Pharmacokinetics and Pharmacodynamics of Biosimilar Insulins: Is Clamp Technology Fit for Purpose?

Philip Home

Diabetes Care 2015;38:2234–2236 | DOI: 10.2337/dc15-1046

The euglycemic glucose clamp was first used to assess the new human insulins in the early 1980s by comparing pharmacodynamics (PD) of square-wave intravenous infusions in terms of the clamp glucose infusion rate (1). Shortly afterward, the technique was adapted to study the profile of action of subcutaneously injected insulin (2) and in people with type 1 diabetes rather than people without diabetes. One major advantage of the clamp is that it allows the study at the same time of both the pharmacokinetics (PK), the plasma concentration absorption profile of injected insulin, and PD in terms of measures such as onset, peak, peak:trough ratio, duration, and area under the curve (Table 1). Attractively, the time-action profiles can be visualized. Although initially used for mealtime insulins, the technique was soon applied to extended-acting insulins, comparing insulin-action profiles of nominally similar insulins (NPH preparations) from different manufacturers (3).

Mealtime insulins can be compared, to a useful extent, in people with type 1 diabetes (C-peptide negative) using standardized or usual meals on a background of steady-state basal insulin or infusion (4). Such an option is not available for long-acting insulins, so glucose clamp studies are particularly important for assessing and comparing these. Thus, while general guidelines for comparing a biosimilar medication (a copy) with the original product emphasize PK/PD studies (5,6), specific guidelines for insulin as drawn up by the European regulators go into considerable detail on glucose clamp studies (7). In this issue of *Diabetes Care,* Linnebjerg et al. (8), in an article comparing the Lilly glargine preparation to the reference Sanofi glargine, report three glucose clamp studies in people without diabetes. Additionally, studies have been performed in people with type 1 diabetes and to assess dose ranging (9,10).

Although we have three decades of experience in the techniques used, debate still rages on methodology and interpretation of the data—indeed for both the PK and PD findings. Some of the issues are discussed in the article by Swinnen et al. (11), written after experts in the field failed to reach consensus over methodology, and some advantages and issues are listed in Table 1.

The PK issues are perhaps the more surprising. What could be easier than measuring insulin concentrations after injection for 24 h or more while fasting, indeed even in the absence of a clamp? But first, if people without diabetes are studied (or more problematically those with type 2 diabetes), then allowance has to be made for changing endogenous insulin secretion. Insulin:C-peptide ratios are usually used for this purpose, referenced to the preinjection baseline ratio. Although C-peptide has a much longer plasma half-life (20 min) than insulin (4 min), this approach will generally remain valid, provided the clamp is of good quality (absence of rapid up-and-down glucose concentration excursions changing the stimulus to endogenous secretion) (Table 1) (12). However in the study by Linnebjerg et al. (8), while the mean PK profiles are identical between the insulins despite high variance at all time points, the recorded profile is not credible, jumping from zero (before injection) to half maximum in just 30 min, very different from what is expected for insulin glargine (13). This unexplained bias probably continues for the full 24 h of study, as the levels at 24 h are higher than might be expected from our knowledge of the

Institute for Cellular Medicine-Diabetes, Newcastle University, Newcastle upon Tyne, U.K.

Corresponding author: Philip Home, philip.home@ncl.ac.uk.

See accompanying articles, pp. 2200, 2204, 2211, 2217, 2226, 2237, 2241, 2250, 2258, 2266, 2274, and 2282.

