EFFECT OF BENFOTIAMINE AND SILIBININON POSTPRANDIAL HYPERGLYCEMIA OF HEALTHY SUBJECTS CHALLENGED WITH SUCROSE LOAD: COMPARATIVE STUDY WITH ACARBOSE

TAVGA A. AZIZ, BUSHRA H. MAROUF, ZHEEN A. AHMED, SAAD A. HUSSAIN

1Department of Pharmacology and Toxicology, School of Pharmacy, Faculty of Medical Sciences, University of Sulaimani, Kurdistan, 2Department of Pharmacology, School of Medicine, Faculty of Medical Sciences, University of Sulaimani, Kurdistan, 3Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq. *Email: saad_alzaid@yahoo.com

ABSTRACT

Objective: To evaluate the acute effect of single doses of benfotiamine and silibinin on postprandial hyperglycaemia after sucrose challenge in healthy subjects.

Methods: Thirteen normal healthy subjects with normal glucose tolerance were enrolled in an open label, crossover study. They received 5 types of treatments separated by 72 hrs washing period. After overnight fasting, either placebo, 50mg acarbose, 100mg acarbose, 300mg benfotiamine or 200mg silibinin were administered, followed (after 60min) by oral sucrose loading (1g/kg dissolved in 150ml of water), then blood glucose levels were measured at 0, 15, 30, 60, 90, 120, 180 min postprandially. The results of the tested compounds were compared with the standard drug acarbose and control.

Results: Pre-treatment with single doses of benfotiamine (300mg) and silibinin (200mg) results in blood glucose levels comparable to that produced by placebo and 50mg acarbose and higher than that produced by 100mg acarbose 30min after sucrose load. Acarbose 100mg only significantly decreases the AUC of glucose excursions after sucrose load, while not all other types of treatments showed significant results compared to control.

Conclusion: Single doses of benfotiamine and silibinin do not reduce postprandial hyperglycaemia after sucrose load in healthy subjects.

Keywords: Benfotiamine, silibinin, Postprandial glycaemia, Sucrose challenge

INTRODUCTION

There has been increasing evidence that the postprandial state is an important contributing factor to the development of many complications, including atherosclerosis and other endothelium-related vascular changes [1,2]. High concentration of blood glucose as well as high glucose fluctuation during postprandial period correlates with the increase in reactive oxygen species or oxidative stress [3], which triggers with time atherogenic changes, including increases in low-density lipoprotein oxidation, sympathetic tone, vasoconstriction, and thrombogenicity [4]. Accordingly, glucose control is an important goal to diminish the risk of long-term health complications of type 2 diabetes. In addition to glycated hemoglobin and fasting plasma glucose, postprandial glucose is recently recommended as essential target for diabetes management [5]. In addition to the use of insulin and many other hypoglycemic agents for controlling extended postprandial hyperglycaemia and its fluctuations [6], many supplements with potential antioxidant properties are used for the same purpose [7,8]. Benfotiamine, a commonly used supplement in the treatment of diabetic neuropathy [9], is a transketolase activator that directs glucose substrates to the pentose phosphate pathway; it prevents experimental diabetic retinopathy [10] and in vitro hyperglycemia-induced endothelial dysfunction [11]. Silibinin is the major compound of the silymarin isolated from seeds of Mediterranean milk thistle, Silybum marianum (L.) Gaertn. (Asteraceae), and clinically used as a hepatoprotectant [12]. Silibinin was effective in stabilizing the mitochondrial membrane, enhancing oxidation and glycogenolysis [13]; it can also rescue beta-cell function in alloxan-treated rats [14]. In addition to the use of insulin and many other hypoglycemic agents for controlling extended postprandial hyperglycaemia and its fluctuations, many supplements with potential antioxidant properties are used for the same purpose. Many of these agents, especially some polyphenols, are tried for their capacity to inhibit a-glucosidase activity and dampen postprandial hyperglycaemia [15]. Such type of activity was mostly achieved with long-term and regular consumption of pharmaceutical doses of these agents [16,17]; however, the acute effect of single doses is not well established. Accordingly, the present study was designed to evaluate the effects of single oral doses of benfotiamine and silibinin dihemisuccinate on postprandial glucose spikes after oral sucrose load in healthy subjects.

