Basal Insulin Therapy

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2020-07-10

INSULIN

The most powerful agent we have to control glucose

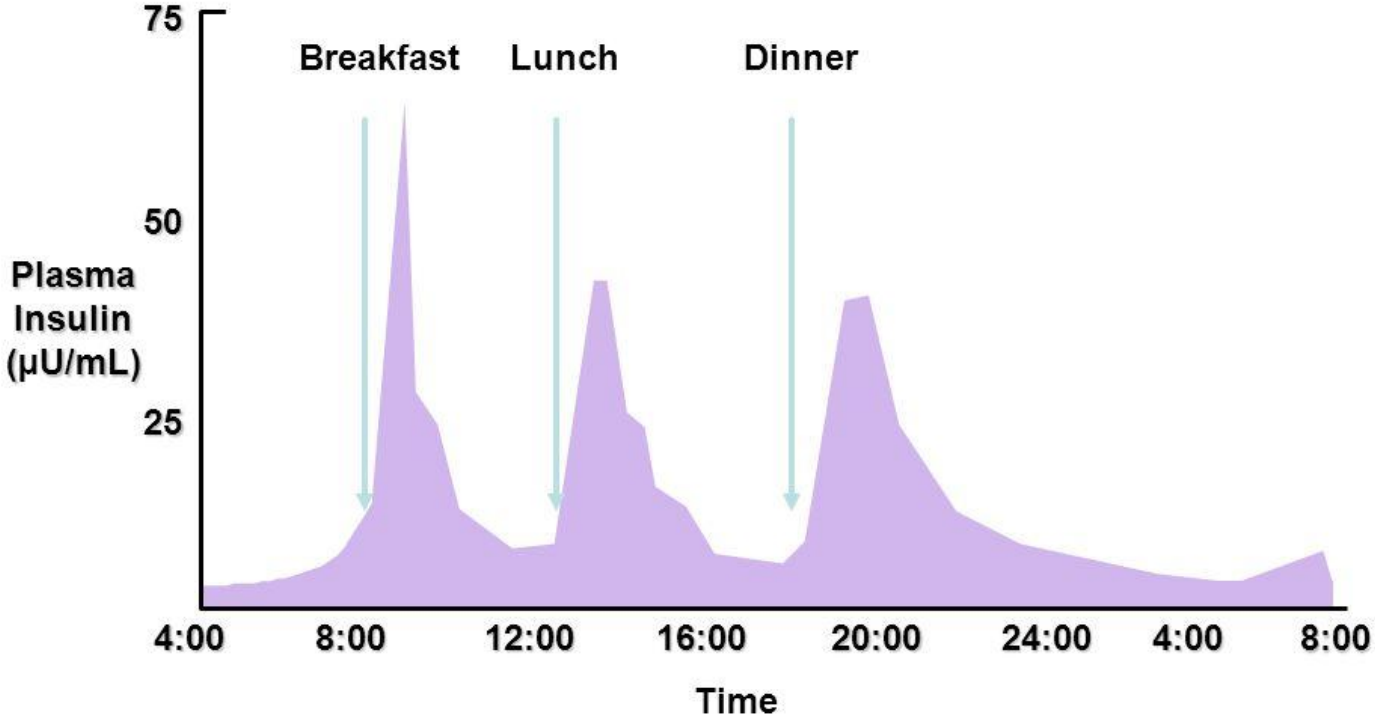
Summer 1921, Banting and Best

Isolation of pancreatic extracts (Isletin) from dog pancreas,
Administration of Isletin to diabetic dogs

OUTLINES

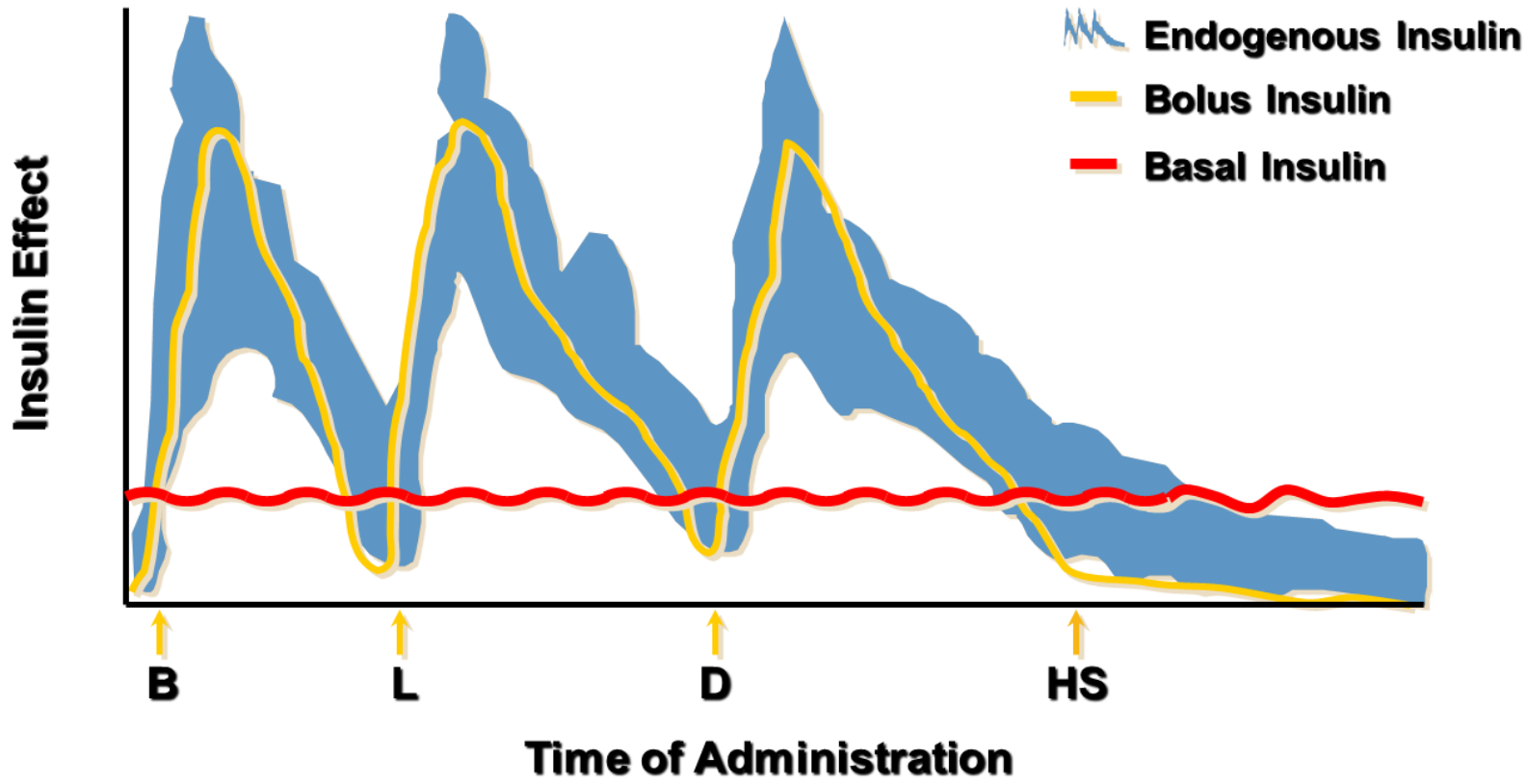
- Action-profile
- Types of basal insulin
- How to begin &Titrate basal
- Glargin & Biosimilar

Physiologic Blood Insulin Secretion Profile



Adapted from White JR, Campbell RK, Hirsch I. Postgraduate Medicine. June 2003;113(6):30-36.

