Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(4):103-107

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Interaction of Metformin and Nifedipine in Type II Diabetic Patients with Hypertension

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ABSTRACT

Diabetes and high blood pressure tend to occur together because they share certain physiological traits.Most patients with diabetes will require combination therapy with multiple antihypertensive drugs to achieve good control. Metformin is widely used in Nigeria to manage Type II diabetes. 1000 mg of metformin was administered alone and with 30 mg of Nifedipine to patients newly diagnosed for diabetes with hypertension. The wash out period was two weeks. HPLC method was used to analyse the serum samples of the patients using Hypersil C18 column at a wavelength of 238 nm. Solvent system was acetonitrile with methanol and buffer. Plasma glucose levels were determined using the standard glucose oxidase method. The maximum absorption concentration of Metformin increased significantly, $p<0.05$ from1890.67 ± 0.22 ng/ml when administered alone to 2357. 16 ± 0.5 ng/ml when co-administered with nifedipine at maximum absorption time of 3 hrs. Area under curve of plasma drug concentration time curve San$(AUC)_{0\text{-}8h}$ also significantly increased from 8882.10 ng/ml/h alone to 10724.57 ng/ml/h when interacted with nifedipine, $p<0.05$. All other pharmacokinetic parameters were not significantly altered. The increased absorption increased the AUC. The effects were followed with non-significant increase in hypoglyceamic effect. Diabetic patients on metformin can be prescribed nifedipine without risk of side effects.

Keywords: Metformin; Nifedipine; Interaction

INTRODUCTION

Diabetes and high blood pressure tend to occur together because they share certain physiological traits. Most patients with diabetes will require combination therapy with multiple antihypertensive drugs to achieve good control [1]. In studies of type 2 diabetes, data has shown that almost 75% of patients with kidney problems (a common complication) had high blood pressure. In those with type 2 diabetics but no kidney problems, the rate of high blood pressure was about 40%. Overall, when averaged across diabetes type 2 and age range, about 35% of all people with diabetes have high blood pressure [2].

One of the most widely used drugs for the treatment of type 2 diabetes is the biguanide, metformin. It works primarily by reducing liver release of blood glucose from glycogen stores and secondarily by provoking some increase in cellular uptake of glucose in body tissues [3]. Nifedipine is used to treat hypertension and chronic stable angina. It inhibits the influx of calcium in smooth muscle cells, hence, prevents calcium-dependent myocyte contraction and vasoconstriction. This co-administration of drugs would likely leads to drug-drug interactions due to their metabolic link [4], hence the need to investigate the clinical implications of the interaction.

MATERIALS AND METHODS

Major equipment used for this research were the followings:
* Digital weighing balance OHAUS model EP 64 BY Ohaus Corporation, Switzerland
* U.V. detector T80 + U.V/Vis spectrometer by PG instrument Ltd U.K
* High Performance Liquid Chromatography; Agilent Technologies, 1120LC series, USA.
* Centrifuge: Heraeus (labafuge 300) D-37520 ostence mated: 2003, serial No40267581, BN: 75003230.

Similarly, Solvents and reagents used are were of analytical grade

- Methanol: Sigma – Aldrich ≥ 99.9% U.K , Mntd: Sept 14, 2011
- Acetnitrile: Sigma – Aldrich ≥ 99.9%, U.K ,Mntd: Sept 14, 2011
- Potassium Dihydrogen phosphate (Buffer) by J.T Baker 99.5% USA
- Metformin HCL reference Standard
- Sulfadoxine: Internal standard source: Rambax Pharmaceutical Ltd, Lagos.

Methodology

Quality Control of Nifedipine and metformin were carried out and the result is within acceptable range. Thereafter, 6 patients were screened to participate in the study. Their ages ranged between 28-45 years. They were also free from liver and kidney diseases and the fasting blood sugar (FBS) test and blood pressure (B.P) were taken before and after the study. Free drug blood samples at fasting state were taken from the patients, after which, 1 g of metformin tablets were administered with 200 ml of water. The patients were allowed to take food after 30 minutes. This is to avoid hypoglycemia in the patients. 3 ml blood samples were withdrawn at 0.0, 0.5, 1.5, 3, 4, 5, 6, 8, hours. The blood sugar levels and blood pressure were determined for the subjects immediately. Blood were collected inside anticoagulant bottles, centrifuged and stored in a refrigerator at -4°C.
The 6 patients were co-administered with 1 g metformin and 30 mg nifedipine with 200 ml of water after 7 days washout period. Blood samples, 3 ml were withdrawn at 0, 0.5. 1. 5, 3, 4, 5, 6 and 8 hours for blood sugar level and metformin concentration determination.

