International Journal of Pharmacology

ISSN 1811-7775

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OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2020.416.421

Research Article
Effect of Lipase Inhibitor (Orlistat) on Gliclazide and Metformin in Response to High-Fat Meal in Rat's Gastrointestinal Tract

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Abstract

Background and Objective: Orlistat decreases the absorption of fat from the gastrointestinal tract by inhibiting pancreatic and gastric lipases, so encourage weight loss. Orlistat is clinically beneficial in reducing body weight in patients with Type 2 diabetes. The objective of the following study is the investigation of the influence of Orlistat in the bioavailability of selective concomitant medications for type 2 diabetes with different lipophilicity; Metformin (MT) and Gliclazide (GZ). **Materials and Methods:** Sprague-Dawley rats, either sex rats were selected as the animal model. The oral glucose loading animal model used for evaluation of bioavailability of both drugs GZ and MT. The effects of the concomitant intake of Orlistat with both drug as well as oily or aqueous meal evaluated through evaluation of blood glucose level lowering. **Results:** Orlistat affects the bioavailability of gliclazide, with high fat content-meal, p-value 0.128, on the other hand, MT not affected. The results suggest the administration of Orlistat and GZ with the presence of high-fat meals will significantly affect GZ bioavailability. **Conclusion:** Based on the glycaemic lowering effects of orlistat seen here. Attention must be raised for concomitant dosing of Orlistat with GZ, especially as the case of a high-fat meal for diabetic patients. More research needed to specify the time interval limit for dose delay between GZ and Orlistat.

Key words: Orlistat, Type 2 diabetes mellitus, antidiabetic agents, gliclazide, metformin, food composition, glycaemic effect

Citation: Afaf H. Al-Nadaf, 2020. Effect of lipase inhibitor (Orlistat) on gliclazide and metformin in response to high-fat meal in rat's gastrointestinal tract. Int. J. Pharmacol., 16: 416-421.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Tetrahydrolipstatin blocks the absorption of 30% of ingested fat[1]. It is one of five approved drugs by the US Food and Drug Administration (FDA) for the long-term management of obesity (Fig. 1)[2]. Orlistat decreases the absorption of fat from the gastrointestinal tract by inhibiting pancreatic and gastric lipases, so encourage weight loss. Its recommended dose is about 60 to 120 mg three times daily during fat meals or up to one hour after[1]. It works within the gut; therefore, no systemic adverse effects attributed. Just mild to moderate adverse gastrointestinal effects appeared, which generally decreased by dietary modification. These side effects may increase when a drug is taken with a diet high in fat (30% total daily calories from fat) or if the recommended daily fat intake is not distributed over three meals[2].

More side effects may affect its use as an anti-obesity drug: Fecal urgency, oily stool and fecal incontinence, but it may carry out a role as another medicine for patients who are constipated on other anti-obesity pharmacotherapy[3]. Because of its mechanism of action, there is a potential for Orlistat to affect the absorption of other drugs, especially fat-soluble drugs as well as fat-soluble vitamins. Orlistat interacted with fat-soluble vitamins without affecting their clinical values[4,5]. Several studies carried out to evaluate potential interactions between Orlistat and potential concomitant medications like Amitriptyline, Atorvastatin, Cyclosporine, Losartan, Metformin, Phentermine, Warfarin, Sibutramine, fat-soluble vitamins and alcohol[6-10]. There was a statistically significant reduction in fat-soluble vitamins except for 1, 25-hydroxyvitamin D[11]. Orlistat appears to impair the absorption of fat-soluble but not water-soluble drugs. This effect predicted as the octanol-water partition coefficient. The clinical significance of interaction must judge within the context of how a drug used. As it's available for weight reduction in obese patients or those who are overweight with the incidence of conditions like type 2 diabetes, large numbers of patients have been treated with Orlistat with concomitant medications such as glucose-lowering agents appetite suppressants, hypolipidemic, antidepressant drugs, immunosuppressant and antihypertensive drugs[12]. Numerous interaction studies carried out to evaluate potential interactions between Orlistat and potential concomitant medications[7-10]. Upon our knowledge, there is no study available about the interaction between Gliclazide and Orlistat. The objective of the following study is to investigate the influence of Orlistat on the bioavailability of selective concomitant medications for type 2 diabetes with different lipophilicity; metformin (hydrophilic) and lipophilic, which is gliclazide (Fig. 1). Moreover, the effect of the concomitant fat-rich meal intake will be evaluated. We hypothesize that Orlistat may affect the bioavailability of gliclazide as it has a lipophilic character.

MATERIALS AND METHODS

Study area: The study was carried out at the department of pharmaceutical chemistry at Applied science University and Mutah University (November 2015 to March 2016).