Normal Insulin Secretion: The Basal-Bolus Insulin Concept



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

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

The Basal/Bolus Insulin Concept
MIMICKING NATURE WITH INSULIN THERAPY

Basal Insulin

- Suppresses glucose production between meals and overnight
- Nearly constant levels
- 50% of daily needs

Bolus Insulin (Mealtime or Prandial)

- Limits hyperglycemia after meals
- Immediate rise and sharp peak at 1 hour
- 10% to 20% of total daily insulin requirement at each meal

BASAL INSULIN

- Intermediate acting

  NPH
- Long acting

  Glargine

  Detemir

  Glargine biosimilar (Basaglar-Basalin)
- Ultra-long-acting insulins

  Degludec U100,U200

  Glargine U300

Diabetes Care. 2018 Jan;41(Suppl 1):S152-S153

Insulins	Compounds	Dosage form/product
Intermediate-acting analogs	Human NPH	U-100 vial U-100 prefilled pen
Basal analogs	Glargine Biosimilar Detemir Degludec	U-100 vial; U-100 prefilled pen;U-300 prefilled pen; U-100 prefilled pen U-100 vial; U-100 prefilled pen U-100 prefilled pen; U-200 prefilled pen

U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used

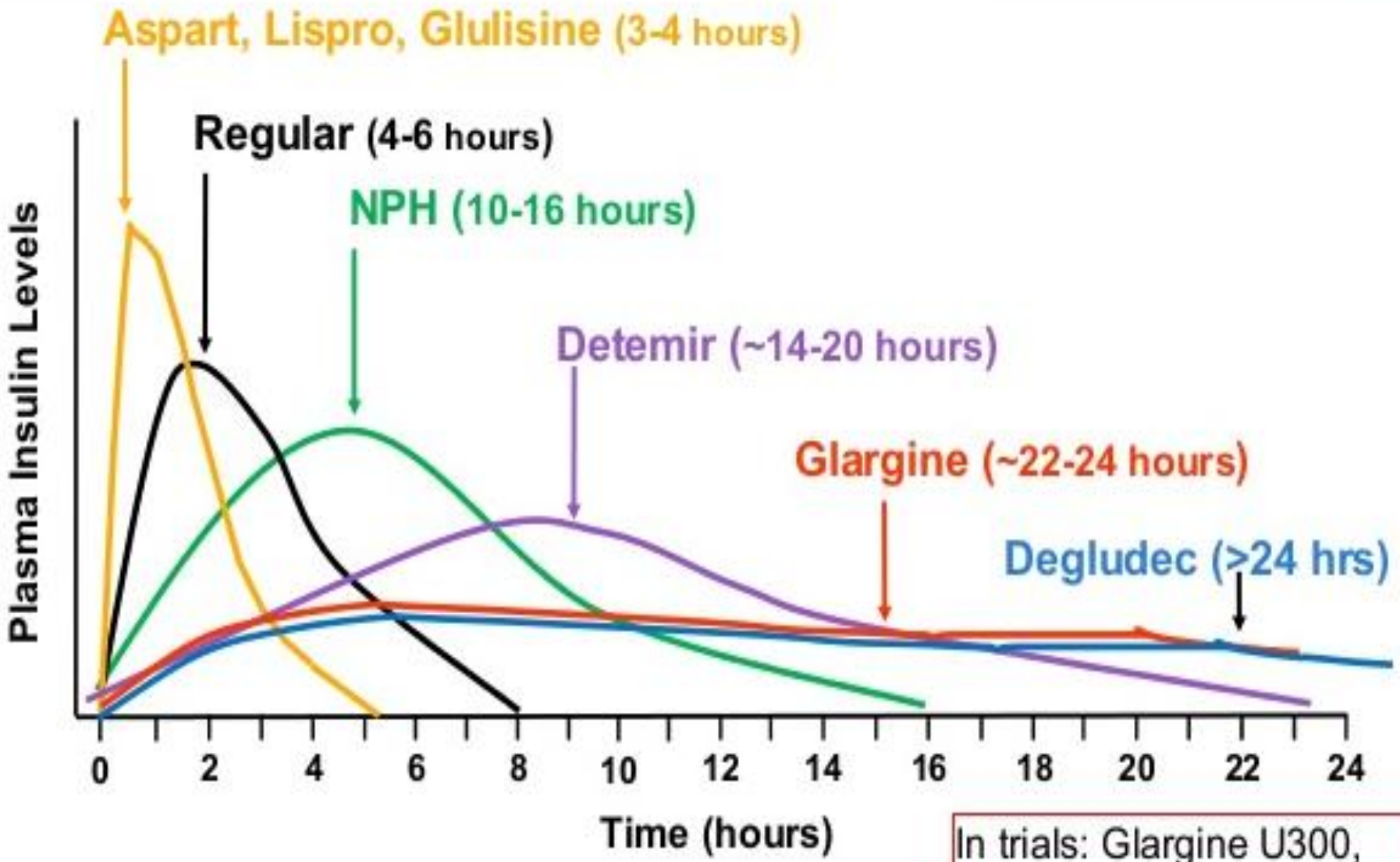
Diabetes Care. 2018 Jan;41(Suppl 1):S73-S85

Basal / Long Acting Insulins

Insulin	Onset	Peak	Duration
glargine U100 (Lantus)	1-2 hr	None	≤ 24 hr
biosimilar glargine U100	1-2 hr	None	≤ 24 hr
detemir (Levemir)	1.8 hr	None	≤ 24 hr
glargine U300 (Toujeo)	1-2 hr	None	24 - 36 hr
degludec U100 / U200 (Tresiba)	1 hr	None	36 - 42 hr
Humulin R - U 500	1-2 hr	6-8 hr	10 - 20 hr
glargine, lixisenatide (GLP1) combo	Soliqua 100/33		

The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.

Insulins Available



In trials: Glargine U300,

Comparison of Human Insulins and Analogues

Insulin Preparations	Onset of Action	Peak (h)	Duration of Action (h)
Lispro/Aspart/Glulisine	10 - 15 min	1 - 2	3 - 6
Regular human	30 - 60 min	2 - 4	6 - 8
Human NPH	1 - 2 h	4 - 8	12 - 16
Detemir	2 - 4 h	flat/ 6-8 *	14-20 *
Insulin Glargine	2 - 4 h	flat	UP TO 24

Time course of action of any insulin can vary in different people or at different times in the same person; thus, time periods indicated here should be considered general guidelines only.

