Diabetology International (2019) 10:77–82
https://doi.org/10.1007/s13340-018-0372-0

SHORT COMMUNICATION

Effect of deglutition aids on the inhibitory effect of orally disintegrating tablets of voglibose on the postprandial elevation of blood glucose levels: a case investigating the interaction between xanthan gum and voglibose

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Received: 11 December 2017 / Accepted: 27 August 2018 / Published online: 5 September 2018

Abstract

In this study, we first performed a disintegration test of the voglibose orally disintegrating (V-OD) tablet immersed in jelly-wafer (JW, V-ODims/jw) for 10 min and compared it with the disintegration time of V-OD that was not immersed in JW. We then orally administered the V-ODims/jw tablet to 7 healthy adults and compared the shift in blood glucose levels (BGLs), after loading with a sucrose solution (Suc-sol, 100 g/150 mL), with that after administration of the non-immersed V-OD tablet. The disintegration time of V-ODims/jw tablet was shorter than that of V-OD. When administered to healthy adults, the BGL after loading with Suc-sol was higher with V-ODims/jw tablet administration than with V-OD tablet. We predict that the expression of the efficacy of voglibose is reduced as a result of the interaction between voglibose and the polysaccharide, xanthan gum (XG), since it is a common additive in JW. This study shows that deglutition aids with additives that do not affect pharmacokinetics must be carefully selected for administering along with pharmaceuticals, because of a suggested possibility that the interaction between these pharmaceuticals and the additives in the deglutition aids weaken the drug efficacy. A more careful selection of deglutition aids from the wide selection of medication is especially important when administered to patients who use these deglutition aids often, such as elderly individuals or individuals with a deglutition disorder.

Keywords Xanthan gum · Jelly-wafer · Voglibose · Orally disintegrating tablet · Blood glucose elevation

Abbreviations

AUIC	Area under the incremental concentration–time curve
BGLs	Blood glucose levels
FT	Food thickener
JP17	The Japanese Pharmacopoeia, 17th edition
JW	Jelly-wafer
Suc-sol	Sucrose solution
V-OD	Voglibose orally disintegrating tablet
V-ODims/ft	Voglibose orally disintegrating tablet immersed in food thickener
V-ODims/jw	Voglibose orally disintegrating tablet immersed in jelly-wafer
XG	Xanthan gum

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Introduction

Food thickeners (FT) are swallowing supplements that are useful for elderly individuals, or individuals with eating or swallowing disorders. These thickeners are not only useful when eating food, but also when taking oral drug formulations, such as tablets [1, 2]. However, undissolved tablets have been observed in the stool of patients taking magnesium oxide tablets that had been immersed in FT [3].

FTs affect the disintegration and dissolution of magnesium oxide tablets [4]. They also affect the disintegration of quick-dissolving tablets, such as orally disintegrating tablets [5, 6]. In addition, the use of FTs along with administration of pharmaceuticals is challenging. Orally disintegrating tablets of voglibose immersed in an FT, are reported to exhibit extended disintegration times and suppressed inhibitory effects on the elevation of BGLs [7].

Nevertheless, medical institutions and nursing care facilities use swallowing aid jellies, which are deglutition aids specially developed for administering pharmaceuticals to elderly individuals or individuals with a deglutition disorder. In this report, we examined the effect of a swallowing aid jelly on the inhibitory effect on the elevation of blood-glucose levels in orally disintegrating tablets of voglibose (frequently administered with the aim of improving postprandial hyperglycemia in patients with diabetes) and conducted a comparative investigation of the inhibitory effect on the elevation of blood-glucose levels when using FT.

Materials and methods

1. Sample: Basen® OD tablet (Takeda Pharmaceutical Company Ltd., 0.2 mg, manufacturing number: OJ163) was used as a model voglibose orally disintegrating (V-OD) tablet. We used Swallowing Aid Jelly (Magic Jelly, RakuRaku) (Ryukakusan Co. Ltd.) as the deglutition aid jelly-wafer (JW).
2. Disintegration test: We immersed V-OD tablets into JW (8 g/tablet) and considered the tablets that had been standing for 10 min as JW immersed (V-ODims/jw) tablets. Further, we immediately performed the disintegration test as per Pharmacopoeia of Japan [disintegration tester: NT-40H (Toyama Sangyo Co., Ltd.), testing liquid: purified water, concentration 37 ± 2 °C, disc: disuse] and measured the disintegration time. After immersion, we defined the sample used in the disintegration test as V-ODims/jw tablet with 8 g of JW and the disintegration time as the time required for V-ODims/jw to completely disintegrate. We defined the control as the disintegration time of V-OD tablet that was not immersed in JW.

