Response to Comment on Russell-Jones et al. Diabetes Care 2017;40:943–950. Comment on Bowering et al. Diabetes Care 2017;40:951–957

Bruce W. Bode,[1] Keith Bowering,[2] and David Russell-Jones[3]

Diabetes Care 2018;41:e29–e30 | https://doi.org/10.2337/dci17-0051

We appreciate the relevant comments raised by Wu et al. (1) regarding the challenges faced by clinicians in safely achieving postprandial, and overall, glycemic control for patients with diabetes in the face of individual needs and physiological variation (including varying rates of gastric emptying/gastroparesis). Increasing awareness and understanding of factors affecting the complex physiology of postprandial glucose regulation, together with an understanding of the clinical pharmacological profile, are key in guiding appropriate dosing and timing of any mealtime insulin therapy. In the onset 1 and 2 trials, both mealtime (0–2 min before the meal) and postmeal dosing (20 min after the start of a meal investigated in onset 1) of fast-acting insulin aspart (faster aspart) demonstrated noninferior overall glycemic control compared with mealtime conventional insulin aspart. Importantly, no statistically significant differences in the overall rates of hypoglycemia were found in these trials comparing faster aspart with insulin aspart in type 1 or type 2 diabetes, with low and similar rates of severe hypoglycemia in both trials (2,3). In line with the consistent left shift of the clinical pharmacological profile of faster aspart previously demonstrated (4), as well as the greater early suppression of endogenous glucose production by faster aspart (5), occurrence of hypoglycemic episodes may occur in closer relation to the meal. This translates to statistically significantly higher rate ratios of those few episodes occurring within 1–2 h of the meal, whereas no differences were found for the overall rates of hypoglycemia. The considerations highlighted here and the clinical findings are also recognized by regulatory authorities and reflected, e.g., in the EU label, which states, "The timing of hypoglycaemia usually reflects the time-action profile of the administered insulin formulation. Hypoglycaemia may occur earlier after an injection/infusion when compared to other mealtime insulins due to the earlier onset of action" and "the time to onset of action must be taken into account when prescribing to patients with concomitant diseases or treatment where a delayed absorption of food might be expected" (6).

In all patients, both with and without formal diagnosis of gastroparesis, the clinical utility of faster aspart in relation to both meals and potential correction of hyperglycemia must always respect the need for individualization of treatment. In summary, the left shift of the pharmacological profile and the suppression of endogenous glucose production by faster aspart allows one to bolus premeal with better postprandial control in both type 1 and type 2 diabetes, or bolus up to 20 min postmeal with no compromise in overall glycemic control in type 1 diabetes. As with any mealtime insulin, timing of the insulin injection must be individualized to minimize hypoglycemia and improve postprandial glucose control. Fortunately, the increased use and availability of continuous or flash glucose monitoring will allow health care providers and patients to improve both postprandial and overall glycemic control by choosing the appropriate insulins for that individual.

Acknowledgments and Funding. The authors are grateful to Theis Gondolf of Novo Nordisk and to Helen Marshall of Watermeadow Medical, an Ashfield Company, part of UDG Healthcare plc, for editorial support (funded by Novo Nordisk).

Duality of Interest. B.W.B. has participated in advisory panels for Novo Nordisk, Sanofi, and Adocia; has been a consultant for Medtronic, Sanofi, and Novo Nordisk; received research support from Abbott, Boehringer Ingelheim/Lilly, BD, Dexcom, Janssen, Lexicon, Medtronic, Novo Nordisk, Sanofi, and Sensonics; participated in speakers' bureaus for AstraZeneca, Insulet, Janssen, Medtronic, Novo Nordisk, and Sanofi; and holds stock in Glytec. K.B. has participated in advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Johnson & Johnson and in speakers' bureaus for Novo Nordisk and Sanofi. D.R.-J. has participated in advisory panels; been a board member and a consultant for AstraZeneca, Sanofi, Lilly, and Novo Nordisk; received research support from AstraZeneca, Sanofi, Novartis, and Novo Nordisk;

[1]*Atlanta Diabetes Associates, Atlanta, GA*
[2]*Division of Endocrinology and Metabolism, University of Alberta, Edmonton, Alberta, Canada*
[3]*Diabetes and Endocrinology, Royal Surrey County Hospital, and University of Surrey, Guildford, U.K.*

Corresponding author: Bruce W. Bode, bbode001@aol.com.

Clinical trial reg. nos. NCT01831765 (onset 1) and NCT01819129 (onset 2), clinicaltrials.gov.

and participated in speakers' bureaus for AstraZeneca, Sanofi, Lilly, Novo Nordisk, Janssen, Takeda, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

References

1. Wu T, Marathe CS, Horowitz M, Jones KL, Rayner CK. Comment on Russell-Jones et al. Diabetes Care 2017;40:943–950. Comment on Bowering et al. Diabetes Care 2017;40:951–957 (Letter) Diabetes Care 2018;41:e27–e28. https://doi.org/10.2337/dc17-1916

2. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950

3. Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. Diabetes Care 2017;40:951–957

4. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clin Pharmacokinet 2017;56:551–559

5. Pieber TR, Basu A, Hansen AK, et al. Greater early postprandial suppression of endogenous glucose production is achieved with fast-acting insulin aspart compared to insulin aspart. Diabetologia 2017;60(Suppl. 1):S315

6. European Medicines Agency. Fiasp: EPAR - product information [Internet], 2017. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004046/human_med_002063.jsp. Accessed 25 October 2017