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Full Length Research Paper

Sex differences in the neuroprotective effect of insulin against chemically-induced convulsions in mice

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Insulin, an important regulator of peripheral metabolism, has been reported to interact with many neurotransmitter systems including those associated with convulsion. The effect of insulin against pentylenetetrazole and strychnine-induced convulsions in mice, as well as possible sex differences, were evaluated in this study. Mice of both sexes weighing between 20 and 25 g were administered insulin intraperitoneally at doses of 1, 2, 4 and 8 IU/kg. Each mouse received a convulsive dose of pentylenetetrazole (100 mg/kg, i.p.) or strychnine (2 mg/kg, i.p.) and was observed for the onset of convulsions and occurrence of death. Against pentylenetetrazole-induced convulsions, all the doses of insulin used significantly ($p < 0.05$) prolonged the onset of convulsions and significantly delayed the time of death in male mice when compared with control. However, in female mice, only insulin 8 IU/kg significantly prolonged the onset of convulsions, while insulin 4 IU/kg significantly delayed the time of death. Against strychnine-induced convulsions, insulin at the doses of 2 and 4 IU/kg significantly ($p < 0.05$) prolonged the onset of convulsions in male mice relative to control, while 8 IU/kg insulin significantly prolonged the time of death in male mice compared to control. However, none of the doses of insulin administered to female mice were effective against strychnine-induced convulsions. These results show that insulin produced sex-related protective effects against chemically-induced convulsions in mice.

Keywords: Insulin, convulsion, pentylenetetrazole, strychnine, male mice, female mice.

INTRODUCTION

Insulin, a polypeptide hormone produced by the β -cells of the Islets of Langerhans in the pancreas, interacts with its receptors in peripheral tissues like liver, fat and muscle to

stimulate the uptake of glucose, fatty acids and amino acids leading to their storage as glycogen, fats and proteins respectively. The central nervous system (CNS)

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was previously thought to be insulin insensitive, but the discovery of insulin and its receptors in the CNS in 1967 and 1978 respectively, radically changed this view (Wada et al., 2005; Huang et al., 2010). Since then, there has been extensive research into the activities of insulin and its receptors in the brain and spinal cord.

Insulin receptors in the CNS and those in peripheral tissues share similar structural and functional characteristics. The insulin receptor, a member of the tyrosine kinase receptor family, is a big trans-membrane glycoprotein formed from two 135,000 Da α subunits and two 95,000 Da β subunits linked by disulphide bonds to form a β - α - α - β heterotetramer (Bedse et al., 2015). When insulin binds to its receptors in the CNS, diverse neuronal effects are produced. Insulin and its receptors in the CNS have been found to play various roles far beyond their traditional peripheral effects. They are now known to play important roles in the growth, structure and function of neurons, and promote cognitive functions such as learning and memory, while impaired insulin receptor signaling has been linked to the pathogenesis of neurodegenerative diseases like Alzheimer's and Parkinson's diseases (Chiu and Cline, 2010; Bedse et al., 2015; Neth and Craft, 2017). Previous works have also reported the neuromodulatory actions of insulin in the CNS by regulating receptor density and affinity at the membrane surface and tyrosine phosphorylation of receptor subunits (Wan et al., 1997; Caraiscos et al., 2007; Ferrario and Regan, 2018). Insulin receptor signaling has thus been implicated in the regulation of synaptic neurotransmission, playing an important role in synaptic plasticity, learning and memory.

Convulsions or seizures result from disturbances in both excitatory and inhibitory neurotransmitter systems, including the glutamatergic and gabaergic systems (Koutroumanidou et al., 2013). Insulin receptor signaling has been reported to modulate the gabaergic, NMDA and glycinergic systems, among other neurotransmitter systems (Caraiscos et al., 2007; Neth and Craft, 2017; Trujeque-Ramos et al., 2018). Therefore, this study investigated the effect of insulin on convulsions induced by the administration of pentylenetetrazole and strychnine in mice. Due to the reported existence of sex differences in some metabolic effects of insulin (Woods et al., 2003; Clegg et al., 2006; Hallschmid et al., 2012), possible sex-related differences in the effect of insulin on convulsions were explored by the use of both male and female mice.