METHODS

Thirteen normal healthy subjects with age range of 23-40 years and normal glucose tolerance were enrolled in an open label, crossover study. The Ethical Committee of the University of Sulaimani, Faculty of Medical Sciences, School of Pharmacy, in accordance with Helsinki declaration, approved the study protocol; the volunteers have signed an informed consent after a full explanation of the study protocol before starting the study. Before starting the study, the eligibility of the volunteers have been screened by evaluating their 12 hr fasting blood glucose and only those who had FBG less than 90mg/dl were enrolled in the study; their body weight, height, medical and drug history have also been checked. Pure powders of both benfotiamine (Sigma, USA) and silibinin dihemisuccinate (Tolbiac Co, Argentina) were used in the study, and formulated as capsule dosage form containing either 300mg benfotiamine or 200mg silibinin. Blood samples for glucose level measurement were obtained by finger prick, using lancing device of an electrochemical biosensor technology Xitux Diagnostic GLAB Self-Monitoring Blood Glucose System (HMM Diagnostics GmbH, Germany). The subjects were enrolled, through a crossover design, in 5 types of treatments separated by 72 hrs washing period. After overnight fasting, either placebo, 50mg acarbose, 100mg acarbose, 300mg benfotiamine or 200mg silibinin were administered, followed (after 60min) by oral sucrose loading (1g/kg dissolved in 150ml of water), then blood glucose levels were measured at 0, 15, 30, 60, 90, 120, 180 min postprandially. The results of the tested drugs were compared with the standard drug acarbose and control.

Statistical Analysis

The data were expressed as mean±SD. The change in plasma glucose level with respect to baseline and time was estimated to represent area under the curve. Statistical significance was performed by one
way factorial analysis of variance (ANOVA), followed by Benferroni’s post hoc comparisons to compare means of AUC, using graph-pad prism 5 for windows software. \( P \) values less than 0.05 were considered statistically significant.

**RESULTS**

Oral administration of sucrose (1.0g/kg) increases blood glucose level in healthy subjects (control group) and maximum concentration (C\(_{\text{max}}\)) of glucose (140mg/dl) was achieved within 30 min (T\(_{\text{max}}\)) after ingestion of sucrose, while pretreatment with two single doses of acarbose (50 and 100mg) resulted in C\(_{\text{max}}\) of 103 and 98mg/dl respectively, 30 min post sucrose load (Figure 1). Meanwhile, pre-treatment with single doses of benfotiamine (300mg) and silibinin (200mg) results in C\(_{\text{max}}\) of 140 and 137mg/dl respectively, 30 min after sucrose load (Figure 1). In figure 2, the two doses of acarbose (50 and 100mg) significantly decrease blood glucose levels at T\(_{\text{max}}\) (30 min), compared with control, benfotiamine and silibinin groups and the effect of acarbose was dose-dependent, where the 100mg dose decreases blood glucose significantly, compared to 50mg dose at this time point (\( P < 0.05 \)). Moreover, both benfotiamine and silibinin did not decrease blood glucose levels significantly at that time point (\( P > 0.05 \)), compared with control group. In figure 3, estimation of integrated AUC\(_{0-180}\) over 3 hr period revealed that acarbose 100mg only produced significant decrease in the AUC\(_{0-180}\) of glucose excursions after sucrose load, while all other types of treatments (50mg acarbose, 300mg benfotiamine and 200mg silibinin) did not show significant results compared to control (Figure 3).

---

**Fig. 1:** Effects of single doses of benfotiamine, silibinin and acarbose on blood glucose excursions during 180 min after sucrose load in healthy subjects; \( n = 13 \) subjects.

**Fig. 2:** Effects of single dose of benfotiamine, silibinin and acarbose on blood glucose levels 30 min after sucrose load in normal healthy subjects; \( n = 13 \) subjects; values with different letters (a,b,c) are considered significantly different (\( P < 0.05 \)).

**Fig. 3:** Effects of single doses of benfotiamine, silibinin and acarbose on the area under the curve (AUC\(_{0-180}\)) of glucose levels after sucrose challenge in healthy subjects; \( n = 13 \) subjects; values with different letters (a,b) are considered significantly different (\( P < 0.05 \)).
DISCUSSION

Rapid absorption of glucose challenges the regulatory mechanisms of glucose homoeostasis, and habitual consumption of high glucose diets may therefore increase the risk of diabetic complications and cardiovascular diseases [18]. Diet rich in carbohydrates produces sharp rise in the blood glucose levels, as the complex carbohydrates in the food are rapidly digested, and absorbed as glucose in the intestine aided by the effect of the digestive enzymes a-amylase and a-glucosidases, which break down dietary carbohydrates into absorbable glucose [19]. Actually, controlling postprandial blood glucose level is critical in the early treatment of DM and in reducing chronic vascular complications. Therefore, interference with the processes of digestopolysaccharides would reduce the rate of glucose release and absorption, and consequently suppress postprandial hyperglycemia [20].

