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Case Report / *Olgu Sunumu*

A Sweet Dream with SGLT2 Inhibitors

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ABSTRACT

Aim: Glucose is an osmotic agent in the peritoneal dialysis fluid (PDF) to absorb water, sodium and other toxins. Glucose absorption from PDF to blood impairs peritoneal dialysis (PD) efficiency and cause glycemic burden. This extra glycemic load leads to poor glycemic control in diabetic dialysis patients with PD program.

Studies have shown sodium-glucose co-transporter (SGLT)-2 expression in peritoneal mesothelial cells. Blockade of peritoneal SGLT reduced blood glucose increment and increased peritoneal glucose retention in mice. In rat models, it was shown that high glucose PDF promotes the peritoneal fibrosis by upregulating the expression of glucose transporter (GLUT) and SGLT, and addition of phlorizin to PDF leads to downregulation of GLUT and SGLT expression and reduced peritoneal degeneration.

Case: According to these information, we want to share our experience of using empagliflozin in a poor glycemic controlled type 2 diabetic patient, who was on PD program for end-stage renal disease.

Result: We hypothesized that if we administer empagliflozin to our patient we can reduce glycemic burden caused by PDF and increase the ultrafiltration volume.

Keywords: *SGLT2 inhibitors, Peritoneal dialysis, Glycemic burden*

SGLT2 İnhibitörleri ile Tatlı Bir Rüya

ÖZ

Amaç: Glukoz; su, sodyum ve diğer toksinleri absorbe için periton diyaliz sıvısında bulunan ozmotik bir ajandır. Periton diyaliz sıvısından kana glukoz emilimi periton diyalizi (PD) verimini bozar ve glisemik yüke neden olur. Bu ekstra glisemik yük, PD programındaki diyabetik diyaliz hastalarında kötü glisemik kontrole yol açar.

Çalışmalar, peritondaki mezotelyal hücrelerde sodyum-glikoz ko-transporter-2 (SGLT2) ekspresyonunu göstermiştir. Peritoneal SGLT'nin blokajı, farelerde kan glukoz artışını düşürmüş ve peritonal glukoz tutulmasını artırmıştır. Sıçan modellerinde, yüksek glukozlu periton diyaliz sıvısının, glikoz taşıyıcılarını (GLUT) ve SGLT'nin ekspresyonunu artırarak peritoneal fibrozu indüklediği ve periton diyaliz sıvısına florizin eklenmesinin GLUT ve SGLT ekspresyonunu azaltarak ve periton dejenerasyonunun azalmasına neden olduğu gösterilmiştir.

Olgu: Bu bilgilere göre, son dönem böbrek hastalığı için PD programında olan kötü glisemik kontrollü tip 2 diyabetik bir hastada empagliflozin kullanma deneyimimizi paylaşmak istiyoruz.

Sonuç: Hastamıza empagliflozin uygulayarak, periton diyaliz sıvısının neden olduğu glisemik yükü azaltabileceğimizi ve ultrafiltrasyon hacmini artırabileceğimizi varsaydık.

Anahtar Sözcükler: *SGLT2 inhibitörleri, Periton diyalizi, Glisemik yük*

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INTRODUCTION

After announcement of the EMPA-REG, CANVAS, CVD-REAL trials the game was changed by sodium-glucose co-transporter (SGLT)-2 inhibitors. These trials reported the unique benefit of the SGLT2 inhibitors for secondary prevention of cardiovascular disease and heart failure. Furthermore, EMPA-REG and CREDENCE trials showed benefits for renal protection (1-3).

Also, mild weight loss was seen with SGLT2 inhibitors and some trials showed promising results for the treatment of nonalcoholic steatohepatitis (NASH). There is growing evidence for the use of SGLT2 inhibitors adjunctive to insulin in type 1 diabetes with insufficient glycemic control (4). In patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among who received dapagliflozin than those who received placebo, regardless of the presence or absence of diabetes (5).

When we look at ongoing studies, we can see that the indications of use to SGLT2 inhibitors increase day by day. In accordance with this trend, we want to share our experience of using empagliflozin in a poor glycemic controlled type 2 diabetic patient, who was on peritoneal dialysis (PD) program for end-stage renal disease.

CASE REPORT

A 45-year-old male with type 2 diabetes mellitus who had been on PD for 2 years with estimated glomerular filtration rate (eGFR) of 8 mL/min/1.73m^2. He had bilateral 2+ pretibial edema and his blood pressure was 150/90 mmHg without any antihypertensive treatment. Despite life style interventions and basal-bolus insulin regimen, he had poor glycemic control, with HbA1c level of 7.8% and five-day self-monitored fasting/postprandial glucose levels in the ranges of 150-210/200-240 mg/dl, respectively.