MATERIALS AND METHODS

Animals

Adult mice of both sexes (Vom strain, National Veterinary Research Institute, Jos, Nigeria) weighing between 20.0 and 25.0 g were used in this study. They were inbred and maintained under natural

daylight/night condition at the Animal House of Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife. Females were kept separately from males to prevent mating. All animals were fed with standard feeds (Pfizer Feed Plc, Lagos, Nigeria) and had access to food and water *ad libitum*. The experimental protocols followed the internationally accepted principles for laboratory animal use and care (EEC directive of 1986; 86/609/EEC; Ethical clearance certificate number for the use of animals: PHP11/12/H/2764).

Drugs

Insulin (Actrapid®: Novo Nordisk, Bagsvaard, Denmark), pentylenetetrazole (Sigma Chemicals, St. Louis, USA), strychnine (Sigma-Aldrich, Switzerland), phenobarbital (Evans Medical, London, United Kingdom) and diazepam (Roche, Basel, Switzerland), dextrose 50% solution (Unique Pharmaceuticals, Sango-Ota, Nigeria) were used. Fresh solutions of appropriate concentrations of the drugs were prepared just before the test for each series of experiment. Drugs were administered to the animals intraperitoneally at a volume of 1 ml/100 g body weight.

Evaluation of pentylenetetrazole-induced convulsions

Six groups of mice (n = 16; males = 8, females = 8) were administered normal saline 10 ml/kg (i.p.), diazepam 2 mg/kg (i.p.) and insulin 1, 2, 4 and 8 IU/kg (i.p.) respectively. The mice administered normal saline or diazepam received a subsequent dose of normal saline 10 ml/kg (i.p.), while the mice that were administered insulin received a subsequent dose of dextrose solution 3 g/kg (i.p.) in order to offset the hypoglycemic effect due to insulin (Uysal et al., 1996; Siegel et al., 2014). Twenty minutes after the administration of normal saline, and insulin, and 30 minutes after diazepam administration, each mouse received a convulsive dose of pentylenetetrazole 100 mg/kg (i.p.). The onset of convulsions (in seconds) and time of death (in seconds), within a period of 1 and 24 h respectively, were recorded as previously described (Hamad et al., 2014).

Evaluation of strychnine-induced convulsions

Six groups of mice (n = 16; males = 8, females = 8) received normal saline 10 ml/kg (i.p.), phenobarbital 30 mg/kg (i.p.) and insulin 1, 2, 4 and 8 IU/kg (i.p.) respectively. The mice administered normal saline or phenobarbital received a subsequent dose of normal saline 10 ml/kg (i.p.), while the mice that were administered insulin received a subsequent dose of dextrose solution 3 g/kg (i.p.) in order to offset the hypoglycemic effect due to insulin (Uysal et al., 1996; Siegel et al., 2014). 20 min after the administration of normal saline and insulin, and 30 min after phenobarbital administration, each mouse received a convulsive dose of strychnine 2 mg/kg (i.p.). The onset of convulsions (in seconds) and time of death (in seconds), within a period of 1 and 24 h respectively, were recorded as previously described (Salahdeen and Yemitan, 2006; Hamad et al., 2014).

Statistical analysis

All data was analyzed by one-way analysis of variance (ANOVA), and Student – Newman – Keuls post-hoc test was carried out to determine a significant effect. Analyses were undertaken using the Primer of Biostatistics software (Version 3.01, 1992) and GraphPad Prism software (Version 5.01, 2007). Results were expressed as

Table 1. Effect of insulin administration on the onset of pentylenetetrazole-induced convulsions in male and female mice.

SEX	Group 1 (NS +NS)	Group 2 (DZP+NS)	Group 3 (1 IU+DEX)	Group 4 (2 IU + DEX)	Group 5 (4 IU+ DEX)	Group 6 (8 IU+DEX)
Males	62.71±5.83	>>3600.00*	117.30±8.76*	94.38±9.70*	103.70±11.46*	96.63±6.25*
Females	58.88±4.64	>>3600.00*	90.75±13.33	85.25±5.15	89.00±11.47	105.50±20.46*

NS: normal saline 10 ml/kg; DZP: Diazepam 2 mg/kg; 1 IU, 2 IU, 4 IU and 8 IU: Insulin dose (IU/Kg); DEX: Dextrose solution 3 g/kg. * $p < 0.05$.

Table 2. Effect of insulin administration on the time of death following pentylenetetrazole-induced convulsions in male and female mice.

