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**To: Scholtz HE, Pretorius SG, Wessels DH, Becker RHA (2005)
Pharmacokinetic and glucodynamic variability: assessment
of insulin glargine, NPH insulin and insulin ultralente in healthy
volunteers using a euglycaemic clamp technique. Diabetologia
48:1988–1995**

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To the Editor: Scholtz et al. present a comprehensive clamp study on pharmacokinetics, pharmacodynamics and variability of insulins NPH, ultralente and glargine [1]. Figure 1a from their article (Fig. 1), reproduced below, illustrates the pharmacodynamic data for insulin glargine. The glucose infusion rate (GIR) is maximal approximately 12 h after injection at a rate of $\pm 3 \text{ mg kg}^{-1} \text{ min}^{-1}$. Six hours earlier and 6 h later, GIR is $\pm 2 \text{ mg kg}^{-1} \text{ min}^{-1}$. Throughout their manuscript, the authors consistently label this as a flat profile. Webster's dictionary defines 'flat' as 'without peaks or valleys'. Of course, this definition is open to interpretation. I asked physicians working at a large academic department of internal medicine whether they agreed that 'flat' is an adequate description of the profile. Most of these physicians were native Dutch, and can thus be trusted to have a fairly good concept of what is flat and what is not. No physician labelled the profile as 'flat'.

The notion that the pharmacodynamic profile of insulin glargine is best characterised as waxing and waning is supported by the profiles shown in a paper comparing insulins NPH, glargine and detemir [2]. The idea that insulin glargine's profile is flat originates from a paper that is difficult to interpret unequivocally [3]. In this study, subjects were clamped to a target glucose level of 7.2 mmol/l. In the methods section it is stated that 'IV glucose was withdrawn when plasma glucose increased to $>7.5 \text{ mmol/l}$ '. In the results section, it reads 'with glargine, plasma glucose was at the target value until 15 h and then increased slightly to $7.8 \pm 0.3 \text{ mmol/l}$ between 16 and 24 h.' Thus, in more than half of the patients glucose infusion must have been stopped be-

Fig. 1 Pharmacodynamic profile of insulin glargine, reproduced from Scholtz et al. (Fig. 1a) [1]. The two lines denote the median GIR after subcutaneous injection of insulin glargine in twelve healthy volunteers, clamped at two different occasions

tween 16 and 24 h after injection, GIR being 0 at that time. Nevertheless, GIR was said to be 'nearly constant between 3 and 24 h ($0.78 \pm 0.6 \text{ mg kg}^{-1} \text{ min}^{-1}$)'. Finally, in all clamp studies, subjects remain fasting for 24 h. Increasing insulin sensitivity at the end of the clamp procedure tends to augment GIR and thereby leads to overestimation of both the duration and magnitude of action of long-acting insulins at the end of the clamp.

We acknowledge that Dutch physicians may hold too rigid opinions on what is flat and what is not. Also, from a marketing point of view it may seem logical to describe the insulin with the smallest peak known so far as an insulin with a flat profile. However, from a scientific point of view, all subcutaneous injected insulins show a waxing and waning pharmacodynamic profile.

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