Without change in concentration and volume of peritoneal dialysis fluid (PDF), we added oral empagliflozin 10 mg/day to his regular treatment with linagliptin. A peritoneal equilibration test (PET) was performed prior to empagliflozin treatment to assess the baseline peritoneal membrane characteristic. PET had shown a high/average solid dialysate-to-plasma ratio (D/P) and low/average D/D0 glucose. The patient's daily average ultrafiltration volume was 430 cc and had 700 ml residual urinary volume before the empagliflozin treatment. After six months of empagliflozin treatment, PET was performed again for comparison of post treatment variability. PET showed high/average D/D0 glucose, but the solid clearance was unchanged. The patient's average ultrafiltration volume increased to 580 cc and residual urine volume was unchanged. Pretibial edema regressed within the first month of treatment and self-monitored blood pressure was <140/90 mmHg at home.

After the six months of empagliflozin treatment, average HbA1c level decreased to 7% and five-day self-monitored average fasting/postprandial glucose levels were 110-140/140-180 mg/dl respectively. The patient never reported hypotension and hypoglycemia in this observation period.

DISCUSSION

Glucose is the osmotic agent in the PDF to absorb water, sodium and other toxins. Glucose absorption from PDF to blood, impairs PD efficiency and cause glycemic burden. This extra glycemic load leads to poor glycemic control in diabetic dialysis patients with PD program.

Peritoneal membrane transport status can be determined with PET in patients who was on PD program. D/P means that transport across the peritoneal membrane for a given solute. High solute D/P means that transport of a solute across the membrane occurs quickly. D/P ratios are typically assessed for various solutes including urea, creatinine, and sodium (6).

The other concept is the D/D0 glucose, it defined as the dialysate glucose at 4 hours versus the dialysate glucose at time zero, if glucose absorption occurs, the osmotic gradient dissipates and ultrafiltration is lost. A high D/D0 glucose indicates slow glucose absorption and sustained ultrafiltration. Using the D/P ratio of creatinine and D/D0 glucose, patients can be classified into one of four transport categories: High, high average, low average, and low (7).

Studies have shown SGLT2 expression in peritoneal mesothelial cells, but the main SGLT in the peritoneum is SGLT1 (8). Phlorizin is a nonselective SGLT inhibitor, blockade of peritoneal SGLT by subcutaneous injection of phlorizin reduced blood glucose increment and increased peritoneal glucose retention in mice. In rat models, it was shown that high glucose PDF promotes the peritoneal fibrosis by upregulating the expression of glucose transporter (GLUT) and SGLT, and addition of phlorizin to PDF leads to downregulation of GLUT and SGLT expression and reduced peritoneal degeneration. In a further rat model, high peritoneal glucose transporter status was not prevented by intraperitoneal adminstration of dapagliflozin but dapagliflozin significantly reduced peritoneal thickening and fibrosis, leading to improved ultrafiltration (UF).

SGLT inhibitor use is not recommended in patient with GFR <30 mL/min/1.73m^2 due to lack of effectiveness in glucose-lowering properties, not for its pharmacokinetic properties. Glucuronidation is the major metabolic pathway for

empagliflozin, and no major metabolite of empagliflozin was detected in plasma; 11-19% of the administered dose is excreted unchanged in urine (9). Studies that investigated the effect of impaired kidney function on the pharmacokinetics of empagliflozin showed that, compared to healthy subjects, empagliflozin area under the curve (AUC) values increased by approximately 66% and 48% in subjects with severe chronic kidney disease (CKD) and end stage renal disease (ESRD), respectively (10). There was no dose adjustment required for empagliflozin in patients with CKD because the increase in drug exposure remained rather limited and Cmax values were similar among all renal function groups. Compared with normal renal function, in patients with mild, moderate and severe CKD, adjusted geometric mean ratios for the extent of exposure to empagliflozin were modestly increased. Pharmacokinetic data suggest that no dose adjustment of empagliflozin is necessary in CKD because of the mere 2-fold increase. However, to our knowledge, there has been no study that has investigated the pharmacokinetic properties of empagliflozin in peritoneal dialysis patients.

In conclusion, based on the available information, we hypothesized that if we administer empagliflozin to our patient we can reduce glycemic burden caused by PD fluid and increase the ultrafiltration volume. Thus, better glycemic and volume control would be provided.

In our case, PET showed that the amount of glucose remaining in the peritoneum increased after empagliflozin treatment, thus ultrafiltration volume increased and the patient glycemic control improved. We know that the efficacy of empagliflozin decreases as GFR decrease, so it cannot be speculated that increased glycemic control in our patient is only due to glucose loss in urine.

There has been no study that examined the excretion of empagliflozin with peritoneal dialysis. If the reduction of glycemic-load and consequent increase in dialysis efficiency can be demonstrated with systemic or intraperitoneal empagliflozin in a randomized blind trial, a lot of patients with peritoneal dialysis can wake up from their nightmare.

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Author Contributions

Utku Erdem Soyaltın and **Ilgın Yıldırım Şimşir** wrote the manuscript. **Utku Erdem Soyaltın** and **Ayşe Bengü Kandemir** researched data and literature. **Meltem Seziş** and **Şevki Çetinkalp** reviewed/edited the manuscript.

Conflict of Interests

Authors declare no potential conflicts of interest, whether of a financial or other nature.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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