

Pharmacodynamics Drug Interactions of Metformin with Aspirin and Nifedipine

Khidir A. M. Hassan^{1*}, Mahmoud M. E. Mudawi² and Mansour I. Sulaiman²

¹Department of Pharmaceutics, Faculty of Pharmacy, Northern Border University, KSA; khidiragab@yahoo.com

²Department of Pharmacology and Toxicology, Faculty of Pharmacy, Northern Border University, KSA

Abstract

Metformin is now being recognized as the standard therapy in T2D patients who are overweight. Metformin has many drug-disease interactions that can increase the risk of metformin-associated lactic acidosis. Therefore this study was conducted to evaluate any possible pharmacodynamic interactions between metformin and drugs used to treat chronic diseases e.g. Hypertension. The rats were fasted overnight before inducing diabetes with streptozotocin. The rats were given an intraperitoneal injection of streptozotocin (50 mg kg⁻¹) freshly prepared in 0.1M sodium citrate buffer. The diabetic state was confirmed 72 h after streptozotocin injection. Diabetic rats were grouped into seven groups each group of five rats and distributed among the normal control group diabetic control group and the treatment groups. The treatment continued for 10 days. Blood samples were taken before treatment and after 10 days and analyzed for serum glucose, cholesterol, HDL, LDL, and triglycerides. In the diabetic control group which was given STZ alone the blood glucose level decreased significantly ($p < 0.05$) after 10 days but still above the hyperglycemic level (200mg/dl). The same was observed in the group treated with metformin. The group treated with nifedipine and aspirin showed significant reduction ($p < 0.01$) in the glucose level below the hyperglycemic level (200mg/dl). While the groups treated with (Metformin + Nifedipine) and (Metformin + Aspirin) showed highly significant reduction ($P < 0.001$) in blood glucose level. These results conclude that the combination of (metformin + Nifedipine) and the combination of (Metformin + Aspirin) have highly significant hypoglycemic effect. It also showed that Nifedipine has promising role in reducing blood glucose level, lipid profile especially LDL-cholesterol, and body weight.

Keywords: Aspirin, Antidiabetic, Metformin, Nifedipine, Streptozotocin

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by a hyperglycemia caused by insulin deficiency, often combined with insulin resistance. In diabetes, the homeostasis of carbohydrate and lipid metabolism is improperly regulated by the pancreatic hormone, insulin; resulting in an increased blood glucose level¹.

Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. Diabetes mellitus is classified on the basis of the pathogenic process

that leads to the hyperglycemia. The broad categories of DM are designated type 1 and type 2².

Metformin lowers blood glucose concentration and improves insulin sensitivity by reducing hepatic gluconeogenesis and enhancing insulin-simulated peripheral glucose uptake. It also inhibits adipose tissue lipolysis, thereby reducing circulating levels of free fatty acids (FFA)³.

Metformin, an oral anti-diabetic drug, is being considered increasingly for treatment and prevention of cancer, obesity as well as for the extension of healthy life span⁴.

*Author for correspondence

Metformin is not metabolised at all but is completely excreted in urine. Metformin may therefore accumulate and cause lactic acidosis if other medications have induced renal failure⁵.

When patients are diagnosed with diabetes, a large number of medications become appropriate therapy. These include medications for dyslipidemia, hypertension, antiplatelet therapy, and glycemic control which may lead to drug interactions with antidiabetic drugs⁶. Metformin has many drug-disease interactions that can increase the risk of metformin-associated lactic acidosis (MALA)⁶.

Drug interactions are often categorized as pharmacodynamic or pharmacokinetic in nature⁶. A pharmacodynamic drug interaction is related to the drug's effect on the body. Pharmacodynamic drug interactions can be either beneficial or detrimental to patients⁶.

Any drug that has the potential to raise blood glucose may produce apparent inefficacy of an oral hypoglycaemic drug. Stopping a drug which causes hyperglycaemia may produce a significant fall in blood glucose. This may require a parallel reduction in the dose of a hypoglycaemic drug⁵.

Some drugs can lower blood glucose, but the mechanisms of action are not well understood. Taking one of these drugs with a hypoglycaemic drug might cause clinically significant hypoglycaemia. The patient may need a lower dose or even have to cease the oral hypoglycaemic drug. Conversely stopping a drug with the potential to lower blood glucose might produce relative inefficacy of a hypoglycaemic drug and create a need for an increased dose⁵.

