

## The Effect of Long Term use of Glibenclamide on Serum and Urinary Sodium and Potassium Level in Type 2 DM Patients

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### Abstract

Long-term use of sulfonylureas including chlorpropamide, is known to potentiate the antidiuretic action of arginine vasopressin (AVP), predisposing to hyponatremia. The present study was designed to evaluate the effect of long term use of glibenclamide on serum and urinary levels of sodium and potassium in Type 2 DM patients in Iraqi DM centers. Ninety eight patients with Type 2 DM who were maintained on different doses of glibenclamide for at least 1 year, attending the centre for Diabetes and Endocrinology in Al-Rusafa, Baghdad, were enrolled in the study, in addition to 15 normal healthy subjects. Patients were allocated into three groups according to the dose of glibenclamide that they received. Blood and urine samples were obtained for evaluation of sodium and potassium levels in these samples by flamephotometry. The results indicated that glibenclamide use resulted in significant elevation in serum levels of sodium and potassium compared to controls, while urinary excretion of these cations was not significantly changed. Stratification of patients according to the dose of glibenclamide revealed that this effect on sodium and potassium was not dose dependent. In conclusion, long term use of glibenclamide impairs normal values of Sodium and potassium independent of the administered dose.

**Key words: Glibenclamide, sodium, potassium.**

### الخلاصة

ان دواء الكلوروبروباميد وهو من مجموعة السلفونيل يوريا يستخدم لعلاج مرضى السكري من النوع الثاني ( غير المعتمد على الانسولين) وهو معروف بتحفيظه لعمل الهرمون المضاد للبول والذي يسبب نقص الصوديوم و يعتقد ان هذا الدواء يعمل مباشرة على مستقبلات هرمون المضاد للبول. في هذا البحث نود دراسة تأثير دواء الكليبينكلاميد وهو من نفس مجموعة الكلوروبروباميد (أي السلفونيل يوريا) على تركيز الصوديوم والبوتاسيوم في الدم (المصل) وكذلك في البول المجموع خلال ٢٤ ساعة في المرضى المصابين بداء السكري النوع الثاني وقد اجريت هذا الدراسة في شهر ايلول ٢٠٠٨ ولغاية شهر كانون الثاني من عام ٢٠٠٩ وقد شارك في هذه الدراسة ٩٨ مريض خارجي من مركز الغدد الصم والسكري في الرصافة ببغداد بالتعاون مع الطبيب الاستشاري هناك و ١٥ شخص سليم وقد اخذت عينات من المصل والبول (البول المجموع خلال ٢٤ ساعة في المنزل) وقد تم قياس تركيز الصوديوم والبوتاسيوم بواسطة جهاز قياس الالوان في اللهب وظهرت النتائج ان الكليبينكلاميد يؤثر بشكل ملحوظ على تركيز الصوديوم والبوتاسيوم في مصل الدم مقارنة مع المجموعة القياسية اما تأثيره على تركيز الصوديوم والبوتاسيم في البول المجموع خلال ٢٤ ساعة لم يكن بشكل ملحوظ.

### Introduction

Glibenclamide is a first line option for treating patients with type 2 diabetes mellitus (DM) who are not overweight or who can not take metformin<sup>(1)</sup>. It is mostly used when diet control and exercise have failed to achieve tight control of plasma glucose level; it also can be used alone or in combination with other hypoglycemic agents to provide better glycemic control<sup>(2)</sup>. Sodium is the important electrolyte in the extracellular space while potassium is the essential one in the intracellular space, this asymmetrical distribution of the electrolytes across the cell membrane requires the active exchange of both cations by the Na<sup>+</sup>/K<sup>+</sup>-ATPase.<sup>(3)</sup> Potassium is the principle electrolyte (cation) of intracellular fluid and the primary buffer within the cell itself. Ninety percent of potassium is contain in blood and bone.