Materials: Orlistat (OR) is a kind gift from Hikma Pharmaceuticals (Amman-Jordan). Metformin (MT) and Gliclazide (GD) (99% pure) are kind gifts from and Jordanian Pharmaceutical Manufacturing Company JPM (Naour-Jordan). Accu-Chek Performa test strips and blood glucose meter purchased from the local market.

Methods: *In vivo* performance of GD and MT in the presence/absence / with a fat-rich meal evaluated in rats using blood glucose level as a pharmacodynamic marker parameter. The oral glucose loading animal model was used for in vivo performance in this study[13].

This method depends on the physiological induction of diabetes mellitus by increase the blood glucose level transiently with no damage to the pancreas, then evaluation of drug absorption by evaluating their effect on blood glucose level[13]. All experimental procedures and sample collection methods approved by the animal ethics committee of Applied

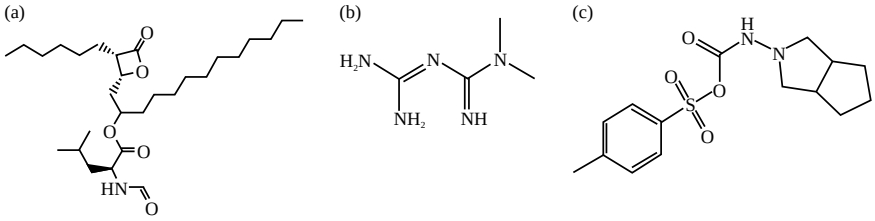

Fig. 1(a-c): Chemical structure for: (a) Orlistat, (b) Metformin and (c) Gliclazide

Table 1: Ingredients and nutrient composition of rat diet as well as study design

	Metformin		Gliclazide		Orlistat		
Food	Oil	Aqueous	Oil	Aqueous	Oil	Aqueous	Glucose
Orlistat	✓	✓	✓	✓			✓
Vehicle	✓	✓	✓	✓	✓	✓	✓

*Metformin dose: 70 mg kg^{-1}, Gliclazide dose: 25 mg kg^{-1}, Glucose dose: 1 mg kg^{-1}, Orlistat dose: 200 mg kg^{-1}, Glucose administered for all groups

Science University (2016/2015-01) and all experiments were carried out by the guidelines of the committee[14]. Sprague-Dawley rats either sex, weighing 200+20 g and aged 8-12 weeks used in this study which normally behaving and not having any pre-existing ailment. Pre-existing diabetes ruled out with the help of blood glucose testing with a glucometer. The environmental parameters in the animal room were: 50-60% humidity and 25°C temperature with continuous ventilation. They divided into two groups of eight (A) and (B). The rats fasted overnight and then (using oral intubation) fed as Table 1. During the experiment, the rats abstained from food and water; blood samples collected from rats' tails and the glucose level was checked using ACCU-CHEK after 0, 20, 40, 70, 110, 170, 230, 290, 350 and 440 min.

Suspensions of gliclazide, metformin were prepared as by adding 0.4 g of carboxymethyl cellulose (CMC) slowly in 50 mL of distilled water heated using a water bath up to 80°C for 15 min, then completing the volume to 100 mL to get a solution of 0.4% CMC. After that 25 mL of this solution was taken and placed on a hot plate at a temperature of 60°C and stirred using magnetic stirrer while 70 mg of sodium laurel sulfate (SLS) is slowly added and dissolved completely. Finally, the drug powder is added in portion with continuous stirring.

Ethical considerations: The experiment was conducted under the Guide for the Care and Use of Laboratory Animals[14] and the proposal of the study was submitted and approved by the ethical review committee of the School of Pharmacy, Mutah University before the commencement of the study.

Statistical analysis: Data are presented using the Mean ± SEM (Standard Error of Mean). The statistical significance among groups was determined using one-way ANOVA and paired sample T-test in SPSS. A p-value >0.05 was considered significant. All statistical analyses were performed using SPSS Advanced Statistics version 22 software, free trial (IBM, Armonk, NY, USA).

RESULTS

The present study designed to discover the influence of orlistat on the bioavailability of lipophilic GZ compared to hydrophilic MT and food content (high-fat food).

The oral glucose loading animal model used for evaluation of bioavailability of both drugs GZ and MT. Table 1 shows study design two groups were used of 8 rats of either sex (MT and GZ group), treated as follows: glucose alone; and all other cases glucose with vehicle; oil-rich meal (1 mL olive oil); drug (GZ or MT); oil and drug (GZ or MT); Orlistat; Orlistat with an oil-rich meal and drug (GZ or MT) finally Orlistat with (GZ or MT).

