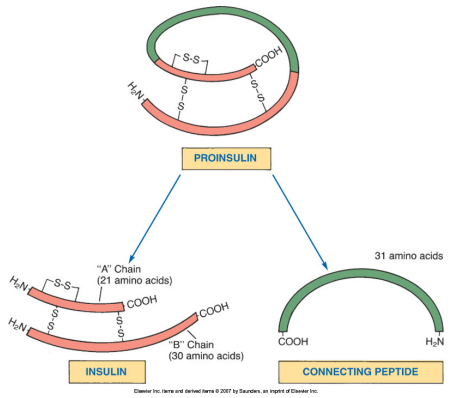
Diabetes Mellitus

Normal Insulin Synthesis

- Prosinsulin is produced in the beta cells
- Before secretion, prosinsulin cleaved into
  - Insulin
  - Connecting peptide (aka C-peptide)
- Effects—Stimulates:
  - Uptake of glucose, amino acids, nucleotides, potassium
  - Synthesis of complex molecules: glycogen, proteins, triglycerides



Insulin Use

- Type I Diabetes
- Type II Diabetes with pancreatic failure
- Diabetic Ketoacidosis
- Hyperkalemia
- Sources:
  - Bovine: no longer produced in U.S.
  - Porcine: may be allergenic
  - Recombinant (Human): most common in U.S.

Types of Insulin

- Natural (Regular)
- Faster than normal
  - Lispro (Humalog)
  - Insulin Aspart (Novolog)
- Slower than normal
  - NPH
  - Semi-lente, Lente, Ultralente
  - Insulin Glargine (Lantus)
- Mixtures

Types of Insulin

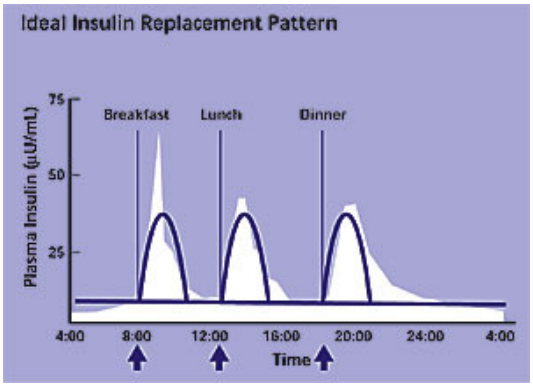
- Primary difference between types of insulins is water solubility
  - The less soluble, the longer it takes to absorb
  - The longer it takes to absorb,
    - More prolonged the effect
    - Slower onset
  - Allergenic Potential
    - NPH: protamine is a foreign substance
- All are given SQ only except
  - Regular insulin may be given IV
  - Intranasal inhalation is being researched

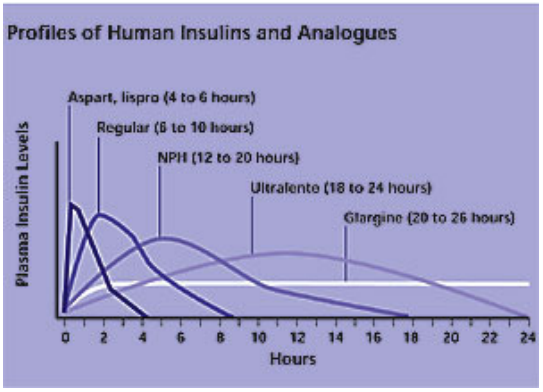
Pharmacokinetics

Drug	Onset (min)	Peak (hrs)	Duration
Regular	30 – 60	1 – 5	6 – 10
Lispro	15 – 30	0.5 – 2.5	3 – 5
Aspart	10 – 20	1 – 3	3 – 5
Lente	60 – 180	6 – 14	16–24
NPH	60 – 180	6 – 14	16–24
Ultralente	240 – 360	8 – 20	24–28
Glargine	70	none	24

Pharmacokinetic Considerations

- How fast does it work?
  - When should the patient eat?
- How long does it last?
  - When should it be given again?
  - When should glucose be checked?
- How do I mix it?
  - Forget clear to cloudy!!!
  - It's a good way to kill a body!!!
  - Glargine is clear, but can **NOT** be mixed!!!