Table 1—Some glucose clamp advantages and limitations in the study of subcutaneous injection profiles of insulin preparations

Advantages
Ability to study PK and PD together and understand relationships
Ability to study PK without possible disturbance of subcutaneous absorption by adrenergic hormone release through hypoglycemia
Ability to study PD without disturbance of glucose dynamics from counterregulatory hormone changes or concentration-driven changes in glucose disposal (glucose uptake and urinary glucose disposal)
Ability to study PD without disturbance of hepatic autoregulation of glucose production
Disadvantages
The technique requires research skills, in particular if conducted in people with type 1 diabetes.
Insulin given to correct or maintain prior blood glucose control will continue to have measurable action for around 1.5 h.
In type 1 diabetes, management of change from prior insulin (usually intravenous) can be problematic and interferes with interpretation of PK until about 0.5 h after this can be discontinued (unless a specific insulin assay is available) and with PD for about 1.5 h (due to half-time of insulin action).
In type 1 diabetes, when loss of action of the studied insulin occurs at end of clamp, insulin must be given or glucose levels left to rise above clamp levels, both options interfering with interpretation of PD and the former with PK (unless a specific insulin assay is available).
In people without diabetes and people with type 2 diabetes, clamp conduct must be good to prevent stimulation of endogenous insulin secretion.
C-peptide measurements can be used to correct for gradual changes in endogenous insulin secretion, but the long plasma half-life of C-peptide (20 min) means this is problematic for studies of faster-acting insulins and that it cannot correct for rapid changes due to poor clamp technique, while in type 2 diabetes, proinsulin (which cross-reacts in many C-peptide assays) poses additional interpretation problems.
PD (glucose infusion rate) estimation has higher variance than insulin concentration (PK) and, in particular, in type 1 diabetes often needs smoothing algorithms for determination of profiles.
In studies of long-acting insulins, the metabolic state is increasingly that of fasting/starvation (glucose infusion rate is low), so the metabolic state changes with time (notably hepatic glucose output); the clamp level, if constant, deviates from physiological levels, and the glucose infusion rate is then artifactually disturbed.
In studies of long-acting insulins, even with larger doses, plasma insulin levels at the beginning and end of the studies are around the LLoQ of the assay and indeed often so in some individuals for long periods: statistical handling of such undetectable levels can create very large changes and uncertainties in the shape of the published profile.
In people with type 1 diabetes and people with type 2 diabetes exposed to insulin, insulin antibody–bound insulin will interfere with interpretation of insulin assays; the interference can be erratic and result in high variance of measured levels.

insulin effect in clinical practice. Some of the problem here may be that many of the measurements made are below the lower level of quantification (LLoQ) of the insulin assay, and indeed the mean level at many time points is just twice that level. The authors imputed a level of half the LLoQ for any result below it and then discarded any result where the endogenous component calculated from C-peptide resulted in negative findings for insulin glargine. These actions would certainly bias the findings throughout the profile in unpredictable ways, mostly at the start and end of the clamp, the periods of most interest.

This might seem to point to an advantage for clamps in people with type 1 diabetes. Unfortunately, this is not the case. Initially and for some hours thereafter people with no endogenous insulin secretion need a tapering insulin infusion to maintain glucose control while absorption of the long-acting insulin begins (Table 1) (14), and this again becomes true late in the clamp in at least some individuals (although some researchers allow hyperglycemia to develop at this point). Furthermore, even low levels of insulin antibodies can interfere with the insulin assays, and perhaps it is this problem that led to the very erratic findings in the Lilly type 1 diabetes biosimilar clamp studies of very wide CIs on the PK data between insulins essentially making the assay data noncontributory to the assessment of biosimilarity (9,10).

The problem of the need for exogenous insulin at the start and end of the clamps in people with type 1 diabetes also bugs the glucose infusion (PD) data (Table 1). As noted above, some researchers have not given extra insulin at those times, but the developing hyperglycemia then means the remaining glucose-lowering effect of the studied insulin is not quantified, being counted as zero or even censored (14). Furthermore, the lack of endogenous insulin secretion means glucose lowering throughout the clamp is more variable, as it is in type 1 diabetes in clinical practice, again adding to statistical uncertainty and resulting in 95% CIs of –54 to 30% for ratio of total glucose infused during the clamp in the Lilly studies (9,10). Furthermore, insulin action in the critical period for extended-acting insulins (18–24 h) will be abnormal in people essentially fasted for that time, meaning the absolute clamp glucose infusion rates will not be a reliable reflection of the glucose-lowering efficacy of the studied insulin at those times (Table 1).