Extraction Method

The extraction method used for thus study was adopted and modified from [5]. 100 µl of metformin hydrochloride solution of appropriate concentration and 100µl of sulfadoxine solution (20 µg ml^{-1}) were added to 900 µl of drug free plasma contained in a clean 5 ml Ria Vial and were properly mixed. To this 50 µl of protein precipitating agent (perchloric acid : acetonitrile 50% v/v each) was added and was vortex for 30 seconds. After centrifugation at 3000 rpm for 10 minutes, 700 µl of the supernatant was evaporated to dryness at 45°C. The residue was reconstituted in 100 µl of mobile phase and 20 µl of this was injected on to the HPLC system.

HPLC Chromatographic Condition

Mobile phase :	Acetonitrile	25 mM KH_2PO_4	Methanol
Ratio :	13	80	7
Column :	ODS Hypersil –C8 4. 6 × 125 mm, 5 um		
Wavelength :	238 nm		
Temperature :	30°C		
Flow rate :	1.00 ml/min		
Run time :	7 minute		
Injection volume :	20 µl		
pH :	5.8 (adjusted with acetic acid)		
Chromatogram :	Metformin	Sulfadixine	
Retention time (min) :	1.111	4.999	

Precision and Accuracy

Precision of the method was determined by selecting 200 ng/ml, 500 ng/ml and 1000 ng/ml concentrations from prepared serial dilution were used to determine within-day and day-to-day variations. For within day variation, three concentrations were run 6 times in the morning and afternoon of same day. The same concentrations were run 6 times a day after to get the inter-day variations. The standard deviations of Peak Height Ratio obtained were calculated followed by coefficient of variation in percentage (Tables 1 and 2).

Calibration Curve

Calibration curve based on peak-height ratio were prepared by spiking drug-free plasma with standard solution of metformin to give concentration range 100 ng – 3 µg/ml and 200 ng/ml of sulfodoxine as internal standard.

Coefficient of Variation and correlation coefficient R^2 (0.994) were computed with a statistical data package SPSS 16.0 and Excel 2007. The results showed good response of the detector at the concentration used.

RESULTS

Result of Precision

Table 1: Intra and inter-day assay variation of metformin

Sample	Concentration ng/ml	CV %	N
Intraday run (Metformin)	200	3.4 ± 0.56	6
	500	1.8 ± 0.87	6
	1000	0.5 ± 0.64	6
Inter-day run (Metformin)	200	4.2 ± 0.23	6
	500	3.5 ± 0.41	6
	1000	1.2 ± 0.04	6

CV = Coefficient of Variation, N= Number of samples

Percentage Extraction Recovery

The percentage extraction recoveries are shown on Table 2.

Table 2: % Recovery of metformin

Sample	Concentration ng/ml	Recovery % ± S.D	N
Metformin	300	97.47 ± 4.2	6
	500	97.58 ± 6.7	6

Calibration Curve of Metformin Standard Solution

The calibration curve obtained from the dilution ratio of standard metformin concentrations 100 ng-3 µg/ml was linear with a correlation coefficient of 0.994 (Figure 1).

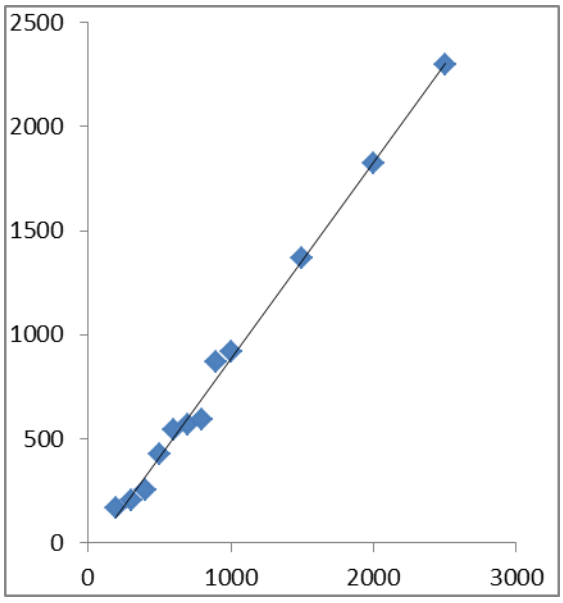

Figure 1: Linear calibration curve of metformin

In-vivo Results

Results of administration of 1 g of metformin alone and when co-administered with nifedipine in type 2 diabetic patients with hypertension as shown in Figure 2.

