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Commentary

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Fasting period after Rybelsus administration influences clinical benefit

Abstract

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been attracted attention for various beneficial effects. Among them, oral semaglutide (Rybelsus) was developed using the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). The relationship between the bioavailability and post-dose fasting time period was analyzed. The results showed that i) its bioavailability with drinking 50mL and 120mL of water together was almost similar, ii) bioavailability for 240mL intake was about 2/3 of 50-120mL, iii) general availability would be about 1.4% for 50-120ml water, and 0.8% for 240mL of water. Tolerability and safety of Rybelsus showed similar results for healthy subjects, patients with renal and/or hepatic impairment. From mentioned above, Rybelsus has been one of the topic agents with characteristic mechanism of SNAC and clinical benefit of GLP-1RA. It will be expected to be applied widely in actual diabetic practice.

Keywords: Glucagon-like peptide 1 receptor agonist (GLP-1 RA), semaglutide, Rybelsus, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), bioavailability

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Diabetes mellitus has been crucial problem worldwide by International Diabetes Federation (IDF) from medical and social points of view.[1] World Health organization (WHO) has also announced recent perspective concerning diabetes mellitus.[2] In Jan 2022, standard guideline of medical care for diabetes was presented by American Diabetes Association (ADA).[3] Thus, various diabetic information has contributed much for adequate diagnosis and therapy of diabetes for years.[4] Among them, recent diabetic topics include several oral hypoglycemic agents (OHAs) and Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) that have been highly evaluated for various beneficial clinical effects.[5]

As GLP-1RA, semaglutide has been estimated for decreasing blood glucose and body weight.[6] Further, it has two ways of administration, which are injectable and oral formulation.[7] Oral agent semaglutide (Rybelsus) was pharmacologically developed for applying absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Authors and collaborators have continued diabetic practice and research for long.[8,9] Recently, we have presented a case report with type 2 diabetes (T2D) treated with Rybelsus.[10] It was provided as increasing dose of 3, 7, 14mg for each month, and significant efficacy was observed with decreased HbA1c 1.4% and weight reduction 5kg for 3 months. The reason of this effect would be from several factors. They include various factors such as oral administration of the agent, intake the agent just after waking up, daily regular lifestyle and meal habit, long fasting time period post-med, influence of gastrointestinal (GI) tract, gastrointestinal adverse events (GIAEs), and others.[11] In this article, pharmacological and medical perspectives of oral semaglutide will be described.

Historically speaking, semaglutide has been originally designed as a once-weekly subcutaneous long-acting GLP-1RA. Semaglutide is a human GLP-1 analog with 94% similarity to natural human GLP-1 but has amino acid changes that improve albumin binding, decrease renal clearance, and boost resistance to DPP-4 destruction.[12] It demonstrated clinical effects for glycemic control and weight reduction compared to placebo and active comparators, such as sitagliptin, exenatide extended-release, dulaglutide, and insulin glargine, in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trials.[13] Furthermore, semaglutide improved cardiovascular outcomes significantly according to several investigations.

Concerning clinical efficacy of oral semaglutide, actual situation of administration per os would be important to be investigated. Using pharmacokinetic model data from clinical studies, the drug delivery system (DDS) of semaglutide was investigated. The purpose of this study was to obtain detail data of absorption, distribution and elimination for the semaglutide concentration in the blood. The protocol included several subjects including healthy, renal or hepatic impairment. Moreover, some condition was varied for the study design, such as water amount to be intake, fasting time period from 15 to 300 minutes. Then, the relationship was investigated between post-dose fasting time (min) and bioavailability (%). The experiment was conducted by application of semaglutide 10mg for single administration and three different water amounts, which were 50mL, 120mL and 240mL. The obtained detail results were calculated from the report of Overgaard et al.

The results were summarized in the Table 1.[14] It showed that i) bioavailability for 50mL and 120mL were almost similar, ii) bioavailability for 240 mL was lower about two-thirds than that of 50-120mL iii) the bioavailability increases along with longer fasting period and iv) it reaches a plateau level approximately 1.4% at 2 hours for 50-120mL. Consequently, the standard administration method would be decided, in which Rybelsus has to be given accompanied with water 50-120 ml and keeping post-dose fasting time period for 30 min. From obtained data, general availability would be about 1.4% for water 50-120ml, and 0.8% for water 240mL.[14] Regarding various subjects, pharmacokinetic investigation was performed. As a result, tolerability and safety of oral semaglutide showed similar results in the cases of healthy subjects, patients with renal impairment or hepatic impairment.[15,16]

As to water intake volume accompanied with Rebelsus, further investigation was conducted. Semaglutide is coformulated together with absorption enhancer, that is Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Regarding the degree of tablet erosion in the stomach, pharmacokinetics was studied for 2 different volumes water associated with evaluation of the relationships of the parameters.[17]

The protocol included semaglutide 10mg and water (50/240 cc) in a randomized, single-center, open-label 2-period crossover trial. The concentrations of semaglutide and SNAC in the blood were followed for 6 and 24 hours after semaglutide administration. For comparative study of 50cc vs 240 cc of water, complete tablet erosion (CTE) was observed 85 min vs 57 min (ratio 1.51, p=0.072). Area Under the Curve (AUC) and maximum concerntration (Cmax) showed 70% higher for 50 cc water. Median time to maximum concentration (Tmax) was 1.5 hours irrespective of water amount. Higher AUC, higher Cmax and longer Tmax showed the positive correlation with longer time for CTE and gastric emptying. Consequently, slower CTE in the stomach may bring higher concentration of semaglutide in the blood.

Table 1 Bioavailabilty of semaglutide in the blood for water amount

Water amount	Data	Bioavailability of semaglutide in the blood (%)					
		15(min)	30(min)	60(min)	120(min)	240(min)	300(min)
50	Measured raw data	0.47	0.82	1.04	1.31		1.56
50-120	Standardized calcul. Data		0.8	1.15	1.39		1.46
240	Measured raw data					0.86	1.01
240	Standardized calcul. Data		0.53	0.74			0.93

In summary, oral semaglutide (Rybelsus) has been in focus as novel type of GLP-1RA. It was evaluated as a novel and effective agent. It was influenced by fasting time period for post-med.[18] It will be expected to be applied widely in actual diabetic practice. This article will be hopefully beneficial for diabetic practice and research.

Conflict of interest

The authors declare no conflict of interest.

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