THE POTENTIAL DRUG-DRUG INTERACTION BETWEEN WARFARIN AND GLIBENCLAMIDE IN DIABETIC AND HYPERCOAGULABLE RATS MODEL

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Diabetic patients are vulnerable to many vascular events. So, diabetic patients treated with oral antidiabetic glibenclamide, may be also treated with oral anticoagulant warfarin, for prophylaxis and treatment of atherothrombotic events. Aim of this study: was to evaluate the possible drug-drug interaction between warfarin and glibenclamide in diabetic and hypercoagulable rats. Material and methods: Fifty adult male albino rats (230-390 gm) were enrolled and subgrouped into; I: control group; II: diabetic and hypercoagulable group; III: as group II but treated with warfarin (0.07 mg/kg) orally for 5 consecutive days; Group IV: as group III but treated with glibenclamide (0.6 mg/kg) orally for 5 consecutive days and group V: as group IV but treated with both warfarin and glibenclamide. The following parameters were then assessed: prothrombin time, activated partial thromboplastin time, clotting time, bleeding time, serum glucose level and glycosylated hemoglobin. Results: The results showed that, PT, aPTT, CT, BT were significantly (p< 0.001) prolonged while the serum glucose level was significantly (p< 0.001) decreased and HbA1c was significantly (p< 0.01) decreased when warfarin and glibenclamide were administered together more than when they were given alone. Conclusion: A drug-drug interaction had occurred when warfarin and glibenclamide were coadministered.

INTRODUCTION

Global diabetes prevalence is expected to be 9.3 percent (463 million people) in 2019, increasing to 10.2 percent (578 million) by 2030 and 10.9 percent (700 million) by 2045. According to the International Diabetes Federation Atlas, it is projected that 15.2 percent of adults in Egypt have diabetes.1

The majority of diabetes-related morbidity and death is due to the disease's detrimental influence on macrovascular and microvascular disorders. T2DM has microvascular consequences such as retinopathy, neuropathy, and nephropathy, as well as macrovascular complications such as ischemic heart disease, cerebrovascular disease, and peripheral vascular disorders. Macrovascular disease develops as a result of underlying obstructive atherosclerotic changes of major arteries which cause functional and structural abnormalities of blood vessels.2 Of the most commonly used in treatment of type DM is glibenclamide that is an insulin secretagogues.3 Warfarin has been used as anticoagulant agent where it inhibits vitamin K epoxide reductase with subsequent no synthesis of vitamin K dependant factors by the liver.4

Diabetes is typically managed by treating concomitant diseases such as thrombosis5. Warfarin is one of the medicines that can be co-administered with glibenclamide in patients with diabetes mellitus for treatment of thrombosis and thromboprophylaxis with the possibility of drug-drug interaction between them.6 The present study aimed to evaluate the possible drug-drug interactions between warfarin and glibenclamide in diabetic and hypercoagulable rats.
MATERIALS AND METHODS

Animals
Fifty adult male albino rats weighing 230-390 grams were obtained from the animal house. They were housed in stainless-steel cages (five rats in each cage). The animals were housed with ideal conditions of temperature (22 ± 2°C) and humidity (55 ± 5%) with 12-light/12-dark cycle. and free access to dry food pellets and tape water. They were kept for one week to adapt the laboratory conditions before starting the experiment. Animal handling and rights were maintained on accordance with the Ethical Committee guidelines of the Faculty of Medicine, Assiut University.

Chemicals
Warfarin and Glibenclamide were obtained from (AK Scientific, Inc., Union City, U.S.A.), Ellagic acid hydrate (Alfa Aesar, Karlsruhe, Germany), Alloxan monohydrate (Alpha Chemika, Mumbai, India), PT and aPTT assay reagents (Biomed Diagnostics, Hannover, Germany), Glucose assay kit (Spinreact, Girona, Spain) and HbA1c assay kit (Teco Diagnostics, Anaheim, U.S.A.).

Induction of DM
Single intraperitoneal (IP) injection of alloxan monohydrate in normal saline at a dose 120 mg/kg after overnight fasting was used to induce DM. To avoid hypoglycaemia, the rats were given 5-10 ml of a 20% glucose solution orally after 6 hours and kept 5% glucose solution for the next 24 hrs. Then, they were stabilized in their cages for 7 days.