SEX	Group 1 (NS +NS)	Group 2 (DZP+NS)	Group 3 (1 IU+DEX)	Group 4 (2 IU + DEX)	Group 5 (4 IU+ DEX)	Group 6 (8 IU+DEX)
Males	304.20±56.77	>>86400.00*	591.60±122.80*	621.90±89.59*	725.30±64.26*	549.80±71.19*
Females	284.60±46.90	>>86400.00*	536.40±77.36	389.00±77.61	604.30±75.29*	481.80±71.08

NS: normal saline 10 ml/kg; DZP: Diazepam 2 mg/kg; 1 IU, 2 IU, 4 IU and 8 IU: Insulin dose (IU/Kg); DEX: Dextrose solution 3 g/kg. * $p < 0.05$.

Table 3. Effect of insulin administration on the onset of strychnine-induced convulsions in male and female mice.

SEX	Group 1 (NS +NS)	Group 2 (PNB+NS)	Group 3 (1 IU+DEX)	Group 4 (2 IU + DEX)	Group 5 (4 IU+ DEX)	Group 6 (8 IU+DEX)
Males	113.30±8.10	203.30±30.51*	130.50±7.56	181.30±26.55*	233.90±13.41*	168.30±7.32
Females	176.10±19.92	200.90±16.78	143.80±10.84	179.50±13.02	193.80±13.36	178.40±17.13

NS: normal saline 10 ml/kg; PNB: Phenobarbital 30 mg/kg; 1 IU, 2 IU, 4 IU and 8 IU: Insulin dose (IU/Kg); DEX: Dextrose solution 3 g/kg. * $p < 0.05$.

mean ± standard error of mean (S.E.M.). $p < 0.05$ was taken as significant difference from control.

RESULTS

Effect of insulin on the onset of convulsions following pentylenetetrazole administration in male and female mice

In both male and female mice, diazepam completely prevented the occurrence of convulsions after pentylenetetrazole administration. In male mice, all the doses of insulin used in this study significantly delayed the onset of convulsions when compared with normal saline. However, only insulin 8 IU/kg significantly delayed the onset of convulsions in females as described in Table 1.

Effect of insulin on the time of death following pentylenetetrazole administration in male and female mice

There was complete prevention of death in the diazepam-treated groups in both male and female mice. Insulin at all the doses used significantly prolonged the time of

death in male mice when compared with normal saline, whereas in female mice only insulin 4 IU/kg significantly prolonged the time of death as shown in Table 2.

Effect of insulin on the onset of convulsions following strychnine administration in male and female mice

The administration of phenobarbital significantly delayed the onset of convulsions in male mice following the administration of strychnine when compared with normal saline, but it did not in females. Insulin doses of 2 and 4 IU/kg significantly delayed the onset of convulsions in males, whereas no insulin dose significantly affected the female mice as presented in Table 3.

Effect of insulin on the time of death following strychnine administration in male and female mice

Phenobarbital administration significantly prolonged the time of death in both male and female mice compared with normal saline. While insulin 8 IU/kg prolonged the time of death significantly in male mice, none of the insulin doses had a significant effect on the time of death

Table 4. Effect of insulin administration on time of death following strychnine-induced convulsions in male and female mice.

SEX	Group 1 (NS +NS)	Group 2 (PNB+NS)	Group 3 (1 IU+DEX)	Group 4 (2 IU + DEX)	Group 5 (4 IU+ DEX)	Group 6 (8 IU+DEX)
Males	263.00±45.04	>>86400.00*	167.50±6.13	223.70±43.56	290.50±24.80	462.00±33.34*
Females	244.60±28.69	513.70±91.80*	201.60±14.03	194.70±11.42	221.10±8.50	230.70±28.36 [†]

NS: normal saline 10 ml/kg; PNB: Phenobarbital 30 mg/kg; 1 IU, 2 IU, 4 IU and 8 IU: Insulin dose (IU/Kg); DEX: Dextrose solution 3 g/kg. * $p < 0.05$.

in female mice as shown in Table 4.

DISCUSSION

The effect of insulin on chemically-induced convulsions in male and female mice was determined using pentylentetrazole and strychnine-induced convulsions in this study. Diazepam, a known benzodiazepine receptor agonist, at the dose of 2 mg/kg (i.p.) completely abolished seizures induced by pentylentetrazole (100 mg/kg, i.p.) in both male and female mice, and prevented mortality within 24 h. Diazepam produces anticonvulsant effect by promoting gabaergic synaptic inhibition in the brain. It binds to its site on the GABA_A receptor and increases the frequency with which the chloride ion channel of the receptor opens, thereby increasing the efficiency of GABA (Nutt and Malizia, 2001). Although insulin did not prevent the incidence of convulsions or mortality due to pentylentetrazole administration in this study, the results obtained are suggestive of a sex-related difference in the protective effect of insulin against pentylentetrazole-induced convulsions. Previous studies have reported a differential sensitivity to insulin in male and female rats which was due to the effect of gonadal hormones (Clegg et al., 2006; Hallschmid et al., 2012). The sex difference observed in insulin's effect in this study could be attributed to hormonal differences between male and female mice. Insulin has been reported to upregulate GABA_A receptors on the post-synaptic membrane through receptor recruitment thereby increasing GABA-mediated inhibition in CNS (Wan et al., 1997; Trujeque-Ramos et al., 2018). This could account for the protective effect that insulin produced against pentylentetrazole-induced convulsion reported in this study.

