The effects of antihypertensive drug therapies on blood glucose levels in maturity onset diabetes patients on oral hypoglycaemic drugs: The case of selected health centres in Lesotho.

Matthias Adorka[1]*, Motseng Letsa[2], Mitonga Kabwebwe Honoré[3]†, Kirk Allen[4]

[1]School of Pharmacy, University of Namibia, Windhoek, Namibia

[2]Faculty of Health Sciences, Department of Pharmacy, National university of Lesotho, Roma 180

[3]School of Public Health, Faculty of Health Sciences, University of Namibia, Windhoek, Namibia

[4]Faculty of Health & Medicine, Lancaster University, Lancaster, England

Received: 24th July, 2016. Accepted: 14th October, 2016. Published: 23rd October, 2016

Abstract

Background: Antihypertensive drugs may cause changes in blood glucose levels. The concurrent use of these medications with hypoglycaemic drugs in diabetic patients may contribute to inadequate control of blood glucose levels. **Objectives:** To describe the effects of prescribed antihypertensive agents on fasting blood glucose levels of non-insulin dependent diabetic patients on treatment with oral hypoglycaemic medications. **Method:** Descriptive data on fasting blood glucose levels of diabetic patients on hypoglycaemic and antihypertensive drug treatments were collected retrospectively for a six-month period. Data sources were medical records of patients attending diabetic clinics in five health centres in the Maseru Health Service Area of Lesotho. The records were categorised into two basic patient groups, namely, patient groups treated with only oral hypoglycaemic agents and patient groups treated with same agents concurrent with antihypertensive agents. Differences in the means of the initial and end of six-months period fasting blood glucose levels of patient treatment groups were determined and

*Deceased

†Corresponding author - Mitonga Kabwebwe Honoré, Tel numbers: +264 652232264 (office), +264 856056256 (Cell); Fax: +264 61254130; Email: hmitonga@unam.na

 ISSN: 2026-7673

compared. **Results:** Patients who received an antidiabetic drug regime concurrent with antihypertensive medication tended to show improved fasting blood glucose levels at six months, whereas patients receiving only antidiabetic drugs did not show improvement. Partly owing to the small sample size (178 patients), the differences were not statistically significant. **Conclusion:** Hydrochlorothiazide prescribed singly or in combination with other antihypertensive drugs was implicated in increased blood glucose levels. Captopril showed better glycaemic control for patients on oral hypoglycaemic agents. Atenolol and nifedipine appeared not to have any effects on patients' fasting blood glucose levels. A prospective case-control study would help clarify these findings in this study's population.

Keywords: Diabetes, hypoglycaemic agents, antihypertensive agents, fasting blood glucose levels, Lesotho

ISTJN 2017; 9:49-60.

1 Background

Hydrochlorothiazide, nifedipine, verapamil, captopril, atenolol and propranolol constitute major antihypertensive medications used in Lesotho [1]. These are invariably prescribed as monotherapy or in combination therapies to treat diabetic patients with hypertension. The combined use of antihypertensive agents to achieve desirable blood pressure in diabetic patients with coexisting hypertension is recommended in medical practice in accordance with provisions of many national Standard Treatment Guidelines (STG) [2]. The biguanide, metformin, and the sulfonylurea, glibenclamide, are the oral hypoglycaemic medications recommended by the Lesotho STG in treating maturity onset diabetes [1]. They are prescribed in various dosage regimens either as sole hypoglycaemic agents or in combination with insulin in the treatment of diabetes as a sole clinical condition or diabetes complicated with hypertension.

Hypertension and diabetes are common comorbidities, and many patients end up being treated with antihypertensive medications concurrently with hypoglycaemic preparations [3]. As the most common classes of antihypertensive agents employed in managing hypertensive patients, studies have shown evidence of calcium channel blockers, ACE-inhibitors, thiazide diuretics and β-blockers either increasing or decreasing blood glucose levels in diabetic persons or animals [4-7]. The clinical significance of the effects of these medications on blood glucose level control of diabetic patients on drug treatment, however, remain controversial [3]. Diabetic patients on concurrent treatment with antihypertensive medications may demonstrate blood glucose levels that become difficult to control.

