MaHTAS
Malaysian Health Technology Assessment Section

Insulin Analogues

Executive Summary

[Adapted from the report by DR JUNAINAH SABIRIN]

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Background

Diabetes mellitus still remains one of the most significant causes of morbidity and mortality in the world, and its global impact is likely to accelerate over the coming decades. The goal of diabetic treatment is to achieve tight glucose control, avoid chronic complications and limit hypoglycaemic episodes frequency in everyday life with minimal weight gain. Success with insulin management ultimately depends on how closely a given regimen can mimic normal physiologic insulin release patterns. The new insulin analogues have been designed to more closely mimic physiologic insulin profiles. However, the cost of insulin analogues is more expensive than conventional human insulin.

Technical Features

The newer insulin analogues have several improvements due to their modified action profile. It is claimed that the main advantages of rapid-acting preparations include faster onset of action and shorter duration of action. Long-acting analogues afford structural changes, which delay the onset of action, allow slow and continuous absorption into the systemic circulation and prolong the duration of action. Thus, producing a time-concentration profiles, imitates the normal insulin basal level and leads to physiological basal glycaemic control with less nocturnal hypoglycaemia. There are three commercially available rapid-acting insulin analogues: insulin lispro, insulin aspart and insulin glulisine. There are two long-acting insulin analogues: insulin glargine and insulin detemir. Three types of fixed-ratio insulin analogues mixes are currently available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, a 70% insulin aspart protamine suspension with 30% insulin aspart. These formulations have been developed to minimise the errors that can occur when patients self-mix insulin combinations. The new insulin analogues can be administered at mealtimes while conventional human insulin is recommended to be administered roughly 30 minutes prior to eating.

Policy Question

In Ministry of Health facilities, should insulin analogues be used for all diabetic patients treated with insulin?

Objective

To assess the safety, efficacy or effectiveness and economic implications of using rapid-acting, long-acting or premixed insulin analogues compared with conventional human insulin for treatment of type 1, type 2, or gestational diabetes mellitus.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R), EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews–Database of Abstracts of Review of Effects, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database and PubMed. No limits were applied to the search, except for publication year from 2006 to current for EBM Reviews-Cochrane Central Register of Controlled Trials. Other database searched include FDA database. The last search was run on 7 March 2012. Additional articles were identified from reviewing the references of retrieved articles and contacting the authors. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool for systematic

2012	review (including HTA reports) and economic evaluation and Jadad scale for RCT. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force. **Result and conclusion** A total of 878 abstracts were screened using the inclusion and exclusion criteria. After reading, appraising and applying the inclusion and exclusion criteria to 172 full text articles, 45 full text articles were included. The 45 full text articles finally selected for this review comprised of five HTA reports, 10 systematic reviews, 16 RCTs, 13 cost-effectiveness analyses and one costing analysis. **Efficacy or Effectiveness of Insulin Analogues** **Rapid-acting insulin analogues** • There was good level of evidence to suggest that treatment with insulin lispro or insulin aspart compared with regular human insulin resulted in small but significantly lower HbA1c values (ranged between 0.09% and 0.14%) in adults with type 1 diabetes mellitus, but not in children. • The HbA1c values were found to be comparable for the two treatment groups in type 2 diabetes mellitus, gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus. Postprandial blood glucose was also found to be significantly lower in groups treated with insulin lispro or insulin aspart compared with regular human insulin (ranged between 0.83 mmol/L and 1.43 mmol/L). However, fasting and preprandial blood glucose was similar for both treatment groups. • There was evidence to suggest greater treatment satisfaction in type 1 diabetes mellitus and in pregnant women with type 1 diabetes mellitus treated with insulin lispro or insulin aspart compared with regular human insulin. **Long-acting insulin analogues** • There was good level of evidence to suggest that treatment with insulin glargine compared with NPH insulin resulted in small but significantly lower HbA1c level by 0.11% in adults with type 1 diabetes mellitus but not in children and adolescents or patients with type 2 diabetes mellitus. Fasting plasma glucose was found to be significantly lower in type 1 diabetes mellitus treated with insulin glargine or insulin detemir (ranged between 0.87 mmol/L and 1.01 mmol/L), while postprandial blood glucose was found to be significantly lower in type 2 diabetes mellitus treated with insulin glargine compared with NPH insulin. • For type 1 and type 2 diabetes mellitus, there was evidence to suggest that quality of life and treatment satisfaction was greater with insulin glargine compared with NPH insulin. • There was fair to good level of evidence to suggest that treatment with insulin detemir was associated with smaller weight gain in children and adults with type 1 diabetes mellitus and in type 2 diabetes mellitus compared with NPH insulin. **Premixed insulin analogues** • There was good level of evidence to suggest that treatment with premixed insulin analogues had similar effect in lowering HbA1c but significantly reduced postprandial blood glucose in type 1 and type 2 diabetes mellitus [ranged between 17.8 mg/dL (0.98 mmol/L) and 30.0 mg/dL (1.68 mmol/L)] compared with premixed human insulin.