Other Considerations

- Concentration
  - U-100 (100 unit/ml) most common in U.S.
  - U-500 (100 unit/ml) special order for patients requiring > 200 units/day
  - U-40 (40 unit/ml) no longer available in U.S.
- Injection
  - Clear: in solution; do not require agitation
  - Cloudy: suspension; must be gently agitated
- Site Regions: back of arm, legs, abdomen
  - Sites vs. regions

Other Considerations

- Only mix compatible insulins
- Store unopened vials in refrigerator
- Opened vials may be stored unrefrigerated up to 4 weeks
  - Keep away from sunlight or excessive heat
  - DON'T put it in your glove compartment in Florida
  - Prefilled syringes should be stored needle up

Delivery Systems

- Old fashioned syringe and needles
- Pen injectors
- Jet injectors
- Portable Insulin Pumps
  - Administers basal plus meal bolus
  - Change sets every three days
  - Microdeposits of crystalline insulin impair absorption
- Implantable Insulin Pumps
- Intranasal: only 10% of dose is absorbed

Tight Control of Hyperglycemia

- DCCT (DM-1)
  - Intensive Insulin therapy
    - 50% less kidney disease
    - 35 – 56% less neuropathy
    - 76% less ophthalmic complications
  - Drawbacks
    - Risk of hypoglycemia
    - Cost 1700/year vs. 4000/year
- UKPDS (DM-2)
  - Improvements not quite as dramatic
- **Bottom line: tight control = ↓microvascular complications**

Dosing

- Insulin Dosing must be matched to need
- Factors
  - Insulin Resistance
  - Current production of insulin
  - Caloric intake
  - Situation
- Increasers of Insulin Need
  - Infection, stress, obesity, growth spurt, sedentary, 2nd and 3rd trimester pregnancy
- Decreasers of Insulin Need:
  - Exercise, 1st trimester pregnancy

Typical Daily Dosages

- 0.1 U/kg – 2.5 U/kg+
- DM-1
  - Initial 0.5 – 0.6 U/kg
- DM-2
  - Initial 0.2 – 0.6 U/kg

Dosing Schedules

- SSI (Sliding Scale Insulin)
  - Usually used while establishing stable dose
  - Also used in Hospital
- Conventional
  - 2/3 of dose in morning, 2/3 in evening
  - NPH or Lente plus Regular
- Intensive
  - Regular used for meals, Ultralente at bed time
  - Lispro used for meals, Glargine used for basal
- Continuous – insulin pump

Complications

- El numero uno: Hypoglycemia: glucose < 50
- Sympathetic response: rapid fall in glucose
  - Tachycardia, palpitations, sweating, nervousness, irritability
  - Blunted by beta blockers
- CNS origins: develop later
  - Headache, confusion, drowsiness, fatigue
  - Convulsions, coma, death
- Pseudohypoglycemia

Hypoglycemia Treatment

- If conscious: PO
  - Orange juice, glucose tablet, honey, non-diet drink
  - Glucagon
  - D50W
- Awareness, Awareness, Awareness
  - Preparation
  - Monitoring
  - Medic Alert bracelet

Other Adverse Effects

- Lipodystrophies
  - Change in subcutaneous fat deposits d/t SC injection
  - Lipoatrophy or Lipohypertrophy
- Allergic reactions
- Drug Interactions
  - Hypoglycemic agents (incl ETOH)
  - Hyperglycemic agents
  - Beta blockers

Oral Hypoglycemics and Misc DM topics

Oral Hypoglycemics

- Secretagogues – aka Squeeze that pancreas
  - Sulfonylureas
  - Meglitinides
- Liver Modifiers
  - Biguanides
- Insulin sensitizers
  - Thiazolidinediones (TZDs)
- Inhibit carb absorption – aka pass the beano
  - Alpha-Glucosidase Inhibitors

Sulfonylureas

- First Oral Hypoglycemics discovered
- Trying to make a better sulfonamide
  - Share cross-sensitivity
- Two generations
  - 2^{nd} generation more potent (mg for mg comparison)
  - 1^{st} generation takes 100s to 1000's of mg
  - 2^{nd} generation take 2 – 40 mg (smaller pills)
- Hardly ever see 1^{st} generation any more

Therapeutic Use

- Mechanism of Action
  - Stimulates beta cells to secrete insulin
  - Will not work in absence of functioning beta cells
    - Do not work for Type I DM
    - May not work in late Type II DM
- Therapeutic Use
  - ***Adjunct*** to lifestyle modification
- Kinetics
  - Readily Absorbed PO
  - Hepatic metabolism
  - Duration ranging from 6 hours to 3 days