In our previous studies, we orally administered V-OD that had been immersed in FT for 10 min (V-ODims/ft). The results showed that blood glucose levels (BGLs) increased, after loading with sucrose solution (Suc-sol, 100 g/150 mL), in individuals administered V-ODims/ft tablets compared to those administered V-OD tablets that had not been immersed [7]. In the present study, we immersed V-OD tablets in JW for 10 min, as was done in the previous oral study of V-ODims/ft [7], to compare the shifts in BGLs in the two oral studies.

3. Oral study: We selected 7 healthy Japanese adult males, aged between 30 and 58 years, with no history of medical allergies, digestive disorders, or diabetes for the clinical trial. Prior to initiating the trial, we thoroughly explained the purpose and details of the study and obtained written consent from all participants. In addition, we obtained approval for the planning of this study from the clinical research ethics committee of Hospital Bando.

We defined the non-immersed V-OD tablets as the control drug and V-ODims/jw, which is V-OD that had been immersed in 8 g of JW for 10 min, as the study drug. The test subjects were administered V-ODims/jw tablets that included 8 g of JW. We defined the number of participants as 7 and administered the study and control drugs in a crossover study. The dosage interval was set to ≥ 7 days because the half-life after a single dose of voglibose (80 mg) in a healthy male test subject is 5.33 h [8]. Before drug administration, the participants were fasted for ≥ 10 h. We administered either the control drug (V-OD) or the study drug (V-ODims/jw) with 150 mL of water directly after collecting a blood sample to measure the fasting BGL. We then immediately administered Suc-sol—100 g of sucrose (special-grade chemical, Koso Chemicals Co., Ltd.) dissolved in 150 mL water.

We also collected blood samples at 15, 30, 45, 60, 75, 90, 105, and 120 min after administering Suc-sol to measure the BGL. The blood samples were collected by the subjects themselves by using a puncturing device (Medisafe® Finetouch®: Terumo Corporation) and a single-use automatic lancet (Medisafe® needle: Terumo Corporation) for self-measurement of BGL. The subjects used a glucose measuring device (Medisafe® Mini GR-102: Terumo Corporation) equipped with a glucose detection kit (Medisafe® Tip: Terumo Corporation).

Before measuring the BGL, we washed our hands and fingers under running water, disinfected the fingertips using ethanol, and dried them sufficiently. Subsequently, we sampled the capillary blood by puncturing with a puncture device for blood collection.

We set the maximum value of BGL 120 min after taking Suc-sol to C_{max}, and the time it took to reach C_{max} to T_{max}. We set the BGL at 0 min subtracted from the temporal BGL after taking of Suc-sol as the blood glucose elevation (ΔC) and calculated the blood glucose elevation area under the incremental concentration–time curve (AUIC) using the trapezoidal formula.

Statistical analysis

We analyzed the disintegration times of the control V-OD and V-ODims/jw tablets using the paired *t* test. We

performed the Wilcoxon signed-rank test to compare the BGLs after administration of the V-ODims/jw and control V-OD tablets. The AUICs after the administration of the V-ODims/jw and control V-OD tablets were analyzed using paired *t* test. All analyses were performed using the IBM SPSS Statistics 25 (IBM Japan, Tokyo, Japan). A *p* value less than 0.05 was considered to be statistically significant.

Results

1. Disintegration test: Median disintegration times for the control V-OD and V-ODims/jw tablets were 27.5 and 22.0 s, respectively. There were significant differences between the control V-OD and V-ODims/jw tablets ($p = 0.007$) (Table 1).
2. Oral study: Fig. 1 shows the shift in BGL after administration of V-OD and V-ODims/jw tablets.

The T_{max} with V-OD tablet administration was 30 min after taking Suc-sol. The T_{max} with V-ODims/jw tablet administration was 45 min after taking Suc-sol, which was 15 min later than that after V-OD tablet administration (Fig. 1).