* Dose dependent

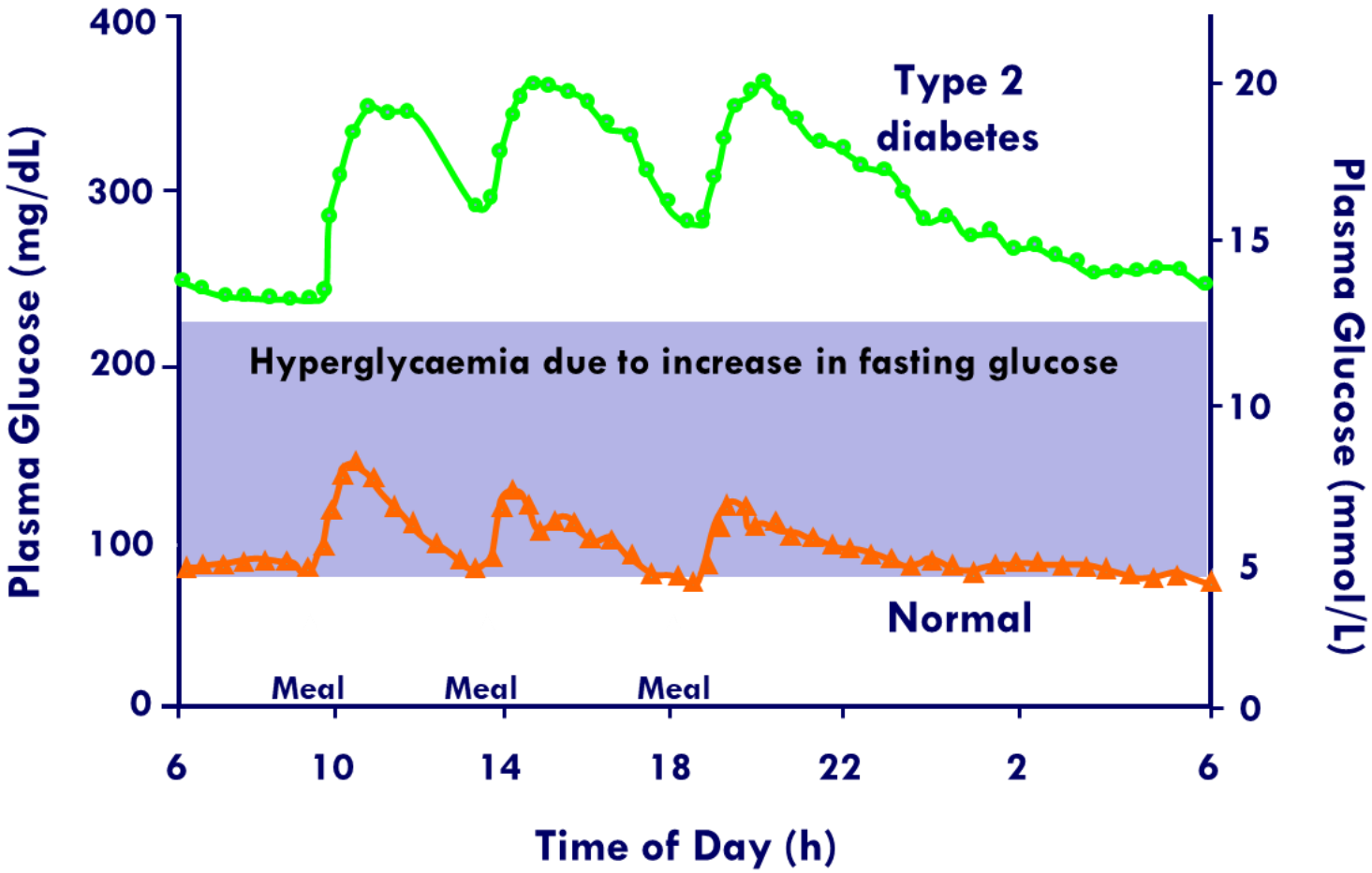
1. Mudaliar S et al. *Endocrinol Metab Clin North Am.* 2001;30:935-982.; 2. Endotext.com

FPG OR PPG?

- FPG and PPG have different contribution to HbA1c
- With mild HbA1c elevations (7.3-8.4%), the proportion of HbA1c elevation attributable to postprandial hyperglycaemia increases to as much as 70% of the glycaemic load
- To reach recommended HbA1c targets <6.5% it is important that postprandial hyperglycaemia is specifically addressed.

Monnier L, et al Diabetes Care 2003; 26: 881–885.

Treating fasting hyperglycemia lowers the entire 24-hour plasma glucose profile



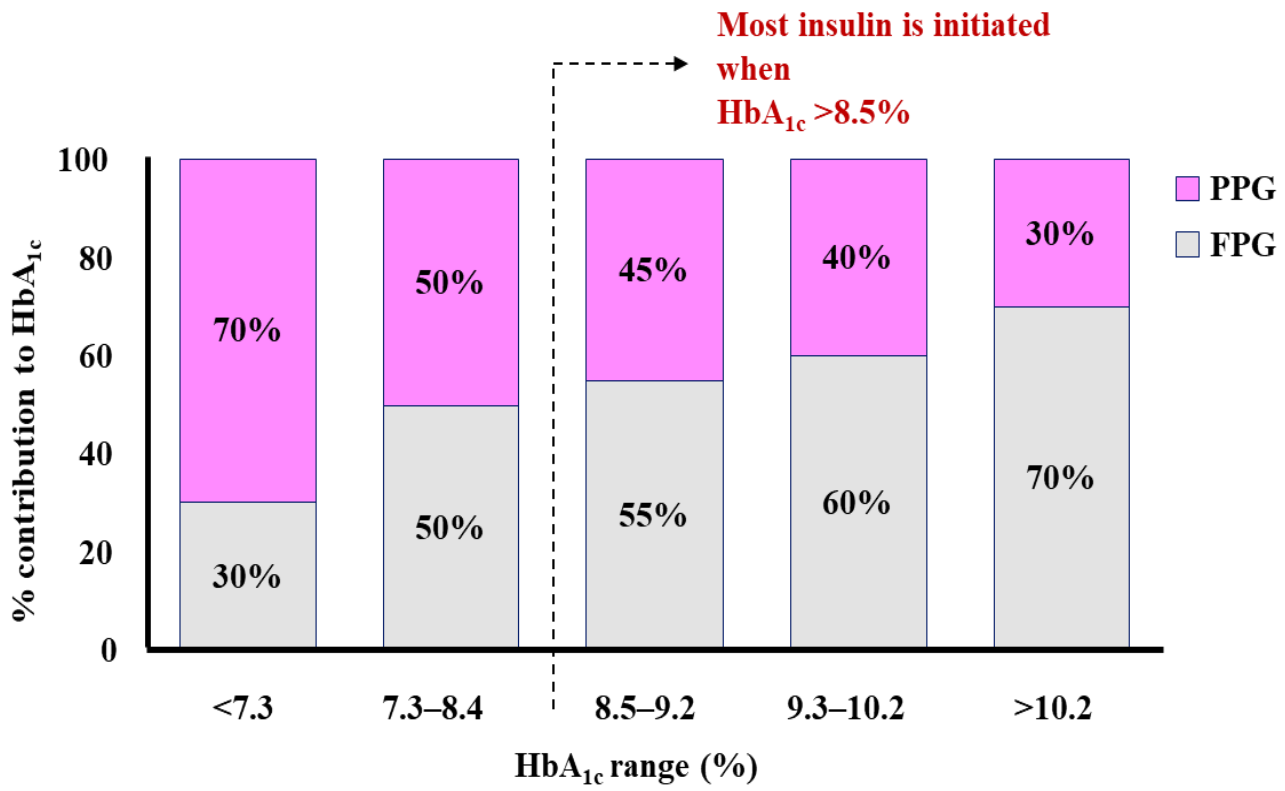
Comparison of 24-hour glucose levels in control subjects vs patients with diabetes ($p<0.001$).
Adapted from Hirsch I, et al. Clin Diabetes 2005;23:78–86.