Assessment the glucose level at 7th day, selected rats should have level above 250 mg/dl and started the treatment by warfarin, glibenclamide or both for 5 consecutive days.

Hypercoagulable state induction
This was performed by IP ellagic acid hydrate at a dose 10.5 mg/kg after 2 hrs from the last dose of treatment and five minutes before collection of the blood samples at the 5th day.

Preliminary experiment to adjust the dose of warfarin in rats
Three groups of animals (3 rats in each group) were used to select the dose of warfarin that would result in a PT of 1.5-2 folds of the control value (25 seconds).

- **Group A:** According to Zaghloul et al., the rats were received warfarin at a dose 0.1 mg/kg orally along five days. The animals showed hemorrhage in the form of ecchymosis, epistaxis, bleeding from mouth then died on the 4th day of treatment. This dose was considered as a toxic dose.

- **Group B:** The rats were received warfarin 0.05 mg/kg orally for 5 consecutive days. On the 5th day of treatment, PT and concentration was measured after 2 hrs. from the last dose of warfarin. It was 32.33 ± 1.45 seconds.

- **Group C:** The rats were received warfarin at a dose 0.07 mg/kg orally for 5 consecutive days. On the 5th day of treatment, PT and concentration was measured after 2 hours from the last dose of warfarin. It was 40.00 ± 1.15 seconds. From the preliminary experiment, 0.07 mg/kg/ day was suitable to produce a PT and concentration range of 1.5-2 folds of control value and considered as a submaximal dose.

Animal groups and treatments
The rats were divided into 5 groups (10 rats in each group) as follow: Group I: (control group); received distilled water followed by 0.05% carboxymethylcellulose (CMC) solution. Diabetic hypercoagulable rats were divided into four groups; Group II: diabetic and hypercoagulable rats were received distilled water followed by 0.05% CMC solution; Group III: diabetic and hypercoagulable rats were received distilled water followed by 0.05% CMC solution; Group IV: diabetic and hypercoagulable rats treated with warfarin at a dose 0.07 mg/kg; Group V: diabetic and hypercoagulable rats treated with warfarin and glibenclamide. All drugs were given orally through gastric tube for 5 consecutive days.

Blood sample collection
After 5 min. from ellagic acid administration, the blood samples were
collected from the retro-orbital sinus under general anesthesia by a capillary tube inserted in the medial canthus medial to the eye globe from each animal after overnight fast. Blood was withdrawn into 3 clean test tubes as follow: First tube (containing 0.1 ml of trisodium citrate 3.8%): About 0.9 ml of blood was withdrawn into it (in a ratio of 9 parts blood: 1 part trisodium citrate). Then, it was centrifuged for 10 minutes at 3000 rpm to separate plasma for determination of PT and aPTT. Second tube (containing ethylene diamine tetra acetic acid (EDTA)): About 0.5 ml of blood was withdrawn into it for determination of HbA1c concentration. Third tube: About 0.5 ml of blood was withdrawn into it and centrifuged for 10 minutes at 3000 rpm to separate serum for determination of glucose level.

Assessment of coagulation parameters
Prothrombin time and activated partial thromboplastin time were determined by using commercial kits. The tests were performed according to the manufacturer's instructions. Bleeding time was determined by making a small cut in the middle of the tail with a scalpel and the stopwatch was started as soon as bleeding started. The cut was dabbed with filter paper every 15 seconds until the paper no longer stained red with blood. Bleeding time was then taken as the time when the blood stopped flowing from the cut.

Clotting time was determined by taking a drop of blood from the tail of each rat then placed on a clean glass slide and a stopwatch was started at the same time. A pin was passed across the drop of blood once every 15 seconds. As soon as threads of fibrin were noticed, the stopwatch was stopped, and the time recorded is the CT.

Measurement of serum glucose level
Serum glucose level was measured by using the commercial assay kit according to the manufacturer's instructions.

Measurement of HbA1c level
HbA1c level was determined by using a glycosylated hemoglobin assay kit. The test was performed according to the manufacturer's instructions.

Statistical analysis of data
The data were presented as means ± standard errors (SE) and analyzed by one-way analysis of variance (ANOVA). For the comparison of statistical significance between two groups, Student’s unpaired t-test was used. A P-value of < 0.05 was adopted as statistically significant. Data analysis was performed by using Graph Pad Prism 5.01 (Graph Pad software Inc., San Diego, USA).

