Brief #5 Comparison rapid vs. standard insulins

Background
This topic proposal was submitted by
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- Kelly Kavanagh, Clinical Pharmacist, Pharmaceutical Services Division, Department of Health and Community Services, Nfld.
- Allen Lytwyn, pharmaceutical consultant, Manitoba Health; in July 2006.

There are four research questions proposed for this topic:
1) Do the new rapid-acting insulins provide clinically meaningful improvements in outcomes over standard insulins? If so, are the benefits proportionate to the cost?
2) What is the evidence to support the use of newer rapid-acting (Novo Rapid) and long-acting (e.g., Lantus) insulins over existing products? Are there specific sub-groups of patients or specific situations where the use of these drugs may be preferred?
3) Should insulin therapy be initiated with rapid-acting insulins?
4) What is the evidence for first-line use of Humalog/Novo Rapid?

Large Deviations from Optimal Utilization
- There is a need to assess this topic based on its budgetary impact on the drug plan and/or healthcare system, potential clinical and non-clinical benefits, as well as scientific controversy on the topic.
- Drug plans are receiving an increasing number of requests for initiation of rapid-acting insulins over standard insulin. It is unknown whether evidence supports this practice.
- As of 2005, regular insulin was listed on all provincial and territorial formularies. Humalog and Novo Rapid were listed only by Alberta, Manitoba, Quebec, PEI, Yukon, Northwest Territories, Nunavut and NIHB (Non-Insured Health Benefits). In all other provinces, they were covered only in special circumstances.1

This briefing paper has been developed to assist in the prioritization of new COMPUS topics at the October 24-25, 2006 face-to-face meeting. The report offers information on the six key criteria for identifying COMPUS topics; large deviations from optimal utilization, size of patient population, impact on health outcomes, impact on cost effectiveness, benefit to multiple stakeholders, measurable outcomes, and potential to effect change in prescribing and use. You are invited to consult with colleagues and consider other factors in the prioritization process (e.g. variation in use, ethical or legal considerations, timeliness of information, public interest and any controversy existing regarding these topics).
Size of Patient Population

- In 1999-2000, about 5.1% of Canadians aged 20 and over (approx. 1.2 million people) had been diagnosed with diabetes.\(^2\)
- The number of people with diabetes is expected to increase to about 2 million people in 2010, and 2.4 million by 2016.\(^3\)
- Health-adjusted life expectancy (HALE) for diabetic men in Ontario is 58.3 years compared to 70 years for men without diabetes; for Ontario women the HALE is 63.8 years compared to 73.5 years.\(^2\)
- 10% of Canadians aged 65 and over have the disease, compared with 3% of Canadians aged 35-64.\(^4\)
- Age-standardized rates of diabetes are three times higher among the aboriginal population than in the general population.\(^2\)
- Diabetes-related healthcare costs were estimated at $4.6 billion in 2000; this is expected to increase by about 75% to about $8 billion in 2016.\(^3\)
- In 1998, the direct cost of hospitalization and drug therapy for diabetes in Canada was almost $400 million.\(^3\)
- British Columbia, Alberta, Ontario and the Territories will see the highest increase in their population of people with diabetes.\(^3\)

Alternatives

- Rapid-acting insulin analogues currently available in Canada include insulin lispro (Humalog, Eli Lilly) and insulin aspart (NovoRapid, Novo Nordisk). Insulin glulisin (Apidra, Aventis) is currently not licensed in Canada.
- Short-acting insulin (also known as regular insulin) is available as human insulin (Humulin R, Novolin R). Although rarely used, regular insulin is also available derived from pork source (Hypurin, Wockhardt UK).

