptor agonists as part of routine physician-led care. Consecutive patients with type 2 diabetes initiated on dapagliflozin from October 2013 to December 2014 were included if they had attended for follow-up assessment. Data were collected on patient demographics, the duration of diabetes, concomitant anti-diabetic medications, body weight, body mass index (BMI), blood pressure and HbA1c before and after dapagliflozin treatment. We compared the effects of dapagliflozin in patients with poor control using an HbA1c value ≥ 80 mmol/mol (9.5%) to define patients with the poorest glycaemic control. This is a level above which physicians would usually be considering insulin therapy rather than additional oral hypoglycaemic agents. The American Diabetes Association (ADA) and

in the UK the National Institute for Health and Care Excellence (NICE) recommend to consider insulin therapy if HbA1c>9% [13,14].

Statistical analysis

Statistical analysis was performed using SPSS (version 22, SPSS Inc., Chicago). Results for continuous variables are presented as mean and standard deviation. Baseline parameters in the two groups were compared by t-test test for continuous variables or chi-square test for categorical variables. The effects of dapagliflozin in patients with baseline HbA1c ≥ 9.5% (80 mmol/mol) were compared with those with baseline HbA1c<9.5% (80 mmol/mol) using repeated measures analysis of variance. Change in each group over time was tested separately if the interaction was significant. A P-value ≤ 0.05 was considered statistically significant.

Ethical consideration

This study was designed as a clinical audit of routine clinical practice to improve patient management. Therefore, this study did not require ethical committee review.

Results

Patients and discontinuations

We identified 187 patients who had been initiated on dapagliflozin and attended ≥ 1 clinic follow-up visit. Twenty-one patients discontinued dapagliflozin. Data is presented on the remaining 166 patients. The reasons for discontinuation included candida infection (3 patients), urinary tract infection (1), polyuria/polydipsia (2), pregnancy (1), myocardial infarction (1), a reduction in estimated glomerular filtration rate (1), campylobacter infection (1), bariatric surgery (1) and non-specific reasons in the remainder.

Patient sample

At baseline, the mean age of the 166 patients was 57.8 ± 9.4 years and duration of diabetes 11.1 ± 6.5 years. Most (99%) were white Caucasian. One hundred and eleven (64%) were male. The characteristics of the two groups (HbA1c ≥ 9.5% or <9.5%) at initiation of dapagliflozin are shown in table 1. There were no significant differences in baseline parameters between the groups and the baseline eGFR was >60 ml/min/1.73m^2 (by MDRD equation) in all. The duration of treatment with dapagliflozin was 6.3 ± 2.6 months.

Efficacy in the whole group

In all the patients grouped together, body weight reduced from 104.2 ± 18.2 to 101.6 ± 18.3 kg (P<0.001), BMI from 35.5 ± 5.9 to 34.5 ± 5.9 kg/m^2 (P<0.001), HbA1c from 9.95 ± 1.42 (85.5 ± 12.2 mmol/mol) to 8.84 ± 1.49% (73.3 ± 12.4 mmol/mol), P<0.001 with 21% of patients receiving dapagliflozin achieving a HbA1c ≤ 7.5% (58 mmol/mol). Mean systolic blood pressure (SBP) decreased from 138.7 ± 17.7 to 134.4 ± 16.9 mmHg (P=0.002). Mean diastolic blood pressure (DBP) decreased from 78.7 ± 11.5 to 75.7 ± 9.8 mmHg (P=0.001).

Effect of dapagliflozin therapy on concomitant medications

One hundred and eleven patients (67%) were receiving insulin therapy. Total daily insulin requirement decreased from 95.4 ± 55.5 to 83.4 ± 44.8 units (P<0.001). Forty-two patients (25%) were treated with GLP-1 receptor agonists. Seven of the 42 were able to discontinue GLP-1 agonist therapy. The number of patients taking a sulphonylurea decreased from 49 to 39; DPP-4 inhibitor treatment from 19 patients to 11; and pioglitazone from 7 to 2. There were 135 patients taking metformin at baseline and 134 at follow-up. The mean dose of metformin did not change (Table 1).

