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Urinary tract infections in patients with diabetes treated with dapagliflozin ☆,☆☆

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ABSTRACT

Aims: Urinary tract infection is common in patients with type 2 diabetes. Possible causative factors include glucosuria, which is a result of treatment with sodium glucose cotransporter 2 (SGLT2) inhibitors. Dapagliflozin is an investigative SGLT2 inhibitor with demonstrated glycemic benefits in patients with diabetes. Data from dapagliflozin multi-trial safety data were analyzed to clarify the association between glucosuria and urinary tract infection.

Methods: Safety data from 12 randomized, placebo-controlled trials were pooled to evaluate the relationship between glucosuria and urinary tract infection in patients with inadequately controlled diabetes (HbA1c >6.5%–12%). Patients were treated with dapagliflozin (2.5, 5, or 10 mg) or placebo once daily, either as monotherapy or add-on to metformin, insulin, sulfonylurea, or thiazolidinedione for 12–24 weeks. The incidence of clinical diagnoses and events suggestive of urinary tract infection were quantified.

Results: This analysis included 3152 patients who received once-daily dapagliflozin (2.5 mg [$n = 814$], 5 mg [$n = 1145$], or 10 mg [$n = 1193$]) as monotherapy or add-on treatment, and 1393 placebo-treated patients. For dapagliflozin 2.5 mg, 5 mg, 10 mg, and placebo, diagnosed infections were reported in 3.6%, 5.7%, 4.3%, and 3.7%, respectively. Urinary glucose levels, but not the incidence of urinary tract infection, increased progressively with dapagliflozin dosage. Most identified infections were those considered typical for patients with diabetes. Discontinuations due to urinary tract infection were rare: 8 (0.3%) dapagliflozin-treated patients and 1 (0.1%) placebo-treated patient. Most diagnosed infections were mild to moderate and responded to standard antimicrobial treatment.

Conclusions: Treatment of type 2 diabetes with once-daily dapagliflozin 5 or 10 mg is accompanied by a slightly increased risk of urinary tract infection. Infections were generally mild to moderate and clinically manageable. This analysis did not demonstrate a definitive dose relationship between glucosuria and urinary tract infection.

1. Introduction

Urinary tract infection (UTI) is a common occurrence in patients with type 2 diabetes (Boyko, Fihn, Scholes, Abraham, & Monsey, 2005; Donders, 2002; Geerlings, 2008; Goswami et al., 2000; Joshi, Caputo, Weitekamp, & Karchmer, 1999), although a precise cause–effect relationship has not been determined. Multiple factors may be involved, such as hyperglycemia, glucosuria, and neurogenic bladder (Geerlings, 2008; Hoepelman, Meiland, & Geerlings, 2003; Rackley, 2011; Rayfield et al., 1982; Sauerwein, 2002). Hyperglycemia can impede the body's resistance to microorganisms and lead to increased adherence of bacteria to uroepithelial cells (Geerlings, 2008; Rayfield et al., 1982). There are inadequate data quantifying the relationship between the level of glucosuria, bacterial growth in the urine, and incidence of UTI. In an analysis of the growth of *Escherichia coli* in human urine, the growth rate of *E. coli* was enhanced when glucose was added to urine, although very high glucose concentrations resulted in a decreased rate when the urinary pH was not kept constant (Geerlings, Brouwer, Gaastra, Verhoef, & Hoepelman, 1999). In a statistical analysis of a retrospective study of women with diabetes, glucosuria was not identified as a risk factor for UTI (Geerlings et al., 2000a, 2000b).

Glucosuria is of particular interest due to its relationship to an investigational class of antidiabetes therapy that targets sodium glucose cotransporter 2 (SGLT2), the protein that mediates reabsorption of

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most of the glucose filtered by the kidney. SGLT2 inhibitors act independently of insulin secretion or action to reduce glucose reabsorption, thus resulting in increased urinary glucose excretion with a corresponding reduction in blood glucose levels (Ghosh, Ghosh, Chawla, & Jasdanwala, 2011; Rahmoune et al., 2005; Salvatore et al., 2011).

Dapagliflozin is a novel, orally administered, selective, potent SGLT2 inhibitor in development for the treatment of type 2 diabetes (Han et al., 2008; Meng et al., 2008). Dapagliflozin has been studied in patients in placebo-controlled clinical studies as monotherapy, as add-on therapy to other standard antidiabetic treatments, and as first-line combination therapy with metformin (Bailey, Gross, Pieters, Bastien, & List, 2010; Ferrannini, Ramos, Salsali, Tang, & List, 2010; List, Woo, Morales, Tang, & Fiedorek, 2009; Rosenstock, Vico, Wei, Salsali, & List, 2012; Strojek et al., 2011; Wilding et al., 2009; Wilding et al., 2012). In each study, patients who received dapagliflozin achieved significantly greater glycemic control than those who received placebo, and dapagliflozin was generally well tolerated. Data from clinical pharmacology studies demonstrated dose-related increases in glucosuria for doses of 2.5, 5, and 10 mg (Parikh et al., 2011); increases were smaller at doses >10 mg (List, Woo, Morales, Tang, & Fiedorek, 2009). Because its mechanism of action leads to increased urinary glucose excretion, controlled clinical trials of dapagliflozin offer an opportunity to evaluate the relationship between glucosuria and UTI.