Adverse Events

- Hypoglycemia
  - Usually mild, but can be fatal
  - Caution in patients with liver dysfunction
  - Educate
- Weight gain
- Pregnancy and Lactation no-no
- Limited evidence that patients treated with sulfonylureas until pancreas failure are more likely to have CV events
- Interactions: ETOH, hypoglycemics, beta blockers

Sulfonylureas

- 1st generation
  - Tolbutamide (Orinase) 6 hr duration
  - Acetohexamide (Dymelor) 12 - 24 hr duration
  - Tolazamide (Tolinase) 12 - 24 hr duration
  - Chorpramide (Diabinase) 24 - 72 hr duration
- 2nd Generation
  - Glipizide IR & SR (Glucotrol) 12 - 24 hr duration
  - Glyburide IR &SR (several) 12 - 24 hr duration
  - Glimepiride (Amaryl) 24 hr duration

Meglitinides

- Newer secretagogues
- Similar action to sulfonylureas
- Shorter durations 2 and 4 hours
- Rapid onset: 0 – 30 minutes
  - PATIENT MUST EAT WITHIN HALF HOUR!!!
- Fewer side effects
- Control PPG better than FPG
- Will not work in patients who do not have functioning beta cells
- Repaglinide (Prandin) and Nateglinide (Starlix)

Biguanides: Metformin

- Only one in United States: Metformin (Glucophage, Glucophage XR)
- Mechanism of Action
  - Decreases gluconeogenesis of liver
  - Enhance glucose uptake by muscle cells
- Kinetics
  - Absorbed slowly PO
  - Excreted by kidneys do not use in insufficiency

Therapeutic Uses

- Glycemic control
  - Combination with TZD and/or secretagogue
    - Synergistic glucose lowering
  - May be used effectively in patients who require insulin (lowers needed insulin amount)
  - Does not cause hypoglycemia
- May prevent progression of prediabetes in younger, obese patients
  - Exercise and diet is better
  - May be related to side effects

Adverse Effects

- GI upset: usually subsides over time
  - Decreased appetite
  - Nausea, diarrhea
- Weight loss
- Toxicity: Lactic Acidosis: emergency
  - RI
  - liver disease, severe infection, shock, heart failure
  - Educate symptoms: hyperventilation, myalgia, malaise, unusual somnolence

Preparations

- Immediate release: BID – TID dosing
- Extended release: QHS dosing
- Combination
  - Glyburide: Glucovance
  - Glipizide: Metaglip
  - Rosiglitazone: (Avandamet)

TZDs (-glitazones)

- Mechanism of Action
  - Increase sensitivity to insulin
  - Animal models: ↑muscle glucose uptake and ↓liver glucose production
  - Takes several weeks for effects to develop
- Therapeutic Use
  - Lower glucose
  - Used alone or in combination with sulfonylurea, insulin, metformin
  - Do not cause hypoglycemia
- Kinetics: well absorbed, metab in liver

Adverse Effects

- Fluid retention
  - Edema
  - May push someone over the edge of heart failure
  - Caution in mild HF: monitor daily weights
  - Contraindicated in Severe HF
  - Dose dependent
- Caution with Insulin
- Mixed Lipid effects
- LFT monitoring

TZDs

- Agents
  - Rosiglitazone (Avandia, Avandamet)
  - Pioglitazone (Actose)
- Were considered third line agents
- Beginning to be seen as first line

Alpha-Glucosidase Inhibitors

- Mechanism of Action
  - Inhibits enzyme responsible for breaking oligo-saccharides and complex carbohydrates into monosaccharides
  - Delays absorption of dietary absorption of carbohydrates
- Uses
  - Adjunct to lifestyle modifications and/or insulin, metformin, sulfonylyurea
  - Works very well
  - Does not cause hypoglycemia

Adverse Effects

- GI effects
- Decreases iron absorption
- Complicates hypoglycemic treatment
  - Can't use sucrose based oral products
- Liver dysfunction

- Agents
  - Acarbose (Precose)
  - Miglitol (Glyset)

Ketoacidosis Management

- Insulin replacement: usually IV
- Bicarbonate
- Water replacement
- Monitor Sodium and Potassium
  - Replace as appropriate
- Careful monitoring of glucose levels

Glucagon

- Used to treat hypoglycemia d/t insulin overdose
  - Moderate Hypoglycemia
  - Glucose (D50W) is preferred for severe
  - Oral glucose for mild
  - Will not work for hypoglycemia d/t anorexia
- Administer SC, IM, IV
  - Takes ~20 minutes before arousal