Phenobarbital, a GABA_A receptor agonist, enhances the effect of GABA by increasing the duration of chloride ion channel opening (Löscher and Rogawski, 2012). In this study, phenobarbital at the dose of 30 mg/kg (i.p.) delayed the occurrence of seizures and prevented mortality due to strychnine-induced convulsion in male mice but not in female mice. Strychnine produces convulsions by binding to glycinergic receptors in the CNS (Maher et al., 2014). There is no report of a sex

difference in the anticonvulsant effect of phenobarbital against strychnine-induced convulsion in previous studies. Insulin at all the doses used in this study did not prevent the incidence of convulsions or mortality resulting from strychnine-induced convulsions in male and female mice, but it conferred some protection against strychnine-induced convulsion in male mice. Insulin has been reported to increase the potency of glycine on its receptors in the CNS (Caraiscos et al., 2007; Yan-Do and MacDonald, 2017). The protective effect of insulin against strychnine-induced convulsion in male mice suggests that insulin facilitated glycine-mediated inhibition in the CNS. However, the doses of insulin that produced protective effects against strychnine-induced convulsions in male mice were not effective in females. Therefore, the effects of insulin as well as phenobarbital against strychnine-induced convulsions in male and female mice revealed sex differences in this study.

CONCLUSION

The results obtained from this study showed that insulin produced protective effects against chemically-induced convulsion in mice, probably via facilitation of the gabaergic and glycinergic inhibitory neurotransmitter systems. This effect of insulin was sex-related as female mice were not protected against pentylentetrazole and strychnine-induced convulsions at certain doses of insulin that protected male mice in this study. Therefore, the results of this work demonstrated sex differences in the response of mice to varying doses of insulin used against chemically-induced convulsions. Further studies are required to elucidate the mechanisms mediating these sex differences.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Effect of amodiaquine on the pharmacokinetics of gliclazide in diabetic subjects

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The study aims at investigating the effect of amodiaquine on the pharmacokinetic profile of gliclazide. It is a one-way single dose cross-over study in two phases. Six freshly diagnosed diabetic volunteers were used. The subjects acted as their own control, and each phase was preceded by an overnight fast. Phase 1 of the study involved the administration of a single oral dose of 80 mg of gliclazide after an overnight fast. After a wash out period of one week, 80 mg gliclazide and 300 mg amodiaquine were co-administered. Serial blood samples were collected over a period of 24 h during each phase into an Ethylenediaminetetraacetic acid (EDTA) vacutainer. After collection, blood samples were processed. A validated High Performance Liquid Chromatography (HPLC) method was used in the estimation of serum gliclazide concentration. Glucose oxidase peroxidase method was used in the estimation of blood glucose concentration. The pharmacokinetic parameters derived by a non-compartmental analysis with two periods (gliclazide alone and in combination with amodiaquine) were compared. The pharmacodynamics as measured by blood glucose concentration was also compared for the 2 phases of the study. Results showed that though amodiaquine affects the rate of absorption of gliclazide, it does not affect the bioavailability and overall disposition of gliclazide after a single oral dose. A lack of pharmacodynamic interactions between amodiaquine and gliclazide was also observed. Conclusively, amodiaquine and gliclazide can be concurrently administered together without fear of loss of activity.

Key words: Diabetes mellitus, gliclazide, amodiaquine, drug Interactions, pharmacokinetics.

INTRODUCTION

Diabetes mellitus is a condition primarily defined by the level of hyperglycaemia, in which the body's cells are

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starved of energy despite high blood glucose levels (WHO, 2016; CDC, 2017a). The diseases are mainly of two types: Type 1 (insulin dependent) usually diagnosed in children, teenagers and young adults; and Type 2 (non-insulin-dependent) often associated with older age. There is also gestational diabetes associated with pregnancy. The disease results in reduced life expectancy, significant morbidity, risk of microvascular damage (Chawla et al., 2016; Mohammedi et al., 2017), increased risk of macrovascular complications, and diminished quality of life (WHO, 2016; Mohammedi et al., 2017). Other complications of diabetes may include increased susceptibility to other diseases, loss of mobility with aging and depression (CDC, 2017b).