Figure 2 shows the blood glucose level for about 8 hours. Appear in part A that orlistat did not affect blood glucose level lowering by GZ using the aqueous vehicle p-value >0.05 (0.128), on the other hand, the interaction was significant in the presence of oil food with a p-value <0.001 (0.000). Interestingly the presence of orlistat (with the absence of oil) led to the higher effect of GZ this effect may conclude an increase of GZ bioavailability as appears for the lowest glucose level in Fig. 2a.

On the other hand, MT effect not interrupted in the presence of oil food alone p-value <0.05 (0.015) as well as, with a concomitant dose of orlistat in presence of oil food as well, a p-value of 0.011 (<0.05) as shown in Fig. 2b.

DISCUSSION

Orlistat interaction with antidiabetic drugs GZ and MT has been evaluated. Also, the evaluation of the food type effect of drug-drug interactions studied. Table 1 shows study design and combinations as well. Significant interaction noticed with food type in case of GZ. In the case of aqueous food presence or absence of Orlistat ends with comparable blood glucose levels while remarkable effect appeared in case of the high fat meal as shown in Fig. 2. No significant interaction appeared in the case of hydrophilic drug MT.

Orlistat mood of action is the covalent binding to the gastric and pancreatic lipase binding sites. Concomitant administration with fat-containing foods that is the exact timing for drug administration, Orlistat partially inhibits hydrolysis of triglycerides, hence reducing the subsequent absorption of monoacylglycerols and free fatty acids[15]. Its gastrointestinal effects side effects are mostly steatorrhea after fatty meals, as it is not absorbed[2]. Its believed that this will affect lipophilic drugs by increasing their loss with steatorrhea, especially with high-fat content food while the minimal effect on hydrophilic drugs as MT.

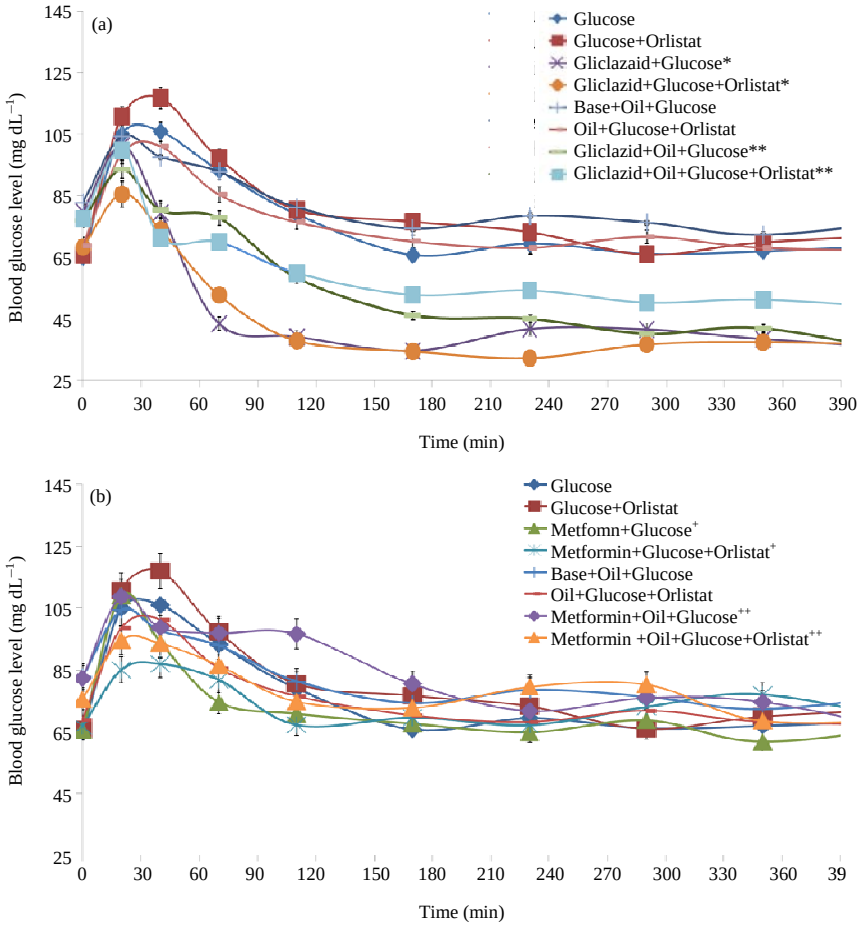

Fig. 2(a-b): Plots for blood glucose level against time after administration of: (a) GZ and (b) MT as indicated in Table 1 and near each curve

*p-value (0.128), **p-value (0.000), +p-value (0.015), ++p-value (0.011)

Metformin (MT) is a popular drug and used by millions worldwide to treat various conditions including Type 2 diabetes mellitus. MT is primarily used as a first-line drug for the treatment of type 2 diabetes mellitus in overweight patients[9]. MT anti-hyperglycemic action postulated by decreased hepatic glucose production by inhibiting gluconeogenesis and increased glucose utilization[10]. At physiological pH, MT ionized with a positive charge. Therefore, its absorption, distribution and excretion depend on Organic Cation Transporters; Monoamine Transporter; Plasma membrane; Multidrug and Toxin Extruders. MT molecular weight is 165.63; log P: -0.92, it's freely soluble in water and is practically insoluble in acetone, ether and chloroform with pKa of 12.4[9].

