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 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 (ml.h^{-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≤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≤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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