Safety

Rapid-acting insulin analogues

- There was good level of evidence to suggest that when compared with regular human insulin, the use of insulin lispro resulted in lower risk for nocturnal hypoglycaemia in adults and adolescents with type 1 diabetes mellitus (reduction by 49% and 39% respectively) and also in type 2 diabetes mellitus in some studies.

- The risk for severe hypoglycaemia was also lower in adult with type 1 diabetes mellitus by 20%.

- Similarly, treatment with insulin aspart resulted in lower risk for nocturnal hypoglycaemia (reduction between 33% and 45%) in type 1 diabetes mellitus.

- There was fair to good level of evidence to suggest that the frequency and type of adverse events were similar between rapid-acting insulin analogues and regular human insulin.

Long-acting insulin analogues

- There was good level of evidence to suggest that there were similar risk for overall, severe and nocturnal hypoglycaemia for type 1 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- In patients with type 2 diabetes mellitus, the risk for nocturnal and overall hypoglycaemia was significantly lower in patients treated with insulin glargine compared with NPH insulin by 34% to 46% and 11% respectively. Five people with type 2 diabetes mellitus needed to use once-daily morning glargine rather than once-daily evening NPH, while eight people with type 2 diabetes needed to use once-daily evening glargine rather than once-daily evening NPH to avoid one person from experiencing a nocturnal symptomatic hypoglycaemic event.

- There was good and fair level of evidence to suggest similar foetal and neonatal outcomes and progression of diabetic retinopathy in patients treated with insulin glargine compared with NPH insulin.

- There was good level of evidence to suggest that treatment with insulin detemir compared with NPH insulin resulted in lower risk for nocturnal hypoglycaemia in type 1 diabetes mellitus (adult, children and adolescents) by 8% to 15%, while severe hypoglycaemia was found to be lower in adult with type 1 diabetes mellitus by 25% to 34%.

- Type 2 diabetes mellitus treated with insulin detemir was found to have significantly lower risk for nocturnal and overall hypoglycaemia (reduction by 34% to 47% and 18% to 32%, respectively).

Premixed insulin analogues

- There was good level of evidence to suggest that the risk for hypoglycaemia was similar for premixed insulin analogues and premixed human insulin.

Cost / cost-effectiveness / economic evaluation

Studies of incremental cost-effectiveness ratio per quality adjusted life year gained generally demonstrated that insulin analogues could be cost-effective compared with conventional human insulin. The drug costs were higher in the insulin analogues group than the conventional human insulin, but this was partly offset by reduced complication costs.

Recommendation

Based on the above review, treatment with insulin analogues compared with conventional human insulin appeared to offer minor benefit in terms of glycaemic control as reflected in HbA1c level, postprandial blood glucose and fasting blood glucose but have advantages in terms of reduced occurrence of hypoglycaemia, particularly nocturnal hypoglycaemia and severe hypoglycaemia as reported in some studies. While the adverse events (excluding hypoglycaemia episodes) were found to be similar in both treatment groups, patients treated with insulin analogues showed greater treatment satisfaction and less weight gain. Hence, it is recommended that insulin analogues should be made available for treatment of all type 1 diabetes mellitus and for type 2 diabetes mellitus who have recurrent hypoglycaemia. However, it is not recommended for gestational diabetes mellitus. More high quality clinical trials are warranted to provide evidence on long term safety and effectiveness of insulin analogues. Although insulin analogues could be considered cost-effective in some countries, generalizability and international comparisons of economic evaluations are limited. Local cost analyses research with the decision maker and societal perspective are encouraged. The price of insulin analogues in Malaysia is much higher compared with conventional human insulin. From literature review, we observed that there were price variations across countries and regions of the world. Hence, we need to negotiate for better pricing package.