Basal Insulins

Tailoring Treatment to Patient Needs

Tom Ransom

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Faculty/presenter disclosure

• **Presenter**: Dr. Tom Ransom, Endocrinologist

• **Relationships with commercial interests**:
  - Grants/Research Support: none
  - Speakers Bureau/Honoraria: NovoNordisk, AstraZeneca, Lilly, Sanofi, Merck, Janssen, Valeant
  - Consulting Fee: none
  - Other: none
Disclosure of commercial support

• This program has received financial/in-kind support from the sponsors listed

• Potential for conflict(s) of interest:
  – Dr. Tom Ransom has received payment/funding, etc. from the companies listed in the disclosures whose products are discussed in the program, including:
    • Sanofi-aventis Canada Inc.: Insulin glargine U100 (Lantus®), Insulin glargine U300 (Toujeo™)
    • Lilly: Basalglar, Humalog, Humilin N
  – Novo Nordisk Canada Inc. distributes three products that will be discussed in this program:
    • Insulin NPH (Novolin® ge)
    • Insulin detemir (Levemir®)
    • Insulin degludec (Tresiba®)*
  – Dr. Tom Ransom will not receive an honorarium for this talk

*Not available in Canada.
Mitigating potential bias

Bias in this program has been mitigated using independent content validation as follows:

• All data have been sourced from clinically accepted evidence

• All support used in justification of patient care recommendations conforms to generally accepted standards, Diabetes Canada 2018 Clinical Practice Guidelines, as well as the most recently available clinical data

• I will be using slides that I have obtained from industry contacts but this has not altered my opinions
Objectives

- Know how insulin modification results in different action profiles.
- Know the rationale of designing insulins with “longer and flatter” profiles.
- Be confident in applying the above to help manage patients with DM2 including starting insulin.
Insulin Release

Into the portal vein $t_{1/2} = \text{minutes}$
Post Transcription Modulation

Endoplasmic reticulum

Golgi apparatus
Preinsulin
Insulin
Happy dog!
Why so unhappy?
Toronto qid
What is a unit of insulin?

Unhappy rabbit
A unit of insulin is...

• One 32\textsuperscript{nd} the amount of insulin required to, within 4 hours of injection, cause a 2 pound fasted rabbit (24 hours) to have a seizure

• Want results to be reproducible/predictable
• Want insulin to be stable
Toronto

• Not fast enough at meal time
• Not long enough for a basal insulin

A need to move on
Subcutaneous Insulin is Slowly Absorbed

The diagram illustrates the process of insulin absorption through the skin. It shows different forms of insulin, such as hexamers, dimers, and monomers, which are in different stages of diffusion through the skin layers. The process is divided into three stages:

- **Minimal diffusion** in the capillary layer, indicating slow entry.
- **Limited diffusion** through the barrier layer, showing a moderate rate of absorption.
- **Rapid diffusion** in the lower layer, suggesting fast absorption.

The diagram also indicates the reversible nature of these forms, with arrows showing the possible transitions between insulin hexamers, dimers, and monomers.
Adjust the Zn concentration
NPH

- neutral protamine Hagedorn
- Human/bovine/porcine
Variability of NPH and UL

- Large inter- and intra-individual variations
- Cloudy - needs to be mixed properly (~20 times)
- Without re-suspension 5 - 214% variability

A: Before (after 24 h sedimentation)
B: After seven cycles
C: After 20 cycles.
insulin homology across species

<table>
<thead>
<tr>
<th>Insulin</th>
<th>B chain</th>
<th>A chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homo</td>
<td>FVNQHLCGSLVEALYLVCGERGFFYTPKT</td>
<td>GIVEQCCTSCISSLQLENYCN</td>
</tr>
<tr>
<td>Pan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorilla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pongo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macaca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macaca fas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorocebus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aotus</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Callithrix</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Microcebus</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Tupaia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canis</td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Wallis Grth Hormon IGF Rsrch 2009
Animal Insulins

• Until 1980’s all commercially available insulin was bovine or porcine extracted

• Impurities – immunologic reactions
  – Allergic, lipo-atrophy/hypertrophy, resistance, variability

• Purification techniques improved over time
Lipo-hypertrophy/atrophy
Modified Human Insulin

Regular Insulin
Hexamers in Zn$^{2+}$ buffer

Neutral Protamine Hagedorn (NPH) Insulin
Medium-sized crystals in protamine-Zn$^{2+}$ buffer

Lente and Ultralente Insulin
Large crystals in acetate-Zn$^{2+}$ buffer
Profiles of Human Insulins

- Regular: 6–8 hours
- NPH: 12–20 hours
- Ultralente: 18–24 hours
Human Insulin

• Starting in the 80’s recombinant DNA technology improved to the point that human insulin predominated

• Regular (Toronto), NPH, Lente, Ultra Lente

• Lente and Ultra Lente fell out of favour due to marked variability
Clinical Efficacy is not lowering of HbA1c, it is the lowering of HbA1c without unacceptable hypoglycemia

Dr. Robert Ratner
Normal Insulin Secretion: The Basal-Bolus Insulin Concept

B, breakfast; L, lunch; D, dinner; HS, bedtime.

Adapted from:
Limitations of Multiple Daily Injections

NPH at AM and HS + Regular AC

NPH at HS + Regular AC

AC (ante cibum), before meals; B, breakfast; L, lunch; D, dinner; HS, bedtime.

Adapted from:
Variability and peak profile for NPH insulin
Pharmacokinetic limitations of subcutaneous exogenous basal insulin

A: Peaked mean profile with high variability
B: Smooth, flat mean profile, but high variability injection to injection
C: Ideal: smooth, flat mean profile, with low variability
With Regards to Basal Insulin

- I hate the liver
- Just a big sugar making machine
- “I woke up with a 12 and I didn’t eat anything!?!?”
The balance between control and tolerability: data from DCCT

![Graph showing the relationship between HbA$_1c$ (%) and the risk of retinopathy and severe hypoglycaemia per 100 patient years.](image)

*Risk of retinopathy per 100 patient years*

*Severe hypoglycaemia per 100 patient years*

*HbA$_1c$ (%)*

Analogs

• Add
• Subtract
• Change
• pH/[Zn]/protamines/etc…

• Either speed up or protract absorption
Faster

Lysine/Proline transposition – steric hinderence dimerization

Substitution of Proline at B28 with negatively charged Aspart enhances repulsion of monomers

Glutamine for Lysine at B29, Aspart for Lysine at Bs results in decreased ability for insulin monomers to self associate
Lys$^{29}$Pro$^{30}$-human insulin
~ concentration (M) $10^{-3}$

formulation

10$^{-3}$

transient

10$^{-3}$

subcutaneous tissue

10$^{-3}$

10$^{-5}$

10$^{-8}$

formulation

Human insulin
~ concentration (M) $10^{-3}$
The Ideal Long-Acting Insulin

- One injection daily covers 24 hours
- No pronounced peak
- Low incidence of hypoglycemia
- Good glycemic control
- Less weight gain
- Safe
- Predictable
- Easy handling
  - Injection at different sites
  - No mixing necessary/clear solution
- High treatment satisfaction and acceptance
Slower

(a) Insulin Glargine

(b) Insulin Detemir

A-CHAIN

C14 fatty acid chain (myristic acid)

Remove Thr

B-CHAIN

(c) Insulin Degludec

(d) Lilly’s Basal Insulin: LY2605541

Glucodynamic Response

Novel engineered insulin goals:
- Less patient variability
- Less hypoglycemia risk
- Better patient control

Status: Phase 1 studies

Derived From Phase 1 Data

Moser Diab Rsrch Clin Prac 2012
Protraction of Glargine

Injection site
Lantus® (clear solution) pH 4
pH 7.4

Microprecipitation
Depot
Hexamers
Dimers
Slow release of Lantus®
Monomers
Capillary membrane
Insulin in blood
Structure of insulin detemir
Insulin detemir: mode of prolonging action

- Self association (hexameric)
- Fatty acid side chains bind to albumin in injection depot

Protracted absorption

- Albumin binding in circulation

‘Buffering’ effect and minor contribution to protraction

Levemir®

(novo nordisk®)
A chain

B chain

dicarboxylic acid

degludec

PEG

LY2605541

R₆ dimers

vial

phenol

ingestion

T₆ polymers

in depot

albumin

in bloodstream
Clamp-profiles for NPH insulin and insulin glargine
Glucose Infusion Rates

SC, subcutaneous; CSII, continuous subcutaneous insulin infusion.
Insulin Glargine Glycemic Control with Less Hypoglycemia

FBG target: ≤6.7 mmol/L

Type 2 DM

FBG, fasting blood glucose.

Benefits of Insulin Glargine Maintained Over 1 Year

**Type 1 DM**

A1C from baseline to endpoint

- **Insulin Glargine (n=61)**
- **NPH Insulin (n=60)**

<table>
<thead>
<tr>
<th>Change in A1C (%)</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.2</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>4.8</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- * Blood glucose < 4 mmol/L (<72 mg/dL).

Weight gain with insulin therapy

- Seen in both type 1 and type 2 diabetes
- May worsen underlying defect in type 2 diabetes
- Barrier to starting insulin therapy in type 2 diabetes
- May decrease compliance with insulin regimens
- May lower self-esteem
Weight gain in type 1 diabetes: DCCT

Initial 12 months

Conventional treatment

Intensive treatment

Insulin Glargine: Glycemic Control with Less Weight Gain

Mean weight gain in type 1 and type 2 diabetes

<table>
<thead>
<tr>
<th>Type</th>
<th>NPH (kg)</th>
<th>LANTUS (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>0.54</td>
<td>0.12*</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.4</td>
<td>0.4†</td>
</tr>
</tbody>
</table>

(n=293) (n=295) (n=231) (n=238)