Table 1 Effect of jelly-wafer immersing on disintegration of voglibose oral disintegrating tablet

	Disintegration time (s)				
	Non immersing		10 min immersing		
	Median[a]	Range	Median[b]	Range	(*b*/*a*)
Jelly-wafer	27.5	26.0–28.0	22.0**	20.0–28.0	(0.8)

**$p < 0.01$ (paired *t* test)

The C_{max} after V-OD tablet administration was 125.9 mg/dL (ΔC: 34.4 mg/dL). However, it was 156.9 mg/dL (ΔC: 65.3 mg/dL) after V-ODims/jw tablet administration, which was 1.25 times (ΔC: 1.90 times) higher than that after V-OD tablet administration. The BGL between 30 and 105 min after taking Suc-sol in subjects administered the V-ODims/jw tablet were higher than in those administered the V-OD tablet; the difference was highest at 45 min after taking Suc-sol. The BGL after V-ODims/jw tablet administration (156.9 mg/dL, ΔC: 65.3 mg/dL) was 1.30 times (ΔC: 2.24 times) higher than that after V-OD tablet administration (120.6 mg/dL, ΔC: 29.1 mg/dL); it was significantly higher that after V-OD tablet administration ($p = 0.020$) (Fig. 1). In addition, the BGL (149.3 mg/dL) in V-ODims/jw tablet-administered subjects, 30 min after taking Suc-sol, was significantly higher than that in V-OD tablet-administered subjects. (125.9 mg/dL, $p = 0.021$) (Fig. 1).

The BGL in V-ODims/jw tablet-administered subjects rapidly increased till 45 min after taking Suc-sol, then rapidly decreased till 120 min. It rapidly increased between 15 and 30 min after taking Suc-sol. The BGL (149.3 mg/dL, ΔC: 57.7 mg/dL) after 30 min of taking Suc-sol was 1.24 times (ΔC: 2.03 times) higher than that after 15 min (120.0 mg/dL, ΔC: 28.4 mg/dL). In addition, the BGL rapidly decreased between 45 and 60 min after taking Suc-sol. The BGL (131.3 mg/dL, ΔC: 39.7 mg/dL) after 60 min of taking Suc-sol decreased by 0.84 times (ΔC: 0.61 times) of that after 45 min (156.9 mg/dL, ΔC: 65.3 mg/dL).

Contrastingly, no fluctuation in BGL after V-OD tablet administration was observed compared to that after V-ODims/jw tablet administration. In particular, BGLs (106.9–107.6 mg/dL) between 90 and 120 min after taking Suc-sol remained unaltered.

The $AUIC_{0\rightarrow 15\ min}$ after V-OD tablet administration till 15 min after taking Suc-sol was higher than that

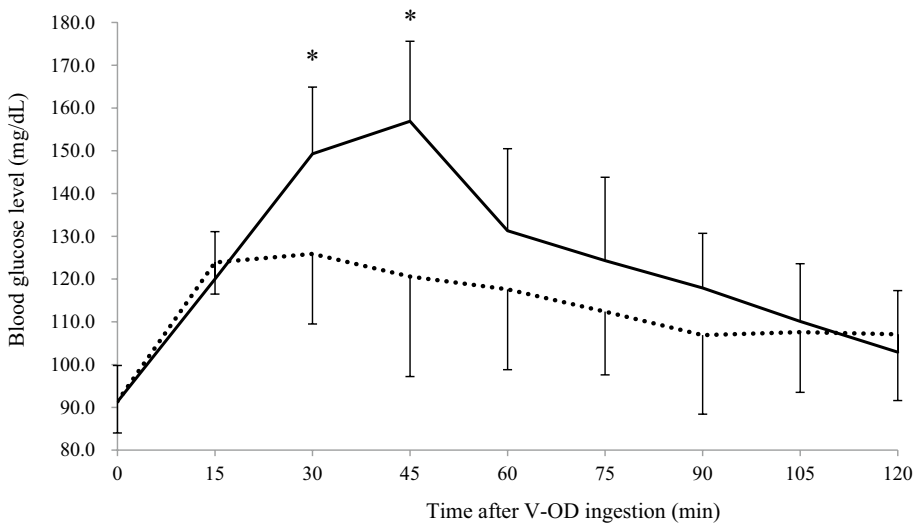

Fig. 1 Effect of immersion in jelly-wafer (JW) on the suppression of postprandial blood glucose level (BGL) by voglibose orally disintegrating tablet (V-OD). The thick line indicates JW immersion; dotted line indicates no JW immersion. Data are shown as the mean ± SD, *$p < 0.05$ (Wilcoxon signed-rank test)

after V-ODims/jw tablet administration. However, AUIC ($AUIC_{0\rightarrow30\ min}$–$AUIC_{0\rightarrow105\ min}$) after V-ODims/jw tablet administration till 30 min after taking Suc-sol was consistently higher than that after V-OD tablet administration. The AUIC ($AUIC_{0\rightarrow30\ min}$–$AUIC_{0\rightarrow105\ min}$) after V-ODims/jw tablet administration between 30 and 105 min after taking Suc-sol was significantly higher than that after V-OD tablet administration (Table 2).