✓In T2DM contribution of fasting hyperglycemia to overall glycaemia increases with worsening diabetes

290 patients with T2DM treated with diet or OHAs without insulin

based on 1-day, four-point daytime glucose profiles

Baseline (normal) plasma glucose defined as <110 mg/dl



Adapted from Monnier L *et al. Diabetes Care* 2003; 26:881–5

The Ideal Basal Insulin

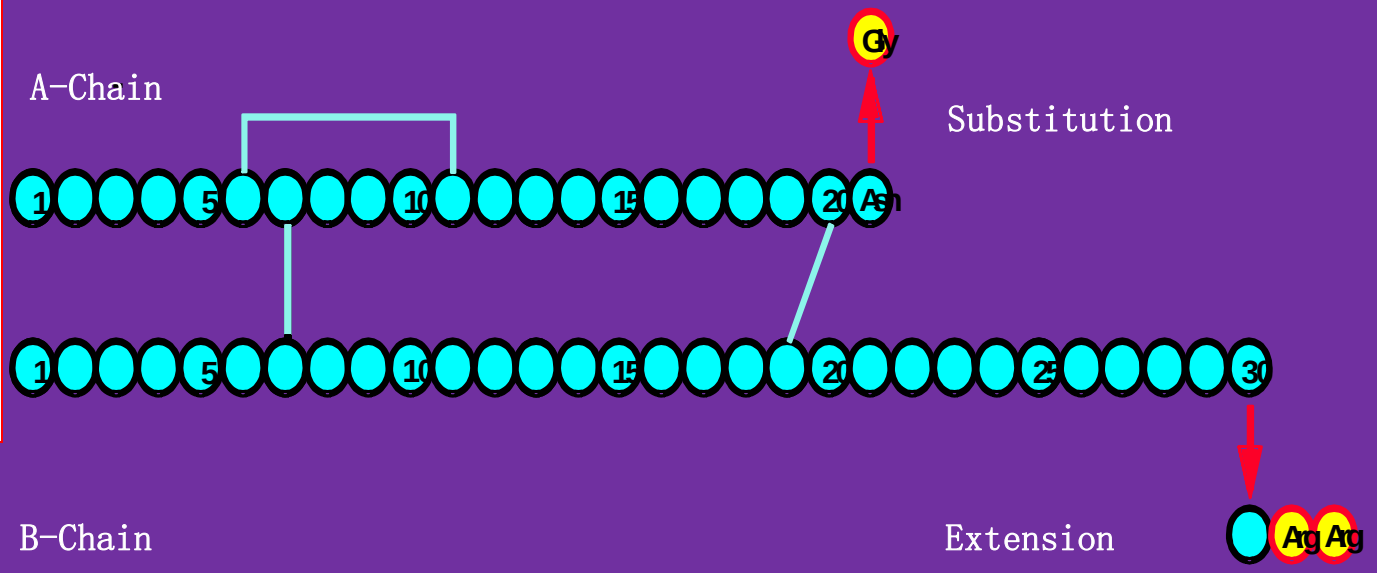
- 1 injection daily covers 24 hours (compliance)
- No peaks
- Low incidence of hypoglycemia (nocturnal hypo)
- Good glycemic control
- Less weight gain
- Safe
- Predictable absorption pattern
- Easy handling
  - Injection at different sites
  - Injection at different times
  - No mixing necessary/clear solution
- High treatment satisfaction and acceptance

Characteristics of Insulin Glargine

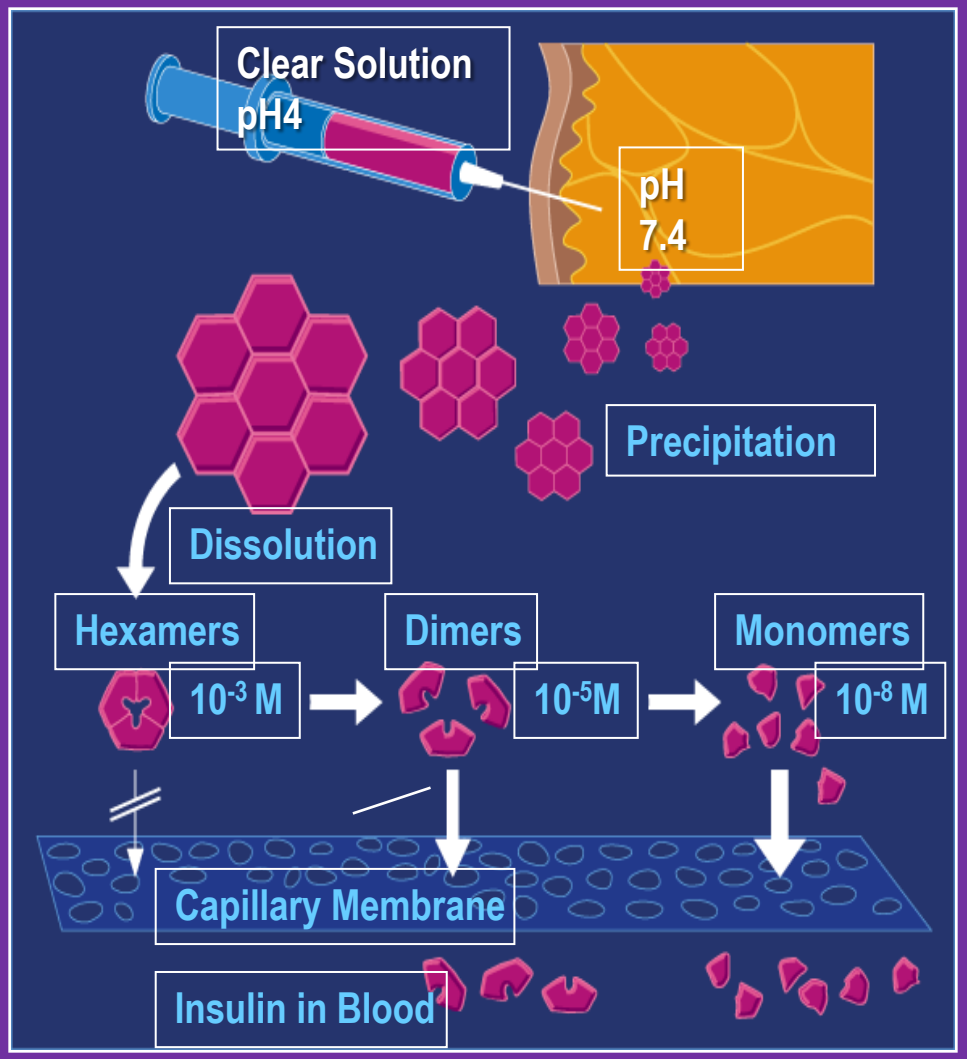
- Recombinant human insulin analogue[1]
- Basal (long-acting) insulin[1]
- Relatively constant peakless concentration over 24 hours[1,2]
- Once-daily SC administration[1]
- For adult and pediatric (aged ≥6 years) patients with type 1 diabetes and adults with type 2 diabetes[1,2]
- Lower risk of hypoglycemia than with traditional basal insulins[1]
- Flexible dosing[1]