The prevalence of diabetes has steadily increased for the past 3 decades and is growing most rapidly in low- and middle-income countries (WHO, 2016). About 1 in 11 adults worldwide have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (Zheng et al., 2017). More than 16 million people were estimated to have diabetes in the AFRO Region and the figure is expected to increase to 41 million to by the year 2045 (IDF, 2016). Polypharmacy is common in clinical practice (Greenblatt et al., 2017; Rodrigues et al., 2017). The chronic treatment with one drug may be supplemented by a further short-term treatment with a second drug, or several drugs may be co-administered on a long-term basis (Greenblatt et al., 2017; Rodrigues et al., 2017). In malarial endemic areas, the need for polypharmacy for diabetic patients becomes obvious in majority of patients (Greenblatt et al., 2017). It is therefore important to consider the possibility of drug interactions (Labaune, 1989).

Drug interactions occur when two or more compounds are administered simultaneously and one drug affects the pharmacokinetics or the pharmacological activity of the other. These may be complex and influenced by many factors (Labaune, 1989; Ogunbona et al., 2014). Among the various hypoglycaemic agents, gliclazide (a sulphonylureas) have been widely used in clinical practice (Colagiuri et al., 2018; Kalra et al., 2018; Leiter et al., 2018). Gliclazide has the advantage of less likely to experienced secondary failure (Wang et al., 2017), owing to their well-established efficacy and safety profile. It is a drug of choice for the treatment of type 2 diabetes mellitus in the elderly (Sola et al., 2015), children and adolescents (Onge et al., 2015), pregnancy and lactation (Kavitha et al., 2013); and those with both micro-vascular and macro-vascular complications (Campbell, 1991; Avogadro, 2012; Azimova et al., 2014). The drug mainly affects insulin secretion in second phase of type 2 diabetes mellitus (Ligtenberg et al., 2001).

Several established antimalarial drugs are known to promote insulin secretion which in certain circumstances may cause or contribute to hypoglycemia (Davis et al., 1997). Amodiaquine, is a cheap synthetic 4-

aminoquinoline antimalarial (O'Neill et al., 2003). Its activity is characterized by a schizonticidal action on the *Plasmodium* species by destroying intra erythrocytic forms. The drug has been used in artemisinin combinations (WHO, 2003, 2006) in the treatment of malaria resistant *Plasmodium falciparum* (Raobela et al., 2018). With such widespread usage of amodiaquine combinations in diabetes patients, drug interactions with gliclazide become a possibility. To the best of our knowledge, there is very little work done on possible interactions of gliclazide with amodiaquine. This study, therefore, is aimed at investigating the effect of amodiaquine on the pharmacokinetic profile of gliclazide in freshly diagnosed diabetic volunteers.

MATERIALS AND METHODS

Subjects and ethical clearance

The subjects were diagnosed of diabetes mellitus at the Medical Outpatient Department of Barau-Dikko Teaching Hospital, in Kaduna, Nigeria. For the purposes of this study, diagnosis of diabetes mellitus was made by the presence of classic symptoms of hyperglycemia and fasting plasma glucose concentration ≥ 130 mg/dL. The study plan was approved by Kaduna State Ministry of Health Ethical Committee (approval number MOH/ADM/744/T/17, dated 29th January, 2010) in accordance with the National Code of Health Research Ethics (2006), Federal Ministry of Health, Nigeria; and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was carried out at Barau-Dikko Teaching Hospital (formerly, Barau-Dikko Specialist Hospital), Kaduna, Nigeria between October and December, 2011. All volunteers gave their written informed consent, which was documented and archived.

Inclusion/exclusion criteria

At baseline, a structured questionnaire was completed for each volunteer that included medical history, prior hospital admissions, and clinical and laboratory data. For inclusion, volunteers for the study are patients freshly diagnosed and were on lifestyle modification, willingness to fill an informed consent form, non-smokers, non-alcohol drinking, and willingness to abstain from heavy exercise. They were not on other medications and caffeine during the study, and have a Body Mass Index (BMI) of less than 30 kg/m^2 . Pregnancy and currently undergoing any medication or planned treatment during the study period were excluded.

