Pharmacodynamics model of the effect of gliclazide therapy on Hemoglobin A1C in response in patients with type 2 diabetes

Abdel Qader Al Bawab[1], Anwaar Jaffal[1], Mohammad Issa Saleh[2]

1: Al-Zaytoonah University of Jordan

2: Jordan University

INTRODUCTION

Diabetes is a global health issue that affects more than 425 million people and is expected to affect over 690 million people by 2045 [1]. Because of its large propagation and related economic costs, diabetes is considered a main public health concern nationally and worldwide [2]. Gliclazide (GLC) is a very commonly used oral hypoglycemic agent that is used in treatment of type 2 diabetes [3]. As per the clinical treatment guidelines; GLC is considered as a second line treatment that is typically used concomitantly with metformin [4]. Predictors to clinical outcome of using GLC (with metformin as a background therapy) is lacking. This study sheds the light of various predictors that are correlated to the effect of GLC on glycated hemoglobin (HbA1c) and facting plasma glucose (FPG).

OBJECTIVES

The aim of the current research work is to:

1. To identify patient characteristics associated with succesful glycemic response in type 2 diabetes patients receiving Gliclazide oral hypoglycemic treatment as an add-on therapy to metformin.
2. To describe longitudinal change in Hemoglobin A1C in response to GLC Therapy.

MATERIALS & METHODS

Male and female type 2 diabetic patients were invited to participate in this study. Key inclusion criteria included: age between 40 and 75 years, an HbA1c of more than 7% and less than 9%, taking metformin or sulfonylureas, and a body mass index of more than 25 kg/m2.

This study was a multicenter, randomized, open label, parallel group study. Each patient had 21 to 27 scheduled visits.

HbA1c and fasting plasma glucose were measured at screening, baseline, and at the end of the following months: 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, and 84 (±14 days).

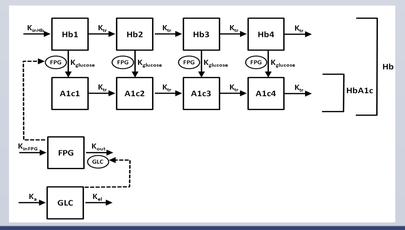
The proposed pharmacodynamic model contain the following components:

Modeling GLC pharmacokinetics

Modeling FPG kinetics

Modeling HbA1c formation and kinetics

And is illustrated as in Figure 1 below:



One compartment pharmacokinetic model with first order absorption and elimination was assumed for GLC.

Fasting Plasma Glucose was assumed to be produced at zero order input rate (KinFPG) and eliminated with a first order rate process with an elimination rate constant of Kout. GLC increases FPG elimination using an Emax model with a baseline.

Four compartments were used to describe nonglycated hemoglobin namely Hb1, Hb2, Hb3, and Hb4. Additional four compartments were used to describe glycated hemoglobin namely A1c1, A1c2, A1c3, and A1c4. Each compartment represents erythrocytes with different age distribution. Glycation of Hb1, Hb2, Hb3, and Hb4 result in A1c1, A1c2, A1c3, and A1c4, respectively.

Erythrocyte lifespan (τ) was previously reported as 120 days (Arias and Arias 2017). According to the model, an erythrocyte spends its lifespan as one of the four age groups (i.e. Hb1-Hb4). The mean residence time an erythrocyte spends as one of these age groups is 30 days. Hence, the transformation rate constant is calculated as the inverse of residence time within each age group:

Finally, Hb is calculated as the sum of nonglycated (Hb1, Hb2, Hb3, and Hb4) and glycated (A1c1, A1c2, A1c3, and A1c4) hemoglobin. On the other hand, HbA1c is the percentage of glycated Hb to the total Hb.

RESULTS

Initially, the basic pharmacodynamic model was fitted using NONMEM without the inclusion of covariates. This resulted in a set of individual parameters for Emax. This was then followed by simple linear regression for each of the covariate (i.e. patient characteristic). This step was done using R. The following were significantly correlated with Emax value (α of 0.05):

Glucose – Fasting

Hemoglobin A1C

Lymphocytes

C-Reactive Protein

Hemoglobin A1C <7.8 %

Plasminogen activator inhibitor type 1 (PAI-1)

