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Diabetes, Obesity and Metabolism 2016.

Switching from sulphonylurea to a sodium–glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia

The aim of the present study was to assess the hypoglycaemia risk and safety of dapagliflozin compared with sulphonylurea during the fasting month of Ramadan. In this 12-week, randomized, open-label, two-arm parallel group study, 110 patients with type 2 diabetes who were receiving sulphonylurea and metformin were randomized either to receive 10 mg (n = 58) of dapagliflozin daily or to continue receiving sulphonylurea (n = 52). The primary outcome was to compare the effects of dapagliflozin and sulphonylurea on the proportions of patients with at least one episode of hypoglycaemia during Ramadan, as well as to assess the safety of dapagliflozin when used to treat patients observing Ramadan. A lower proportion of patients had reported or documented hypoglycaemia in the dapagliflozin group than in the sulphonylurea group: 4 (6.9%) versus 15 (28.8%); p = 0.002. The relative risk of any reported or documented hypoglycaemia in the 4th week of Ramadan was significantly lower in the dapagliflozin group: RR=0.24, 95%CI: 0.09, 0.68; p=0.002. No significance differences were observed between the two groups regarding postural hypotension (13.8 vs 3.8%; p = 0.210) or urinary tract infections (10.3 vs 3.8%; p = 0.277). In conclusion, fewer patients exhibited hypoglycaemia in the dapagliflozin group than in the sulphonylurea group.

Keywords: dapagliflozin, hypoglycaemia, SGLT2 inhibitor, sulphonylurea

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RESEARCH LETTER

Introduction

The population-based Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that patients with type 2 diabetes mellitus (T2DM) who fasted during the month of Ramadan had a 7.5 times higher risk of developing hypoglycaemia [1,2], and the risk varied according to oral antidiabetic agent. The UK VECTOR study revealed that 41.7% of patients receiving sulphonylurea developed hypoglycaemia [3]. No events were reported in patients receiving vildagliptin [3]. It is therefore important to choose agents that can reduce the risk of hypoglycaemia during the fasting period [1,4,5].

Dapagliflozin, a novel glucose-lowering medication, is less likely to cause hypoglycaemia because it acts independently of insulin. It is a selective sodium-glucose co-transporter-2 inhibitor that blocks the reabsorption of glucose in the proximal tubule of the kidneys and promotes excretion of excess glucose in the urine [4,6–8].

The use of dapagliflozin and the risk of hypoglycaemia in patients with T2DM during the fasting month of Ramadan has never been reported.

The aim of the present study was to assess the risk of hypoglycaemia associated with the use of dapagliflozin compared with that of sulphonylurea in patients with T2DM who fast during Ramadan.

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Materials and Methods

Study Design

This was a 12-week (June to September 2014), randomized, open-label, two-arm, parallel-group study conducted in specialist endocrine and primary care clinics in Malaysia. The study was approved by the local institutional review boards. Informed patient consent was obtained.

Study Patients

Eligible patients with T2DM, aged 18–65 years, who intended to fast during Ramadan were recruited to the study. Patients with glycated haemoglobin (HbA1c) levels of 7–10.5%, who were treated with stable doses of sulphonylurea (glimepiride, gliclazide or glibenclamide) and metformin (>1500 mg per day) during the 60 days before screening were included. Patients who were pregnant or breastfeeding as well as those who had impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m^2), recurrent urinary tract infections, alanine transaminase levels >2.5 times the upper normal limit, malignancy, cardiovascular events within the last 90 days, or contraindication for fasting were excluded.

Study Medication, Treatment and Interventions

Of the 4344 patients screened, 325 patients met the eligibility criteria. A total of 119 patients consented to be recruited into

the study (Figure S1, Supporting Information). Patients were randomized at a 1 : 1 ratio using a 'blocked' randomization protocol. Patients in the intervention arm received 10 mg of dapagliflozin daily, and the control group continued to receive sulphonylurea, with each group receiving background metformin therapy. The treatment allocation was revealed to the study investigator and to patients after randomization (Figure S2, Supporting Information).

Demographic information, clinical data (hypoglycaemia and adverse events data), and blood samples were collected at each patient visit (baseline, 4th week of Ramadan, and 6 weeks post Ramadan). Patients were advised to document their blood glucose at five different times per week.