Study design and blood sampling

The protocol adopted was a one-way single dose cross-over study in two periods. Each phase was preceded by an overnight fast. The subjects act as their own control. Phase 1 of the study involved the administration of a single oral dose of 80 mg of gliclazide after an overnight fast. After a wash out period of one week, 80 mg gliclazide and 300 mg amodiaquine were co-administered. Serial blood samples (5 ml) were collected at intervals of 0, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 h during each phase into an EDTA vacutainer.

Blood sample processing

After collection, blood samples centrifuged at 2000 rpm and plasma kept frozen in a freezer maintained at -20°C prior to analysis. For the extraction of gliclazide from the plasma, the frozen plasma was thawed and to 1 ml of plasma were added 0.1 ml of glipizide (internal standard, 20 µg/ml), 0.2 ml of 0.4 mol/l HCl, 5.0 ml of benzene- isopropanol (98:2, v/v) and was vortex-mixed for 2 min. Then mixed samples were centrifuged at 2000 rpm for 5 min. 4.0 ml of the upper layer was transferred into another tube. The extraction was dried in a hot air oven (Memmert 854 Schwalbach, Germany) at 40°C. The residue was resolved with 0.15 ml methanol and 20 µl of solution was injected into the liquid chromatograph.

Determination of plasma gliclazide concentration

A validated High Performance Liquid Chromatography (HPLC) method (Yang et al., 2004) was used in the estimation serum gliclazide concentration using a HPLC instrument (Shimadzu® chromatograph-LC-10 series, Japan). The data was validated for range, accuracy, repeatability, intermediate precision, coefficient correlation, sensitivity and system suitability parameters were calculated. The system used (Shimadzu Corporation, Kyoto Japan) consist of Ultra-Fast LC-20AB prominence with the following accessories: SIL-20AC auto-sampler; DGU-20A3 degasser; SPD-M20A UV-diode array detector; 5 µm VP-ODS C₁₈ and dimensions (4.6 x 150 mm); CTO-20AC column oven, CBM-20Alite system controller and Windows LCsolution software. The chromatographic conditions were made up of a mobile phase: solvent A: water (pH 2.8) 51%; solvent B: acetonitrile 49%; mode: isocratic; flow rate 1 ml/min; injection volume 20 µl detection UV 229 nm Column oven temperature was 40°C. Glipizide was used as an internal standard. The total run time was 7.5 min.

Determination of glucose concentration

Plasma glucose concentration was measured over a period of 24 h at 9 time points-interval. Glucose oxidase peroxidase method (Trinder, 1969) was used. 10 µl of the plasma sample (A_{sample}) or standard (A_{standard}) was pipetted into a 1.5 ml microcentrifuge tube containing 1000 µl of the glucose reagent (Randox) mixed well and incubated for 10 min at 20±5°C. The slightly pink mixture was then transferred to 1 cm path length cuvette and the absorbance of the standard and sample were measured at λ 500 nm against the 1000 µl reagent blank within 30 min. Glucose concentrations were determined according to the following equation: Glucose Concentration (mmol/L) = $\frac{A(\text{sample})}{A(\text{standard})} \times 5.5$. In the plasma glucose concentration for all time points between the two phases of the study were compared.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using a non-compartmental method. The pharmacokinetic parameters were determined for the two phases of the study. The Pharmacokinetic Software - PharmPK software (Joel et al., 2012) was used to generate the following Pharmacokinetic parameters: Maximum plasma concentration (C_{max}), Time to maximum plasma concentration (t_{max}), Total body clearance (Cl), Volume of distribution (VD), Area under the curve from zero hours to last measurable concentration (AUC_{0-t}), Area under the curve (from zero hours to infinity) ($AUC_{0-\infty}$), Area under the Moment curve from zero

hours to last measurable concentration ($AUMC_{0-t}$), Area under the Moment curve from zero hours to infinity ($AUMC_{0-\infty}$), Elimination half- life ($t_{1/2\text{eli}}$), Elimination rate constant (K_{eli}). The method of residual was used to generate Absorption half- life ($t_{1/2\text{abs}}$), Absorption rate constant (K_{abs}) using Microsoft excel. Total body clearance (Cl), volume of distribution (VD) and Mean residence time (MRT).

Statistical analysis

Data were expressed as mean±SEM. GraphPad Prism Version 7.02 software for Windows (San Diego California, USA) was used for data analysis using Wilcoxon (matched-pairs) signed rank test with $p < 0.05$ considered significant.

