Title: Efficacy and Safety of Human versus Animal Insulins

Date: 3 August, 2007

Context and policy issues:
Type 1 diabetes mellitus is a metabolic disorder resulting from a lack of insulin production from the pancreas. Long-term complications of diabetes include blindness, kidney disease, limb amputation, heart disease, and stroke. Results from two pivotal trials clearly demonstrated that intensive insulin therapy in patients with type 1 diabetes led to reductions in long-term complications and mortality. For many years, insulin was produced from the pancreases of pigs and cows. At the time of introduction of human insulin, marketing strategies suggested that the lower immunogenicity of human insulin would offer a clinical advantage for insulin treated patients. Human insulin was produced either by a single amino acid substitution from porcine insulin (termed semi-synthetic human insulin) or using recombinant DNA technology with baker’s yeast or E. coli as the host cell (termed biosynthetic or recombinant human insulin). Both forms of insulin were highly purified. The first human recombinant insulin was manufactured by Eli Lilly and approved for sale in Canada in 1983. In 1993, a second recombinant human insulin, manufactured by Novo Nordisk, entered the Canadian market. Over the next few decades, rapid-acting analogues, analogue mixtures, basal analogues, and other human insulin products and formulations were developed with differences in the time of onset, peak activity and duration of action.

Initially, animal insulins were more immunogenic than human insulins and adverse effects were reported more frequently. However, in the last few years, production techniques have become progressively more sophisticated leading to development of highly purified animal insulins. Adverse effects including lipodystrophy, lipoatrophy, insulin allergy, and insulin resistance seen with the older impure animal insulins are now uncommon with highly purified animal insulins. However, with advances in recombinant human insulin production, the demand for animal insulins has declined. According to Eli Lilly, approximately 0.1% of the Canadian insulin market uses animal
products. This figure represents about 400 people using animal insulin out of approximately 382,000 insulin-dependent Canadians. A further challenge to the production of animal-sourced insulins is the risk of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) transmission. Manufacturers have therefore focused on the production and sale of human insulins. In 1995, Novo Nordisk discontinued the production of mixed bovine/porcine insulin. In 1999, Eli Lilly discontinued its mixed bovine/porcine insulins and in July 2005, announced it would discontinue its last porcine insulins.

Although the majority of patients with diabetes now use human insulin, a small number of patients cannot manage their disease using human insulins. There have been reports of loss of ability to recognize the early warning symptoms of hypoglycemia (e.g., sweating, nervousness, palpitations, weakness, trembling, and intense hunger) after switching to a synthetic human product, termed “hypoglycemia unawareness”. In order to help guide decisions regarding the future availability of animal insulins for these individuals, this report will present the available evidence for safety and efficacy of human versus animal insulins.

Research questions:
What is the evidence of benefit and harm of animal insulin compared to human insulin?

Methods:
A limited literature search was conducted on key health technology assessment resources, including OVID Medline, OVID EMBASE, The Cochrane Library (Issue 2, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. Internet links are provided, where available. Bibliographies of reports were scanned to identify other relevant evidence.

Summary of findings:
Several insulins are currently available in Canada (table1). Following Eli Lilly’s discontinuation of its porcine insulins, Wockhardt UK Ltd received market authorization from Health Canada in January 2006 for Hypurin® Porcine insulins. Hypurin® Bovine insulins are not currently approved for use in Canada but may be imported from Wockhardt UK Ltd via the Special Access Programme.
### Table 1: Insulins Available in Canada†

<table>
<thead>
<tr>
<th>TYPE</th>
<th>BRAND NAMES</th>
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<tbody>
<tr>
<td><strong>Human</strong></td>
<td></td>
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<tr>
<td>Insulin Regular</td>
<td>Humulin®-R, Novolin®ge Toronto</td>
</tr>
<tr>
<td>Insulin NPH</td>
<td>Humulin®-N, Novolin®ge NPH</td>
</tr>
<tr>
<td>Insulin Lente</td>
<td>Humulin®-L</td>
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<tr>
<td><strong>Analogues</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin Aspart</td>
<td>NovoRapid®</td>
</tr>
<tr>
<td>Insulin Lispro</td>
<td>Humalog®</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>Lantus®</td>
</tr>
<tr>
<td>Insulin Detemir</td>
<td>Levemir®</td>
</tr>
<tr>
<td><strong>Premixed</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin Lispro/</td>
<td>Humalog®Mix25™, Humalog®Mix50™</td>
</tr>
<tr>
<td>Insulin Lispro</td>
<td>Humulin® 30/70</td>
</tr>
<tr>
<td>Insulin Lispro Protamine</td>
<td>Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50)</td>
</tr>
<tr>
<td>Insulin NPH</td>
<td>Hypurin® Porcine Regular</td>
</tr>
<tr>
<td>Insulin NPH (Porcine)</td>
<td>Hypurin® Porcine NPH</td>
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† Based on a listing from the Drug Product Database of drugs currently licensed for sale by Health Canada. 19

A Cochrane systematic review 20 provides the highest quality evidence from trials published over the last twenty five years assessing the safety and efficacy of human versus animal insulins. Our search did not retrieve any relevant trials published since this review.

