

Longer Fasting After Rybelsus Administration Contributes Higher Efficacy

Miki K¹, Bando H^{1,2,3,*}, Hayashi K¹, Dohi A³ and Kamoto A¹

¹Hayashi Hospital, Tokushima, Japan

²Tokushima University / Medical Research, Japan

³Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan

*Corresponding author: Bando H, Tokushima University, Medical Research, Japan; E-mail: pianomed@bronze.ocn.ne.jp

Abstract

Recent pharmacological topic for diabetes includes clinical application of Glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Among them, oral semaglutide (Rybelsus) has been developed as the first oral form of GLP-1RA by useful application of sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Semaglutide concentration in the blood was compared when fasting time period after Rybelsus administration would be 15, 30, 60 and 120 minutes. As a result, the concentration ratio after 4 hours was 1.00, 1.67, 2.60 and 3.06, respectively. Authors have experienced a diabetic case of remarkable efficacy as HbA1c -1.4% and weight -5kg, who kept 3-4 hours fasting after Rybelsus intake.

Keywords: Glucagon-like peptide 1 receptor agonists (GLP-1 RAs); Oral semaglutide (Rybelsus); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Fasting time period

Introduction

Non-communicable diseases (NCDs) have been increasing across the world [1]. Among them, type 2 diabetes mellitus (T2DM) has become crucial medical and social problems. Adequate treatment for T2DM includes oral hypoglycemic agents (OHAs), insulin and other injectable agents such as effective Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) [2]. GLP-1RAs have recently evolved rapidly for beneficial efficacy including promoting insulin secretion, decreasing glucagon secretion, reducing hunger and enhancing satiety. As latest novel development, oral semaglutide (Rybelsus) has been introduced to actual practice [3]. This article introduces the points about the basic clinical features of Rybelsus [4].

GLP-1RA has been evaluated as second line treatment for T2DM and also for possible agent for obesity [5]. From cardiovascular (CV) outcome results, it was proved to show reduction of various CV risk for case with established CV problems. This is firstly approved as oral GLP-1RA, and this peptidic agent would be considered as quintessential for actual treatment for T2DM. Thus, in modern clinical practice, drugs that are beneficial for diabetes,

obesity, and cardiovascular disease are significant, and oral drugs are considered to be more useful than injectable drugs. Several types of GLP-1RA have been observed. Among them, only semaglutide has injectable and oral types [6]. Oral semaglutide is the first oral agent of GLP-1RA as brand name Rybelsus [7]. Regarding the molecular structure, semaglutide is 94% homologous to human GLP-1, which has some significant changes to achieve a longer half-life of about 1 week [8,9]. Oral semaglutide was developed as oral agent by the combination of absorption enhancer, that is known as sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC) [10,11]. SNAC will form a non-covalent bond with GLP-1 for a concentration dependent manner. It can elevate lipophilicity degree and increase transcellular absorption of the agent through epithelium of the stomach mucosa [11,12]. Furthermore, it can act as locally pH buffer, increase soluble degree, and protect the degradation of the agent. The activity of SNAC is reversible and short, and then it easily separates from semaglutide on reaching the bloodstream. As semaglutide shows well-defined pharmacokinetics, it will be actually absorbed completely in the stomach. The blood concentration reaches maximum approximately 15-35 min after

Received date: 24 March 2022; **Accepted date:** 30 March 2022; **Published date:** 04 April 2022

Citation: Miki K, Bando H, Hayashi K, Dohi A, Kamoto A. (2022) Longer Fasting After Rybelsus Administration Contributes Higher Efficacy. SunText Rev Med Clin Res 3(1): 150.

DOI: <https://doi.org/10.51737/2766-4813.2022.050>

Copyright: © 2022 Miki K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ingestion [10]. Rybelsus is novel agent of oral semaglutide, which is one of human GLP-1RA. Two kinds of investigation were conducted including food influence before taking agent and fasting time period after taking the agent [13]. Regarding food-influence exam, 78 case were divided to 3 groups, which are i)

fed 30-min pre-dose, ii) fasting overnight and 4-hour post-dose, iii) reference fasting overnight and 30-min-post-dose. As to dosing exam, 161 case were randomized for 8 groups including fasting time duration post-dose 15-30-60-120 minutes with water 50 or 120 cc (Table 1,2).

Table 1 Semaglutide concentration for fasting and reference

protocol	Seamaglutide conc. 2 hours (nmol/L)	Seamaglutide conc. 4 hours (nmol/L)	Seamaglutide conc. 24 hours (nmol/L)	Ratio of conc. 2 hours	Ratio of conc. 4 hours	Ratio of conc. 24 hours
Fasting	18.4	18.6	14.5	1.44	1.50	1.41
Reference	12.8	12.4	10.3	1.00	1.00	1.00

Time (2,4 and 24 hours) shows the period from oral administration.

Table 2 Semaglutide concentration for fasting time

Fasting time (min)	Seamaglutide conc. 2 hours (nmol/L)	Seamaglutide conc. 4 hours (nmol/L)	Seamaglutide conc. 24 hours (nmol/L)	Ratio of conc. 2 hours	Ratio of conc. 4 hours	Ratio of conc. 24 hours
15	8.7	8.6	7.4	1.00	1.00	1.00
30	14.6	14.4	12.3	1.68	1.67	1.66
60	22.5	22.4	18.2	2.59	2.60	2.46
120	28	26.3	22.5	3.22	3.06	3.04

Fasting time means the continuation of fasting after oral administration of semaglutide.