RESULTS

Subjects

Six freshly diagnosed diabetic subjects (2 males and 4 females) on dietary and lifestyle modification met the inclusion criteria. Their mean age (years) were 55.6±5.7, and mean Body Mass Index (BMI) of 27.25±2.3. All subjects completed the treatment periods and were included in the pharmacokinetic analysis.

Plasma gliclazide concentration

Table 2 showed the mean pharmacokinetic parameters generated after a single oral dose of 80 mg of gliclazide alone and when used concomitantly with 300 mg of amodiaquine. Changes observed are: a 46% decrease in C_{max} ($p=0.0313$); 18% decrease in T_{max} ($p=0.8125$); 35% decrease in k_{eli} ($p=0.2188$); 16% increase in T_{eli} ($p=0.8438$); 12% decrease in AUC_{0-t} ($p=0.6875$); 5% increase in $AUC_{0-\infty}$ ($p>0.9999$); 14% increase in $AUMC_{0-t}$ ($p=0.8438$), $AUMC_{0-\infty}$ ($p=0.2188$), MRT ($p=0.1563$); 2% decrease in clearance ($p>0.9999$); 23% increase in VD ($p=0.1563$); and 58% decrease in $T_{1/2\text{abs}}$ ($P=0.0625$); K_{abs} ($p=0.0938$).

Glucose concentrations

Table 3 shows the mean glucose concentration over time. There were no significant changes ($p>0.05$) in the time glucose level profile for the various time points measured.

DISCUSSION

Polypharmacy is common in diabetic patients (Al-mohamadi and Ibrahim, 2015). Despite this growing phenomenon, the influence of diabetes on drug

Table 1. Summary of validation parameters.

S/N	Validation parameter	Value
1	Number of theoretical plates	3486
2	Retention time of Gliclazide (min)	4.8
3	Retention time of internal standard (Glipizide)	3.4
4	Resolution	2.5
5	Asymmetry factor	1.5
6	Tailing factor	1.3
7	LOD ($\mu\text{g/ml}$)	1 $\mu\text{g/ml}$
8	LOQ ($\mu\text{g/ml}$)	3 $\mu\text{g/ml}$
9	Range	5-30.0 $\mu\text{g/ml}$
10	Slope	0.01338312
11	intercept	0.115870857
12	Coefficient correlation (r)	0.9778
13	Accuracy (n=9)	93.0 \pm 0.39 %
14	Repeatability (within run) {n=20}	5.95 \pm 0.38 (CV %)
15	Intermediate precision (between run) {n=20}	6.85 \pm 0.46 (CV %)
16	λ_{max}	229 (nm)

metabolism in polypharmacy has not been fully investigated (Pinnamraju et al., 2018). This study evaluated the effect of 300 mg amodiaquine co-administered with 80 mg gliclazide in freshly diagnosed diabetes subjects which were not yet placed on treatment. This is to preclude the need for concomitant drug intake during the course of the study. Table 1 shows a summary of the validation parameters affirming the suitability of the method for the quantitation of gliclazide in humans.

As shown in the result, all the pharmacokinetic parameters generated (except for C_{max}) were not significantly altered ($p > 0.05$) clearly denoting a lack of significant pharmacokinetic interactions between gliclazide and amodiaquine. The significant decrease in C_{max} even though with non-significant changes in T_{max} ($p = 0.8125$), $T_{1/2\text{abs}}$ ($p = 0.0625$), K_{abs} ($p = 0.0938$) showed that the rate of absorption of gliclazide might still have been affected. However, a non-significant change in AUC denotes that the extent of absorption of gliclazide has not been affected, and non-significant changes in AUMC, shows that the total drug absorption has not been significantly affected. The change in C_{max} may be indicative of drug interaction in the absorptive state. Several factors are known to affect drug absorption through the gastrointestinal tract and this include a change in gastric pH, formation of complexes and motility disorders (Palleria et al., 2013). For most orally administered drugs, drug absorption occurs at a gastric pH of between 2.5 and 3, hence drugs able to increase gastric pH has the possibility of changing the kinetics of

co-administered drugs (Palleria et al., 2013). Amodiaquine is a basic drug with a pKa on the acidic side of 9.2 and basic side of Strongest Basic of 10.23; Co administration with gliclazide (pKa of 5.8) may have the likelihood of increasing gastric pH, thus possibly causing a decrease in drug dissolution and absorption of gliclazide. This effect might still need to be studied after multiple drug administration of the two drugs. The minimum detectable plasma gliclazide concentration obtained at T_{max} above reported values by most studies for hypoglycaemic activity (Czyrski et al., 2018). Thus, the observed changes in the C_{max} may not be of clinical significance.