Endpoints and Assessments

The primary endpoint was the proportion of patients with any reported symptomatic or documented hypoglycaemia. Reported symptomatic hypoglycaemia was defined as typical hypoglycaemia symptoms not accompanied by plasma glucose determinations. Documented hypoglycaemia included asymptomatic hypoglycaemia and symptomatic hypoglycaemia. Asymptomatic hypoglycaemia was defined as an event not accompanied by typical symptoms but with a measured plasma glucose concentration of <3.9 mmol/l [9]. Documented symptomatic hypoglycaemia was defined as typical hypoglycaemia symptoms accompanied by a measured plasma glucose concentration of <3.9 mmol/l [9].

The secondary endpoints included adverse events and glycaemic variables.

Statistical Analysis

Continuous variables are presented as means (standard deviation) or medians (interquartile range). Comparisons between groups were analysed with either an independent t-test or a Mann–Whitney U-test. Categorical variables are presented as proportions and compared using the chi-squared test. A sub-analysis of documented hypoglycaemia was performed using McNemar's test. Glycaemic variables were analysed using repeated measures analysis of variance in a general linear model. Data were analysed using IBM SPSS Statistics Version 22.

Results

Demographic and Baseline Characteristics

The 110 patients included in the final analysis were randomized to receive dapagliflozin (n = 58) or to continue receiving sulphonylurea (n = 52). Nine patients were excluded (Figure S1, Supporting Information). The baseline demographic and clinical characteristics, except systolic blood pressure, were similar in both groups (Table 1). In addition, 24.1% (n = 14) of the patients in the dapagliflozin group and 9.6% (n = 5) in the sulphonylurea group reported symptomatic hypoglycaemia 1 month prior to randomization into the respective drug groups.

Hypoglycaemia

Within the dapagliflozin group, a significant reduction in reported symptomatic hypoglycaemia was observed, from 24.1% at baseline to 3.4% in the 4th week of Ramadan ($p = 0.004$). No significant changes in hypoglycaemia episodes were observed in the sulphonylurea group (Table 2). The relative risk of any reported or documented hypoglycaemia in the treatment group was significantly lower than that in the control group: relative risk 0.24, 95% confidence interval 0.09, 0.68 ($p = 0.002$; Table S1, Supporting Information). Furthermore, a lower proportion of patients with documented hypoglycaemia was found in the dapagliflozin group than in the sulphonylurea group: 7.3 versus 27.1% ($p = 0.007$). None of the patients in either group experienced major hypoglycaemia requiring hospital admission.

Fewer hypoglycaemic events had occurred in the dapagliflozin group than in the sulphonylurea group by the 4th week of Ramadan (5 vs 20 events; $p = 0.005$) and 6 weeks post Ramadan (1 vs 13 events; $p = 0.016$).

Adverse Events

No differences in overall adverse events were observed (Table S2, Supporting Information). Hypoglycaemia was the most common adverse event. Other significant adverse events reported in the dapagliflozin group but not found in the sulphonylurea group included polyuria (3.5%), thirst (3.5%), body itching (1.7%), skin dryness (1.7%), nausea (1.7%) and lethargy (1.7%). In addition, more patients presented with postural hypotension (13.8 vs 5.8%; $p = 0.210$) and urinary tract infections (10.3 vs 3.8%; $p = 0.277$) in the dapagliflozin group, but the difference was not statistically significant. One serious adverse event was reported in each group.

Glycaemic Variables

The mean change in HbA1c was a reduction of 0.05% in the dapagliflozin group and 0.32% in the sulphonylurea group [$F(1,100) = 1.878$, $p = 0.174$; Table S3, Supporting Information]; however, no significant differences in HbA1c, fasting plasma glucose or fructosamine levels were observed between the groups.

Discussion

To our knowledge, this is the first study to date to assess the safety of dapagliflozin treatment in Muslim patients with T2DM who fast during Ramadan.

This study showed that, in combination with metformin, dapagliflozin was associated with a lower risk of hypoglycaemia than sulphonylurea. The proportions of patients with reported symptomatic hypoglycaemia were 3.4% in the dapagliflozin group and 19.2% in the sulphonylurea group. The relative risk reduction of reported or documented hypoglycaemia was 76% in the 4th week of Ramadan. Additionally, a greater reduction in reported symptomatic hypoglycaemia, from 24.1 to 3.4%, was observed when patients were switched from sulphonylurea

Table 1. Patient demographic, clinical and laboratory characteristics at baseline.