RESULTS AND DISCUSSION

Results
Effect on coagulation parameters
As shown in figures 1, 2, 3 and 4, PT, aPTT, BT and CT were significantly (p<0.001) shortened in diabetic and hypercoagulable rats (group II) in comparison with control rats (group I). In diabetic and hypercoagulable rats treated with warfarin 0.07 mg/kg orally for 5 consecutive days (group III), PT, aPTT, BT and CT were significantly (p<0.001) prolonged than non-treated diabetic and hypercoagulable rats (group II).

Fig. 1: Effect of warfarin (0.07 mg/kg), glibenclamide (0.6 mg/kg) and their combination on PT
Data represents the mean ± SE of each group (n=10). ***: Highly significant in comparison with group I (p<0.001). ###: Highly significant in comparison with group II (p<0.001). ns: Not significant in comparison with group II (p>0.05). +++: Highly significant in comparison with group III (p<0.001)
In diabetic and hypercoagulable rats treated with glibenclamide 0.6 mg/kg orally for 5 consecutive days (group IV), PT, aPTT, BT and CT were not significantly changed in comparison with non-treated diabetic and hypercoagulable rats (group II). In diabetic and hypercoagulable rats treated with a combination of warfarin 0.07 mg/kg and glibenclamide 0.6 mg/kg orally for 5 consecutive days (group V), PT, aPTT, BT and CT were significantly (p < 0.001) prolonged than diabetic and hypercoagulable rats treated with warfarin alone (group III).

**Effects on serum glucose level**

As shown in figure 5, serum glucose level was significantly (p < 0.001) increased in diabetic and hypercoagulable rats (group II) in comparison with control rats (group I). In diabetic and hypercoagulable rats treated with warfarin 0.07 mg/kg orally for 5 consecutive days (group III), serum glucose level was not significantly changed in comparison with non-treated diabetic and hypercoagulable rats (group II).

In diabetic and hypercoagulable rats treated with glibenclamide 0.6 mg/kg orally for 5 consecutive days (group IV), serum glucose level was significantly (p < 0.001) decreased in...
comparison with non-treated diabetic and hypercoagulable rats (group II). In diabetic and hypercoagulable rats treated with a combination of warfarin 0.07 mg/kg and glibenclamide 0.6 mg/kg orally for 5 consecutive days (group V), serum glucose level was significantly (p < 0.001) decreased in comparison with diabetic and hypercoagulable rats treated with glibenclamide alone (group IV).

**Effects on HbA1c**

As shown in figure 6, HbA1c was significantly (p < 0.01) increased in diabetic and hypercoagulable rats (group II) in comparison with control rats (group I). In diabetic and hypercoagulable rats treated with warfarin 0.07 mg/kg orally for 5 consecutive days (group III), HbA1c was not significantly changed in comparison with non-treated diabetic and hypercoagulable rats (group II).

In diabetic and hypercoagulable rats treated with glibenclamide 0.6 mg/kg orally for 5 consecutive days (group IV), HbA1c was significantly (p < 0.001) decreased in comparison with non-treated diabetic and hypercoagulable rats (group II). In diabetic and hypercoagulable rats treated with a combination of warfarin 0.07 mg/kg and glibenclamide 0.6 mg/kg orally for 5 consecutive days (group V), HbA1c was significantly (p < 0.01) decreased in comparison with diabetic and hypercoagulable rats treated with glibenclamide alone (group IV).

**Discussion**

Patients with DM who are being treated with sulfonylureas, such as glibenclamide, may also be given warfarin, an oral anticoagulant medication, for the prevention and treatment of thromboembolic consequences of diabetes. In this case, there is a chance of a drug-drug interaction between warfarin and glibenclamide. A potential drug-drug interaction refers to the possibility of one drug to alter the pharmacodynamics and pharmacokinetics of another drug when they had given concurrently.17

In the present study, we had studied the effect of warfarin on the antidiabetic action of glibenclamide as well as the effect of glibenclamide on the anticoagulant action of warfarin in rats. Warfarin action was evaluated by measuring the PT, aPTT, CT and BT.
the antidiabetic action of glibenclamide was evaluated by measuring the serum glucose and HbA1c levels.