INSULIN GLARGINE

- A-chain has an Asparagine to Glycine substituiation at position A21
- Two positively charged Arginine are added at the C terminus of the B chain



GLARGINE: Mechanism of Action

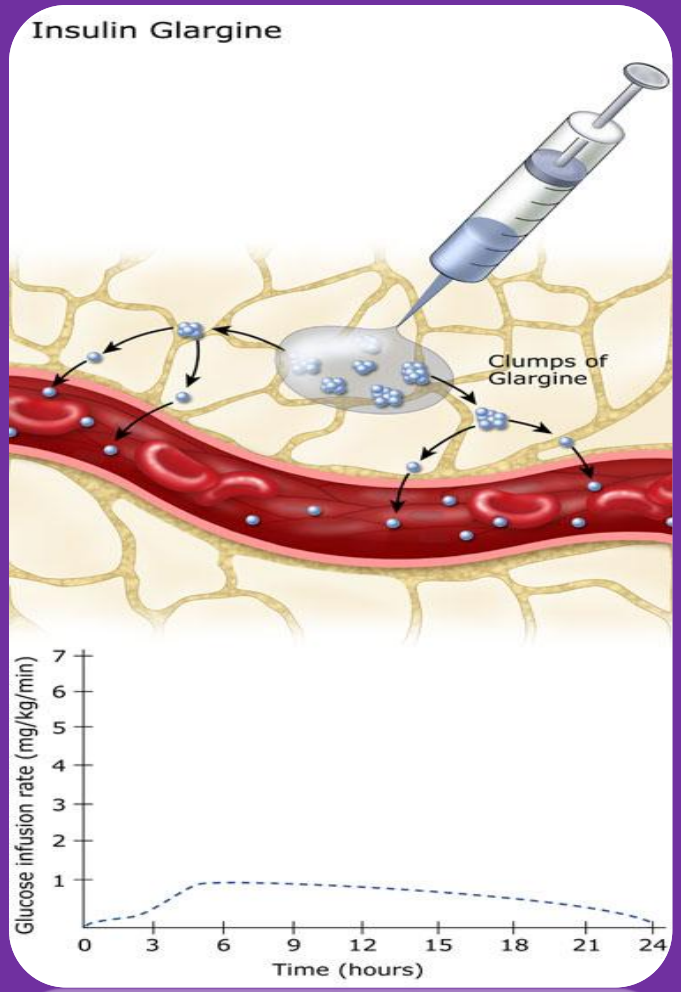


- Injection of an acidic solution (pH 4.0)
- Precipitation of insulin glargine in subcutaneous tissue (pH 7.4)
- Slow dissolution of free insulin glargine hexamers from micro precipitates (stabilized aggregates)
- Protracted action

GLARGINE: PHARMACOKINETICS

Slow dissolution of the Glargine hexamers at the injection site results in a relatively constant release with no pronounced peak over a period of up to 24 hours.

Onset of action= 2 hours
Peak= flat
Duration= 24 hours



Administration of Insulin Glargine Injection

- SC once a day
- Not intended for intravenous administration
- Must not be diluted or mixed with any other insulin or solution
- Available in 10-mL vials and 3-mL Pens and cartridges for injection (100 IU/ml)

Initial Dosing Guidelines for Insulin Glargine

Type 2 Patient	Appropriate Glargine Dosage
Insulin-naïve	Initiate at 10 IU once daily , titrate appropriately
Switched from NPH once daily	Initiate at same dosage; titrate appropriately
Switched from NPH twice daily	Reduced total daily dose by 20%-30% compared to NPH; titrate appropriately

Titration of Glargine to a final dose range of 2 to 100 IU is suggested

Titrate basal insulin as long as FPG > target

INITIATE

- Bedtime or morning long-acting insulin
  Daily dose: 10 units or 0.2 units/kg

Check FPG daily

TITRATE

- Increase dose by 2 units every 3 days until FPG is (70–130 mg/dL)
- If FPG is >180 mg/dL), increase dose by 4 units every 3 days

In the event of hypoglycemia or FPG level < 70 mg/dL

- Reduce bedtime insulin dose by ≥4 units, or by 10% if >60 units

MONITOR

Continue regimen and check HbA_{1c} every 3 months

Biosimilar Glargin Insulin Studies

- Non-clinical Studies
- Clinical Studies
- Running Studies

Non-clinical Studies

Safety Pharmacology

- Effects on Central Nervous System, Cardiovascular System, Respiratory System
- Hypersensitivity and Skin Irritation Test

Evaluation of Toxicity and Toxicokinetic Characteristics

- Organ Toxicity, Immunogenicity, Kinetics data

Primary Pharmacodynamics

- Effects on Blood Glucose

Clinical Studies

A comparison of clinical efficacy and economic value in Basalin and Lantus-treated patients with type 2 diabetes using continuous glucose monitoring system (Phase III)

Studies of pharmacokinetic, pharmacodynamics properties and bioequivalence of Basalin in healthy man (Phase I)

A Glucose Clamp Trial Investigating the Biosimilarity of Basalin with US and EU Lantus Comparator Products in Patients with Type 1 Diabetes Mellitus (Phase I)

Efficacy, safety and immunogenicity of Basalin vs Lantus in patients with diabetes mellitus (Phase III)

Running Studies

An Open-label, randomized, multicenter, phase 3 study to compare the Immunogenicity, Efficacy, and Safety of Basalin to Lantus in adult patients with T2DM **(US)**

An Open-label, randomized, multicenter, phase 3 study to compare the Immunogenicity, Efficacy, and Safety of Basalin to Lantus in adult patients with T1DM **(EU)**

Effects of Replacing Lantus With Basalin on the Glycemic Variation in Patients With T2DM **(China)**

Studies of pharmacokinetic, pharmacodynamic properties and bioequivalence of recombinant insulin glargine injection in healthy man

CHENG Shi-wu,LU Jun-ming,PANG Chang-yum (Department of Endocrinology, Chinese PLA General Hospital, Beijing 100853, China.)

