Taylor & Francis
Taylor & Francis Group

Expert Review of Endocrinology & Metabolism

ISSN: 1744-6651 (Print) 1744-8417 (Online) Journal homepage: informahealthcare.com/journals/iere20

Lixisenatide once daily significantly improves post-prandial glucose throughout the day due to diverse mechanistic effects

Denis Raccah

To cite this article: Denis Raccah (2014) Lixisenatide once daily significantly improves post-prandial glucose throughout the day due to diverse mechanistic effects, Expert Review of Endocrinology & Metabolism, 9:3, 201-203, DOI: 10.1586/17446651.2014.897606

To link to this article: https://doi.org/10.1586/17446651.2014.897606

Lixisenatide once daily significantly improves post-prandial glucose throughout the day due to diverse mechanistic effects

Expert Rev. Endocrinol. Metab. 9(3), 201–203 (2014)

Denis Raccah

Department of Diabetology, University Hospital Sainte Marguerite, 270 Boulevard de Sainte Marguerite, 13009 Marseille, France
denis.raccah@ap-hm.fr

Response to: Donsmark M, Knudsen LB. Lixisenatide in the treatment of Type 2 diabetes. *Expert Rev. Endocrinol. Metab.* 9(3), 197–199 (2014).

I appreciate the interest shown in our recent publication and thank you for providing me with the opportunity to address the issues raised [1].

In response to the concern that the once-daily prandial glucagon-like peptide-1 receptor agonist (GLP-1 RA) lixisenatide may not provide a sufficient therapeutic effect for a full 24 h, Ratner and colleagues have demonstrated that lixisenatide treatment significantly improves glycemic control, with comparable efficacy levels to those observed with once- and twice-daily treatment regimens (20 and 10 μg, respectively) [2], highlighting that once-daily dosing with lixisenatide is sufficient to improve long-term glycemic control.

The assumption made in the query is that less than 2% of the administered dose of lixisenatide is present at the end of the dosing period. This does not take into consideration the time taken to reach the maximum plasma concentration, which, in the case of lixisenatide, is approximately 2 h in humans. Consequently, the pharmacodynamic effect of lixisenatide is present for significantly longer than that proposed in *Lixisenatide in treatment of Type 2 diabetes*. Furthermore, this assumption is based on the requirement that the maximum plasma concentration in the central compartment represents the maximum pharmacodynamic effect. This does not hold true for GLP-1 RAs as they induce their effect through a number of different target tissues, for example, increasing insulin secretion, suppressing glucagon activity and slowing gastric emptying, as well as having central and possibly peripheral effects in the regulation of the feeling of satiety. Lixisenatide is a very potent and selective GLP-1 RA with four times greater binding affinity than that of human GLP-1 [3,4]. Exendin-4 has been shown to have a binding affinity similar to that of human GLP-1 [5]. While no head-to-head comparison of the binding affinities of GLP-1, lixisenatide, exenatide and liraglutide have yet been published, data on functional activity of these compounds on the GLP-1 receptor have been presented at 73rd Scientific Sessions of the American Diabetes Association (ADA), 2013. In this study, lixisenatide, exenatide and native GLP-1 activated the GLP-1 receptor in the RTC 6–23 cell line with similar potency (EC50 = 4.5–8 pmol/l), while liraglutide was 100 times less potent (EC50 = 715 pmol/l) [6].

Notably, data on the blood glucose-lowering activity of lixisenatide 20 μg once-daily reported by Lorenz and colleagues demonstrated that postprandial plasma glucose (PPG) was significantly reduced from baseline to Day 28 during all meals of the day: breakfast ($p < 0.0001$), lunch ($p < 0.0001$) and dinner ($p < 0.05$) [7], showing that lixisenatide treatment reduces PPG throughout the day. Moreover, at the 2013 International Diabetes Federation Congress, Kapitza and colleagues presented data demonstrating that lixisenatide plus metformin provide a greater reduction in PPG after breakfast compared

 10.1586/17446651.2014.897606 ISSN 1744-6651

with liraglutide plus metformin, while PPG results were comparable with those of liraglutide plus metformin at lunch and dinner [8]. The same study showed that the cumulative reduction in premeal adjusted area under the curve PPG over 24 h was significantly greater with lixisenatide plus metformin compared with liraglutide plus metformin [8].

These data support the opinion stated in my recently published review that lixisenatide has a long-lasting effect compared with the sole terminal half-life in the central compartment due to its high affinity for the GLP-1 receptor.