To evaluate the effects of warfarin and glibenclamide, an effective animal model of DM and hypercoagulable state that mimicked the clinical situation was required. According to Maniyar et al, alloxan monohydrate 120 mg/kg intraperitoneally as a single dosage caused experimental diabetes by damaging insulin-producing β cells in the pancreas18.

In experimental animals, alloxan administration has been shown to cause pancreatic damage that is proportional to the dosage provided. The size of the lesion is also related to the amount of insulin in the pancreas. This might explain why, at low or medium doses, the medication does not cause absolute but inadequate insulin shortage in experimental animals19.

As a result of the partial death of pancreatic cells caused by the administration of a lower dose of alloxan monohydrate (120 mg/kg), type 2 diabetes is produced. As a result, these mice have surviving cells and insulin production is feasible, which is necessary for our animal diabetes model20. In comparison to the control rats, the results indicated a substantial increase in blood glucose levels after one week of alloxan administration. These findings are consistent with other studies as.

According to Liu et al.9, an experimental hypercoagulable condition was established by administering 10.5 mg/kg ellagic acid intraperitoneally as a single dose 5 min. before blood samples were collected. Ellagic acid is a polyphenol present in a variety of fruits9. This chemical has been linked to a variety of actions, including reducing inflammation in colon cancer cells21 to free radical scavenging22 and coagulation effects. The coagulation effects have been attributed to their effect on Hageman factor (factor XII) to trigger intrinsic coagulation system23.

The results of the current study showed that ellagic acid used dose had successfully induced a hypercoagulable state as a significant shortening of all coagulation parameters compared to the control rats. These results are consistent with Liu et al. 9.

In the current investigation, warfarin was administered either alone or in combination with glibenclamide. The preliminary studies revealed that the submaximal dosage was 0.07 mg/kg orally once day for 5 days. The findings revealed that warfarin at this dosage protected rats against the hypercoagulable impact of ellagic acid, with all coagulation parameters substantially extended in comparison to non-treated rats.

In comparison to the non-treated diabetic and hypercoagulable rats, this warfarin dosage had no effect on blood glucose levels or HbA1c. This means that warfarin has no antidiabetic effect. Glibenclamide at 0.6 mg/kg was related with lower levels of glucose and HbA1c.

In comparison to the non-treated diabetic and hypercoagulable rats, glibenclamide at 0.6 mg/kg showed no significant effect on coagulation indices. This means that glibenclamide has no anticoagulant effect, while diabetic and hypercoagulable rats treated with both warfarin and glibenclamide resulted in extended coagulation parameters.

In addition, blood glucose and HbA1c levels were substantially lower in diabetic and hypercoagulable rats treated with glibenclamide alone. These data suggest that a drug-drug interaction occurred because glibenclamide improved warfarin's anticoagulant effect and warfarin enhanced glibenclamide's antidiabetic action when both medications were coadministered.

This interaction might be pharmacodynamic or pharmacokinetic. The potential of a pharmacodynamic interaction can be ruled out since warfarin has no antidiabetic effect and glibenclamide has no anticoagulant effect. As a result, it is most likely owing to pharmacokinetic interaction; plasma proteins and the hepatic CYP450 system are typical interaction sites24.

Glibenclamide can modify the anticoagulant action of warfarin through interference with CYP2C9–catalyzed S-warfarin 7-hydroxylation24&25 and to lesser extent on CYP3A4 but it has no effect on CYP 1A2, 2C8, 2C19, 2E1 and 2D626.

Protein-binding displacement might occur24, since sulfonylureas and warfarin bind to plasma albumin, and each medication has been shown to be more than 99 percent bound. The medications may compete for binding sites on plasma albumin. The newly active unbound
drug would be accessible for compensatory activation of metabolism, resulting in an increase in total drug clearance. As a result of this the unbound drug concentration returning to the predisplacement concentration 27&28. Non-ionic force binds glibenclamide to human serum albumin. As a result, ionic medicines such as warfarin do not displace glibenclamide from albumin in the same way as the first generation sulfonylureas do 29. According to these findings, protein binding displacement of warfarin is not a mechanism for medication interaction 30. Furthermore, because of decreased intrinsic clearance caused by metabolic restriction, the elimination of unbound warfarin would have been considerably delayed 27. As a result, suppression of CYP2C9 appears to explain the observed effect of glibenclamide on warfarin's anticoagulant activity.