2. Justification of the Study

It has been reported that diabetic patients may take other drugs to treat concomitant diseases. Diabetic patients may be administered antihypertensive drugs, NSAIDs, anti-ulcer drugs which may interact with metformin. Therefore this study was conducted to evaluate any possible pharmacodynamic interactions between metformin and drugs used to treat chronic diseases e.g. Hypertension

3. Materials and Methods

3.1 Chemicals

Streptozocin (Manufactured by Sigma- Aldrich, USA) was purchased from a local distributor in KSA, Sodium

Citrate (Manufactured by Lobel Chemie, laboratory reagents & fine chemical, India) was availed from the laboratory stock at Northern Border University

Metformin (Glucophage 500 mg, Merck santé, France), Aspirin 100 mg (Bayer, Germany) and Nifedipine (Adalat 20 mg, Bayer, Germany) were purchased from the local market.

3.2 Method of Analysis

Samples were analyzed for serum glucose, cholesterol, HDL, LDL, and triglycerides using the kits of Human Diagnostic Worldwide.

3.3 Experimental Animals

Wistar albino rats of either sex were used (Table 2) were obtained from the animal house at the faculty of pharmacy, Northern Border University. The animals were housed in a standard controlled animal care facility. The animals were maintained under standard nutritional and environmental conditions throughout the experiment and water was given ad libitum.

3.4 Induction of Diabetes

Rats were fasted overnight before inducing diabetes with streptozotocin. Streptozotocin is used to induce both type I and Type II diabetes based on the dose i.e. it is concentration dependent, for the induction of type I, 60 mg/kg is given intraperitoneally or intravenously, and for type II induction 40-50mg/kg is the usual dose used^{1,7,8}. In this study the rats were given an intraperitoneal injection of streptozotocin (50 mg kg⁻¹) freshly prepared in 0.1M sodium citrate buffer. The diabetic state was confirmed 72 h after streptozotocin injection. Threshold value of fasting blood glucose was taken as >200 mg dL⁻¹⁸. Diabetic rats were weighed and matched for body weight and divided into following groups consisting five animals each:

- Group 1: Normal control
- Group 2: Diabetic Control
- Group 3: Diabetic rats administered Metformin 100 mg/kg (10 days, p.o.).
- Group 4: Diabetic rats administered Aspirin 100 mg/kg (10 days, p.o.).
- Group 5: Diabetic rats administered Nifedipine 20 mg/kg (10 days, p.o.).
- Group 6: Diabetic rats administered Metformin 100 mg/kg (10 days, p.o.) + Aspirin 100 mg/kg (10 days, p.o.).

- Group 7: Diabetic rats administered Metformin 100 mg/kg (10 days, p.o.) + Nifedipine 20 mg/kg (10 days, p.o.).

3.5 Blood Glucose Estimation

Blood sample were collected from the retro orbital plexus of the rats and glucose was estimated before (day 0) and after treatment (day 10).

3.6 Blood Lipids Estimation

Blood samples were assessed for total cholesterol, HDL, LDL and triglycerides before (day 0) and after treatment (day 10).

3.7 Body Weight Determination

Weight of rats was recorded before and after the study period of 10 days.

4. Results

As shown in Table 1, a paired- samples t-test was conducted to compare the glucose level in rats with STZ induced hyperglycemia before treatment (time zero) and after 10 days. There was a highly significant difference ($p < 0.001$) in the groups treated with (Metformin + Nifedipine) and (Metformin + Aspirin).

Figure 1 compare the glucose level in rats with STZ induced hyperglycemia before treatment (time zero)

Table 1. Effect of drugs (Metformin, Aspirin, Nifedipine) on fasting blood glucose levels in STZ induced diabetes

Group No.	Treatment (n = 5)	Blood Glucose (mg/dl) (Mean \pm SEM)	
		Day 0	Day 10
1	Diabetic control (STZ)	394.60 \pm 44.35	224.51 \pm 61.90 * \downarrow
2	Metformin	525.53 \pm 15.17	312.09 \pm 43.81 * \downarrow
3	Nifedipine	269.60 \pm 34.76	139.16 \pm 19.10 * \downarrow
4	Metformin + Nifedipine	555.80 \pm 6.89	142.53 \pm 17.60 *** \downarrow
5	Aspirin	229.30 \pm 40.08	150.00 \pm 48.99 * \downarrow
6	Metformin + Aspirin	574.70 \pm 57.47	197.28 \pm 53.41 *** \downarrow

* \downarrow Significant decrease ($p < 0.05$) *** \downarrow Highly significant decrease ($p < 0.001$) (paired samples T-test) compared Day 10 to Day 0.