Damaged cells release potassium into the blood<sup>(4)</sup> Using free flow micropuncture technique in rats, intravenous infusion of glibenclamide (3mg/hr) evoked a natriuresis and diuresis; while potassium excretion remained unchanged. It has been reported that glibenclamide impaires sodium reabsorption in one or more of the nephron segment that comprise the loop of Henle<sup>(5)</sup>. Moreover, other hypothesis indicates that the natriuretic effect of glibenclamide is a consequence of blockade of potassium channels in the apical membrane of the thick ascending part of Henle loop; or it may inhibited a small secretory potassium flux in the proximal tubule<sup>(6)</sup>. The present study was designed to evaluate the effect of long term use of different doses of glibenclamide on serum and urinary levels of sodium and potassium levels of Iraqi patients with type 2 DM.

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## Subjects and methods

Ninety eight patients (54 female and 44 males) with type 2 diabetes mellitus, were referred to the specialized center for Endocrinology and Diabetes, Baghdad during the period from September 2008 to January 2009 were enrolled in the study; their age range was  $52.26 \pm 8.65$  years and diagnosed to have type 2 DM for at least five years (Average duration of type 2 DM  $5.5 \pm 0.4$  years) and maintained on glibenclamide 5 mg, 10 mg or 15 mg at least 1 year with adequate glycemic control (Average fasting blood sugar =  $6.0 \pm 0.94$  mmole/L) and no detectable secondary complications. All patients were informed about the nature of the study and their signed consents were obtained before participation. Additionally, 15 healthy subjects with comparable age to that of patients were utilized as control. After overnight fasting, venous blood samples were obtained from all subjects without using tournique to avoid leakage of cellular potassium, and serum was prepared for evaluation of serum levels of sodium and potassium using flamephotometer (The flamephotometer used is FP 20 seac from Seag Radim company-Italy). Moreover, 24 hours urine sample was collected for evaluation urinary excretion of sodium and potassium using flamephotometry. For 24 hours urine collection, we instructed the patients to void at 8 AM and discard the specimen. Then collect all urine including the final specimen voided at the end of the 24-hour collection period (i.e, 8 AM the next morning)<sup>(7)</sup>. For evaluation of the effect of glibenclamide on serum and urinary levels of sodium and potassium, all patients data were compared with those of controls; Meanwhile, for the evaluation of the effect of glibenclamide dose, patients were classified in three groups, those who are treated with 5 mg/day (n=56), those treated with 10 mg/day (n=29) and those treated with 15 mg/day (n=13). All data were expressed as mean  $\pm$  standard deviation; un-paired students t-test between patients and control and ANOVA test was performed for evaluation of differences between groups and p-values < 0.05 were considered significant. Flame photometry based on atomic emission method for the routine detection of metal salts, principally Na, K, Li, Ca and Ba. Quantitative

analysis of these species is performed by measuring the flame emission of solution containing the metal salts. Solution is aspirated into the flame. The hot flame evaporates the solvent, atomizes the metal, and excites a valence electron to an upper state. Optical filters are used to select the emission wavelength monitored for the analyte species. Comparison of emission intensities of unknowns to either that of standard solutions, or to those of an internal standard, allows quantitative analysis of the analyte metal in the sample solution<sup>(8,9)</sup>

## Results

In the present study, table 1 shows that serum sodium concentration in total number of patients is significantly different ( $P < 0.05$ ) compared to that in control group. Table 1 also shows that both urine sodium and potassium concentrations in total number of patients are not-significantly different ( $P > 0.05$ ) compared to that in control group. In table 2, the average urinary excretion of sodium and potassium was not significantly different ( $P > 0.05$ ) among patients who were using different doses of glibenclamide.