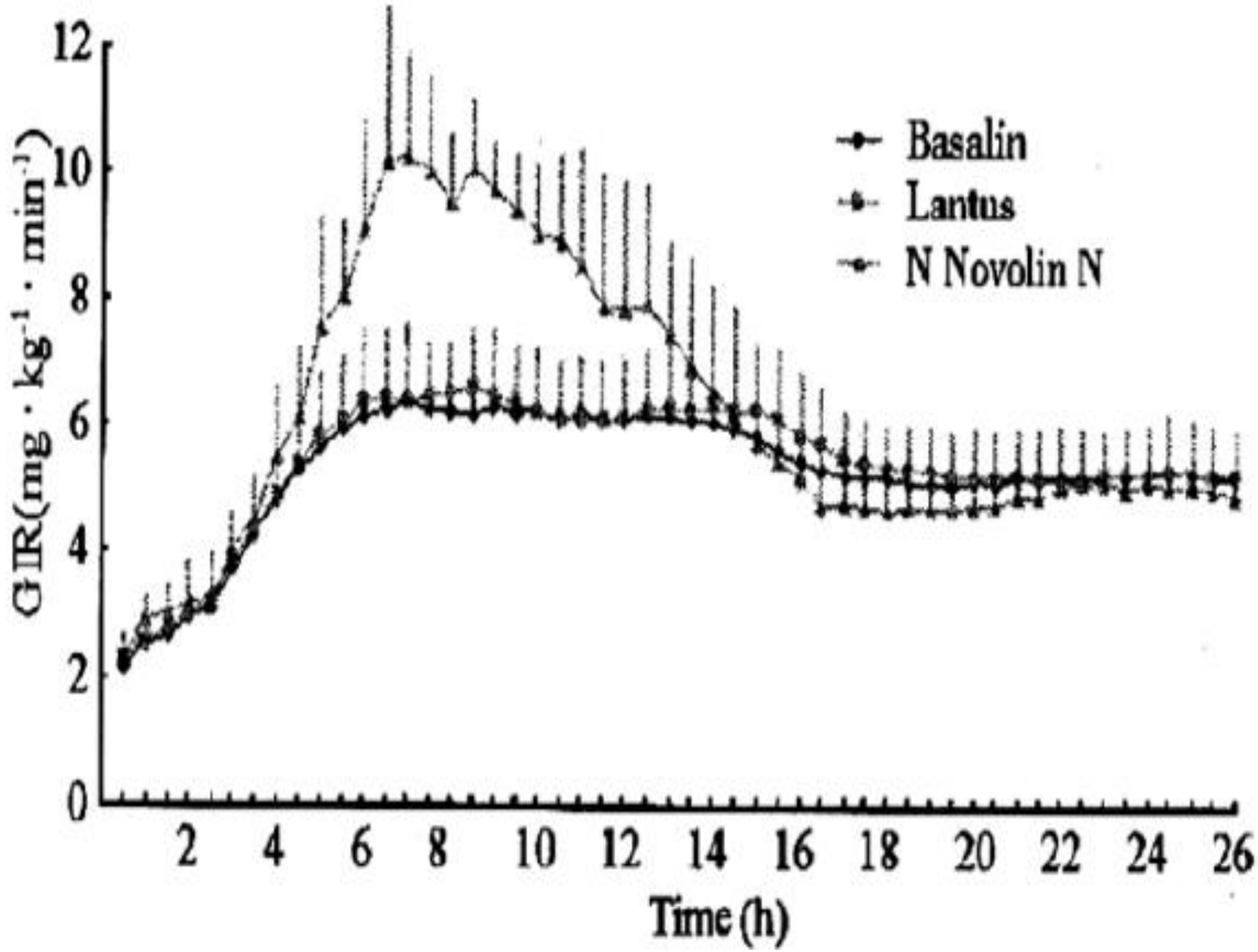
Abstract

Objective: To study the pharmacokinetic and pharmacodynamic properties of the subcutaneously injected long-acting insulin analog-recombinant insulin glargine injections in comparison with those of reference preparation-NPH insulin injection (Novolin® N) in healthy volunteers, and to evaluate the bioequivalence of domestic (Basalin®) and imported (Lantus®) recombinant insulin glargine injection

Phase 1, Single center, randomized, single-blind, three-period, crossover design, China	16 healthy male volunteers received single subcutaneous injection of 0.4 IU/kg body weight of Basalin administration.

Table-1: Comparison of pharmacokinetic and pharmacodynamic parameters among subcutaneous injection of Basalin, Lantus and Novolin N ($\bar{x}\pm S$).

Item	Basalin (G1) (n = 16)	Lantus (G2) (n = 16)	Novolin N (N) (n = 6)	P value G1 vs G2	G1 vs N	G2 vs N
Pharmacodynamic parameter						
GIR						
Basal GIR (mg·kg-1·min-1)	2.96±0.88	3.03±0.55	3.21±0.45	>0.05	>0.05	>0.05
GIRmax (mg·kg-1·min-1)	6.99±1.07	7.30±1.06	11.80±0.98	>0.05	<0.01	<0.01
Tmax(h)	7.38±3.29	7.25±2.78	4.58±1.16	>0.05	<0.05	<0.05
AUC0~4h(g/kg)	1.03±0.20	1.05±0.15	1.25±0.20	>0.05	<0.05	<0.05
AUC0~8h(g/kg)	2.53±0.44	2.60±0.33	3.61±0.34	>0.05	<0.01	<0.01
AUC0~16h(g/kg)	5.33±0.74	5.50±0.66	6.78±0.63	>0.05	<0.01	<0.01
AUC0~24h(g/kg)	7.82±1.05	8.01±0.86	9.15±0.99	>0.05	<0.05	<0.05
Hharmacokinetic parameter						
Ins conc.						
Basal (mU/L)	14.83±5.60	15.34±6.80	12.90±5.37	>0.05	>0.05	>0.05
Cmax (mU/L)	39.87±8.79	43.50±10.68	54.79±8.59	>0.05	<0.05	<0.05
Tmax(h)	12.19±5.78	12.56±5.53	5.67±1.63	>0.05	<0.05	<0.05
AUC0~24h [(mU/L)·h]	4.88±1.00	5.28±1.16	3.97±0.75	>0.05	<0.05	<0.05
C-peptide conc.						
Basal (ng/ml)	1.83±0.68	1.75±0.32	1.67±0.31	>0.05	>0.05	>0.05
Cmin(ng/ml)	0.72±0.22	0.58±0.12	0.61±0.11	>0.05	>0.05	>0.05
Tmin(h)	19.63±4.03	18.38±4.93	14.67±5.77	>0.05	>0.05	>0.05
AUC0~24h [(ng/ml)·h]	32.89±11.22	29.49±5.14	34.08±7.19	>0.05	>0.05	>0.05



GIR Curve after subcutaneous injection of Basalin®, Lantus® or Novolin® N.