Although benfotiamine is known to be useful in the treatment of certain DM complications, including retinopathy and neuropathy [10,21], and mostly long-term administration is necessary for this purpose; it fails, when used as a single dose, to lower glucose spikes in healthy subjects after sucrose load as shown in the present study. This may be attributed to its unique mechanism of action as inhibitor of aldose reductase and stimulation transketolase, which seems to be time dependent [22,23]. The use of alpha glucosidase inhibitor treatment in control of rise in the postprandial glucose level is desirable as it represents a simple effective mechanism for controlling hyperglycemia. In 2004, Kesavan et al. reported the advantage of some plant extracts as alpha glucosidase inhibitors in prevention of postprandial diabetic patients into T2DM patients in addition to controlling the risk of cardiovascular damage [24]. T2DM patients suffer from hyperglycemic spike up after meals, which take almost 4-5 hours to reduce back to the original glucose level. The spike up is attributed to increased disaccharidases activity by 1.5 fold [25] and glucose transporters GLUT2 and SGLT1 activity by almost 3-4 fold in diabetic animals as compared to normal [26].

The increased glucose level for prolong time leads to nonspecific glycation of proteins initiating the mechanism of impaired glucose tolerance (pre DM) and type 2 diabetes mellitus [27]. Hence, control of postprandial glucose levels would be valuable in preventing secondary complications of diabetes. Previous research has been focused on the control of postprandial glucose by the inhibition of pancreatic amylase and the intestinal-alpha-glucosidases, the key enzymes of dietary carbohydrate digestion [28]. Slowing the rate of carbohydrate digestion and/or absorption is the most probable mechanism underlying the potential for attenuated postprandial hyperglycemia, as this condition is associated with the prevention of impaired glucose tolerance (pre-diabetes) and a significant reduction in risk of developing T2DM [29]. It has been reported previously that the treatment with an a-glucosidase inhibitor (acarbose) specifically delays postprandial rise in plasma glucose levels by 40% in healthy volunteers [30]. It is possible that some natural products, including silybin, will prevent or delay developing diabetes in healthy people.

An evidence reports that suppression of postprandial glucose may contribute to decreasing the level of HbA1C resulting in a significant reduction in the incidence of chronic vascular complication such as macro- and micro vascular diseases [31]. In the present study, we examined the acute effect of silybin on the postprandial effects of oral sucrose in healthy subjects. We report that treatment with silybin (200mg) do not reduce the postprandial elevation in blood glucose levels induced by bolus dosing with sucrose; this result was in tune with that reported by Lambert et al., where single acute dose of green tea polyphenols produced no effect on the increase in postprandial blood glucose induced by maltose orglucose [32]. Therefore, these results suggest that silybin may modulate an aspect of carbohydrate metabolism that is unique to postprandial, and might be the result of inhibition of a-amylase by silybin. However, although the present study includes only healthysubjects, it may nevertheless apply to individuals with diabetes, as hyperglycemia is an independent predictor of future cardiovascular events in both healthy and diabetic individuals. Therefore, we assume that an intake of silybin might help people with T2DM to control the postprandial hyperglycemia asthereby prevent the progression of diabetic complications. The recently published data showed that silybin (200mg/day) reduces fasting plasma glucose, postprandial hyperglycemia and HbA1c level in diabetic patients after four months of supplementation [16].

However, the effect of single acute dose of silybin on postprandial glucose level in healthy subjects remains controversial. Further studies are needed to determine the acute effect of silybin in diabetic subjects focusing on examining postprandial glucose and HbA1c level, which could yield important new insights into the preventive of diabetic complications. Another recent report suggested that a lifetime intake of dietary polyphenols, assuming the same mechanism, has a comparable potential to reduce diabetes risk [33], but more studies are required to fully test the effect of modulating postprandial blood glucose in healthy subjects and those with DM. In conclusion, single acute doses of benfotiamine and silybin do not affect postprandial glucose excursions after sucrose load in healthy subjects.

ACKNOWLEDGEMENT

The authors thank University of Sulaimani, Faculty of Medical Sciences for supporting the project.

REFERENCES


