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Expert Opinion

Insulin glargine: commentary on the duration of action and lower risk of nocturnal hypoglycaemia in patients with diabetes

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Dear Editor,

We read with interest the review by McAulay and Frier [1] on insulin analogues and other developments in insulin therapy for diabetes. The review provides a very thorough understanding of the progress that has been made in insulin therapy so far and the options that are now open to physicians and their patients with diabetes who need insulin. The authors state that insulin glargine (Lantus®, Aventis Pharmaceuticals), the first long-acting basal insulin, may not have a 24-h duration of action in all patients. A study by Hamann *et al.* [2] in patients with Type 1 diabetes is cited, where insulin glargine was injected either before breakfast, before dinner or at bedtime, which indicated that injection of insulin glargine before breakfast is less likely to induce nocturnal hypoglycaemia than administration at bedtime. This data has been interpreted to indicate that the duration of insulin glargine action may not last throughout the night. However, in this same study, the data demonstrates that the mean nocturnal blood glucose measured at 03.00 h was lower at end point in the group injecting insulin glargine before breakfast, compared with those injecting insulin glargine before dinner and at bedtime. This data would suggest that the effect of insulin glargine is not waning at night in the prebreakfast-treated group [2]. In addition, an isoglycaemic clamp study by Fanelli *et al.* [3] demonstrated that after just 7 days of insulin glargine administration, the duration of action of insulin glargine in patients with Type 1 diabetes was 23.2 ± 1.3 h, compared with 20.5 ± 3.7 h after a single administration of insulin glargine on day 1. This study clearly confirms that the duration of insulin glargine action is very close to 24 h when steady-states are reached [3].

One of the key factors that should be taken into consideration when administering insulin glargine is that the correct and individualised dose is given to ensure that the 24-h duration of action is achieved with a once-daily dose. The flat profile of action of insulin glargine enables the dose to be increased with less risk of nocturnal hypoglycaemia compared with insulin isophane suspension (NPH). In a study in patients with Type 1 diabetes cited in this review, insulin glargine administered at dinnertime or bedtime was compared with insulin NPH administered four times a day [4]. HbA_{1c} with insulin NPH treatment did not change over 3 months but did decrease by ~ 0.4% in both insulin glargine groups. Although the total doses of insulin did not differ between the three groups, there was a decrease in mealtime insulin lispro and an increase in basal insulin glargine requirements. This increase in the dose of insulin glargine was, however, not accompanied by an increased risk of nocturnal hypoglycaemia. Similarly, in people with Type 2 diabetes, the 'Treat-to-Target' study demonstrated that more patients reached target HbA_{1c} levels of 7.0% with a reduced risk of nocturnal hypoglycaemia with insulin glargine compared with insulin NPH [5]. These results were further endorsed by a meta-analysis of people with Type 2 diabetes taking part in Phase III/IIIb trials, which showed that the risk of nocturnal hypoglycaemia was reduced by 29% in

patients receiving insulin glargine compared with those receiving insulin NPH [6].

The authors suggest that the duration of effect of insulin glargine is < 24 h in some people with Type 1 diabetes, especially when used at low doses and that these individuals require twice-daily injections, which negates the benefit of a single daily administration. We would bring to the authors' attention a study that was published at the recent International Diabetes Federation meeting in Paris [7]. In this study, in people with Type 1 diabetes, the authors demonstrated that equivalent glycaemic control was achieved with insulin glargine in the morning, in the evening or as a split dose, morning and evening (7.4 ± 0.2, 7.5 ± 0.2 and 7.5 ± 0.1%, respectively) and that there was no difference between the groups in terms of episodes of severe hypoglycaemia or weight gain. This study demonstrated that dividing the insulin glargine dose did not provide any additional benefit whatsoever for the people involved.