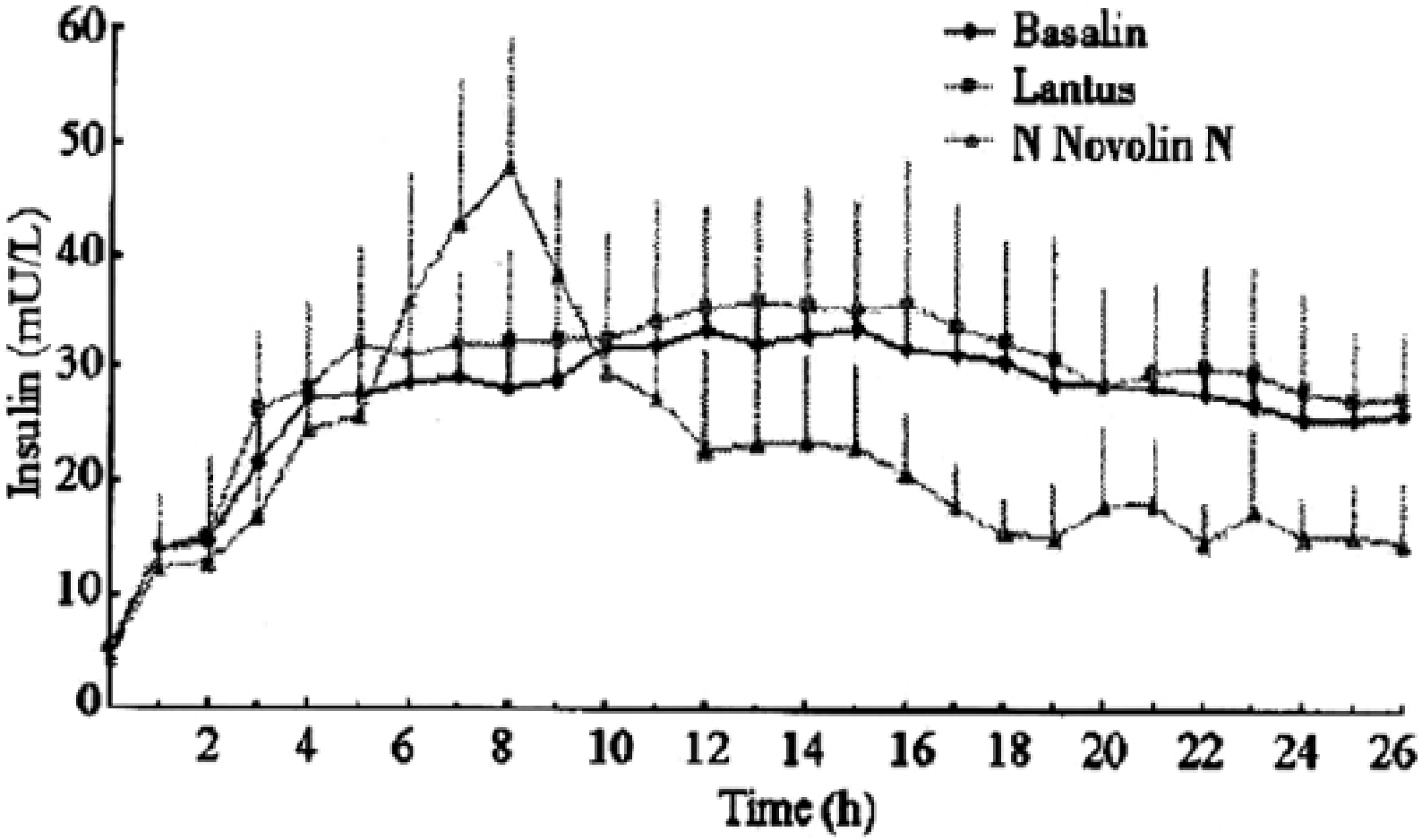


Figure-2: Plasma insulin curve after subcutaneous injection of Basalin®, Lantus® or Novolin® N.

Plasma insulin concentrations (P >0.05) showed a constant metabolic activity over 24-hour study period.

There were no significant differences in INS-AUC0~24h, Cmax and Tmax between Basalin and Lantus (P >0.05).

There were no significant differences in FBG, basal glucose and blood glucose among 3 groups in the trial period (P > 0.05).

1 TITLE PAGE

A Glucose Clamp Trial Investigating the Biosimilarity of Gan & Lee Insulin Glargine Injection (Insulin Glargine 100 U/mL) with US and EU Lantus® Comparator Products in Patients with Type 1 Diabetes Mellitus

A randomized, double-blind, multicenter, single-dose, 3-way crossover, 3-treatment, euglycemic glucose clamp trial in male subjects with type 1 diabetes mellitus

Trial Phase: I

Sponsor: Gan & Lee Pharmaceuticals USA Corporation
520 US Highway 22 East - Suite 302
Bridgewater NJ 08807 USA

A Glucose Clamp Trial Investigating the Biosimilarity of Basalin with US and EU Lantus in Patients with Type 1 Diabetes Mellitus

Phase 1, A randomized, double-blind, multicenter, single-dose, 3-way crossover, 3-treatment, Euglycemic glucose clamp trial (Germany)	114 male subjects with type 1 diabetes mellitus

Primary Pharmacokinetic Endpoints

- AUC ins.0-24h
- C ins.max

Primary Pharmacodynamic Endpoints

- AUC GIR.0-24h
- GIR max

Secondary Pharmacokinetic Endpoints

- AUC ins.0-12h
- Tmax ins

Secondary Pharmacodynamic Endpoints

- AUC GIR.0-12h
- AUC GIR.0-last
- Tmax GIR

Safety Endpoints

- AEs
- Local tolerability
- Laboratory safety parameters
- Physical examination
- Vital signs
- ECGs
- Blood glucose
- Anti-insulin antibodies

Conclusion

- The primary objectives of the trial were met, Basalin demonstrated both pharmacokinetic and pharmacodynamic similarities to Lantus US RLD and to Lantus EU RP, and there were no clinically meaningful differences between the AE profiles of Basalin, Lantus US RLD and Lantus EU RP.

Clinical study of the efficacy, safety and immunogenicity of Basalin and Lantus in patients with diabetes mellitus

Open-label, comparative, randomized, multicenter, Russia	59 patients in each group, evaluate for 12 months

Primary Efficacy Endpoint

- Change of HbA1c level 6 months after the start of treatment compared to baseline
- Number of patients with HbA1c level < 7.0% after 6 months of treatment
- HbA1c level pattern
- Fasting glucose level pattern

Secondary Endpoints

- Incidence and severity of hypoglycemia
- Body weight and BMI patterns
- Lipid profile pattern
- Treatment satisfaction assessment (DTSQS and DTSQC questionnaires)

Safety assessment Safety Endpoints

- Assessment of changes of laboratory findings
- Incidence of ketoacidosis
- Incidence of other adverse events

Immunogenicity Endpoints

- Incidence of immune response (formation of antibodies against insulin) in the groups of the study drug and comparison drug.
- Comparison of the mean antibody titer in the studied groups.
- Analysis of the dynamic changes of the antibody titer after the end of treatment and during the treatment compared to the screening data.