Many factors ranging from drug therapy-related problems like patients' noncompliance to medication regimens to individual patient's genetic dispositions may rightly be implicated in the development of such clinical scenarios. In events where antihypertensive agents are prescribed together with hypoglycaemic drugs in treating diabetic patients with hypertension, the possibility of the concurrent use of the former agents being a contributing factor to uncontrolled FBGLs in the patient group cannot be ruled out. Failure to achieve adequate levels of glycaemic control in diabetic patients is a predictor for the development of diabetic complications [2]. This makes it imperative for clinicians to endeavour to meet diabetic treatment goals which target normoglycaemia (4.0 - 7.0 mmols/L) for fasting and pre-prandial blood glucose levels [8]) as they manage their patients. Knowing what effects specific antihypertensive drugs have on blood glucose levels of diabetic patients on hypoglycaemic drug treatment will empower clinicians to select antihypertensive drugs appropriate in treating the patient group. In view of this we consider it being of therapeutic relevance to investigate and report in this study as our objective, the effects of commonly prescribed antihypertensive medications on FBGLs of diabetic patients on treatment with oral hypoglycaemic medications.

2 Methods

2.1 Study design and data collection

The research was an observational cohort study with two time points. Patient treatment data were collected retrospectively from patient treatment booklets at pharmacies of the study site clinics from June 11, 2012, to July 11, 2012. Sites of study were confined to five outpatient clinics in urban Maseru, Lesotho, and included the Mabote, Domiciliary, Quoaling and Likotsi filter clinics. The clinics attended to ambulatory patients and provided healthcare services for diabetes and hypertension patients as well as patients with other ailments, either chronic or acute. Specifically data were collected on patients' demographic characteristics; specific drug treatments they received for diabetes, hypertension or other concurrent ailments; and also blood glucose measurements recorded for them on days of their initial and subsequent clinic visits every three months. Fasting blood glucose levels in all four clinics were measured using glucometers of same make (Accu-Chek Aviva™) as supplied to the clinics by the nation's central medical store. Anti-diabetic and antihypertensive medications were prescribed in quantities sufficient to last patients until their next clinic visit in 3 months. Other medications commonly prescribed for patients' on their days of clinic visit were either vitamins or medications for acute treatments of ailments contracted while on treatment for diabetes.

2.2 Procedures and Data analysis

We investigated effects of antihypertensive drugs on blood glucose levels for patient groups for whom fasting blood glucose levels (FBGLs) were recorded continuously for two clinic visits in six months. We hypothesised that there were no differences between the means of differences in FBGLs between paired patient groups who took given antidiabetic drug only and those who took same treatments with indicated antihypertensive medications. We assumed blood glucose levels recorded on patients' clinic visit days were not affected by any medications they were prescribed for acute treatment of conditions they might have presented on their previous diabetic clinic visit days. We reasoned that such medications would lose effectiveness at controlling blood glucose levels by the next diabetic clinic visit, nearly three months after the use of the prescribed medication, when the patient's blood glucose levels would be determined.

We categorised patient records into two basic groups, namely, patient groups who received antidiabetic drug treatment only (Group A) and patient groups who received antidiabetic drugs concurrent with antihypertensive drugs (Group B). The categorisation produced paired subgroups of patients that comprised those who received a given hypoglycaemic drug treatment regimen without antihypertensive agents and those who were treated with same hypoglycaemic drugs with prescribed antihypertensive medication regimens. We considered patient groups of sample sizes of four and above and ignored those with sample sizes smaller than this. We calculated the differences between the initial ($\text{FBGL}_{\text{initial}}$) and the average fasting blood glucose levels at the end of 6-months period of treatment ($\text{FBGL}_{\text{6-months}}$) following initial treatment for patients in various treatment groups. The differences were calculated as $\text{FBGL}_{\text{6-months}}$ minus $\text{FBGL}_{\text{initial}}$. Positive and negative differences were indicative of increases and decreases in blood glucose levels at the end of a treatment period.