Efficacy in patients with baseline HbA1c ≥ 9.5% (80 mmol/mol) versus those with baseline HbA1c <9.5% (80 mmol/mol)

At baseline the characteristics of both groups were similar (Table 1). Mean changes from baseline in HbA1c, body weight, blood pressure and daily insulin requirement are shown in table 2. In the group with a HbA1c ≥ 9.5% the mean HbA1c decreased from 10.83% (95.1 mmol/mol) to 9.30% (78.3 mmol/mol) whereas in those with a HbA1c<9.5% (80 mmol/mol), the mean HbA1c decreased from 8.60% (70.6 mmol/mol) to 8.13% (65.4 mmol/mol). The ANOVA showed an interaction (P<0.001) indicating significantly greater response in patients with poorest glycaemic control. Fifty-four patients had a clinically insignificant reduction in HbA1c (<0.5%). These consisted of 33 (33 of 65:51%) in the group with HbA1c<9.5% and 21 (21 of 101: 21%) in the group with an HBA1c ≥ 9.5%.

With respect to body weight the reverse association was observed. Weight decreased from 104.3 to 102.5 kg in the HBA1c ≥ 9.5% group

	Patients with HbA1c<9.5% (n=65)	Patients with HbA1c ≥ 9.5% (n=101)
Male (n (%)) n=166	45 (69)	62 (61)
Age (years) n=166	58.6 ± 10.8	57.3 ± 8.5
Duration of diabetes (years) n=137	11.7 ± 7.1	10.7 ± 6.1
Weight (kg) n=163	104.0 ± 17.6	104.3 ± 18.7
BMI (kg/m^2) n=161	34.5 ± 5.4	36.1 ± 6.1
HbA1c (%) (mmol/mol) n=166	8.60 ± 0.58 70.6 ± 4.8	10.83 ± 1.07 95.1 ± 9.4
SBP (mmHg) n=157	137.9 ± 17.2	139.2 ± 18.0
DBP (mmHg) n=157	79.1 ± 12.7	78.5 ± 10.7
Insulin (n (%))	42 (65)	69 (68)
Insulin TDD (IU) n=111	102.1 ± 50.3	91.3 ± 58.5
GLP-1 Therapy (n (%)) n=41	17 (25)	25 (25)
Metformin (n (%)) n=134	48 (74)	86 (85)
Metformin TDD (mg) n=134	2022 ± 657	2065 ± 583
Duration of treatment (months) n=166	6.8 ± 3.0	6.0 ± 2.8

Table 1: Patient characteristics grouped by degree of glycaemic control at initiation of dapagliflozin

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TDD: TOTAL daily dose; GLP1: Glucagon like peptide 1.

None of the parameters show significant difference between the groups (except HbA1c)

	Patients with HbA1c <9.5 (n=65)	Patients with HbA1c ≥ 9.5 (n=101)
HbA1c (%)		
Baseline ± SD	8.60 ± 0.58	10.83 ± 1.07
Change (95% CI)	-0.46 (-0.21, -0.72)	-1.53(-1.23, -1.83)
P	0.001	<0.001
Weight (kg)		
Baseline ± SD	104.0 ± 17.6	104.3 ± 18.7
Change (95% CI)	-3.7(-2.7, - 4.7)	-1.8(-1.1, -2.4)
P	<0.001	<0.001
BMI (kg/m^2)		
Baseline ± SD	34.5 ± 5.4	36.1 ± 6.1
Change (95% CI)	-1.31(-0.97, -1.66)	-0.82(-0.56, -1.09)
P	<0.001	<0.001
SBP (mmHg)		
Baseline ± SD	137.9 ± 17.2	139.2 ± 18.0
Change (95% CI)	-5.4(-1.1, -9.7)	-3.5(-0.02, -7.0)
P	0.002	
DBP (mmHg)		
Baseline ± SD	79.1 ± 12.7	78.5 ± 10.7
Change (95% CI)	-3.9(-0.4, -7.4)	-2.6(-0.5, -4.7)
P	= 0.001	
Insulin TDD (IU)	n=42	n=69
Baseline ± SD	102.1 ± 50.3	91.3 ± 58.5
Change(95% CI)	-19.6(-10.1, -29.1)	-7.0(-1.2, -12.8)
P	<0.001	0.021

Table 2: Mean changes in efficacy parameters in those with baseline HbA1c<9.5% (80 mmol/mol) & those with baseline HbA1c ≥ 9.5% (80 mmol/mol)

BMI: Body mass index; SBP: Systolic blood pressure.