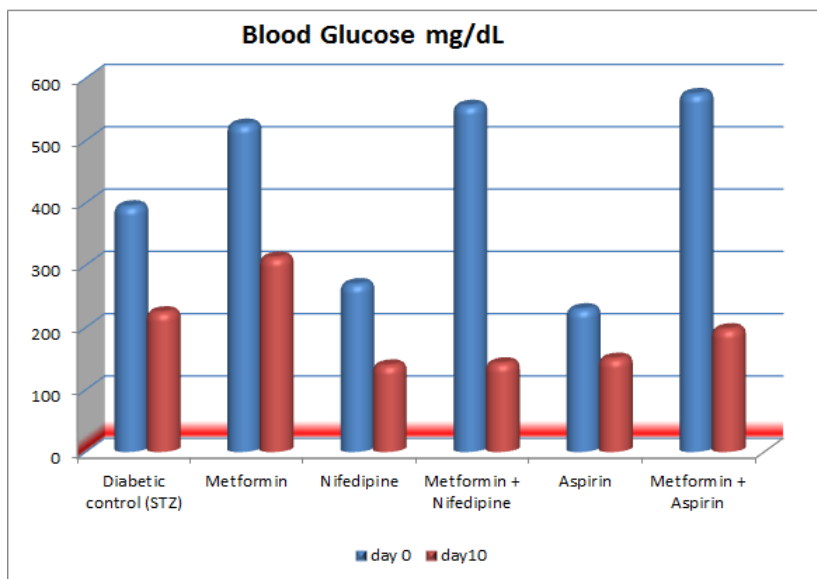


Figure 1. Effect of metformin, nifedipine and Aspirin on fasting glucose level.

and after 10 days of treatment in different treatment groups.

Table 2 shows a paired- samples t-test was conducted to compare the body weight in rats with STZ induced hyperglycemia before treatment (time zero) and after 10 days. There was a highly significant reduction ($p < 0.001$) in the group treated with Nifedipine.

Figure 2 show a comparison of body weight in rats with STZ induced hyperglycemia before treatment (time zero) and after 10 days of treatment in different treatment groups.

As shown in Table 3 a paired- samples t-test was conducted to compare the lipids level in rats with STZ induced

hyperglycemia before treatment (time zero) and after 10 days. There was a highly significant reduction ($p < 0.001$) in LDL – cholesterol concentration in the group treated with Nifedipine.

Figure 3 compare the lipid profile in rats with STZ induced hyperglycemia before treatment (time zero) and after 10 days of treatment in different treatment groups.

5. Discussion

The prevalence of diabetes is high among the Saudi population and represents a major clinical and public health problem^{9,10} and many patients taking antidiabetic drugs

Table 2. Effect of Metformin, Aspirin, and Nifedipine on body weight in STZ induced diabetes

Group No.	Treatment (n = 5)	Body weight (g) (Mean ± SEM)	
		Day 0	Day 10
1	Diabetic control (STZ)	176.00 ± 11.99	191.66 ± 10.75 *↑
2	Metformin	177.00 ± 5.35	178.50 ± 6.84
3	Nifedipine	228.40 ± 9.23	192.00 ± 8.79 ***↓
4	Metformin + Nifedipine	181.60 ± 8.41	184.50 ± 9.08
5	Aspirin	195.40 ± 13.11	201.00 ± 21.46
6	Metformin + Aspirin	167.20 ± 5.64	167.50 ± 4.61

*↓ Significant decrease ($p < 0.05$) ***↓ Highly significant decrease ($p < 0.001$) (paired samples T-test) compared Day 10 to Day 0.