The mean differences in blood glucose levels for the respective patient groups were further analysed to determine what effects concurrent use of given antihypertensive drug treatments have on FBGLs of patients treated with the given hypoglycaemic drug regimens. T-test was used to assess the effects of subjects' gender on differences in the means of initial and end of 6-months FBGLs. We further correlated subjects' age and the differences between their $\text{FBGL}_{\text{initial}}$ and $\text{FBGL}_{\text{6-months}}$ to find what correlation there was between subjects age and differences in their initial and six months period FBGLs. We used a two-sample t-test with a level of significance of $p < 0.05$ in testing our hypothesis to determine whether or not the use of prescribed antihypertensive agents or their combinations have any effect on measured FBGLs of patients who took only hypoglycaemic medications as prescribed.

2.3 Study subject inclusion and exclusion criteria

All patients with maturity onset diabetes who attended diabetic clinics at the indicated study sites and who were prescribed oral hypoglycaemic medications with or without antihypertensive medications, were included in the study. To avoid effects of other drugs on FBGLs as there might, we excluded the following patient categories from the study: (i) patients who were prescribed other drugs either for long term prophylactic use or treatment of any other ailment apart from diabetes or hypertension and (ii) subjects included in the study but visited clinics with other complaints and were prescribed other medications in the course of their three month treatment period following a diabetic clinic visit. There were patient groups who took various metformin dosage regimens in oral hypoglycaemic mono-therapies. These had sample sizes of less than three and we excluded them from our statistical analysis in which we compared means of differences in $FBGL_{6\text{-months}}$ and average $FBGL_{initial}$ (Table 4).

2.4 Ethical considerations

This study was approved by the Lesotho Ministry of Health and Social Welfare Ethics Committee and the Netcare Management which runs three of the four study site clinics. Informed consents were received from patients to participate in the study. Patient's codes were used in the data collection forms to maintain anonymity.

Table 1: Frequency distributions of subjects according to demographic categories.

Demographic category	Number	Percentage frequency
Gender		
Male	34	19.1
Female	144	80.9
Total	178	100
Age		
$\leq 25 - < 50$ yrs	42	23.6
$\geq$50 yrs	136	76.4
Total	178	100

3 Results

A majority (80% out of 178) of all prescription records analysed were for female patients, compared with a 20% for males. Records for patients in the age group of 50 or more

years similarly constituted the majority (76%) of all records analysed (Table 1). A one-way Analysis of Variance (ANOVA) of the differences of FBGLs between males and females were not statistically significant, indicating no effect of subjects' gender on their FBGLs ($p = 0.83 > 0.05$). A correlation analysis of subjects' age and the differences between their $FBGL_{initial}$ and $FBGL_{6\text{-months}}$ similarly indicated no statistically significant correlation between age and differences in subjects' initial and six months period FBGLs ($p = 0.79 > 0.05$).

Table 2: Relative frequencies of prescribed hypoglycaemic drug regimens.

Anti-diabetic drug regimen	Number	Relative frequency
Metformin 500mg thrice daily (M1)	16	9.1
Metformin 850 mg thrice daily (M2)	12	6.9
Glibenclamide 10 mg once daily (G2)	1	0.6
Metformin 500mg thrice daily (M1) + Glibenclamide 5 mg od (G1)	12	6.9
Metformin 500mg thrice daily (M1) + Glibenclamide 10 mg od (G2)	5	2.9
Metformin 850 mg thrice daily (M2) + Glibenclamide 5 mg od (G1)	23	13.1
Metformin 850 mg thrice daily (M2) + Glibenclamide 10 mg od (G2)	24	13.7
Metformin 850 mg thrice daily (M2) + Glibenclamide 15 mg od (G3)	2	1.1
Metformin 1g thrice daily (M3) + Glibenclamide 5 mg od (G1)	2	1.1
Metformin 1g thrice daily (M3) + Glibenclamide 10 mg od (G2)	6	3.4
Metformin 1g thrice daily (M3) + Glibenclamide 15 mg od (G3)	2	1.1
Actraphane 10 iu a.m & 5 iu p.m âĂŞ 20 iu a.m. and 10 iu p.m. (ACT1)	4	2.3
Actraphane 24 iu a.m & 12 iu p.m âĂŞ 30 iu a.m. and 15 iu p.m. (ACT2)	20	11.4
Actraphane 32 iu a.m & 16 iu p.m âĂŞ 40 iu a.m. and 20 p.m. (ACT3)	6	3.4
Actraphane >40 iu a.m & >20 iu p.m (ACT4)	4	2.3
ACT1 + M1	3	1.7
ACT1 + M2	2	1.1
ACT1 + M3	1	0.6
ACT2 + M1	9	5.1
ACT2 + M2	8	4.6
ACT2 + M3	0	0
ACT3 + M1	6	3.4
ACT3 + M2	4	2.3
ACT3 + M3	1	0.6
ACT4 + M1	1	0.6
ACT4 + M2	1	0.6
Total	175	100