Impact on Health Outcomes

- Insulin analogues have been developed to more closely mimic the action of endogenous insulin in non-diabetic patients; potential advantages include better glycemic control with a reduced risk of hypoglycemia.
- A recent Cochrane meta-analysis of 49 randomized controlled studies showed that HbA1c was reduced to a small but statistically significant extent with rapid-acting insulin analogues compared with regular human insulin in patients with type 1 diabetes [-0.1% (95% CI –0.2 to –0.1)]. Based on these results, approximately 650 patients would have to be treated with analogues for one year to prevent the development of retinopathy in one patient.\(^5\)
- Continuous subcutaneous insulin infusion (CSII) with insulin analogues compared to regular human insulin showed a statistically significant reduction in HbA1c [-0.2% (95% CI –0.3 to –0.1)].\(^5,6\)
- No difference in reduction in HbA1c between treatments was observed in children with type 1 diabetes, pregnant women with type 1 diabetes, women with gestational diabetes, or patients with type 2 diabetes.\(^5\)
- Overall, no reduction in hypoglycemic episodes was found in patients using rapid-acting insulin analogues or regular human insulin. However, severe hypoglycemia occurred less often in patients on rapid-acting insulin analogues (median 21.8 vs 46.1 episodes per 100 person-years, respectively).\(^5\)
Insulin analogues are effective in attenuating postprandial hyperglycemia episodes; however, whether this will result in a decrease in the incidence of cardiovascular disease and mortality is unknown.\textsuperscript{7,8}

In type 1 diabetes, there is a lower incidence of major nocturnal hypoglycemia episodes reported with the rapid-acting insulin analogues.\textsuperscript{9}

Rapid-acting insulin analogues are usually injected 5-15 minutes before a meal. This compares to regular human insulin, which needs to be injected 30-60 minutes prior to eating. As a result, quality of life and treatment satisfaction have been improved in the insulin analogue group in some studies; however, this has not been consistently observed in all trials.\textsuperscript{5}

The Canadian Diabetes Association recommends insulin aspart or insulin lispro, in combination with adequate basal insulin in preference to regular insulin. As well, the rapid-acting insulin analogues should be used when CSII is used in patients with type 1 diabetes.\textsuperscript{10}

### Impact on Cost-Effectiveness

<table>
<thead>
<tr>
<th>Product</th>
<th>Price*</th>
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<tbody>
<tr>
<td>Humalog (insulin lispro) 100 U/mL (10 mL vial)</td>
<td>$25.14</td>
</tr>
<tr>
<td>NovoRapid (insulin aspart) 100 U/mL (10 mL vial)</td>
<td>$24.12</td>
</tr>
<tr>
<td>Novolin Toronto 100 U/mL (10 mL vial)</td>
<td>$17.46</td>
</tr>
<tr>
<td>Humulin R 100 U/mL (10 mL vial)</td>
<td>$16.72</td>
</tr>
</tbody>
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*Manufacturer’s wholesale price as at September 2006.*

Based on these prices, there would be an approximately 30% price increase if a patient were to be switched from regular to rapid-acting insulin.

- There is limited cost-effectiveness data currently available for the rapid-acting insulin analogues.\textsuperscript{11} Studies have shown that patients have a preference for rapid-acting insulin analogues and have been shown to be willing to pay for the advantages these products offer.
- Insulin lispro patients compared with regular insulin patients had significantly higher diabetes-related and nondiabetes-related pharmacy costs while having similar or lower diabetes-related and total medical costs as a result of fewer inpatient hospitalizations.\textsuperscript{12}
- The incremental cost-effectiveness ratios (ICERs) for insulin aspart versus human insulin were below 30,000 Euros per quality-adjusted life year gained.\textsuperscript{13}

### Benefit to Multiple Stakeholders

- Audience would include private and public drug plans, endocrinologists and family physicians, pharmacists, diabetes educators, academic detailing programs and patients with diabetes.
- The anticipated message from a review of this topic might be that rapid-acting insulins may lead to a small clinical improvement and potentially an improved quality of life at an added cost.
Measurable outcomes

- A drug utilization evaluation could be conducted to determine usage of rapid-acting insulins in Canada.

Potential to effect change in prescribing and use

- Educational programs should be primarily targeted towards endocrinologists, with information also provided to diabetic educators, family physicians and pharmacists.

Evidence

- One Cochrane Collaboration review\(^5\) and one meta-analysis\(^1^4\) were identified that evaluated rapid-acting insulin analogues. In addition, two reviews evaluated insulin analogues.\(^8^9\)

- There are three economic analyses that evaluated rapid-acting insulin analogues.\(^1^1^1^3\)
References