2. Subjects, materials and methods

2.1. Clinical trials and patients

Data from 12 randomized, placebo-controlled trials (Appendix 1) were pooled to evaluate the relationship between pharmacologically induced urinary glucose excretion and UTI in patients with type 2 diabetes treated with dapagliflozin. Details regarding the methodologies of these trials are provided in the accompanying article "Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin" (Johnsson et al., 2013). Patients with a history or risk factors for UTI were not excluded from participation in the clinical trials.

All studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and were approved by the institutional review boards or independent ethics committee of each participating center. All patients provided written informed consent to participate in their respective clinical trials.

2.2. Safety signal detection and quantification

Due to the potential for an increased risk in the incidence of UTI associated with treatment-induced glucosuria, a comprehensive approach was undertaken to broaden the potential for detection of any signal indicating an increased risk. Throughout the dapagliflozin clinical trials program, a rigorous effort was made to capture all signs, symptoms and events suggestive of UTI. In addition to spontaneous reports of symptoms by study participants, investigators proactively questioned patients at each visit about symptoms suggestive of UTI (either experienced currently or since the previous study visit). This proactive questioning was designed to address the possibility that patients might not recognize certain symptoms as being relevant. Supplemental case-report forms were provided to obtain more detailed information for assessment.

For the initial analysis, a broad net was generated using a set of 63 prespecified, preferred terms (Appendix 2) from the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 to capture signs and symptoms (eg, dysuria) suggestive of UTI, as well as specific clinical diagnoses. These preferred terms were referred to as "events suggestive of UTI." When a prespecified, preferred term was reported, a case-report questionnaire was completed by the investigator to fully describe the case and the risk factors.

In a second, more specific analysis, 49 prespecified, preferred terms for clinical diagnosis were used to quantify diagnosed UTIs (Appendix 2). To increase the specificity of diagnosis, investigators were also asked to obtain a urine culture to confirm diagnosis in patients with suspected UTI. Study protocol required the drug to be withheld in patients with clinical evidence of pyelonephritis or presumed urosepsis until treatment of the infection was complete and clinical recovery had occurred.

3. Results

3.1. Patients

The population for this analysis included 4545 patients from the 12 clinical trials. Treatment groups included 3152 patients who received once-daily dapagliflozin (2.5 mg [$n = 814$], 5 mg [$n = 1145$], or 10 mg [$n = 1193$]) and 1393 patients who received placebo. These study groups were generally balanced with respect to baseline demographics and disease characteristics (Table 1). Baseline mean HbA1c was 8.1% to 8.4%. More than 85% of patients had BMI ≥ 25 kg/m^2, and >55% had BMI ≥ 30 kg/m^2. A varied range of disease duration (mean 5.3–6.7 years) and progression were represented in the patient population. In dapagliflozin-treated patients, mean exposure ranged from 148.2 to 150.5 days. Mean duration of exposure for those treated with placebo was 149.4 days.

A dose-dependent increase in glucosuria was documented at 24 weeks in this pooled analysis; mean change from baseline in spot fasting urine glucose excretion for placebo, 2.5 mg, 5 mg, and 10 mg was −241.0 mg/dL (SE 36.2), +1480.5 mg/dL (SE 68.6), +2149.9 (SE 66.7), and +2592.3 (SE 65.6), respectively. Where long-term data for glucose excretion were available, levels were consistent with the short-term analysis.

3.2. Events suggestive of UTI

Of the 63 prespecified, preferred MedDRA terms used to capture signs, symptoms, and events suggestive of UTI, 16 were reported in ≥1 patient (Appendix 2 Figure). Greater proportions of patients in the dapagliflozin 5- and 10-mg groups experienced events suggestive of UTI (7.3% and 6.5%, respectively) than did patients in the dapagliflozin 2.5-mg group and the placebo group (4.2% and 4.5%, respectively) (Appendix 3 Figure). Most episodes were mild or moderate in intensity across all treatment groups. These events were more common in women than in men in all treatment groups. Signs, symptoms, and events suggestive of UTI that were reported in ≥1% of women in one or more of the dapagliflozin groups were the diagnosis of UTI, the symptom of dysuria, and the diagnosis of cystitis (Table 2). UTI and cystitis also occurred in ≥1% of women in the placebo group. Dysuria and UTI were reported in ≥1% of men in one or more of the dapagliflozin groups but not in the placebo group.

Urine cultures were obtained in 39% to 50% of dapagliflozin patients and in 50% of placebo patients with events suggestive of UTI. Approximately two thirds of the cultures across all treatment groups were positive; most of the organisms identified were those commonly seen in patients with type 2 diabetes (eg, *E. coli*, *Klebsiella pneumoniae*, and *Proteus*).

To begin to understand the potential risk factors for UTI, incidence rates were determined based on various subgroups, including categories of baseline HbA1c (<8%, ≥8% to <9%, and ≥9%), age (<65 and ≥65 years), gender, and history of recurrent infection (Fig. 1). For all subgroups, there was variation in the background rates of events suggestive of UTI; however, within each subgroup, there was a proportionate increase in incidence for dapagliflozin vs placebo. There