As demonstrated by Kapitza and colleagues, mean supine heart rate measured 24 h after dosing decreased with lixisenatide treatment and increased with liraglutide treatment [9], with no difference observed for systolic and diastolic blood pressure between the two drugs, making it unlikely that the increase in heart rate seen with liraglutide is a compensatory one. Furthermore, there is insufficient evidence to conclude that lixisenatide no longer has an effect on 24 h postadministration simply because an increase in heart rate is no longer observed, although I do support the conclusion that these data may warrant further investigation. The mechanism behind the change in heart rate following administration of incretin-based treatment is currently unknown, although increased resting heart rate has been associated with an increased risk of death, and cardiovascular complications as an independent risk factor in a large study of patients with Type 2 diabetes mellitus (T2DM) [10].

In the QT/QTc study, performed in healthy volunteers, an increase in heart rate was observed with lixisenatide 20 µg once-daily dosing after 2 h and up to approximately 10 h following lixisenatide administration. This increase ranged from 2 to 7.3 b.p.m., with the peak of 7.3 b.p.m. observed 4 h after lixisenatide administration [11]. These effects are indeed different from those observed in a similar study with liraglutide, where the increase in heart rate was observed at all time points throughout the 24-h period [12]. However, as mentioned before, the mechanism of the effect of GLP-1 RAs on heart rate is currently unknown and certainly cannot be used as a surrogate of their effect of glycemic control in patients with T2DM. Rather, it could be used as an additional measure to assess the risk–benefit ratio of potential therapeutic options for patients in need of treatment intensification.

Finally, when considering whether a GLP-1 RA can be considered 'prandial' or not, the classification of a treatment as prandial is not due to its ability to reduce the absolute value of PPG, but the glycemic delta, that is, the difference between postprandial and preprandial glucose, or the area under the curve of glycemia after the meal. The long-acting GLP-1 RAs, such as liraglutide, have only a modest impact on the glycemic delta, whereas the short-acting GLP-1 RAs have a strong effect, mainly due to the delay in gastric emptying they induce. Reduction in the absolute PPG by the long-acting GLP-1 RAs is largely via the reduction of the fasting and preprandial glucose, with only a modest prandial treatment effect compared with the short-acting GLP-1 RAs. Bearing in mind these mechanistic differences, the choice between the different GLP-1 RAs should be made according to the glycemic profile of the individual patient.

In summary, Phase III clinical trials demonstrated that lixisenatide is an effective treatment option for patients with T2DM, improving glycemic control, including significant reductions in PPG excursions, especially in those not currently achieving HbA_{1c} targets despite ongoing therapy.

Financial & competing interests disclosure

The author was supported by Sanofi. D Raccah is a member of advisory boards and speaker in symposia for Lilly, Novo Nordisk, Sanofi, MSD, BMS, Astra Zeneca, Merck Serono, Boehringer Ingelheim, Novartis. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. The author would like to thank S Barnes, Caudex Medical (London, UK) for providing writing assistance, which was funded by Sanofi.

References

1. Raccah D. Efficacy and safety of lixisenatide in the treatment of Type 2 diabetes mellitus: a review of Phase III clinical data. Expert Rev Endocrinol Metab 2013;8(2):105-21
2. Ratner RE, Rosenstock J, Boka G. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. Diabet Med 2010;27(9):1024-32
3. Werner U, Haschke G, Herling AW, et al. Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. Regul Pept 2010;164(2-3):58-64
4. Thorkildsen C, Neve S, Larsen BD, et al. Glucagon-like peptide 1 receptor agonist ZP10A increases insulin mRNA expression and prevents diabetic progression in db/db mice. J Pharmacol Exp Ther 2003;307(2): 490-6
5. Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regul Pept 2004;117(2): 77-88
6. Schwahn U, Stengelin S, Werner U. Functional activity of lixisenatide and GLP-1 receptor expression in in-vitro thyroid C-cells of rat and human origin. Diabetes 2013;62(Suppl 1):A259
7. Lorenz M, Pfeiffer C, Steinstrasser A, et al. Effects of lixisenatide once daily on gastric emptying in type 2 diabetes - Relationship to postprandial glycemia. Regul Pept 2013;185C:1-8
8. Kapitza C, Coester HV, Berria R, et al. Pharmacodynamic profiles of lixisenatide vs. liraglutide in patients with type 2 diabetes mellitus on metformin. International Diabetes Federation; 2013. P-1066
9. Kapitza C, Forst T, Coester HV, et al. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes Obes Metab 2013;15(7):642-9
10. Hillis GS, Woodward M, Rodgers A, et al. Resting heart rate and the risk of death and

cardiovascular complications in patients with type 2 diabetes mellitus. Diabetologia 2012; 55(5):1283-90

11. Sanofi-Aventis. Lyxumia EMA submission. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002445/WC500140449.pdf

12. Victoza liraglutide. Product mongraphy. Available from: http://www.novonordisk.ca/PDF_Files/VictozaProductMonographEnglish.pdf