Metformin prescribed in dosage regimens of 500mg or 850mg three times a day was the preferred oral hypoglycaemic medication prescribed as a single agent in treating maturity onset diabetes patients (Table 2). In dosage regimens of 850 mg three times a day, this medication was also prescribed most frequently in combination with glibenclamide 5mg (13.1%) or glibenclamide 10mg (13.7%) once a day when combination therapies of oral hypoglycaemic agents were desired (Table 2). The most used antihypertensive drug regimens in treating diabetic patients presenting with hypertension were hydrochlorothiazide 25 mg once daily (H1), prescribed as a single agent (15.7%) or prescribed in combination with captopril 25mg three times a day (H1+C1) (26.4%), atenolol 100mg daily (H1+A2) (12.1%), or captopril

25mg three times a day with nifedipine 10mg three times a day (C1+H1+N1) (13.6%) or captopril 25mg three times a day with atenolol 10mg three times a day (C1+H1+A2) (9.3%) (Table 3).

Table 3: Relative frequencies of prescribed antihypertensive drug regimens.

Antihypertensive drug regimen	Number	Relative frequency
Hydrochlorothiadize 25 mg daily (H1)	22	15.7
Captopril 25 mg tid (C1)	4	2.9
H1+C1	37	26.4
H1+A2	17	12.1
H1+N1	8	5.7
C1+A2	4	2.9
C1+N1	1	0.71
A2+N1	1	0.71
C1+H1+A2	13	9.3
C1+H1+N1	19	13.6
C1+N1+A2	3	2.1
C1+H1+A2+N1	2	1.4
C1+MOD	2	1.4
H1 + A2 + HY	2	1.4
C1+H1+A2	5	3.6
Total	140	100

Patient groups who were treated with mono therapies of metformin dosage regimens concurrent with hydrochlorothiazide alone or hydrochlorothiazide in combination with captopril or atenolol, demonstrated average $FBGL_{6\text{-months}}$ that were higher than $FBGL_{initial}$ for the groups (Table 4). Patient groups treated with metformin 500mg three times daily (M1) concurrent with captopril 25 mg three times a day (C1) and atenolol 100 mg once a day (A2) on the contrary exhibited average six-month treatment period FBGLs that were lower than initial FBGLs for the groups (Table 4).

Patient groups who took M1 with H1 in combinations with C1 or A2 or those who took metformin 850mg three times daily (M2) concurrent with H1 all demonstrated increased mean FBGLs at the end of the six-month treatment period. Patient groups treated with M1 and M2 in combination with glibenclamide 5mg daily (G1), i.e. M1+G1 and M2+G1, concurrent with H1 alone or H1+C1 or H1+A2 similarly had increased FBGLs at the end of the six-month treatment period. Group B patients who received M2 and glibenclamide 10mg once daily (G2) ie (M2+G2) concurrent with H1 combined with either captopril, atenolol or nifedipine showed increased FBGLs generally (Table 4). The patient group which took M1 concurrent with C1+A2 on the other hand showed decreased mean FBGLs at the end of the six-month treatment period (Table 4). Comparisons of the means of differences between $FBGL_{6\text{-months}}$ and $FBGL_{initial}$ of Group A and corresponding Group B patients showed no significant differences between means of FBGLs of paired patient groups (p values > 0.05 in all cases) (Table 4).

Table 4: Frequency distributions of infection types according to numbers of antibiotics per prescription and prescription appropriateness.