Conclusion

- Non-inferior efficacy and safety of Basalin compared to Lantus.

J Endocrinol Invest
DOI 10.1007/s40618-017-0712-0

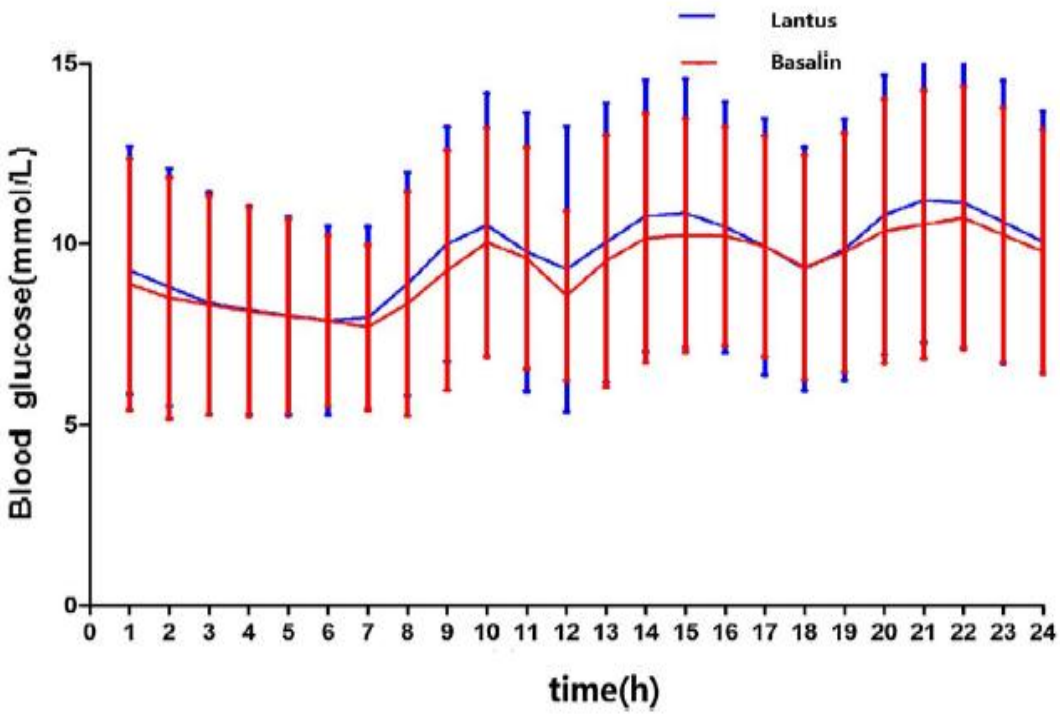
ORIGINAL ARTICLE

A comparison of clinical efficacy and economic value in Basalin- and Lantus-treated patients with type 2 diabetes using continuous glucose monitoring system

H. Q. Li[1] · C. F. Lu[1] · J. Wang[1] · G. P. Yin[1] · R. Sun[1] · X. H. Xu[1] · B. L. Liu[1] · F. F. Li[1] · T. Jing[1] · K. O. Lee[2] · L. Ye[3] · J. H. Ma[1] · X. F. Su[1]

Double blind, randomized, Single center, China	To determine the clinical non-inferiority in treatment of type 2 diabetes mellitus (50 patients in each group)

Fig. 1 24-h CGMS glucose profile of patients having Lantus or Basalin



Glargine	24hMBG (mmol/L)	24hSDBG (mmol/L)	24hMAGE (mmol/L)	24hNGE (number)
Basalin	9.35 ± 2.39	2.17 ± 0.88	5.22 ± 2.71	1.99 ± 1.716
Lantus	9.67 ± 2.75	2.24 ± 0.96	5.50 ± 2.69	2.06 ± 2.119
p	0.378	0.563	0.474	0.797

Glargine	1 h before breakfast MBG (mmol/L)	1 h before lunch MBG (mmol/L)	1 h before dinner MBG (mmol/L)	10 P.M. to 6 A.M. MBG (mmol/L)
Basalin	7.55 ± 2.10	8.95 ± 3.19	9.01 ± 2.81	8.75 ± 2.48
Lantus	7.73 ± 2.38	9.26 ± 4.01	9.33 ± 3.45	8.79 ± 2.77
p	0.562	0.559	0.489	0.905

Parameters of glucose variation calculated from CGMS 24-hour standard deviation of blood glucose(SDBG), 24-hour mean amplitude of glycemic excursion(MAGE) and number of glycemic excursion every 24 h(NGE) were calculated

Glargine	0–6 h (mmol/L)	6–12 h (mmol/L)	12–18 h (mmol/L)	18–24 h (mmol/L)
Basalin	8.27 ± 2.82	9.01 ± 2.49	9.92 ± 2.80	10.30 ± 3.09
Lantus	8.40 ± 2.85	9.42 ± 2.86	10.22 ± 3.26	10.62 ± 3.48
p	0.749	0.292	0.482	0.496

h hour

MBG of every 6-h interval

	Glargine	AUC			Percentage of time	
	BG < 3.9 mmol/L	3.9 ≤ BG ≤ 10 mmol/L	BG > 10 mmol/L	BG < 3.9 mmol/L	3.9 ≤ BG ≤ 10 mmol/L	BG > 10 mmol/L
Basalin	0.00 ± 0.01	4.50 ± 1.26	1.05 ± 1.48	0.01 ± 0.02	0.64 ± 0.28	0.35 ± 0.28
Lantus	0.01 ± 0.03	4.47 ± 1.28	1.29 ± 1.78	0.01 ± 0.03	0.61 ± 0.30	0.38 ± 0.31
p	0.154	0.902	0.318	0.9	0.461	0.478

Glucose area under the curve (AUC) and time below 3.9 mmol/L, between 3.9 and 10.0 mmol/L, and above10 mmol/L

24-hour mean blood glucose, 24-hour standard deviation of blood glucose, 24-hour mean amplitude of glycemic excursion and number of glycemic excursion every 24 h were calculated.

No significant difference of 24hMBG, 24hSDBG, 24hMAGE, and 24hNGE ($p > 0.05$ for all) was found between Basalin and Lantus treatments.

The glucose area under the curve and time when blood glucose was below 3.9 mmol/L, between 3.9 and 10.0 mmol/L, or above 10.0 mmol/L were similar between Basalin and Lantus treatment.

The frequency of hypoglycemic episodes was also similar. However, the mean cost of Basalin was only 72% of Lantus's in one treatment course.

Basalin is non-inferior in clinical efficacy compared to Lantus.

Thanks for your patience