**Table 1 : Effect of glibenclamide on serum and urinary levels of sodium and potassium in type 2 patients.**

Parameter	Control subjects (n=15)	DM patients treated with glibenclamide (n=98)
Serum sodium (meq/L)	$139.95 \pm 3.859$	$142.29 \pm 6.67^*$
Serum potassium (meq/L)	$4.13 \pm 0.56$	$4.71 \pm 0.663^*$
Urine sodium (meq/L)	$103.14 \pm 26.25$	$100.64 \pm 48.8$
Urine potassium (meq/L)	$62.02 \pm 33.2$	$51.76 \pm 25.12$

Values were expressed as mean  $\pm$  SD; n= number of subjects; \* = significantly different from control ( $p < 0.05$ ).

**Table 2: Effect of 5 mg /day , 10 mg/day and 15 mg/day Glibenclamide on serum and urinary sodium and potassium levels in type 2 DM patients.**

parameter	Patients treated with 5 mg /day glibenclamide N=56	Patients treated with 10 mg /day glibenclamide N=29	Patients treated with 15 mg /day glibenclamide N=13
Serum sodium ( meq/L)	142.3 ± 4.5 <sup>a</sup>	142.7 ± 7.8 <sup>a</sup>	141.53±4.33 <sup>a</sup>
Serum potassium ( meq/L)	4.746 ± 0.659 <sup>a</sup>	4.648 ± 0.748 <sup>a</sup>	4.73 ± 0.496 <sup>a</sup>
Urine sodium ( meq/L)	109.08 ± 52.28 <sup>a</sup>	96.4 ± 41.58 <sup>a</sup>	73.75 ± 46.89 <sup>a</sup>
Urine potassium (meq / L)	55.39 ± 21.59 <sup>a</sup>	41.85 ± 24.77 <sup>a</sup>	54.75 ± 35.964 <sup>a</sup>

Values were expressed as mean ± SD; n= number of subjects; values with identical superscripts (a) were considered non significantly different (P>0.05) (ANOVA).

## Discussion

Systemic administration of glibenclamide inhibits sodium reabsorption in the loop of Henle<sup>(6)</sup>; this extra-pancreatic effect of glibenclamide reveal natriuretic activity<sup>(10)</sup>, which is attributed to elevation of functional sodium delivery to the distal tubules. Moreover, glibenclamide impairs sodium reabsorption in one or more of the nephron segments that comprise the loop of Henle<sup>(5)</sup>. In the present study, long term use of glibenclamide by DM patients resulted in significant elevation in serum levels of sodium and potassium (table 1); this effect may be attributed to enhancement of free water excretion induced by glibenclamide in patients with DM<sup>(11)</sup>. In clinical practice, administration of 5 mg single oral dose of glibenclamide in patients with type 2 DM did not essentially affect sodium and potassium excretion<sup>(12)</sup>. Several agents belong to sulfonylureas group, including glibenclamide, have diuretic action in well hydrated normal subjects<sup>(11)</sup>, and glibenclamide enhances water excretion in patient with diabetes insipidus<sup>(13,14)</sup>, and diabetes mellitus<sup>(11)</sup>. In this respect, the reported elevation in serum levels of sodium and potassium (in the present study), without affecting urinary levels, may be explained on the bases of improper hydration status of enrolled patients, especially when associated with excessive of water excretion. The data presented in table 2 indicated that there is no dose-related effect for glibenclamide on sodium and potassium homeostasis; this observation may indicate that the reported elevation in serum levels of the cation is beyond the pharmacodynamic activity of glibenclamide. Moreover, the limitation of patients' sample, duration of follow up multifactorial pathophysiology may have potential interference in this respect. Accordingly, larger patients sample with proper selection criteria could be a proper approach for clear definition of the problems.

## Conclusion

In this study we conclude that glibenclamide dose not satisfy syndrome of inappropriate antidiuretic hormone secretion (SIADH) criteria because no hyponatremia occur (SIADH criteria are hyponatremia and urinary sodium concentration >20mmol/L)<sup>(15, 16)</sup>. Also we conclude that long-term use of different doses of glibenclamide in type 2 DM may impaire sodium and potassium homeostasis unrelated to the administered dose.

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