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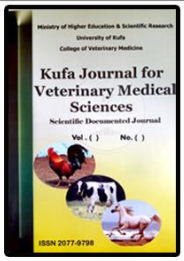

The effects of dapagliflozin on serum electrolytes concentration in adult male rats

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Abstract

Hyperkalemia hazard is increased in diabetes, especially in patients with renal disease or those receiving angiotensin-converting enzyme (ACE) medications, angiotensin receptor blockers (ARBs) or potassium-sparing diuretics. Also, other diuretics can increase hypokalemia danger. Recently, We assessed the effects of dapagliflozin in ameliorate the serum calcium, sodium, potassium(Ca^{+2}, Na^{+2}, K^{+}) and uric acid concentration in adults male rats. In this study were erolled 18 adult male rats randomly assigned to three groups(n=6) as following: control group (I) 0.5 ml/kg B.W of normal saline.

Group II and III receive orally by gavage for 30 days 0.53 mg/kg and 1.06 mg/kg B.W of dapagliflozin. The end of experiment the blood were collected for measuring the following parameter: blood glucose, Ca^{+2}, Na^{+2}, K^{+}) , and uric acid concentration. The results of the present study revealed the following: there was significant ($P\leq0.05$) increase in body weight, K^{+}, Ca^{+2} and uric acid concentration of treated II, and III groups compared with control. On the other hand, there was significant ($P\leq0.05$) decrease in Na^{+2} concentration of treated compared with control.

The experiment was concluded that Dapagliflozin in dose dependent pattern produce significant effects in reduction body weight in II and III groups compared with I group, furthermore, shows that changes in serum concentrations of potassium, calcium and uric acid in treated groups compared to normal where as no effects on sodium concentration was found. Also there is no differences in blood glucose concentration in treated group compared to normal, rather than hypoglycemic and all groups are normal groups.

Key Words: Dapagliflozin, T2DM, SGLT2, , Na^{+2}, K^{+} Ca^{+2}.

تأثير ديباكليفوزون على تركيز الشوارد في مصل الدم على ذكور الجرذ البالغة

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الخلاصة

تضمنت الدراسة تقييم علاج ديباكليفوزون في تحسين تركيز الصوديوم , البوتاسيوم والكالسيوم في الدم. خطر زيادة تركيز الشوارد في مرضى السكري وخصوصا في المرضى الذين يعانون من أمراض الكلى والقلب والذين يتعاطون علاجات ACEو ARBs والعلاجات المدره عن طريق البوتاسيوم. ضمت الدراسة 18 ذكر جرد بالغ وقسمت عشوائيا على ثلاثة مجاميع بواقع 6 جرد لكل مجموعه. مجموعه السيطرة أعطيت محلول ملحي 0.5 مل لكل جرد. ومجموعتي العلاج الأولى أعطيت 0.53 ملغم /كغم والمجموعة الثانية أعطيت 1.06 ملغم/كغم كل المجاميع الثلاثة أعطيت عن طريق الفم ويوميا ولمده

30 يوما بواسطه اللي ألفمي. بعد الانتهاء من التجربة تم تخدير كل جرد والتضحية بهم لغرض جمع عينات الدم وقياس مستوى السكر بالدم, تركيز الصوديوم ,البوتاسيوم, الكالسيوم وحمض اليورك. وقد أشارت النتائج إلى زيادة في الوزن الكلي للجسم وكذالك زيادة معنوية ($p<0.05$) بتركيز مستوى الكالسيوم والبوتاسيوم وحمض اليورك في مجاميع IIو III واللاتي تم علاجهن بالديباكليفوزون مقارنتا بمجوعه السيطرة والتي تم علاجه بالمحلول الملحي من جانب أخر هناك انخفاض معنوي ($p<0.05$) بتركيز الصوديوم في مجاميع IIو III مقارنتا بمجوعه السيطرة. نسنتج من التجربه ان الديباكليفوزن له ثاتير في انقاص الوزنوتقليل الكالسيوم وزياده في الصويوم والبوتاسيوم.

Introduction

Hyperkalemia hazard is increased in diabetes, especially in patients with renal diseases or those receiving angiotensin-converting enzyme (ACE) medications, potassium-sparing diuretic. Also, other diuretics can increase hypokalemia danger(1). Diabetes mellitus is a complex metabolic disease that affects about 382 million adults worldwide (2).