Nam et al. 31 discovered that when taken concurrently with a sulfonylurea in type 2 diabetes, warfarin was linked with an increased risk of severe hypoglycemia, which was more evident after extended concomitant treatment. As a result, patients are at a higher risk of hypoglycemia, which might lead to hospitalization or admission. These individuals should be continuously followed in order to decrease their risk of hypoglycemia and improve their quality of care 31. However, decreased intrinsic clearance caused by metabolic restriction, the elimination of unbound warfarin would have been considerably delayed 27. As a result, suppression of CYP2C9 appears to explain the observed effect of glibenclamide on warfarin's anticoagulant activity.

These findings might be explained by warfarin's suppression of osteocalcin carboxylation and a positive feedback loop. Osteocalcin is a protein that osteoblasts generate during bone growth. Its uncarboxylated form increases insulin secretion both directly on pancreatic islet cells and indirectly by increasing glucagon-like peptide-1 production from the small intestine 32. Furthermore, uncarboxylated osteocalcin enhances insulin sensitivity 33, with the combined impact predicted to lower blood glucose. The conversion of osteocalcin to its carboxylated form, which has no effect on glucose metabolism, requires vitamin K and is blocked by warfarin 34.

In conclusion, our data suggest that doctors and patients should be aware of the increased risk of severe hypoglycemia associated with the use of warfarin during sulfonylurea treatment. When using warfarin and glibenclamide together, the doses of both drugs must be reduced to avoid severe drug-drug interactions such as bleeding and hypoglycemia. These patients must be monitored more closely to reduce their risk of hypoglycemia and improve their quality of care.

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التفاعل الدوائي المحتمل بين الوارفارين والجليبينكلاميد في نموذج الجرذان المصاب بداء السكري وفرط التخثر

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الخلفية: إنمرضى السكري معرضون لعدد من الظواهر في الأوعية الدموية. لذلك، مرضا السكري الذين يعالجون بالأدوية المضادة لمرض السكر عن طريق الفم مثل جليبينكلاميد، يمكن علاجهم أيضاً بدولة مضادة للتخثر عن طريق الفم أيضا مثل الوارفارين، للوقاية والعلاج من ظواهر جدال الن 보면يات الأولية (الدوية أو (التخثر العصيدي).

الهدف من الدراسة: أجريت الدراسة الحالية لتقييم التفاعلات الدوائية المحتملة بين الوارفارين والجليبينكلاميد في الفئران المصاب بداء السكري وحالة فرط التخثر.

المواضب والطرق المستخدمة: تم توزيع خمسين من ذكور الجرذان البالغة (30-39 جم) وتوزيعها في مجموعات فرعية: أولا: مجموعة المقارنة. ثانيا: المجموعة المصاببة بمرض السكر وفرط التخثر. ثالثا: الجرذان المصاببة بمرض السكر وفرط التخثر التي عولجت بالوارفارين (0.2 مجم / كجم) عن طريق الفم لمدة 5 أيام متناوبة; المجموعة الرابعة: الجرذان المصاببة بمرض السكر وفرط التخثر المعالجة بالجليبينكلاميد (0.2 مجم / كجم) عن طريق الفم لمدة 5 أيام متناوبة.

والمجموعة الخامسة: الجرذان المصاببة بمرض السكر وفرط التخثر والمعالجة بالوارفارين (0.2 مجم / كجم) والجليبينكلاميد (0.1 مجم / كجم) عن طريق الفم لمدة 5 أيام متناوبة. تم تقسيم المعايير التالية بعد خمسة أيام، زمن البروترومبين، زمن الترومبولاستين الجزيئي المنشط، زمن التخثر، زمن النزف، ومستوى الجلوكوز في الدم والهيموجلوكوبين الجليكونيلي.

النتائج: أظهرت النتائج أن زمن البروترومبين، زمن الترومبولاستين الجزيئي المنشط، زمن التخثر، زمن النزف، قد تم إطالة ألمها بشكل كبير بينما تم تقليل أو انخفاض مستوى الجلوكوز في الدم والهيموجلوكوبين الجليكونيلي بشكل ملحوظ عندما تم إعطاء الوارفارين والجليبينكلاميد معاً أكثر من إعطاء كل منهما بمفرده.

الاستنتاج: حدوث تفاعلات بين الأدوية عندما تم تناول الوارفارين والجليبينكلاميد معاً.