Patient group A: Received antidiabetic drug treatment only				**Patient Group B: Received same antidiabetic drug treatment as Patient Group A concurrent with specified antihypertensive drugs**				p-values of comparisons of means of differences in initial and end of 6-month treatment period average FBGLs
Antidiabetic drug treatment regimen	Mean initial FBGL	Average FBGL at end of 6 months	Differences: Mean FBGL - Initial	Antihypertensive drug treatment regimens received by subgroups of Group B patients	Mean initial FBGL	Average FBGL at end of 6 months	Differences: Mean FBGL - Initial	Means of differences of Group A and corresponding Group B patients compared
Mono hypoglycaemic therapies								
M1	-	-	-	H1	6.43	6.54	0.11	-
M1	-	-	-	H1+C1	6.25	7.55	1.3	-
M1	-	-	-	H1+A2	8.35	8.68	0.33	-
M1	-	-	-	C1 +A2	7.07	6.68	-0.39	-
M2	-	-	-	H1	6.96	7.37	0.41	-
Multiple hypoglycaemic therapies								
M1+G1	6.20	6.78	0.58	H1+C1	9.40	10.75	1.35	0.192
M2+G1	6.20	6.70	0.50	H1+C1	9.56	7.84	-1.72	0.917
				H1+A2	8.37	6.52	-1.85	0.511
M2+G2	11.53	12.53	1.00	H1	9.6	10.38	0.78	0.430
				H1+C1	9.78	9.03	-0.75	0.095
				H1+A2	9.03	8.54	-0.49	0.988
				C1+H1+A2	10.45	10.09	-0.36	0.860
				C1+H1+N1	9.557	8.96	-0.59	0.630

‡Abbreviations: M1: Metformin 500mg 3x daily; M2: Metformin 850mg 3x daily; G1: Glibenclamide 5mg daily; G2: Glibenclamide 10mg daily; H1: Hydrochlorothiazide 25 mg daily;C1: Captopril 25mg 3x daily; A1: Atenolol 50mg daily; A2: Atenolol 100mg daily; N1: Nifedipine 3x daily; FBGL: Fasting blood glucose level

4 Discussion

The main oral hypoglycaemic agents used in the management of maturity onset diabetes within the circumscribed area of this study were metformin and glibenclamide. Hydrochlorothiazide, captopril, atenolol and nifedipine similarly were the major antihypertensive agents used in treating hypertension coexisting with diabetes. All the above noted drugs were among medications recommended by the Lesotho STG in treating diabetes and hypertension as isolated clinical conditions.

We noticed increases in FBGLs, particularly in cases of patients who took hydrochlorothiazide or its combinations with captopril, atenolol and nifedipine concurrently with hypoglycaemic treatments with metformin 500mg or 850 mg three times a day (Table 4). Higher dosage regimens of metformin and glibenclamide were used in the treatment of subgroups of patient Group A who, presumably, were unresponsive to lower doses of the drugs. These higher regimens of the medications however did not decrease FBGLs at the end of six months following their initial use in treating the condition. We found it difficult, hence, to attribute uncontrolled increases in FBGLs in the corresponding patient groups to effects of the antihypertensive drugs they took concurrently with the prescribed hypoglycaemic medications. There was a decrease, however, in FBGLs at the end of the six month treatment period following the initial therapy in the particular patient group that took metformin 500mg

three times daily with captopril 25mg three times and atenolol 100mg once daily. We are led to infer from this result that captopril and atenolol prescribed together may not cause any increases in blood glucose levels in diabetic patients on hypoglycaemic drug treatment.

We also inferred that increases observed in FBGLs in the concurrent use of antidiabetic drugs with antihypertensive drug regimens that included hydrochlorothiazide may be caused to some extent, by the thiazide diuretic. Captopril and hydrochlorothiazide are known to increase and decrease insulin sensitivity, respectively [11]. The drugs thus may be responsible for the decreases and increases in blood glucose levels of our study subjects as results demonstrated. Unlike captopril, atenolol may worsen glucose and insulin metabolism and cause increased FBGLs in diabetic patients [12]. This, however, may occur only in the likely events of high dose usage of the drug. At high doses beta-1 adrenergic receptor blockers like atenolol may as well block beta-2 receptors through which hyperglycaemic effects of the beta blockers are mediated. Blockade of beta-2 adrenergic receptors in skeletal blood vessels and muscles reduces peripheral blood flow and directs blood away from sites of glucose uptake to reduce glucose disposal [13]. The observed decrease in blood glucose levels noticed for the patient subgroup on captopril and atenolol concurrent with hypoglycaemic drug treatments may be due to captopril rather than atenolol. In their review paper on antihypertensive medications and blood sugar, Blackburn and Wilson indicated that angiotensin converting enzyme inhibitors (ACEI) like captopril reduce angiotensin II mediated vasoconstriction that is favourable to improving insulin receptor sensitivity and peripheral glucose uptake. The authors further indicated that calcium channel blockers, nifedipine inclusive, are not associated with hyperglycaemic effects [13].