Among various results of the study, meaningful data was summarized and measured from related figures [13]. Semaglutide concentration in the blood was compared between fasting situations and non-fasting with fed before taking medicine (reference). As a result, the blood concentration showed 1.41-1.50 times higher in fasting condition. Semaglutide concentration in the blood was compared when fasting time period after taking medicine as 15-120 min. When the standard level is set 1.00 at 15 min, concentration ratio for 4 hours would be elevated 1.67, 2.60 and 3.06 times in 30, 60 and 120 min, respectively. Furthermore, water amount of 50ml and 120ml revealed no significant changes. These data would indicate stable beneficial effect of combined semaglutide and SNAC in the actual clinical practice. Consequently, the standard method of intake for Rybelsus was decided as i) taking medicine just after waking up in the morning for fasting condition, ii) at least 30 min fasting time period is necessary after taking the agent, iii) water intake is between 50 to 120 mL [14]. These data for recommended amount were from previous study of phase 3 clinical trials [15,16].

Author's diabetic research group has experienced a case with T2DM, which had remarkable improvement by Rybelsus for 3mg, 7mg and 14mg in every month. The changes in HbA1c and weight were 8.5% to 7.1% and 96kg to 91kg for 3 months [17]. The case has continued regular lifestyle habit with no breakfast and then fasting time was 3-4 hours after taking Rybelsus. This situation may be involved in the satisfactory result. When fasting period is longer, clinical effect becomes higher. Rybelsus will provide broad benefit for patients, physicians and medical staffs

because of clinically useful and convenient treatment method [18,19]. Consequently, primary care physician can provide adequate management for maintaining diabetic better control of lots of patients with T2DM [2]. This article will hopefully give a impressive key to health and happiness to people.

Conflict of Interest

The authors declare no conflict of interest.

Funding

There was no funding received for this paper.

References

1. World Health Organization. 2021.
2. Fernando K, Bain SC, Holmes P, Jones PN, Patel DC. Glucagon-Like Peptide 1 receptor agonist usage in type 2 diabetes in primary care for the UK and Beyond: A Narrative Review. *Diabetes Ther.* 2021; 12: 2267-2288.
3. Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingway I, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. *Diabetes Obes Metab.* 2022; 24: 94-105.
4. Bando H. Useful oral administration of glucagon-like peptide 1 receptor agonist (GLP-1RA) as Semaglutide (Rybelsus) for Type 2 diabetes mellitus (T2DM). *Asp Biomed Clin Case Rep.* 2022; 5: 38-41.
5. Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits

- for management of type 2 diabetes. *Rev Endocr Metab Disord.* 2022; 7: 1-19.
6. Tak YJ, Lee SY. Anti-Obesity drugs: long-term efficacy and safety: an updated review. *World J Mens Health.* 2021; 39: 208-221.
7. Bando H. Effective oral formulation of semaglutide (Rybelsus) for diabetes and obesity due to absorption enhancer development. *Int J Endocrinol Diabetes.* 2022; 5: 130.
8. Lau J, Bloch P, Schaffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue Semaglutide. *J Med Chem.* 2015; 58: 7370-7380.
9. Jensen L, Helleberg H, Roffel A, van Lier JJ, Bjornsdottir I, Pedersen PJ, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. *Eur J Pharm Sci.* 2017; 104: 31-41.
10. Beglinger C, Poller B, Arbit E, Ganzoni C, Gass S, Orellana IG, et al. Pharmacokinetics and pharmacodynamics effects of oral GLP-1 and PYY3-36: a proof-of-concept study in healthy subjects. *Clin Pharmacol Ther.* 2008; 84: 468-474.
11. Andersen A, Knop FK, Vilsboll T. A Pharmacological and clinical overview of oral Semaglutide for the Treatment of Type 2 Diabetes. *Drugs.* 2021; 81: 1003-1030.
12. Buckley ST, Baekdal TA, Vegge A, Maarbjaerg SJ, Pyke C, Ahnfelt-Ronne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med.* 2018; 14: 10.
13. Bækdal TA, Breitschaft A, Donsmark M, Maarbjaerg SJ, Sondergaard FL, Borregaard J. Effect of Various dosing conditions on the pharmacokinetics of oral Semaglutide, a human glucagon-Like Peptide-1 analogue in a tablet formulation. *Diabetes Ther.* 2021; 12: 1915-1927.
14. Rybelsus. Available online: <http://www.novo-pi.com/rybelsus.pdf>. <https://www.novo-pi.com/rybelsus.pdf>
15. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SO, et al. Pioneer 2 Investigators. Oral Semaglutide versus Empagliflozin in Patients with Type 2 diabetes uncontrolled on metformin: The PIONEER 2 Trial. *Diabetes Care.* 2019; 42: 2272-2281.
16. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, et al. Pioneer 3 investigators. Effect of additional oral Semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA.* 2019; 321: 1466-1480.
17. Bando H, Yamashita H, Kato Y, Kato Y, Ogura K, Kawata T, et al. Remarkable efficacy of blood glucose and weight by oral Semaglutide (Rybelsus) for short period. *SunText Rev Case Rep Image.* 2022; 3: 143.
18. Yabe D, Deenadayalan S, Horio H, Kaneto H, Jensen TB, Terauchi Y, et al. Efficacy and safety of oral Semaglutide in Japanese patients with type 2 diabetes: A subgroup analysis by baseline variables in the PIONEER 9 and PIONEER 10 trials. *J Diabetes Investig.* 2022.
19. Bando H. Clinical trials of novel perspectives on Semaglutide with injectable and oral formulations. *SunText Rev Endocrine Care.* 2022; 2: 107.