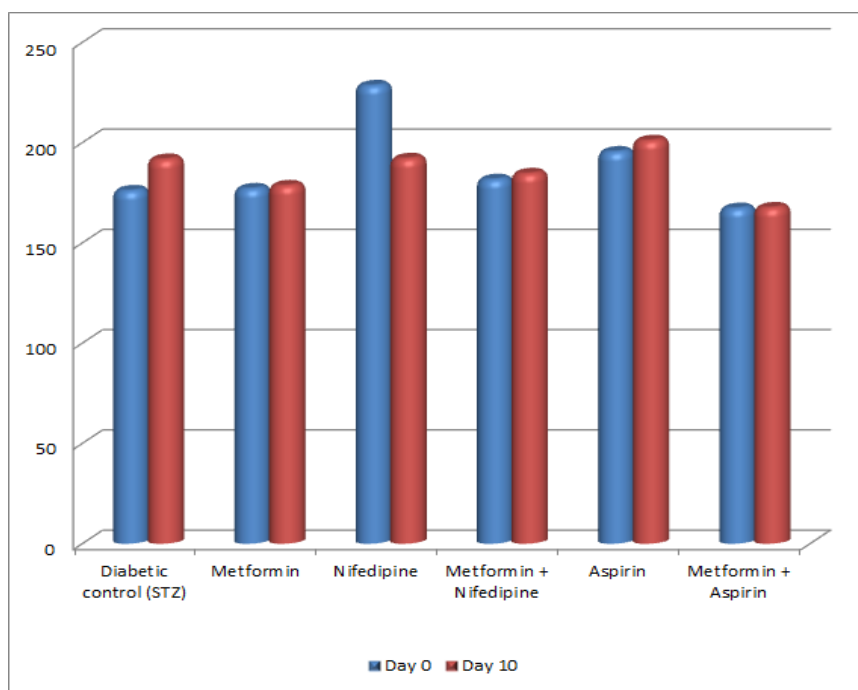
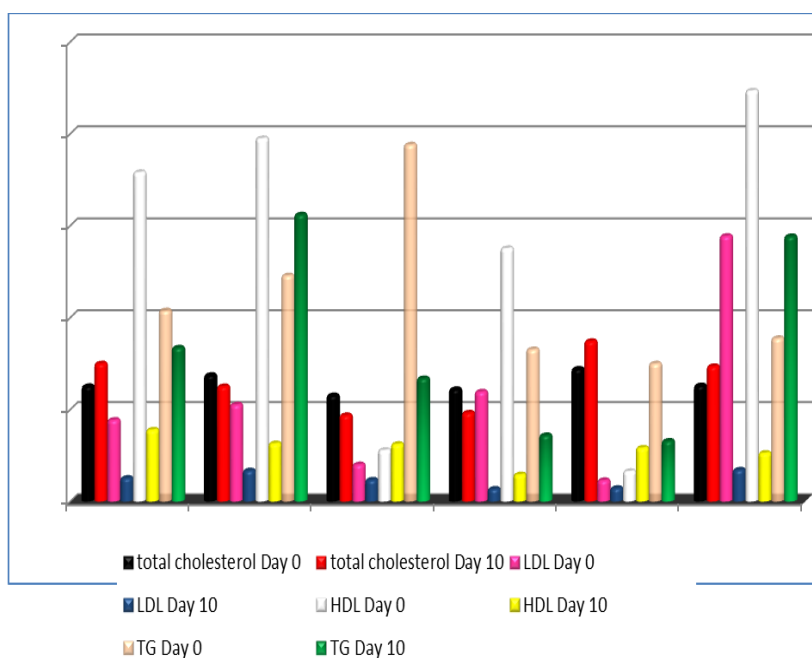


Figure 2. Effect of metformin, aspirin, and nifedipine on body weight.

Table 3. Effect of Metformin, Aspirin, and Nifedipine on blood lipid levels in STZ induced diabetes

Group No.	Treatment (n = 5)	Total Cholesterol (mg/dl) (Mean ± SEM)		LDL (mg/dl) (Mean ± SEM)		HDL (mg/dl) (Mean ± SEM)		TG (mg/dl) (Mean ± SEM)	
		Day 0	Day 10	Day 0	Day 10	Day 0	Day 10	Day 0	Day 10
1	Diabetic control (STZ)	62.63± 7.08	74.98 ± 7.19 *↑	44.31 ± 6.87	12.72 ± 4.50 *↓	178.98± 62.56	38.94 ± 8.88	103.84 ± 24.06	83.59 ± 14.59
2	Metformin	68.69 ± 6.70	62.55 ± 13.30	52.64 ± 4.13	16.76 ± 4.35*↓	197.40 ± 58.42	31.52± 6.07	122.85 ± 19.52	155.99 ± 64.54
3	Nifedipine	57.63 ± 11.74	46.84 ± 5.32	20.05 ± 2.41	11.73 ± 2.22 ***↓	27.85 ± 5.23	31.13 ± 4.17	194.02 ± 71.29	66.90 ± 36.48
4	Metformin + Nifedipine	61.01 ± 9.87	48.20 ± 5.65	59.66 ± 13.96	6.80 ± 1.48 *↓	137.62 ± 33.24	14.60 ± 2.98 *↓	82.65 ± 8.34	35.93 ± 4.65 *↓
5	Aspirin	72.07 ± 8.25	87.11 ± 23.17	11.47 ± 2.58	7.23 ± 3.55	16.36 ± 5.73	29.10 ± 7.76	74.94 ± 12.59	32.90 ± 11.03 *↓
6	Metformin + Aspirin	63.03 ± 3.81	73.47 ± 7.95	144.32 ± 88.68	17.19 ± 1.85	223.34 ± 80.63	26.32 ± 6.25	88.74 ± 28.66	144.19 ± 52.95

*↓ Significant decrease ($p < 0.05$) ***↓ Highly significant decrease ($p < 0.001$) (paired samples T-test) compared Day 10 to Day 0.