After an extensive search of the literature, 45 randomized controlled trials (n=2156) were included in the review, 50% of which were published before 1987. 20 Details of the review are presented in table 2. Many of the trials examined glycemic control and/or hypoglycemic events during the transition from animal to human synthetic insulin. Purified porcine and semi-synthetic human insulin were most often investigated. Due to poor methodological quality and clinical heterogeneity of the included studies, glycemic control, as measured by a lowering of glycosylated hemoglobin (HbA\textsubscript{1c}), was the only parameter used for pooled meta-analysis. Results indicated that there were no significant differences in glycemic control between human and animal insulins. However, lack of standardization for HbA1c measurements and reference ranges resulted in significant heterogeneity between studies, and the authors note that these results should be interpreted with caution. Unpooled data did not show a significant difference between insulins in terms of frequency or severity of hypoglycemic episodes.
Five studies examining immunogenicity of human and animal insulin were difficult to compare because of the different assays for insulin antibodies. The average duration of these trials was 10 months. In general, an initial decline in insulin antibodies was observed following transfer from animal to human insulin which tended to level off in trials of six months or longer. Authors rarely reported significant differences by the end of the trial. Therefore, despite previous claims of reduced antigenicity with human insulins, insulin dose and insulin antibodies did not demonstrate clinically relevant differences. Adverse effects apart from hypoglycemic episodes were rarely reported so no clear conclusions could be made as to whether any differences existed between insulins. Furthermore, many patient-oriented outcomes including health-related quality of life, long-term diabetic complications, and mortality were never investigated. The authors concluded that the available evidence does not show that human insulin is clinically superior to animal insulin in terms of efficacy or safety.

While there are a number of evidence-based guidelines for diabetes, few guidelines specifically address the use of human versus animal insulins. Current guidelines from the Canadian Diabetes Association state that patients switching from animal to human insulin do not require counseling about any change in frequency or perception of hypoglycemia. Some guidelines recommend that all new patients be started on human insulin preparations while others state that insulin preparations of any species may be used.
Table 2: Evidence from a systematic review examining human versus animal insulin

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESIGN</th>
<th>MAJOR RESULTS</th>
<th>CONCLUSIONS</th>
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| Richter et al., 2005<sup>20</sup> | **Included Studies:** 45 RCTs (n=2156) Median duration of 6 months  
**Patient Population:** All individuals with a diagnosis of diabetes mellitus  
26 trials (58%) trials examined type 1 diabetics  
41 trials (91%) studied adults  
**Human Insulins:** Semi-synthetic (36 trials) Recombinant DNA (9 trials)  
**Animal Insulins:** Purified porcine (33 trials)  
Purified porcine/bovine (9 trials)  
Purified bovine (2 trials)  
Unknown (1 trial)  
**Outcome Measures:** Glycemic control (HbA<sub>1c</sub>)  
Frequency, severity, and symptoms of hypoglycemia  
Diabetic complications (e.g., retinopathy, nephropathy, neuropathy)  
Fasting plasma glucose  
Adverse effects (apart from hypoglycemia)  
Mortality  
Health-related quality of life  
Compliance  
Costs  
Socio-economic effects (e.g., hospital stay, sick leave days, emergency room admissions)  
**Efficacy:** Lowering of HbA<sub>1c</sub> was not significantly different in patients receiving human insulin compared to those receiving animal insulin.  
WMD 0.17%  
(95% CI: -1.05-0.72%)  
The test for study heterogeneity was significant (p=0.046).  
Unweighted means of post treatment insulin dose showed no significant difference.  
Human insulin= 43 U/day  
Animal insulin= 47 U/day  
**Safety:** Unweighted means showed no significant differences in the frequency, severity, and presentation of hypoglycemic episodes for different insulin preparations.  
There is no evidence that human insulins are superior in terms of glycemic control or hypoglycemic episodes to animal insulins.  
**Limitations:** Significant heterogeneity in patient population and study design.  
Crossover studies did not use a washout period.  
Few studies mentioned method of randomization, allocation concealment, or blinding.  
Intention-to-treat analysis was reported in only one study.  
No study systematically measured compliance.  
Long-term outcomes including diabetic complications or mortality were not assessed and adverse effects apart from hypoglycemic episodes were rarely reported.  

RCT=Randomized Controlled Trial, WMD=Weighted Mean Difference.
Conclusions and implications for decision or policy making:
Available evidence does not support claims that human insulin is associated with decreased immunogenicity or a greater risk for hypoglycemia unawareness. However, high quality clinical trials are required to confirm these findings as well as address potential differences in long-term outcomes including diabetic-related mortality and complications, adverse effects including local and systemic reactions, and socio-economic factors. Studies examining hypoglycemic events during the transition from animal to synthetic insulin have been the focus of most of the clinical trials, with an absence of data for those who have never used animal insulin. No randomized controlled trials have yet assessed the safety and efficacy of insulin analogues versus animal insulins. Current evidence suggests that it is unlikely that improvement in glycemic control can be achieved by merely switching from animal to human insulin. Therefore, the decision regarding choice of insulin should be based on clinical experience and patient-preference.

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