	Dapagliflozin + metformin, n = 58	Sulphonylurea + metformin, n = 52	p
Age, years	53 (9.1)	56 (9.1)	0.13
Gender, n (%)			
Male	35 (60.3)	31 (59.6)	0.938
Female	23 (39.7)	21 (40.4)	
Clinical characteristics			
Weight, kg	77.5 (13.96)	75.6 (15.35)	0.501†
BMI, kg/m^2	29.9 (4.84)	29.64 (4.44)	0.777†
Systolic blood pressure, mmHg~	141 (129.5, 147.0)	147 (132.0, 158.3)	0.013‡
Diastolic blood pressure, mmHg~	80 (73.8, 85.3)	85 (76.0, 89.0)	0.113‡
Duration of diabetes, years	5.0 (3.0, 9.0)	6.0 (3.0, 10.3)	0.365‡
Comorbidity, n (%)			
Hypertension	39 (67.2)	40 (76.9)	0.26
Dyslipidaemia	49 (84.5)	46 (88.5)	0.544
Obesity	52 (89.7)	45 (86.5)	0.412
Smoking habit	25 (43.1)	17 (32.7)	0.175
Complications, n (%)			
Retinopathy	10 (17.2)	7 (13.5)	0.584
Nephropathy	9 (15.5)	13 (25)	0.214
Peripheral neuropathy	23 (39.7)	15 (28.8)	0.234
Cardiovascular disease	3 (5.2)	3 (5.8)	0.03
Cerebrovascular events	3 (5.2)	3 (5.8)	1.0§
Peripheral vascular disease	0 (0)	1 (19)	0.497§
Laboratory characteristics			
Fasting plasma glucose, mmol/mol	8.1 (2.34)	8.1 (2.27)	0.968†
Fructosamine, µmol/l~	309.5 (285.25, 345.5)	325.5 (291.35, 369.5)	0.17‡
HbA1c, %~	7.7 (7.08, 8.43)	7.6 (6.9, 8.1)	0.367‡
Creatinine, µmol/l	83 (20.2)	86 (21.2)	0.468†
Hypoglycaemia data			
No. of patients with reported symptomatic hypoglycaemia 1 month before Ramadan*	14 (24.1)	5 (9.6)	0.044
No. of reported hypoglycaemic events	25	10	0.054
Hospital admissions as a result of hypoglycaemia	2 (3.4)	2 (3.8)	1.0

BMI, body mass index; HbA1c, glycated haemoglobin; IQR, interquartile range; s.d., standard deviation.
Statistical test used for categorical variables: Pearson's chi-squared test, unless otherwise indicated.
Data are number of patients (%) or mean (sd) unless stated otherwise.
~Median (IQR).
*Level of significance $p < 0.05$ for between-group comparisons.
†Independent sample t-test for continuous data, unless otherwise indicated.
‡Wilcoxon Mann–Whitney test.
§Fisher's exact test.

to dapagliflozin. Unlike insulin secretagogues, which enhance insulin secretion, dapagliflozin blocks glucose reuptake in the proximal tubules in an insulin-independent manner without impeding the counter-regulatory hormones. This leads to a lower risk of hypoglycaemia [7,10,13].

Previous studies have shown that 3.3% of patients who receive dapagliflozin with metformin develop hypoglycaemia, which is similar to the rate found for metformin alone [11]. Another study, by Nauck et al. [6], reported fewer hypoglycaemic events in patients treated with dapagliflozin than in those treated with glipizide in combination with metformin (3.4 vs 39.7%). In the present study, although the risk of hypoglycaemia in the dapagliflozin group was higher (6.9%), it was significantly lower than that of the sulphonylurea group. No major hypoglycaemic events leading to discontinuation of the study occurred.

The present study also showed that the majority of patients in either group did not experience any symptoms of hypoglycaemia. None of the patients in the dapagliflozin group reported any documented symptomatic hypoglycaemia. This could be attributable to mild hypoglycaemia, which does not trigger autonomic symptoms. Another explanation is unawareness of hypoglycaemia, secondary to the previously frequent hypoglycaemia experienced when receiving sulphonylurea.

No difference in overall adverse events was observed between the dapagliflozin and sulphonylurea groups. Although more urinary tract infections were reported in patients receiving dapagliflozin, this condition is not uncommon in patients with diabetes and is resolved with standard medical treatment. The higher rate of circumcision among male Muslims patients may explain the lower risk of genital tract infection (5.3%) in the present study than in another study, by

Table 2. Proportion of patients with hypoglycaemia and number of hypoglycaemic events.