With regard to the safety of insulin glargine, the authors cite a publication by Kurtzhals *et al.* [8], which indicated that insulin glargine had a higher affinity for IGF-1 receptors and a greater ability to promote DNA synthesis compared with regular human insulin. This result was obtained in human osteosarcoma and human mammary epithelial cell lines, both of which have a predominantly high expression of IGF-1 receptors. However, in a study with human skeletal muscle cells (a more physiologically relevant cell type), insulin glargine and regular human insulin had equivalent affinities for the IGF-1 receptor and equivalent sensitivity and potency for DNA synthesis [9]. With regard to the relationship between IGF-1 receptor signalling and the regulation of retinal revascularisation, insulin glargine is not associated with the development of optic disk swelling [10], which is the most commonly associated retinopathy symptom resulting from IGF-1 treatment [11,12]. It is therefore unlikely that insulin glargine has any adverse effect on retinopathy progression [10].

In conclusion, the introduction of insulin glargine has finally provided people with both Type 1 and Type 2 diabetes with a 'long-acting' truly basal insulin supply that can be achieved with a once-daily dose titrated to individual patient needs [13,14]. As clinicians and patients become more familiar with the use of insulin glargine, it is expected to enable them to Treat-to-Target HbA_{1c} goals of < 7.0% and < 6.5% recommended by the American Diabetes Association and International Diabetes Federation, respectively, with a lower risk of hypoglycaemia, the major barrier to reaching target [15,16].

Author's response

We thank Owens and Rosenstock for their perceptive comments on our review article and would make the following observations in reply. They argue that in the published study by Hamman *et al.* [2], the action of insulin glargine does not wane overnight, and lasts for 24 h. However, in that study, the relevant value is not the nocturnal blood glucose at 03.00 h as they quote, but the mean blood glucose concentration before breakfast (06.00 – 09.00 h), which was measured ~ 24 h after the previous dose of insulin glargine had been administered. It is evident that this morning (fasting) blood glucose was higher in the group of patients who received insulin glargine in the morning (at breakfast) compared with administration at dinner and at bedtime. This would be consistent with our interpretation that in some people with Type 1 diabetes, the duration of action of insulin glargine is < 24 h. Furthermore, this fasting hyperglycaemia occurred despite the fact that subjects who received insulin glargine at breakfast had the highest increment in insulin dose over the study period [2]. This would not be surprising as pharmacokinetic studies of insulin glargine have demonstrated the mean duration of action to be < 24 h [13], and in clinical practice, a significant proportion of patients (~ 10%) require twice-daily administration. This is not necessarily an undesirable property of this insulin analogue, as it can be used to advantage in people who are prone to nocturnal hypoglycaemia.

Rosenstock and Owens also highlight data that was presented at the recent meeting of the International Diabetes Federation in Paris, which suggest no difference in glycaemic control between once- or twice-daily administered insulin glargine [7]. However, this retrospective, non-randomised study by Garg *et al*. raises the question as to why the majority of patients in that study were administering insulin glargine twice-daily? Presumably the necessity for this will be explained when the full paper is published. The study by Fanelli et al. [3], has also been cited, in which the investigators found that the duration of action of insulin glargine appeared to be closer to 24 h when insulin glargine was administered daily for a total of 7 days. In this study, the mean duration of action of insulin glargine after a single administration was 20.5 ± 3.7 h, which is identical to the time quoted in the paper by Lepore *et al*. [13]. Indeed, in this latter study, the glucose infusion had to be discontinued in 4 of the 20 patients receiving insulin glargine in accordance with the study protocol, because of persistent hyperglycaemia [13]. The obvious conclusion from this observation is that while insulin glargine may last for 24 h in many people, it acts for a shorter period in some patients with Type 1 diabetes, a finding that has been observed by many clinicians using this insulin analogue.

With reference to the study by Rosetti *et al*. [4], Rosenstock and Owens state that the increase in dose of insulin glargine was not accompanied by an increased risk of nocturnal hypoglycaemia and that the mealtime insulin lispro dose was lower. However, the lower dose of fast-acting insulin may have contributed to a lesser degree of hyperinsulinaemia at night and so reduced the risk of nocturnal hypoglycaemia.

In clinical practice the use of insulin glargine is still undergoing refinement and at present we would agree with Bolli and Owens that the outcome of long-term clinical studies will answer the important question of safety of this valuable insulin analogue [11].

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