CASE REPORT

Caution advised with dapagliflozin in the setting of male urinary tract outlet obstruction

Victoria Hall,¹ Jason Kwong,² Douglas Johnson,¹ Elif Ilhan Ekinci^{3,4}¹General Medicine, Austin Health, Heidelberg, Victoria, Australia²Infectious Diseases, Austin Health, Heidelberg, Victoria, Australia³Endocrinology, Austin Health, Heidelberg, Victoria, Australia⁴Department of Medicine, Austin Health, The University of Melbourne

Correspondence to

Dr Victoria Hall,
victoria.hall@austin.org.au

Accepted 9 May 2017

SUMMARY

We describe an adverse outcome in a 70-year-old man with type 2 diabetes mellitus treated with sodium–glucose cotransporter type 2 (SGLT2) inhibitor dapagliflozin. SGLT2 inhibitors act in the proximal tubules to prevent glucose reabsorption and induce urinary glucose excretion, they have been associated with increased risk of urinary tract infection (UTI). Our patient presented to hospital with *Escherichia coli* septicaemia with positive urine and blood cultures on the background of two previous UTIs occurring post commencement of dapagliflozin in the community. Renal tract ultrasound in hospital revealed incomplete bladder emptying with evidence of urinary stasis, and a postvoid residual volume of 180 mL. His dapagliflozin was ceased, and he has had no further episodes of UTI. This case suggests there may be an increased risk of UTI in patients prescribed SGLT2 inhibitors who also have evidence of bladder outlet obstruction—caution is advised in the prescribing of SGLT2 inhibitors in this setting.

BACKGROUND

- First observed case in literature of possible increased risk of urinary tract infection (UTI) in the setting of urinary stasis with the sodium–glucose cotransporter type 2 (SGLT2) inhibitor dapagliflozin.
- These novel hypoglycaemic agents are increasingly being prescribed in the community and in hospital—this case report will help to create awareness about this possible adverse effect and therefore to exercise caution prior to prescribing.

CASE PRESENTATION

We describe a potentially preventable adverse outcome in a 70-year-old man with long-standing type 2 diabetes mellitus treated with the sodium–glucose cotransporter type 2 (SGLT2) inhibitor dapagliflozin. Concomitant medications included exenatide and metformin, with evidence of poorly controlled diabetes with recent haemoglobin A1C of 9.0%. He also had hypertension and hypercholesterolaemia, managed on perindopril 5 mg and rosuvastatin 20 mg daily. He gave a 6-month history of lower urinary tract symptoms, including urge incontinence, investigated with a previous ultrasound displaying a raised postvoid residual and trabeculated bladder, indicating the possibility of chronic bladder outlet obstruction. Renal function was normal.

He presented to our hospital with *Escherichia coli* septicaemia with positive urine and blood cultures. This was on the background of two previous separate episodes of urinary tract infection (UTI), both occurring while on maximum dose dapagliflozin (10 mg daily), commenced 1 year prior. Previous to this, the patient did not give a history of UTI. Despite these episodes and the known bladder outlet obstruction, his dapagliflozin had been continued in the community.

INVESTIGATIONS

A renal tract ultrasound was repeated in hospital which again revealed incomplete bladder emptying, evidence of urinary stasis and a postvoid residual volume of 180 mL. Prostate volume was normal.

OUTCOME AND FOLLOW-UP

The dapagliflozin was subsequently ceased and switched to an alternate oral hypoglycaemic. On outpatient follow-up now 1 year later, there have been no further episodes of UTI.

DISCUSSION

Urinary tract infections are commonly seen in patients with type 2 diabetes, the underlying mechanism is not known but may be related to hyperglycaemia, glucosuria and neurogenic bladder.¹ A study conducted by Truzzi *et al*² found that men with a postvoid residual of 180 mL are at high risk of bacteriuria, requiring either pharmacological or surgical intervention to facilitate bladder emptying. Johnsson *et al*³ in their pooled safety data analysis for dapagliflozin investigated the relationship between urinary glucose excretion, dose of dapagliflozin and incidence of UTI. Although urinary glucose excretion levels increased with increased dose of dapagliflozin, incidence of UTI did not.³ Both this study and another large randomised, placebo-controlled trial, however, demonstrated an increase in the risk of UTI in patients treated with dapagliflozin and other SGLT2 inhibitors above and beyond the presence of type 2 diabetes.^{3,4} Monami *et al*⁴ found an increased incidence of UTI in the treatment group with an OR of 1.23 (1.03–1.47), $p=0.02$.⁴ Infections were usually mild to moderate, rarely leading to cessation of dapagliflozin.^{3,4} Pyelonephritis was a rare event occurring at similar frequency in treatment and placebo groups.³ There was one event of urosepsis in the dapagliflozin 10 mg group. Reasons for discontinuation included pyelonephritis and UTI.⁴

CrossMark

To cite: Hall V, Kwong J, Johnson D, *et al*. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-219335

There is no specific mention of exclusion of patients with evidence of chronic bladder outlet obstruction from these trials.^{3,4} Although making up a small proportion of the treatment groups (2.0%–2.8%), there was no clear trend for recurrence of UTI in patients with a history of recurrent UTI with dapagliflozin versus placebo.³

On review of the literature, the effect of dapagliflozin causing an increased incidence of UTI in the setting of lower urinary tract obstruction with urinary stasis has not been studied, nor has urinary obstruction been cited as a reason for discontinuation of SGLT2 inhibitors.^{1,2,4,5} Prescriber information does not regard it as a precaution prior to prescribing.⁵ Further investigation is required to determine whether SGLT2 inhibitor use in

these patients increases the risk of UTI beyond attributable risk to either of these risk factors in isolation.

The temporal association, however, of UTI in our patient with the commencement of the dapagliflozin, and on cessation lack of further episodes, suggests an increased risk in the setting of likely long-standing residual postvoiding urinary volume. Given that both residual urinary volume and dapagliflozin are independent risk factors for UTI, we would recommend using SGLT2 inhibitors with caution in patients with evidence of incomplete bladder emptying.^{1,2}

Contributors VH researched, identified case and wrote the letter. JK helped identify case and edited the letter. DJ helped identify the case and edited the letter. EIE offered advice and edited the letter.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

Learning points

- ▶ In safety trials, dapagliflozin has been shown to cause an increased risk of urinary tract infection (UTI).
- ▶ Our patient did not start having UTI until he was commenced on dapagliflozin. This was in the setting of a long-standing increased postvoid residual. With the literature in mind, we recommend exercising caution in the prescription of SGLT2 inhibitors in patients with proven or suspected urinary tract outlet obstruction due to potential increased risk of UTI.
- ▶ Further investigation is required to determine whether SGLT2 inhibitor use in patients with increased postvoid residual increases the risk of UTI.

REFERENCES

- 1 Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs* 2015;75:33–59.
- 2 Truzzi JC, Almeida FM, Nunes EC, *et al*. Residual urinary volume and urinary tract infection—when are they linked? *J Urol* 2008;180:182–5.
- 3 Johnsson KM, Ptaszynska A, Schmitz B, *et al*. Urinary tract infections in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 2013;27:473–8.
- 4 Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2014;16:457–66.
- 5 Monthly Index of Medical Specialties. Dapagliflozin. 2015 https://www.mimsonline.com.au.acs.hcn.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=Dapagliflozin&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=96850001_2.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow