

Innovations in Insulin Analogue Therapy

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Disclosure Statement

Dr. Goldenberg has received honoraria or consultancy fees from:

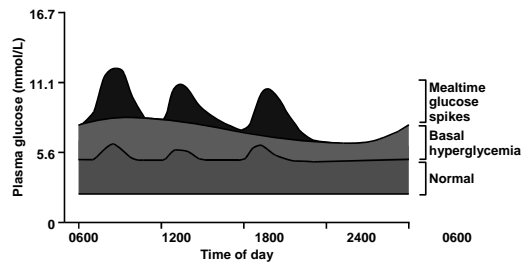
- Eli Lilly
- GlaxoSmithKline
- Sanofi-Aventis

Objectives

- Review the basal-bolus insulin concept
- Discuss basal insulin analogues: glargine & detemir
- Discuss premixed insulin analogues: Lispro Mix 25 and BiAsp 30
- Understand physiologic insulin replacement with basal and rapid analogues

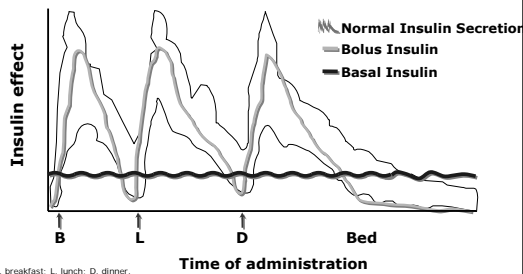
Glucose Patterns: Normal and Diabetes

Therapy Should Address Basal and Mealtime Hyperglycemia in Type 2 Diabetes



Riddle MC. Diabetes Care 1990;13:676-86

Normal Insulin Secretion: The Basal-Bolus Insulin Concept



B, breakfast; L, lunch; D, dinner.
Adapted from:
1. Leahy JL, Inz: Leahy JL, Cefalu WT, eds. *Insulin Therapy*. New York, NY: Marcel Dekker, Inc.; 2002.
2. Bolli GB, et al. *Diabetologia*. 1999;42:1151-1167.

Comparison of Human Insulins / Analogues: Basal Insulins

Insulin preparations	Onset of action	Peak	Duration of action
NPH	1 - 3 h	5 - 8 h	up to 18 h
Glargine	90 min	Flat	24 h
Detemir	1 - 2 h	6 - 9 h	12 - 23 h*

* Dose dependent

Comparison of Human Insulins / Analogues: Bolus Insulins

Insulin preparations	Onset of action	Peak	Duration of action
Regular	30 - 60 min	2 - 4 h	5 - 8 h
Aspart/Lispro	10 - 15 min	60 - 90 min	4 - 5 h

Starting With Basal Insulin Advantages

- 1 injection at bedtime
- Safe
- Simple to adjust dose based on fasting glucose
- Limited weight gain
- Effective improvement in glucose control
- Consider for A1C 7 – 10%

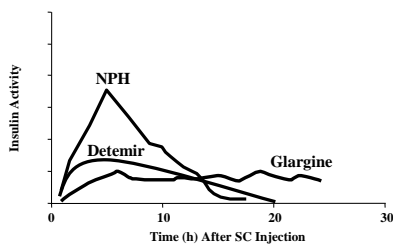
Limitations of Human NPH as Basal Insulin

- Does not mimic basal insulin profile
 - Variable absorption and poor predictability
 - Pronounced peak
 - Less than 24-hour duration of action
 - Requires twice-daily injections to provide 24-hour basal insulin coverage
- Causes unpredictable hypoglycemia
 - Major factor limiting insulin adjustments
 - Weight gain

Features of Basal Insulins Glargine & Detemir

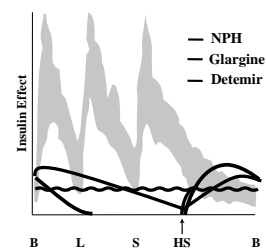
- Analogue basal insulins
- Flatter insulin action profile than NPH
- Prolonged duration of action allows once daily dosing for glargine; detemir once or twice daily
- Predictability better than NPH
- Comparable or better glucose control than NPH
- Lower risk of clinically important hypoglycemic events than NPH, esp. overnight
- Less weight gain than NPH in some studies

Insulin Activity Profiles of Basal Insulins



Lepore, et al. *Diabetes*. 1999;48(suppl 1):A97.
Phink J, et al. *Diabetes Care*. 2005;28(5):1107-12

Bedtime Basal Insulin NPH or Glargine or Detemir



Starting Basal Insulin in Type 2 Diabetes

- Continue oral agent(s) at same dosage (may stop TZD)
- Add single, HS insulin dose (around 10 U or 0.1-0.2U/kg)
 - NPH
 - Gargine
 - Detemir
- Adjust dose by fasting SMBG
- Titrate insulin dose as needed
- Treat to target (e.g., fasting glucose ≤ 5.5 mmol/L)

Titration Algorithms for Bedtime Basal Insulin

- 1) **Treat-to Target Trial:** Start with 10 IU/d bedtime basal insulin and adjust weekly; target FPG ≤ 5.5 mmol/L

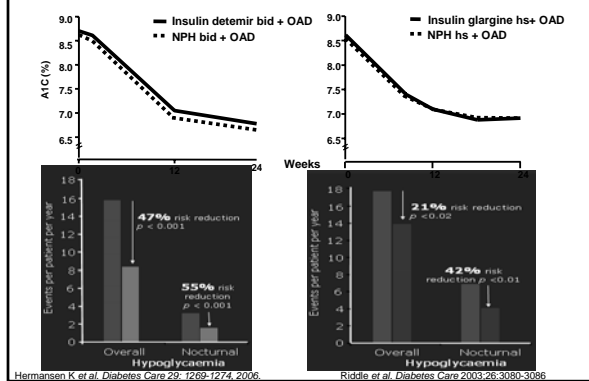
Self-monitored FPG (mean of last 2 days), mmol/L	↑ Insulin dose, IU/d
≥ 10.0	8
7.8-10.0	6
6.7-7.8	4
5.6-6.7	2

- 2) **The INSIGHT Trial:** Start with 10 IU at bedtime and adjust daily

Increase by 1 IU daily until FPG ≤ 5.5 mmol/L

Riddle M, et al. *Diabetes Care*. 2003; 26: 3080-3086.
Gerstein H et al. *Diabet Med*. 2006; 23: 736-742

Comparison of detemir and glargine treat-to-target trials



Hermansen K et al. *Diabetes Care* 29: 1269-1274, 2006

Riddle et al. *Diabetes Care* 2003; 26: 3080-3086

Detemir (hs or bid) vs Glargine (hs) as add-on to Oral Agents over 52 Weeks

Type 2 DM, n= 582, failing 1 or 2 oral agents, A1C 7.5-10% (mean 8.6%)

ITT Analysis	Insulin Glargine	Detemir
FPG mmol/L	7.0	7.1 <i>P = ns</i>
A1C, %	7.1	7.2 <i>P = ns</i>
Final A1C $\leq 7\%$ (% patients)	52	52 <i>P = ns</i>
Overall or nocturnal hypoglycemia		<i>P = ns</i>
Weight gain (kg)	3.9	3.0 <i>P = 0.012</i>
Within-patient variation in FPG or pre-supper PG		<i>P = ns</i>

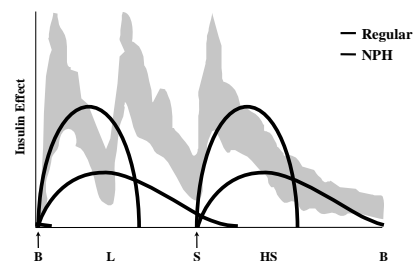
Rosestock J et al. ADA 66th Scientific Sessions, June 2006, Washington, DC, Abstract 555-P.

Premixed Insulins

	Rapid analog	Protamine analogue
Lispro Mix25	25%	75%
BIAsp 30	30%	70%
Inject 0-15 min. before meals	Regular (Short)	NPH (Intermediate)
Premix 10/90*	10%	90%
Premix 20/80*	20%	80%
Premix 30/70	30%	70%
Premix 40/60	40%	60%
Premix 50/50	50%	50%
Inject 30 minutes before meals	(* will be discontinued July 2007)	

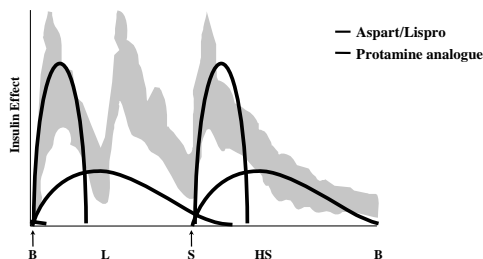
Twice-daily Pre-mixed Regimens

Premix Regular/NPH Twice Daily (e.g., 30/70)



Twice-daily Pre-mixed Regimens

Premix Analogue (e.g. Lispro Mix 25, BiAsp 30)



Premixed Insulin Regimens (e.g., 30/70, Lispro Mix25, BIAsp 30)

- Convenience and simplicity of 2 injections per day
- Requires consistent daily routine
- Often used for those reluctant or unable to do MDI
- Some gaps in insulin coverage
- Little flexibility, as can't separate basal and bolus adjustments
- Premix with rapid analogue (e.g., Lispro Mix25, BIAsp 30) is more convenient (inject & eat) & provides more physiologic rapid insulin with better postprandial glucose control and less hypoglycemia than premixes using regular insulin (e.g. 30/70)
- Initiated at 0.3 – 0.5 U/kg/day, with 2/3 in am and 1/3 in pm (e.g., 80 kg = 24units/day = 16u in am and 8u in pm)

The Basal/Bolus Insulin Concept

- **Basal Insulin**
 - Suppresses glucose production between meals and overnight
 - Nearly constant levels
 - 40 - 50% of daily needs
 - Evening dose adjusted based on fasting glucose
- **Bolus Insulin (Mealtime)**
 - Limits glucose spikes after meals
 - Immediate rise and sharp peak at 1 hour
 - ≈20% of total daily insulin requirement at each meal
 - Dose adjusted based on carb. intake (e.g., 1U/10g carb)
 - Sensitivity factor for premeal hyperglycemia (100/TDD) is amount of glucose lowering per 1 extra unit of bolus insulin analogue

Advancing To Basal/Bolus Insulin (MDI)

- **Indicated when FPG acceptable on basal alone, but**
 - A1C >7% and/or
 - 2hrs post-meal glucose > 10 mmol/L
- **Insulin options**
 - Basal: NPH hs or bid; Glargine od; Detemir hs or bid
 - Bolus: Regular, Lispro, or Aspart before meals
- **Initiation**
 - Total daily dose is 0.5U/kg (e.g., 70 kg = 35 units)
 - Basal : 40% of daily dose (e.g, 14 U NPH /Detemir/Glargine)
 - Bolus: doses are 20% of total daily dose before meals (e.g., 7 units before meals)
- **Oral agent options in Type 2 diabetes & MDI**
 - Usually stop insulin secretagogue
 - Continue metformin for weight control and lower insulin dose
 - Continue TZD in some cases

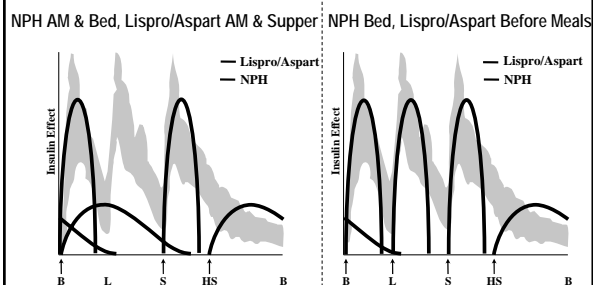
Short-acting Analogues: *Lispro* and *Aspart*

Advantages vs Regular Insulin as Bolus Therapy

- **Convenient administration immediately prior to meals**
- **Faster onset of action**
- **Limit postmeal glucose peaks**
- **Shorter duration of activity**
 - Reduce delayed *hypoglycemia*
 - Frequent delayed *hyperglycemia* without optimal basal insulin

Multiple Daily Injections (MDI)

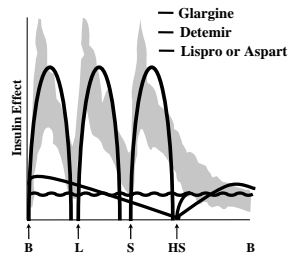
NPH + Mealtime Lispro or Aspart



Multiple Daily Injections (MDI)

Glargine or Detemir at hs + Mealtime Lispro or Aspart

Lispro/Aspart Before Meals, Glargine or Detemir Bed



Innovations in Insulin Analogue Therapy

- **Start with 1 injection at hs of basal insulin analogue**
- **Consider twice daily premix analogue in select patients**
- **Advance to basal-bolus therapy as necessary**
- **Analogue bolus (lispro, aspart) and analogue basal (detemir, glargine) is most physiologic therapy**
- **Glargine or Detemir as basal has better predictability and less hypoglycemia than NPH**
- **Treat to target**