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Review

A review of human and analogue insulin trials☆

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Abstract

A recent meta-analysis evaluated trials of the rapid-acting analogues insulin lispro and insulin aspart, performed before the introduction of the basal analogues, insulin glargine and insulin detemir. This article reviews the effect of rapid-acting and basal insulin analogues separately and in combination, relative to human insulin. Outcomes evaluated include HbA_{1c}, hypoglycaemia, postprandial glucose (PPG), and weight changes. Results from trials that matched defined criteria are presented in tables. In type 1 diabetes, compared with human insulin, the rapid-acting analogues generally reduced hypoglycaemia and postprandial glucose, whereas the basal analogues tended to reduce hypoglycaemia – particularly nocturnal hypoglycaemia. Weight gain may also be reduced with basal analogues, compared with human basal insulin. In type 2 diabetes, premix rapid-acting analogues controlled postprandial glucose better than human insulin mixes; basal analogues used as basal-only therapy reduced hypoglycaemia compared with NPH insulin; and some advantages were apparent with analogues in basal-bolus therapy. Whilst the benefits on individual metabolic and clinical outcomes appear modest, almost all studies report some advantage when using insulin analogues in type 1 and type 2 diabetes. Significant benefits, including PPG lowering with the rapid-acting analogues and the potential for reduction in cardiovascular risk, should be investigated further.
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Keywords: Insulin analogues; Hypoglycaemia; Postprandial glucose

Contents

Abbreviations: AACE, American Association of Clinical Endocrinologists; AUC, area under the curve; BG, blood glucose; BHI, premix human insulin; BIAsp, premix insulin aspart; bid, twice daily; FBG, fasting blood glucose; FPG, fasting plasma glucose; HI, human insulin; IAsp, insulin aspart; IDet, insulin detemir; IGlarg, insulin glargine; IGlu, insulin glulisine; ILis, insulin lispro; Mix25, premix insulin lispro; NPH, NPH insulin; NS, not significant; OADs, oral antidiabetic agents; od, once daily; PG, plasma glucose; PPG, postprandial glucose; RR, relative risk; SM, self-monitored

☆ The author has received honoraria for lectures and meeting attendance from Novo Nordisk, Eli Lilly, Sanofi Aventis and Pfizer.

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1. Introduction

Insulin analogues designed to overcome the shortcomings of human insulin have become available for patients with diabetes, to more closely simulate the endogenous release of insulin seen in healthy individuals and reduce long-term complications. The rapid-acting analogues (insulin lispro [ILis; HumaLog®, Eli Lilly] and insulin aspart [IAsp; NovoRapid®, Novo Nordisk]) were the first analogues to become available. Two basal insulin analogues, insulin glargine (IGlarg; Lantus®, Sanofi-Aventis) and insulin detemir (IDet; Levemir®, Novo Nordisk) subsequently become available, and more recently a third rapid-acting analogue, insulin glulisine (IGlu; Apidra™, Sanofi-Aventis), has also been licensed. Relative to human insulin, the rapid-acting analogues dissociate more rapidly after injection and, therefore, have a more rapid onset of action, with a higher peak serum concentration and a more rapid tailing off effect. The longer duration of action of the basal analogues, relative to protaminated or zinc-retarded human insulin, potentially offer better coverage over the between-meal period. Their flatter pharmacodynamic profile, with a much lower peak of action, may also reduce the risk of hypoglycaemia.

Numerous clinical trials have shown that the potential pharmacokinetic advantages of the insulin analogues may translate into clinical efficacy in both type 1 and type 2 diabetes. However, a recent meta-analysis suggested that the rapid-acting analogues provide only a small advantage in terms of HbA_{1c}, and no advantage for hypoglycaemia, compared with regular human insulin [1,2]. The purpose of this review, therefore, is to assess the effects, not only of the rapid-acting analogues, but also basal insulin analogues separately and in combination, relative to human insulin, on key clinical outcomes, bearing in mind the higher cost of the analogues relative to human insulin. In addition to HbA_{1c} and hypoglycaemia, fasting plasma glucose, postprandial glucose, 24 h glucose profiles and changes in weight, when recorded, were also reviewed.

2. Materials and methods

2.1. Types of studies

For type 1 diabetes, trials of basal-bolus therapy are covered, including trials up to and including December 2005. For type 2 diabetes, trials comparing analogues versus human insulin as premixes, basal insulin, or basal-bolus therapy are considered over the same time period. Studies on continuous subcutaneous insulin infusion are not covered in the present review. References dated 2006 cover studies for which earlier abstracts were available.

2.2. Selection of references

Trials were limited to randomised controlled trials and were identified by reference to the previously published meta-analysis [1], PubMed searches using the name of each analogue combined with ‘diabetes’ and limited to randomised controlled trials, and searching of European Association for the Study of Diabetes and American Diabetes Association abstracts for 2003–2005 inclusive. The three major insulin manufacturers in the UK, Eli Lilly, Novo Nordisk and Sanofi-Aventis, were also contacted for abstract information and details of papers in press.

Trials were included if they compared analogue insulin with human insulin, generally with treatment groups of at least 50 patients each (where few reports were available some smaller trials were included, as noted in the tables), had a treatment duration of at least 3 months, and if they reported clinical outcomes (HbA_{1c}, fasting blood glucose [FPG], postprandial blood glucose [PPG], hypoglycaemia, or change in weight). Although short-term studies are useful to establish

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