In the same manner, non-significant changes in the clearance, MRT shows that duration of action of gliclazide might not been affected by amodiaquine. It has been reported that gliclazide is highly protein bound with a protein binding of 84-99% (Campbell et al., 1991). The low volume of distribution (VD) observed, thus further confirms the protein binding properties of gliclazide. The non-significant change in the VD of gliclazide makes displacement by amodiaquine from protein binding sites very unlikely. There were no significant changes ($p > 0.05$) in the time glucose level profile for the various time points measured. This suggests amodiaquine does not have significant effect on the pharmacodynamics of gliclazide after a single oral dose. These data support the use of amodiaquine in malaria infected diabetic patients on gliclazide treatment. The time glucose profile also shows a monophasic blood glucose reduction further explaining the monophasic blood gliclazide time profile.

Table 2. Mean pharmacokinetics parameters of gliclazide (n=6).

Variable	Control (Gliclazide alone)		Gliclazide+Amodiaquine		Wilcoxon (matched-pairs) signed rank test (p-Value)	
	Mean	SEM(\pm)	Mean	SEM(\pm)		
C _{max} ($\mu\text{g/ml}$)	4.057	0.195	2.205	0.108	*p<0.05	(p=0.0313)
T _{max} (h)	5.667	0.272	4.667	0.276	p>0.05	(p=0.8125)
K _{eli} (h ⁻¹)	0.122	0.044	0.079	0.030	p>0.05	(p=0.2188)
T _{1/2 eli} (h)	8.434	0.438	9.744	0.295	p>0.05	(p=0.8438)
AUC _{0-t} ($\mu\text{g.h/ml}$)	30.636	0.508	27.034	0.455	p>0.05	(p=0.6875)
AUC _{0-inf} ($\mu\text{g.h/ml}$)	33.528	0.609	35.117	0.570	p>0.05	(p>0.9999)
AUMC _{0-t} ($\mu\text{g.h}^2/\text{ml}$)	213.552	1.394	267.862	1.709	p>0.05	(p=0.8438)
AUMC _{0-inf} ($\mu\text{g.h}^2/\text{ml}$)	235.481	1.715	403.757	2.196	p>0.05	(p=0.2188)
MRT (h)	7.044	0.295	11.120	0.264	p>0.05	(p=0.1563)
Cl (mlh ⁻¹)	2610.625	5.241	2557.648	6.617	p>0.05	(p>0.9999)
VD (ml)	26759.117	22.020	33045.591	18.314	p>0.05	(p=0.1563)
T _{1/2 abs} (h)	2.299	0.189	0.968	0.173	p>0.05	(p=0.0625)
K _{abs} (h ⁻¹)	0.340	0.070	1.194	0.155	p>0.05	(p=0.0938)

*Significant at p \leq 0.05.**Table 3.** Mean Glucose Conc. (mmol/l) (n=6).

Time (h)	Control (Gliclazide alone)		Gliclazide+Amodiaquine		Wilcoxon (matched-pairs) signed rank test(p-value)	
	Mean	SEM(\pm)	Mean 2	SEM(\pm)		
0	11.279	0.288	9.882	0.255	p>0.05	(p=0.3125)
0.5	10.219	0.310	10.096	0.284	p>0.05	(p=0.8438)
1	9.382	0.310	9.704	0.288	p>0.05	(p>0.9999)
2	8.867	0.293	8.661	0.314	p>0.05	(p>0.9999)
4	9.369	0.311	7.209	0.299	p>0.05	(p=0.5625)
8	10.251	0.319	9.387	0.151	p>0.05	(p=0.0625)
12	10.119	0.302	9.895	0.325	p>0.05	(p=0.8438)
16	10.832	0.295	11.533	0.279	p>0.05	(p=0.5625)
24	11.158	0.288	13.349	0.287	p>0.05	(p=0.3125)

*Significant at p \leq 0.05.

Conclusion

The studies showed that though amodiaquine affects the rate of absorption of gliclazide, it does not affect the bioavailability and overall disposition of gliclazide after a single oral dose. A lack of a pharmacodynamic interaction between amodiaquine and gliclazide was also observed hence, the drugs may be co-administered. Study after a multiple dose administration of these drugs is therefore suggested to see if similar effects can be validated.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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