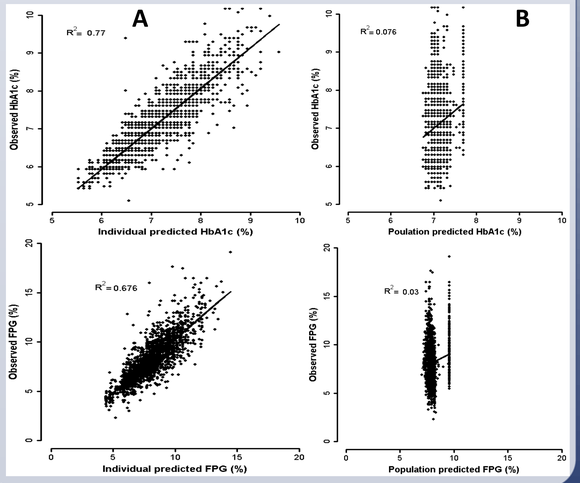
The multiple linear regression of the significant covariates is illustrated in Table 1 below:

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	-1.73	0.1866	-9.271	0.0000
Glucose – Fasting	0.055	0.0138	4.0180	0.0000
C-Reactive Protein	0.014	0.0043	3.3590	0.0010
Lymphocytes	-0.117	0.0551	-2.1290	0.0340
Plasminogen activator inhibitor type 1 (PAI-1)	0.001	0.0003	2.1470	0.0330

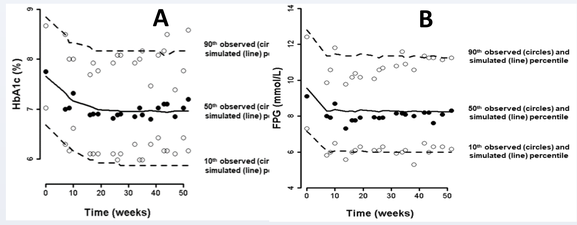
According to the developed model, the estimated pharmacodynamics parameters are presented in Table 2.

Parameter	Description	Typical population estimate
Ka, hr-1	GLC absorption rate constant	0.525 (fixed parameter)
t1/2, hr	GLC elimination half-life	14.3 (fixed parameter)
FPG0, mmol/L	Baseline fasting plasma glucose	9.54
FPG0-IIV	Inter-individual variability in FPG0 values	0.026
Kout, hr-1	Glucose elimination rate constant	0.997
Emax_0, mmol/(L.hr)	Baseline Emax value	0.213
B1	A regression parameter that describes the effect of baseline fasting plasma glucose (FPG0) on Emax	0.531
B2	A regression parameter that describes the effect of baseline lymphocytes (LYMPH0) on Emax	-0.374
Emax-IIV	Inter-individual variability in Emax values	0.446
EA50, mg	A parameter that describes the effect of GLC on glucose elimination:	783
Gam	A parameter that describes the effect of glucose on Glycation of hemoglobin to form Hemoglobin A1C (HbA1c)	0.475
Kglucose, L/(hr.mmol)	Rate constant for the formation of HbA1c	0.000373
Kglucose -IIV	Inter-individual variability in Kglucose values	0.00397
τ, day	Red blood cell life span	120 (fixed parameter)
KinHb, G/(L.hr)	Hemoglobin production rate	1.16
KinHb -IIV	Inter-individual variability in KinHb values	0.00667

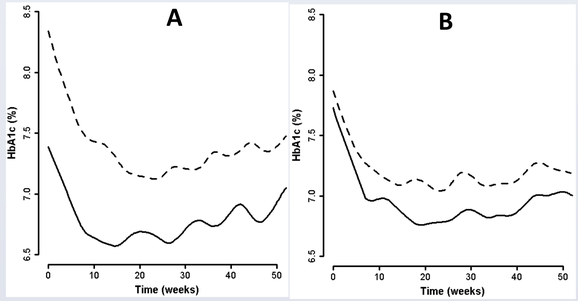
Observed versus individual (A) and population (B) predicted Hemoglobin A1c (HbA1c) and FBG% are presented in Figure 2.



The Visual predictive check of HbA1C (A) and FBG (B) are shown in Figure 3.



Prediction of glycated hemoglobin (HbA1c) for patients with high (dashed) and low (solid) baseline FPG (A) and lymphocytes (B) are shown in Figure 4.



CONCLUSION

Longitudinal change in HbA1c and FPG following GLC therapy was described using a mechanistic pharmacodynamic model. Having a higher baseline FPG was associated with increased magnitude of reduction in HbA1c overtime resulting from GLC therapy. Having a higher baseline lymphocytes was associated with smaller reduction in HbA1c.

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