During the testing period, none of the subjects showed any symptoms of sucrose overload, such as digestive abnormalities.

Discussion

Oral administration of the disaccharide hydrolase-inhibiting voglibose inhibits α-glucosidase, found in the small intestine, and limits postprandial elevation of BGL by restraining the creation of glucose derived from sugar found in food substances. Voglibose is commercially available both as a plain tablet that can be taken with water and as an OD tablet that can be taken without water.

The OD Tablets are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. The OD Tablets are expected to be beneficial to elderly individuals, or individuals with eating or swallowing disorders.

The disintegration test is a test to confirm that the tablets disintegrate within a specified time in the General Tests section of the Japanese Pharmacopoeia, 17th edition (JP17). An OD tablet is defined in the General Rules for Preparations section of the JP17 as a tablet that is quickly dissolved or disintegrated in the oral cavity and shows optimum disintegration. However, it is not specifically defined in the Disintegration Test section of the JP17. Therefore, we defined them as plain tablets of immediate-release drugs that disintegrate within 30 min. In the guidance of the US Food and Drug Administration (FDA), the disintegration time of orally disintegrating tablets by collapse test is said to be within 30 s [9]. The median disintegration time of the V-OD tablets used in this study was 27.5 s. Indicating a sufficiently fast disintegration, the V-OD tablets used in this study were considered to have OD properties. Furthermore, the median disintegration time for V-ODims/jw tablets was 0.8 times shorter than that of V-OD tablets. These disintegration test results are no problem for the administration. Generally, water is required to penetrate the interior of a tablet to disintegrate it and the tablet is disintegrated when the added disintegrating agent absorbs the water that penetrated the tablet. Although the particular mechanisms that shorten the disintegration time for V-ODims/jw tablets are unclear, we believe that the thickening agents, including JW, have an effect. JW contains Japanese agar gelatin and the thickening agent, xanthan gum (XG). Since water easily separates from Japanese agar gelatin, we expected water to penetrate the interior of the V-ODims/jw tablet during immersion in JW, containing Japanese agar gelatin. Accordingly, we believe that V-ODims/jw tablets disintegrate faster than V-OD tablets due to water penetrating the interior of the tablet during immersion.

Our previous studies show that the disintegration time of the V-OD tablet immersed in FT (V-ODims/ft) is longer than that of the V-OD tablet. Further, administration of the V-ODims/ft tablet exhibited a higher BGL after Suc-sol loading than administration of the V-OD tablet. We believe that addition of the slightly viscous dextrin along with XG to FT extended the disintegration time of the V-ODims/ft tablet, since the FT coating on the outside of the tablet decreases the rate at which water penetrates the interior of the tablet. This is caused by the additive action of the viscous properties of XG and dextrin. Furthermore, we assume that the extended disintegration time reduced the efficacy of voglibose. Results of this study showed that the inhibitory effect on the elevation of blood-glucose levels of V-ODims/jw tablet was reduced in a manner similar to that of V-ODims/ft, despite the shorter disintegration time of V-ODims/jw tablets than that of V-OD tablets. This suggests that reduction in the inhibitory effect on the elevation of blood-glucose level by voglibose is not caused by the extended disintegration time of the tablet. In addition, an in vitro experiment to measure the rate of absorption of acetaminophen by XG solution clarified that XG absorbs acetaminophen and that the absorption rate decreases following a decrease in the coefficient of viscosity of the XG solution [10]. Further, in an in vivo experiment, a single dose of acetaminophen (100 mg/kg) was administered in the stomach of rats, following a 60-min continuous dosage

Table 2 Effect of jelly-wafer (JW) Immersing on restraint of postprandial area under the blood glucose concentration–time curve (AUC) by voglibose oral disintegrating tablet (V-OD)

Time after V-OD ingestion (min)	Post-prandial AUC (mg/dL/min)	
	Without JW immersing	With JW immersing
	Mean ± SD	Mean ± SD
0–15	243 ± 34	213 ± 71
0–30*	501 ± 109	646 ± 129
0–45**	720 ± 175	1136 ± 246
0–60**	916 ± 265	1434 ± 363
0–75*	1074 ± 336	1679 ± 429
0–90*	1189 ± 397	1876 ± 474
0–105*	1310 ± 481	2015 ± 468
0–120	1428 ± 546	2100 ± 426