Insulin detemir: mode of protraction

- Self association (hexameric)
- Fatty acid side chains bind to albumin in injection depot
- Albumin binding in circulation

Protracted absorption

‘Buffering’ effect and minor contribution to protraction
Receptor binding, metabolic and mitogenic potency of insulin analogues

<table>
<thead>
<tr>
<th></th>
<th>Insulin receptor affinity</th>
<th>Metabolic potency</th>
<th>IGF-I receptor affinity</th>
<th>IGF-IR/IR affinity</th>
<th>Mitogenic potency (Saos/B10 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>B10 Asp</td>
<td>205 ± 20</td>
<td>207 ± 14</td>
<td>587 ± 50</td>
<td>2.9</td>
<td>975 ± 173</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>84 ± 6</td>
<td>82 ± 3</td>
<td>156 ± 16</td>
<td>1.9</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>92 ± 6</td>
<td>101 ± 2</td>
<td>81 ± 9</td>
<td>0.9</td>
<td>58 ± 22</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>86 ± 3</td>
<td>60 ± 3</td>
<td>641 ± 51</td>
<td>7.5</td>
<td>783 ± 13</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>~18 - 46</td>
<td>~ 27</td>
<td>16 ± 1</td>
<td>0.9</td>
<td>~ 11</td>
</tr>
</tbody>
</table>

## Basal Insulins

<table>
<thead>
<tr>
<th>Basal insulins</th>
<th>onset of action</th>
<th>peak</th>
<th>duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intermediate-acting (cloudy) Insulin neutral protamine Hagedorn (Humulin®-N, Novolin® NPH)</td>
<td>1-3h</td>
<td>5-8h</td>
<td>Up to 18h</td>
</tr>
<tr>
<td>• Long-acting insulin (clear) Insulin detemir (Levemir®)</td>
<td>90min</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>• Insulin glargine U-100 (Lantus®)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Insulin glargine U-300 (Toujeo®)</td>
<td></td>
<td></td>
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<tr>
<td>• Insulin glargine biosimilar (Basaglar®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Degludec U-100, U-200 (Tresiba®)</td>
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</tbody>
</table>

- U-100 glargine 24h, detemir 16-24h
- U-300 glargine >30h
- Degludec 42h
Long acting insulin analogs:

- Efficacy in lowering A1C levels greater than or comparable to NPH insulin in adults and the elderly
- Less variability in fasting blood glucose levels than with NPH insulin
- Less symptomatic hypoglycemia than with NPH insulin
- Less symptomatic nocturnal hypoglycemia than with NPH insulin
- Minimal or no effect on weight
- Well tolerated
Future Insulins

- Even faster, even longer
- **Mode of administration**
  - Inhaled
  - Buccal
  - Transcutaneous
  - Oral
  - Peritoneal
- “Smart” insulins
Summary So Far

- Don’t hold your breath for a cure
- With advancements in insulin technology management will become “easier”
  - Profiles that match normal physiology better
  - Predictable
  - Safe
  - Different modes of delivery
Starting Insulin
Type 2 Diabetes is progressive
Needing Insulin is NOT a Sign of Failure!

• It is just another tool to help patients achieve optimal glycemic control

• Patients should never feel guilty about needing insulin
Time-Action profiles of bolus & basal insulins

Diagrammatic representation
Action curves are approximations taken from different data sources. Actual patient response will vary.
Some of my favorite “lines” that I’ve adopted

• Think like a pancreas
• Start low and go slow (when appropriate)
• I’m not trying to guess what you need. I’m deliberately giving you less than you need so you can titrate up safely. I want you to be comfortable making adjustments.
• We are better at checking and reacting than predicting
• Start on a weekend
It sits in your skin

Not This                          This

It’s the formulation that effects how long it lasts and how fast it acts
MDI Basal

- I hate the liver!
  - Unrelenting glucose production
  - Daily rhythm
  - It’s not a scam. Sugars are higher in the morning
  - The basal handles the liver
MDI Bolus

• You need more insulin for a bowel of Cheerios at breakfast than at supper

– less

more

• My pancreas squirts out more insulin for pasta with garlic bread than for a Caesar salad with chicken strips
How much to start?

• As long as you have a titration schedule you will get there soon enough so always start safe
  – 6 or 10 or dose = FBG
  – +/- high A1c
  – +/- obese
How to titrate?

- 1 unit per day
- 2 units every 3-4 days (twice per week)
- 4 units weekly (for really long acting)

- “patient was instructed to do a forced titration of there bedtime insulin to get their FBG to...”
- I could take 2 units of insulin right now and not worry
Titration

• No max dose
  – Lily has a u 500 of R
  – Once you hit 62 do 30 and 32
  – You are going to tell me how much you need
    • Every one is different
Other than Bed Time?

• Convienience
• Pre breakfast lows
• bid ?
  – If on lower dose (usually less than 30 units) patern may dictate a trial of bid

• Remember extra checking while titrating
Final thoughts

• Safety first
• Basal analogs are incrementally “better”
• Develop a routine for yourself