The Incidence of type 2 diabetes mellitus (T2DM) has been increased worldwide over the past years, a phenomenon often described as "epidemic" or "dramatic", thus emphasizing not only as high numbers, but also the complexity of the problem (3). Global projections suggest that about 592 million people will have T2DM by 2035, and another 471 million people will have impaired glucose tolerance and will be at higher risk of developing T2DM in next year's (3). The core defects of T2DM include quantitative and qualitative β-cell dysfunction, peripheral insulin resistance, and elevated glucose production by the liver, as well as increased lipolysis when obesity is suspected (4). However, it is becoming accepted that other known mechanisms, including increased glucagon, decreased incretin effects, increased glucose reabsorption in the kidneys and some neurotransmitter dysfunction, are also involved in the pathophysiology of T2DM (4). Several lines of evidences suggest that there is increased in the tubular Na^+-glucose reabsorption in uncontrolled diabetes mellitus, due to the increase in filtered glucose load and the increased expression of sodium glucose co-transporter 1 (SGLT1), SGLT2 and glucose transporter isotype 2 (GLUT2) transporters in proximal convoluted tubule cells (5). So there is a growing interest in SGLT inhibitors to treat diabetic patients there by inhibiting SGLTs in the kidney (6). These proteins responsible for transport of glucose across the membranes of the proximal convoluted tubule epithelial cells in an active process that involves sodium transport, facilitated by sodium gradient between the tubule and the cell, which supports secondary active co-transport of glucose (7). Glucose then will passively diffuse into the intercellular space mainly via the GLUT2 carrier (7). When the concentration of glucose in plasma exceeds that which can be reabsorbed via the SGLT proteins which approximately 198 mg/dL, then the excessive amount of glucose will be excreted in the urine (8). Data from preclinical studies suggest that hyperglycemic state in T2DM is associated with significantly higher expression of SGLT2 and GLUT2 proteins, together with an increased in the level of renal glucose reabsorption (9). Chronic exposure to high blood glucose levels will induce harmful metabolic effects, known as "glucose toxicity" which is a strong determinant of β-cell dysfunction and promoter of the vicious cycle of diabetes pathogenesis (10). SGLT2 inhibitors are indicated to improve glycemic control in patients with T2DM by reducing the reabsorption of filtered glucose (11). They can also lower the renal threshold for glucose, thereby increasing urinary glucose excretion (12). The efficacy of SGLT2 inhibitors is influenced by the

blood glucose level and renal function and not by insulin, their action becoming negligible when a plasma concentration drops below 90 mg/dL; this translates into a lower risk of hypoglycemia compared with insulin-dependent antidiabetic drugs (12). Dapagliflozin (Forxiga) is the first SGLT2 inhibitor approved in the world, in 2011; it was followed by canagliflozin (Invokana) and empagliflozin (Jardiance) (13). Dapagliflozin is indicated for T2DM patients over 18 years as monotherapy to improve glycemic control in patients with inadequate glycemic control who are intolerant to metformin, and as an adjunct to diet and exercise in combination with other glucose-lowering agents in patients which inadequately controlled on existing antidiabetic medications, including insulin(14). However In patients with moderate renal impairment dapagliflozin has been shown to be less effective (15). Thus, with reduced renal function, dapagliflozin is expected to be less efficacious (16). The effectiveness of SGLT2 inhibitors on suppressing glucose fluctuations in patients with T2DM has not been clarified (17). So the present study tried to investigate antihyperglycemic effects of dapagliflozin in addition to its effects on serum electrolytes, uric acid, hematocrit and kidney.

Materials and Methods

Eighteen male rats(*Rattus Norvegicus*), 13±1 weeks olds, weighing 220±10g were used in this experiment. They were received free access to standard rat pellets and tap water. Dapagliflozin (Forxiga 10 mg tablet) was brought from pharmacy, then dissolve 10 mg in normal saline after that calculated doses were administered to animals. Rats were divided randomly into three groups(n=6): group I is control group receive 0.5ml of normal saline daily for 30 day by oral gavage. Elsewhere, the treated group II and III receive dapagliflozin 0.53 and 1.06 mg/kg daily for 1 month by oral gavage as a suspention in 0.5 ml of normal saline. The end of experiment all rats, where anesthetized and scarified for blood sampling c was obtained from vena cava by 5ml syringe. Blood concentration of Ca^{+2} mg/dl, Na+2 mg/dl, K+ mg/dl and uric acid mg/dl were evaluated using spectrophotometer kits (Bico-Germany). All results were expressed as mean ±SEM. The significance of differences between treated groups was determined using Student's t-test and one-way analysis of variance (ANOVA). P-values < 0.05 were considered significant.

Results

Table(1) illustrated the effects of dapagliflzin on total body weight, shows that the total body weight was a significantly ($p<0.05$) increased in both dapagliflozin II, III groups compared with control group. There was no significant differences among groups in blood glucose concentration(table 2) that illustrated effects of dapagliflozin on sserum glucose concentration.

Table (3) illustrated effects of dapagliflozin on serum Na^{+2}, K^{+} and $Ca^{+2\ t}$ that showed there were significant ($p\leq0.05$) decreased in serum sodium level of dapagliflozin groups compared with control group. While, a significant ($p\leq0.05$) increased in serum level of K^{+} and Ca^{+2} of dapagliflozin II, III groups compared with control group.

Table (4) revealed to effects of dapagliflozin on uric acid that showed there was significant ($p\leq0.05$) decreased in serum level of uric acid in both dapagllflozin II, III groups compared with control group.