Pharmacokinetic Parameters Calculation

The pharmacokinetic parameters were calculated from the concentrations derived from the corresponding Peak Height Ratio observed in HPLC machine. Residual method and a software package, PKF Microsoft excel were used to compute the pharmacokinetic parameters as shown in the following table below; (Tables 3 and 4).

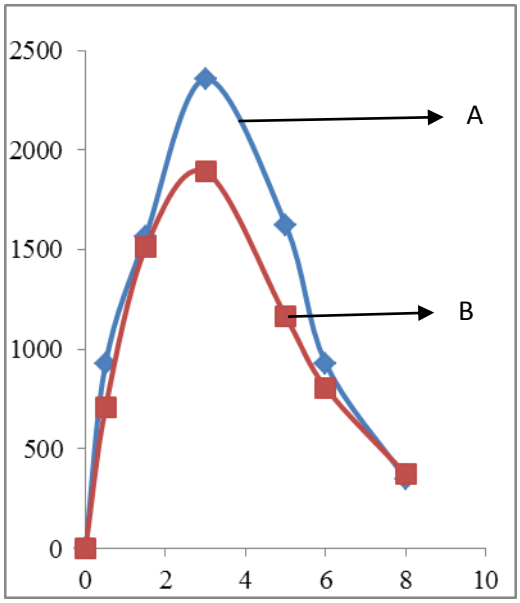

Figure 2: Mean concentration of metformin alone (B) and when co-administered with nifedipine (A)

Table 3: Comparison of pharmacokinetics of metformin (mean, n=6) alone and when co-administered with Nifedipine in patients

Pharmacokinetic Parameter	MET. Alone	MET.+Nifedipine	P-Value
Lag time(h)	0.12 ± 001	0.1 ± 0.701	P>0.05
t ½ abs (h)	1.45 ± 0.016	1.12 ± 0.031	P>0.05
K abs (/h)	0.478 ± 0.002	0.619 ± 0.057	P<0.05
Cmax (ng/ml)	1890.67 ± 0.107	2357.16 ± 0.101	P<0.05
AUC_{0-8} (ng/ml/h)	8882.10 ± 0.205	10724.57 ± 0.001	P<0.05
$AUC_{0-\infty}$ (ng/ml/h)	12106.87 ± 0.061	13238.58 ± 0.011	P<0.05
Vd (L)	112.59 ± 0.062	93.24 ± 0.430	P>0.05
t ½ el (h)	6.0 ± 0.000	5.0 ± 0.310	P>0.05
K el (/h)	0.116 ± 0.000	0.138 ± 0.003	P>0.05
T max (h)	3.0 ± 0.000	3.0 ± 0.000	P>0.05
CL(ml/h)	970.7 ± 0.330	675.65 ± 0.020	P<0.05

Table 4: Comparison of mean sugar level in metformin alone in type 2 patient with hypertension and when co-administered with nifedipine

Time(h)	MET. Alone (mmol/L) (mean)	MET.+ Nifedipine (mmol/L) (mean)	P-Value
0	6.3	3.8	P<0.05
2	7.9	7.1	P>0.05
3	6.4	5.5	P>0.05
5	8	4.3	P<0.05
8	8	1	P<0.05

DISCUSSION

C_{max}, AUCs and CL significantly increased (P<0.05) but the changes in other pharmacokinetic parameters are statistically insignificant. This observation is in agreement with what has been reported [6]. The later reported increased in C_{max} and AUC when metformin was co-administered with nifedipine. This is because nifedipine might have enhanced the absorption of metformin by enhancing stomach and intestinal absorption [7]. It was also observed that blood sugar level dropped from 7.1 mmol/L at 2 hrs to 1.0 mmol/L at 8 hrs.

Blood pressure on the other hand only dropped from 136 mmHg at 0 hr to 130 mmHg at 3 hrs and remained constant, thereafter. Significant reduction of blood glucose levels were observed at 5 and 8 hrs when metformin was co-administered with nifedipine as compared with metformin administered alone. As C_{max} and AUC increased the blood glucose level decreased. There was direct relationship in the clinical effect observed and the increment in the serum levels of metformin when co-administered with nifedipine.

CONCLUSION

The results of metformin interaction with nifedipine showed that it enhances the concentration of metformin. Therefore, there was a direct relationship between the hypoglycemic response of metformin at the absorptive phase when administered alone or with the drugs (nifedipine) investigated.

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