So do the clamps in normal people give confidence that Lilly and Sanofi insulin glargine are clinically similar? For the metrics that probably matter to people with diabetes and clinicians (namely, comparative efficacy at 24 h from injection and the ratio of peak:24-h PK and PD), no data are given, but the published profiles are visually reassuring. The summary data that are given, for example, 24-h area under the curve, are not very helpful—it could be similar for insulins with very different time-action profiles. But even those data do suggest the clamps can only perform to 95% confidence limits of about ±10%, and sometimes much worse (8,10). Clinicians will need to ask themselves whether they are happy that nominally similar ("biosimilar") insulins could be different by 10%, particularly if substitution within the individual person with diabetes is contemplated or mandated.

Fortunately for the Lilly insulin glargine, other information is available, including clinical studies that ascertained other metrics of clinical importance, such as fasting plasma glucose and hypoglycemia incidence. It is that complete package of data that lends credence to Lilly's claim of biosimilarity

rather than the clamp data in isolation (10,15).

Acknowledgments. The author is grateful to many colleagues involved in insulin development for lively discussions of some of the issues addressed in this article.

Duality of Interest. P.H., or institutions with which he is associated, receives funding for his research, advisory, and lecturing activities from actual and potential insulin manufacturers of original products or copies, including AntriaBio, Biocon-Mylan, Eli Lilly, Hanmi, Merck, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Home PD, Shepherd GA, Noy G, et al. Comparison of the activity and pharmacokinetics of porcine insulin and human insulin (Novo) as assessed by the glucose clamp technique in normal and diabetic man. Diabetes Care 1983; 6(Suppl. 1):23–28
2. Gardner DF, Arakaki RF, Podet EJ, Nell LJ, Thomas JW, Field JB. The pharmacokinetics of subcutaneous regular insulin in type I diabetic patients: assessment using a glucose clamp technique. J Clin Endocrinol Metab 1986;63:689–694
3. Starke AA, Heinemann L, Hohmann A, Berger M. The action profiles of human NPH insulin preparations. Diabet Med 1989;6:239–244
4. Home PD, Lindholm A, Hylleberg B, Round P; UK Insulin Aspart Study Group. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. Diabetes Care 1998; 21:1904–1909
5. U.S. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product [Internet], 2012. Available from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed 13 August 2014
6. Heinemann L, Khatami H, McKinnon R, Home P. An overview of current regulatory requirements for approval of biosimilar insulins. Diabetes Technol Ther 2015;17:510–526
7. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues [Internet], 2015. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184161.pdf. Accessed 25 March 2015
8. Linnebjerg H, Lam ECQ, Seger ME, et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies. Diabetes Care 2015;38:2226–2233
9. Heise T, Zhang X, Quin Lam EC, et al. Duration of action of 2 insulin glargine products, LY2963016 and Lantus, in subjects with type 1 diabetes mellitus (T1DM). Abstract 891-P. Presented at the 74th Annual Meeting of the American Diabetes Association, 13–17 June 2014, San Francisco, California
10. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). EPAR summary for the public: Abrasia; insulin glargine [Internet], 2014. Available from www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf. Accessed 31 December 2014
11. Swinnen SG, Holleman F, DeVries JH. The interpretation of glucose clamp studies of long-acting insulin analogues: from physiology to marketing and back. Diabetologia 2008;51: 1790–1795
12. Owens DR. *Human Insulin: Clinical Pharmacological Studies in Normal Man*. Lancaster, MTP Press, 1986, p. 138
13. Luzio S, Dunseath G, Peter R, Pauvaday V, Owens DR. Comparison of the pharmacokinetics and pharmacodynamics of biphasic insulin aspart and insulin glargine in people with type 2 diabetes. Diabetologia 2006;49: 1163–1168
14. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000; 49:2142–2148
15. Heinemann L, Home PD, Hompesch M. Biosimilar insulins: guidance for data interpretation by clinicians and users. Diabetes Obes Metab 2015;17:911–918