**Figure 3.** Effect of metformin, nifedipine and aspirin on blood lipid levels in STZ induced diabetes.

and antihypertensive drugs concomitantly which may lead to various drug-drug interactions. Therefore the main objective of this work was to study the pharmacodynamic interactions between metformin, nifedipine, and aspirin and their effects on blood glucose level, lipid profile and body weight.

In this study streptozocin (STZ) when administered intraperitoneally (IP) to rats the blood glucose

level increased above 200 mg/dl within 48-72 hours which considered hyperglycemic. In the diabetic control group which was given STZ alone the blood glucose level decreased significantly ($p < 0.05$) after 10 days but still above the hyperglycemic level (200mg/dl). The same was observed in the group treated with metformin. On the other hand the group treated with nifedipine and aspirin showed significant reduction (p

< 0.01) in the glucose level below the hyperglycemic level (200mg/dl).

Interestingly, the groups treated with (Metformin + Nifedipine) and (Metformin +Aspirin) showed highly significant reduction ($P < 0.001$) in blood glucose level. Taking one of these drugs with a hypoglycemic drug might cause clinically significant hypoglycaemia. The patient may need a lower dose or even have to cease the oral hypoglycemic drug. Conversely stopping a drug with the potential to lower blood glucose might produce relative inefficacy of a hypoglycemic drug and create a need for an increased dose⁵. Therefore patients taking metformin with nifedipine or aspirin need close monitoring for blood glucose level.

Suresha et al. reported that Nifedipine worsens glycemic control in normal rats after glucose challenge through inhibition of basal insulin secretion¹¹. Jobran Al Qahtani et al. also reported that Nifedipine has induced hyperglycemia in an infant¹². These results does not go on line with our finding regarding the effect of Nifedipine, in which Nifedipine has reduced blood glucose level in STZ induced hyperglycemia in rats. However, our finding agreed with the finding of Kaymaz et al. who concluded that calcium channel blockers (Nifedipine) have beneficial effects on body weight, glycated hemoglobin and blood glucose level¹³. Choi and Lee reported that the combination of nifedipine and metformin caused reduction in blood glucose level which may be due to the fact that both metformin and nifedipine are commonly metabolized via hepatic CYP2C and 3A subfamilies in rats. Therefore; simultaneous administration of both drugs may lead to an increase of the bioavailability of both drugs due to competitive inhibition for the metabolism of nifedipine and metformin by each other via intestinal CYP3A1/2 in addition to competitive inhibition for hepatic metabolism of each drug¹⁴.

In a study performed to investigate the beneficial effects of nifedipine on abnormalities of platelets and lipid metabolism in patients with type II diabetes mellitus, it was found nifedipine produced significant reduction of lipid profiles except for HDL which showed significant increase¹⁵. This result agrees with our findings which demonstrated that nifedipine produced highly significant reduction in LDL-cholesterol blood level in rats.

Many studies documented that Aspirin can significantly decrease blood glucose level¹⁶ which is in agree with our findings in this study. It is claimed that Aspirin

can cause decrease in basal rates of hepatic glucose production, enhances tissue insulin sensitivity, decreases insulin clearance, and decreases oxidative stress in diabetic patients^{17,18}.

In this study Nifedipine produced highly significant reduction ($P > 0.001$) in body weight in the rats with STZ induced hyperglycemia. In addition Nifedipine showed highly significant ($P < 0.001$) decrease in LDL-cholesterol concentration compared to day zero for the same group; While Aspirin produced significant ($p < 0.05$) reduction in triglycerides (TG) concentration.

6. Conclusion

From this study we conclude that the combination of (metformin + Nifedipine) and the combination of (Metformin + Aspirin) have highly significant antidiabetic effect which might be helpful for diabetic patients with concomitant hypertension. Our study showed that Nifedipine has promising role in reducing blood glucose level, lipid profile especially LDL-cholesterol, and body weight.

7. Acknowledgement

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8. Conflict of Interest

None to declare

9. References

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