*$p < 0.05$, **$p < 0.01$ (paired t test)

of 0.1% (w/v) XG solution through a gastric catheter. A significantly decreased concentration of acetaminophen was detected in the portal vein blood sample, 45–60 min after the dosing compared to that in the control group (the group that was not administered XG) [11]. Voglibose has an epi-inositol framework and there is a possibility that it can interact with polyalcohols or sugars. Therefore, we can infer that voglibose is absorbed by the polysaccharide XG present in FT or JW, in a manner similar to absorption of acetaminophen. We postulate that the interaction (absorption) of voglibose with XG leads to the reduction in its efficacy. Due to this interaction (absorption), the BGLs after Suc-sol loading with administration of V-ODims/ft or V-ODims/jw tablets were higher than that with administration of the V-OD tablet.

Voglibose is an imino-based compound with a p*K*a of 7.06. However, JW is acidic with a pH of approximately 3.7. In the case of V-ODims/jw tablet immersed in JW, we believe that voglibose exists more in the ionic form than in the molecular form, since the pH of the penetrated water is acidic. Therefore, we can infer that the ionic form of voglibose, under acidic conditions of JW, is absorbed by XG due to its ion absorption properties.

The results of a previous study show that during collection of capillary blood from the fingertips, if the hands are not adequately clean, despite disinfection using ethanol, the fructose and glucose adhering to the fingertips may lead to false high values of BGLs [12]. Therefore, to obtain accurate values of BGLs, we washed the hands and fingers under running water, disinfected them with ethanol, and adequately dried them before collection of blood. In addition, false low BGL values are observed when capillary blood is collected from the fingertips of patients in shock, those with peripheral circulatory disorders, or those who are dehydrated [13–15]. The subjects in our study were healthy adults with unrestricted water intake; thus, the impact of false low values was not likely.

The BGLs vary depending on the site from which the sample is obtained; moreover, the BGLs change markedly after meals, and when the blood sugar level is low immediately after administration of the drug, the blood obtained from the forearms using a subcutaneous injection has lower response to change in BGLs than the blood collected from the fingertips [16]. In this study, we collected blood from the fingertips rather than from the forearms to accurately monitor the changes in the blood sugar levels after administration of voglibose without a time lag.

The BGL with V-ODims/jw tablet administration, between 15 and 45 min after Suc-sol loading, was higher than that with V-OD tablet administration. This shows that when patients with diabetes take V-OD to stabilize BGLs along with JW, it is possible that JW may severely diminish the postprandial inhibitory effect on the elevation of BGLs. Therefore, it is necessary to ascertain changes in postprandial BGLs when V-OD is taken along with JW.

This study revealed a rapid decrease in the BGL with V-ODims/jw tablet administration, between 45 and 60 min after Suc-sol loading, in contrast to the steady shift in BGL with V-OD tablet administration. Typically, exercise therapy for improving postprandial high blood glucose is initiated 1–2 h after eating. If a diabetes patient taking a V-OD tablet with JW begins exercise therapy 1 h after eating, there is a risk of developing hypoglycemia due to decrease in blood sugar caused by the exercise therapy in addition to the rapid decrease in blood sugar mediated by the V-ODims/jw tablet. Therefore, it is necessary to take preventive measures against low blood sugar levels.

In this report, we have shown that deglutition aids have an effect on the pharmacological effects of voglibose on postprandial hyperglycemia. Moreover, α-glucosidase inhibitors, including voglibose, can possibly exhibit poor control over BGLs if patients with diabetes who take diabetes treatment drugs, such as voglibose, to stabilize BGLs use JW with said treatment. This is due to the interaction between the additives in deglutition aids and the antidiabetic drugs because there are many cases of interactions with other diabetes treatment drugs. Accordingly, it is important to frequently measure the BGLs of patients upon initiating, terminating, or changing the type of JW.

According to this report, products with additives that do not affect pharmacokinetics must be carefully selected for administration along with pharmaceuticals because of a suggested possibility that the interaction between these pharmaceuticals and additives in the deglutition aids weaken the drug efficacy. A more careful selection of deglutition aids from the wide selection of medication is especially important for patients who frequently use these deglutition aids, such as elderly individuals or individuals with a deglutition disorder.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest associated with this study.

Ethical standards This study was carried out in accordance with the Declaration of Helsinki of 1964 and later versions and approved by the ethics committee of Hospital BANDO (approval number: not applicable, approval date: 8 March 2017).

Informed consent The healthy Japanese adult males gave their written informed consent to participate in this study and its results to be published.

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