The changes in HbA1c, body weight and BMI with dapagliflozin were different between the two glycaemic control groups (interactions significant) but not in the case of SBP and DBP where similar reductions were seen.

compared to 104.0 to 100.3 kg in the group with HbA1c<9.5% (interaction P=0.001). As expected the same association was observed for BMI with a decrease from 36.1 to 35.3 in the HBA1c ≥ 9.5% compared to 34.5 to 33.1 in the group with a HbA1c<9.5% (interaction P=0.028). The reductions in SBP and DBP were similar between the two groups (interactions not significant). The insulin total daily dose decreased from 91 to 84 U/day in the HBA1c ≥ 9.5% group but there was a greater reduction from 102 to 83 U/day in the HBA1c<9.5% group (interaction: P=0.017).

Discussion

Previous phase 3 clinical trials have shown that dapagliflozin is effective in reducing HbA1c as monotherapy (-0.89%) [6]; as add-on to metformin (-0.78%) [10]; as triple therapy with add-on to metformin and sulphonylurea (-0.69%) [9]; and as add-on to insulin (-0.96%) [11]. In our routine clinical evaluation we observed a greater mean reduction of 1.11% (12 mmol/mol) (P<0.001) for the whole group. Of note, our patient sample had a higher baseline HbA1c of 9.95 ± 1.42% (85.5 ± 12.2 mmol/mol) compared to those recruited into published phase 3 clinical trials with dapagliflozin. We observed that the efficacy of dapagliflozin in reducing HbA1c was significantly greater in those patients with higher baseline HbA1c ≥ 9.5%. This is consistent with subgroup analysis from trials [6,9,12] and data from clinical practice [15]. The efficacy of dapagliflozin on glucose control appears to be associated with baseline blood glucose levels and renal function [4]. Thus, unlike other oral agents, dapagliflozin is an option for the treatment of more poorly controlled patients and may be an alternative to starting or increasing insulin therapy.

Twenty-one patients with a HbA1c ≥ 9.5% showed no clinically significant effect with a reduction in HbA1c of less than 0.5%. It is possible these patients were non compliant with therapy, particularly since SGLT2 inhibitors are not without unwanted effects. Alternatively, perhaps these patients did not benefit from the reduction in glucose load that the increased glycosuria achieves, and therefore were truly insulin dependent, a judgement that is often difficult to make in the clinic. These results may be related to the design of this observational study and associated limitations when compared to a randomised, placebo-controlled prospective study. Out patients had a relatively long duration of recognised diabetes (11 years), which may be associated with a greater chance of beta-cell dysfunction. Nevertheless, it does seem that the majority of our poorly controlled type 2 patients need a reduction in glucose load to achieve better HbA1c, and this is achieved by SGLT2 inhibition. The response to SGLT2 therapy may assist in the identification of genuinely insulin dependent type 2 diabetic patients.

SGLT2 inhibitors generate a net loss of 200-300 kilocalories per day as urinary glucose and have produced weight loss of between 2.1-3.2 kg in clinical trials [6,10,11,16]. In addition, the osmotic diuresis and natriuretic effect of SGLT2 inhibition has been associated with a clinically significant reduction in blood pressure. We observed similar significant reductions in weight, BMI and blood pressure. Greater reduction in body weight and BMI occurred in the lower HbA1c group and was associated with a greater reduction in insulin dose.

A previous clinic-based analysis has also shown that dapagliflozin is associated with a reduction in the need for concomitant diabetes medication [15]. Within our study, there were no significant changes in metformin total daily dose, but 20% of patients treated with a sulfonylurea and 17% of those treated with a GLP-1 agonist were able to discontinue these medications. The total daily insulin dose decreased by 11.7 units/day. Thus in routine clinical practice, significant reductions in HbA1c is achieved despite reductions in other diabetes medications. A reduction in daily insulin dose is likely to make it easier for obese patients to lose weight. Reductions in weight and blood pressure may translate into improved long-term outcome. These changes and reductions in medications are well appreciated by patients and have additional cost benefits. We observed a low prevalence of reported genital and urinary tract infection, leading to discontinuation of therapy. Phase 3 clinical trials have reported variable rates from <1% to 8-9% [17]. It seems likely that poorly controlled patients will have significant glycosuria prior to SGLT2 treatment such that this therapy will make little difference in this group.

In summary, when used in routine clinical practice, dapagliflozin has a greater efficacy when used in patients with a HbA1c ≥ 9.5%. This has not been demonstrated well in the published phase 3 trials available to date. We also observed significant reductions in concomitant medicine use including insulin and GLP-1 agonists with a low discontinuation rate of treatment.

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Disclosures

The authors declare no conflict of interest, nor disclosures associated with this manuscript. This study was conceived and conducted independently of the companies that manufacture and market dapagliflozin.

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