Table 1: the effect of dapagliflozin on total body weight in adult male rats n=6

Group number	Total body weight differences **(g)**
Group I	26.84±1.61 a
Group II	23.5±1.82 b
Group III	17.50±2.61 c
LSD	0.33

Data are expressed as mean ± standard error; N=6 in each group, different letters represent significant difference at (p≤0.05).

Table 2: the effects of dapagliflozin on blood glucose concentration in adult male rats n=6

Group number	Blood glucose **mg/dl**
Group I	197.33±4.73 a
Group II	196.66±3.92 a
Group III	195±6.04 a
LSD	8.83

Data are expressed as mean ± standard error; N=6 in each group, different letters represent significant difference at (p≤0.05).

Table 3: the effects of dapagliflozin on serum electrolytes Na^{+2}, K^{+}, and Ca^{+2} in adult rat male n==6

Group number	Na^{+2} **mg/dl**	K^{+} **mg/dl**	Ca^{+2} **mg/dl**
Group I	164.22±8.06 a	5.73±0.25 c	8.63±0.25 b
Group II	155.66±9.19 c	6.33±1.20 a	8.90±0.14 a
Group III	160.0 ±8.09 b	6.46±0.84 a	9.11±0.14 a
LSD	3.66	0.13	0.33

Data are expressed as mean ± standard error; N=6 in each group, different letters represent significant difference at (p≤0.05).

Table 4 : the effects of dapagliflozin on blood uric acid concentration in adult rat male n=6

Group number	Uric acid **mg/dl**
Group I	3.33±1.57 a
Group II	2.33±0.88 b
Group III	2.20±0.88 b
LSD	0.13

Data are expressed as mean ± standard error; N=6 in each group, different letters represent significant difference at (p≤0.05).

Discussion

The present study tried to investigate variable effects of different doses of dapagliflozin on healthy rats; it was found that there is a significant weight reduction in both treated groups compared to control group by measuring mean of weight differences between day one and at the end of study as illustrated in table 1; this is appears to be attributable to the loss of glucose energy, lower insulin levels and increased oxidative metabolism of fat (18). Also, dapagliflozin appears to have a mild diuretic effect; the weight loss could result from fluid loss secondary to osmotic dieresis (19, 20).

A previous study was performed to determine whether weight reduction is due to loss of glucose or osmotic diuretic effect, although the initial reduction in body weight may be due, in large part, to osmotic diuresis, the gradual continuous reduction and subsequent stabilization of body weight is likely the result of caloric loss *via* increased glucose excretion (19).

There is no significant effect in blood glucose level among treated groups compared to control group this is may attributed to that dapagliflozin is considered as antihyperglycemic and all rat was healthy so dapagliflozin will act when blood glucose will exceed the filtration capacity of the kidney(18).

Also present study shows that there is no significant changes in the concentration of Na^{+2} between control group and treated groups while there are a significant changes in K^{+} and Ca^{+2} in both treated groups compared to control group which can be explain as the following: The renal medulla is the primary site for urine concentration (21).

There are three major transport proteins in the renal medulla that work in combination to produce an osmotic gradient that is necessary to produce concentrated urine: the UT-A1 urea transporter, the aquaporin-2 (AQP2) water channel, and the Na-K-2Cl co-transporter (21). In the outer medulla, NaCl is the main constituent of the osmotic gradient and Na-K-2Cl co-transporter, located in the medullary thick ascending limb, is chiefly responsible for the absorption of NaCl (22).

However previous study showed that sodium glucose transport isotype 2 ($SGLT_2$) inhibitor treatment may affect the medullary transport expression by unknown mechanism which my responsible for alteration in the serum electrolytes (Na^{+2}, K^{+}, Na^{+2}) concentrations in treated groups compared to control group (23). There is a previous literature support that there are a significant elevation in serum magnesium concentration, and the possibly increased phosphate level, might be the result from osmotic diuresis caused by sodium glucose transport isotype 2 inhibitors, but the precise mechanisms still unknown (23). Abnormally high magnesium concentration is predictive of total mortality in patients with heart failure and critically ill patients (24), also in those receiving haemodialysis (25).

Therefore, caution must to be exercised in those patients with disturbed renal function, like in case of severe chronic renal failure (25). This result is corresponding with Seigo Sugiyama, *et al.*, 2018 who reported that dapagliflozin exhibited significant renoprotective effects, with improvement of urine albumin-tocreatinineratioUACR and uNAG and increased kidney length and radiation attenuation in patients with uncontrolled T2DM.

Conclusion

Dapagliflozin in dose dependent pattern produce significant effects in reduction body weight in treated groups compared to normal, changes in serum levels of potassium, calcium and uric acid in treated groups compared to normal where as no effects on sodium level was found. Also there is no differences in blood glucose level in treated group compared to normal because it act as anti hyper glycemic rather than hypoglycemic and all groups are normal groups.

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