	Dapagliflozin + metformin, n (%)	Sulphonylurea + metformin, n (%)	p
4th week of Ramadan	**n = 58**	**n = 52**	
Proportion of patients with hypoglycaemia			
Any reported symptomatic or documented hypoglycaemia*	4 (6.9)	15 (28.8)	0.002
i) Reported symptomatic hypoglycaemia*	2 (3.4)	10 (19.2)	0.008
ii) Documented hypoglycaemia	4 (7.3)	13 (27.1)	0.007
Symptomatic hypoglycaemia‡	0 (0)	5 (38.5)	
Asymptomatic hypoglycaemia‡	4 (100)	8 (61.5)	
Hypoglycaemic events			
No. of documented hypoglycaemic events†	5	20	0.005
No. of patients experiencing 1 hypoglycaemic event	3	5	
No. of patients experiencing 2 hypoglycaemic events	1	7	
No. of patients experiencing 3 hypoglycaemic events	0	1	
6 weeks post Ramadan	**n = 54**	**n = 50**	
Proportion of patients with hypoglycaemia			
Any reported symptomatic or documented hypoglycaemia*	4 (7.4)	13 (26.0)	0.010
i) Reported symptomatic hypoglycaemia	4 (6.9)	9 (17.3)	0.103
ii) Documented hypoglycaemia	1 (1.9)	7 (15.2)	0.024
Symptomatic hypoglycaemia§	0 (0)	1 (14.3)	
Asymptomatic hypoglycaemia§	1 (100)	6 (85.7)	
Hypoglycaemic events			
No. of documented hypoglycaemic events†	1	13	0.016
No. of patients experiencing 1 hypoglycaemic event	1	3	
No. of patients experiencing 2 hypoglycaemic events	0	2	
No. of patients experiencing 3 hypoglycaemic events	0	2	

*Indicates statistical significance ($p < 0.05$). Data are proportions (%).
Categorical variables analysed using the chi-squared test and numerical variables using †Mann–Whitney test. Documented hypoglycaemia included symptomatic and asymptomatic hypoglycaemia obtained from patient's diary. McNemar's t-test comparing symptomatic vs asymptomatic hypoglycaemia in patients with documented hypoglycaemia at ‡4th week of Ramadan ($p = 0.261$) and §6 weeks post Ramadan ($p = 1.0$).

Bailey et al. [12]. Apart from hypoglycaemia, other adverse events reported in the dapagliflozin group were mild and self-limiting.

Throughout the 12-week study period, a numerically 0.05% reduction in the mean HbA1c level was observed in the dapagliflozin group compared with a 0.32% reduction in the sulphonylurea group ($p = 0.174$). A study by Nauck et al. [6] showed a greater reduction in the HbA1c level in patients receiving sulphonylurea at week 24; however, dapagliflozin proved to be more stable and achieved equivalent efficacy at week 52. Another 4-year study by del Prato et al. [8] reported a lower hypoglycaemia rate as well as more sustained glycaemic control with dapagliflozin.

The results of the present study suggest that switching from sulphonylurea to dapagliflozin is associated with a lower risk of hypoglycaemia while retaining a similar glycaemic efficacy. Thus, this can be considered an alternative approach for preventing hypoglycaemia during the fasting month of Ramadan. Limitations of this study include the lack of data regarding treatment adherence because of the short clinical visit in the 4th week of Ramadan, bias attributable to the unblinded study design and the small sample size used to assess adverse events.

In summary, the present study showed that dapagliflozin was associated with fewer cases of hypoglycaemia and was well tolerated during Ramadan. In addition, there was no difference in glycaemic efficacy between the groups.

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Conflict of Interest

N. A. K. has been a member of the advisory board with AstraZeneca Malaysia. W. J. WS., N. K., S. R., H. O., N. MN., N. M., N. AW. and N. S have no conflict of interest.

W. J. WS., N. M. and N. A. K. participated in the study concept and design. W. J. WS., N. K., S. R., N. S., H. O., N. M. and N. AW. participated in acquisition of data. W. J. WS., N. MN. and N. A. K. participated in the analysis and interpretation of data. W. J. WS., N. MN. and N. A. K contributed to writing and revising the report.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study flow.

Figure S2. Trial profile.

Table S1. Relative risk ratio of different forms of hypoglycaemia.

Table S2. Safety and tolerability of dapagliflozin and sulphonylurea.

Table S3. Mean change in glycaemic variables.

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