As a sulphonylurea GZ has a half-life of 11 hours; extensive metabolism; as well as low renal clearance[16]. GZ reduces the hepatic glucose production as well as clearance with no effect on the insulin receptor. This effect leads to a low incidence of hypoglycemia and body weight gain if compared to other drugs within the same group[17]. GZ molecular weight is 323.4; its a weak acid with a pKa of 5.8, which has great lipid solubility with a partition coefficient between buffer (pH 7.4) and chloroform of greater than 1000 and log P 1.73. More than 80% of an oral dose of GZ is absorbed with peak levels occurring after approximately[16,17] 3 to 4 h.

GZ and MT used in diabetic patients with a high chance to be overweight or obese. Because of GZ high lipophilicity, its absorption may depend on the presence of a lipid phase in the gastrointestinal environment, which may be affected by the pharmacological action of Orlistat. Orlistat inhibits dietary fat absorption by about 30%. Consequently, it is theoretically possible that orlistat may alter the absorption kinetics of highly lipophilic drugs[12].

As with previous reports, Orlistat affects the pharmacokinetic profile of highly lipophilic drug Amiodarone[7] by 20% to 25%. This effect was not with all drugs with lipophilic character as within the same study no effect reported with Fluoxetine and Simvastatin when coadministered with Orlistat in healthy volunteer[7]. Another study explored possible interactions with drugs like glucose-lowering agents (Metformin hydrochloride), antidepressant drugs (Amitriptyline hydrochloride), appetite suppressants (Phentermine hydrochloride and Sibutramine hydrochloride monohydrate), immunosuppressants (Cyclosporine) and hypolipidemic (Atorvastatin calcium) and antihypertensive drugs (Losartan potassium)[6-12]. Selection for these groups based on the possibility of the high risk of these diseases with obese patients. Cyclosporine was the only affected with this group of drugs[4]. Similar studies reported with warfarin[6]; gliburide[18]; phenytoin[19], atenolol, furosemide, nifedipine and captopril[8] results in no significant alteration the pharmacokinetic parameters for these drugs. Reports support that considering direct drug-drug interaction can correlate[20] to drug log P. compounds with more than log P value of 6.5 are affected by Orlistat[20]. Vitamin E; β-carotene kinetics were affected by orlistat[5,11].

All these reports investigated the drug-drug interactions without considering the effect of food type. Herein the work evaluated and proved the theory that indirect interaction has to be taken into consideration when talking about orlistat drug-drug interaction. GZ blood-glucose-lowering effect reduced in the presence of high-fat content more than an aqueous partner. Orlistat reduced fat absorption and promotes its secretion while GZ as its chemical character directed more to the lipophilic character that is toward the fatty stool. This effect has to be investigated with other drugs that have a narrow therapeutic index as it may affect their effect profile.

As a result, Orlistat did not affect GZ availability via direct drug-drug interaction. This behavior is followed by MT as well. While in concomitant food intake the type of food affects GZ bioavailability rather than MT, which has more hydrophilic properties than GZ. For diabetic patients, that need to receive doses of Orlistat must pay attention, especially with GZ.

CONCLUSIONS

Orlistat affects the bioavailability of gliclazide. This effect appeared with high fat content-meal. GZ may lose with fat food into feces, as blood glucose level is higher with the fat meal that is significantly differing from the aqueous meal (p-value 0.128). GZ may lose with feces as it may be solubilized with fatty meals. This effect didn't appear with hydrophilic metformin as it will not interact with oil. More research needed to specify the time interval limit for dose delay between GZ and Orlistat.

SIGNIFICANCE STATEMENT

This study discovered the possible effect of high-fat food on drug-drug interaction regarding orlistat and lipophilic drugs such as GZ. This study helps researchers to go thoroughly through Orlistat interaction with other drugs, as previous studies didn't concentrate deeply on the effect of food type and meal content when they explored their kinetics behavior with concomitant administration with Orlistat. Thus more studies needed to decide dose regimen modification for and the lag period between Orlistat and other drugs with patients receiving this important lipid-lowering agent.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Applied Science University, for allowing the use of the animal house. The authors acknowledge Professor Imad Hamdan.

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