Comparisons of the means of differences between initial and end of six-month treatment period FBGL measurements in paired subgroups of Group A and Group B patients showed that observed differences in $FBGL_{6\text{-months}}$ and $FBGL_{initial}$ as reported were not statistically significant (p values >0.05) (Table 4). We failed, hence, to reject our null hypothesis of no differences existing in the means of initial and end of six-month treatment period FBGLs for paired patient subgroups who took hypoglycaemic agents without (Group A) or with (Group B) specified antihypertensive medications. Thiazide diuretics are known to cause hyperglycaemia as earlier documented [14]. On this basis and on the basis of the observed increases in FBGLs reported for patient groups who took the medication, we recommend hydrochlorothiazide to be used with caution or avoided if possible in diabetic patients. Captopril, atenolol and nifedipine on the other hand may be prescribed as antihypertensive drugs of choice in the treatment of hypertensive complications in diabetic patients. This said, however, we recommend captopril and for that matter any ACEI, to be prescribed with caution for diabetic patients on hypoglycaemic drug treatment. The drugs have the potential of causing hypoglycaemia in this patient group [5].

4.1 Study Limitations

The use of retrospective data limited us to report on patient treatment groups with rather small sample sizes. This hindered our ability to investigate effects of more antihypertensive drugs as prescribed for the management of hypertension among diabetic patients on hypoglycaemic drug treatment. The study also had the limitation of not being able to determine extents of patients' compliance in taking their prescribed medications. This to some extent may compromise the accuracy of FBGL data. We recommend further studies on the topic using a methodological design that opts for the use of prospective instead of retrospective data to aid causal inference. By this means it would be possible to use data generated from adequate sample sizes of patient treatment groups and afford a means of addressing other limitations. The influence of confounding factors on blood glucose control in diabetic patients was not investigated in this study though they may affect fasting blood glucose data as analysed. On the basis of culture and genetics, these factors, however, could be considered population related. It is relevant therefore to determine their existence as well as their therapeutic significance among the population of study to allow for a more meaningful interpretation of results.

Not all records could be used to determine relative frequencies of hypoglycaemic and antihypertensive drug regimens prescribed in the concurrent treatments of diabetes and hypertension (Tables 2 and 3). This is because some prescription records with missing values were not included in either case of totals of records analysed for these determinations.

5 Conclusion

Results of the study showed differences in FBGLs of diabetic patients treated with only oral hypoglycaemic medications and those treated with same hypoglycaemic treatment concurrent with antihypertensive drug treatments. Observed in patient groups treated with minimum metformin dosage regimen of 500mg three times daily, captopril, in doses of 25mg three times daily, appeared to decrease blood glucose levels of diabetic patients on oral hypoglycaemic agents. In therapeutic doses as prescribed, atenolol and nifedipine showed no effects on patients' FBGLs. Hydrochlorothiazide prescribed in doses of 25mg daily either singly or in combination with other antihypertensive drugs in the treatment of hypertension in diabetic patients, appeared to be implicated in increased blood glucose levels observed in the patient group. Caution is required in its use in treating hypertension in diabetic patients.

Acknowledgements

We acknowledge students of the Diploma in Pharmacy Technology Programme of the National Health

Training College of Lesotho, who collected and electronically captured data for this study. No authors received remunerations for their roles in conducting this research and preparing this manuscript. MA, ML and MKH provided funding for the study and also for the preparation of this manuscript from their personal resources.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MA and ML participated in the design and collection of data. MKH and KA analysed the data. All authors participated in data interpretation and manuscript writing.

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