


Practice Tips and Tools in the Use of U-500 Insulin for Patients with High Dose Insulin Requirements

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Disclosures to Participants


Presenter: Elaine Cochran-None

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Off-Label Use:
Insulin pump as a subcutaneous infusion device for U-500 insulin






Outline of Talk—"Tips and Tools"


- High Dose Insulin Requirements-History of Treatment
 - Examples of severe insulin resistance
 - Identifying patients with "other" forms of diabetes
 - Impact of energy intake on insulin sensitivity
 - "High-Dose Insulin Requirements"—Mechanical issues
- Principles of treating to target glycemia
 - DCCT, DPP, UKPDS
- Use of Insulin therapy
 - U-500 insulin
 - Pharmacology and Availability
 - Manufactured by Lilly USA, LLC
 - Pharmacologic profile
 - Cost






Outline ("Tips and Tools", cont.)

- Deciding when to begin U-500 insulin
 - Principles that guide practice
 - Determining patient's U-500 requirements
- Dosing of U-500 Insulin
 - >100-299, 300-599, >600 units/day
 - Dose adjustments
- Specifics with Insulin Pumps
- Practical Issues in Administration
 - Inpatient Setting
 - Outpatient Setting
- Impact of Diet
 - Examples of diet therapy on insulin requirements



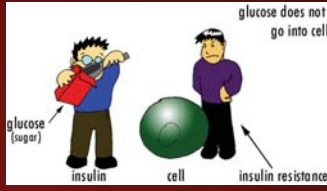
Outline ("Tips and Tools", cont.)

- Teaching Points
 - Encourage decrease caloric intake
 - Examples of Regimen Handouts
 - Teaching patients how to express their regimen to others
- Conclusions
 - Weight loss and decreased caloric intake, and increasing activity are essential to controlling insulin doses
 - U-500 insulin is effective and cost efficient in high dose insulin requiring patient
 - Diabetes educator plays key role in teaching patient to use and administer U-500 insulin




Patients with "High-Dose Insulin Requirements"

- Most notably defined as "severe insulin resistance"
- Patients requiring more than 200 units of insulin/day, for > 2 days
- Pediatric (and in general in terms of weight) patients requiring more than 2-3 units/kg/day





The diagram shows a person on the left holding a red bag labeled 'insulin'. An arrow points from the bag to a green sphere labeled 'cell'. A second person on the right is also holding a red bag labeled 'insulin', but an arrow points from the bag to the text 'insulin resistance' instead of the cell. Above the cell, text reads 'glucose does not go into cell'.



Insulin Requirements


- Influenced by type of diabetes
- Influenced by energy intake
 - Insulin requirements when fasting
 - Insulin requirements after bariatric surgery
- Influenced by device/mechanical issues:
 - Pumps with bolus rate limits of 1 unit per 40 seconds, maximum bolus of 25-30 units, and cartridge that holds 180-300 units
 - Pens with maximum amount of 60 unit or 80 unit bolus
- Cost and insurance







ADA Classification of Diabetes

- Type 1 Diabetes
- Type 2 Diabetes
- Gestational Diabetes
- Other specific types of diabetes




*All can be associated with severe insulin resistance





Review of "Other" Diabetes

- Genetic defects of β cell function
- Genetic defects of Insulin Action
 - Studies at NIH of patients with Type A, Leprechaunism, Lipodystrophy. Typically most commonly associated with use of U-500 insulin
- Type B (also associated with U-500)
- Endocrinopathies (Acromegaly, Cushing's)
- Drug induced (steroids, etc)



Type 2 vs "Other"—Simple Screening


- Laboratory findings
 - Fasting TG's level
 - Severity of insulin resistance (i.e. insulin or c-peptide levels)
- Insulin requirements on weight maintenance/weight loss diet
- Physical symptoms of hyperinsulinemia
- Age of Patient: Young vs "Older"

Typical Insulin Requirements for Various Forms of Diabetes Mellitus

Diabetes Type	Insulin Requirement (U/kg/day)	% of Patients
Type 1 diabetes	0.25 - 1.0	~80%
Type 2 diabetes	1.0 - 2.5	~15%
Other	2.5 - 3.0	~5%


Theoretical Dose Response Curves for Insulin in Diabetes


Insulin Dose (units)	Type 1 DM Response (%)	IR Syndromes Response (%)	Type 2 DM Response (%)
0	0	0	0
50	~80	~60	~10
100	~90	~80	~20
150	~95	~90	~30
200	~98	~95	~35
250	~100	~98	~40
300	~100	~100	~45
350	~100	~100	~48
400	~100	~100	~50



Role of Energy Expenditure and Weight


- Previous graphs show daily insulin requirements as units/kg/day
- Weight has direct effect on insulin dose
- Insulin resistance also impacts dose
- Obesity is related to insulin resistance






Role of Excessive Energy Intake

- Taking in more energy than utilizing
- When you reduce it with modest changes in body weight (5-6%), decreased energy intake effects glucose energy metabolism
 - Evidence in the literature:
 - Acute dietary
 - DPP
 - Bariatric surgery





Excess energy intake... (cont.)


Fluctuations in the Affinity and Concentration of Insulin Receptors on Circulating Monocytes of Obese Patients

EFFECTS OF STARVATION, REFEEDING, AND DIETING

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One of the first articles, describing a study done at our Institute, looking at the acute physiologic effects of decreased energy intake on insulin sensitivity.



Excess energy intake...(cont.)

Findings of the Diabetes Prevention Program:

This is another example, and well known, of how weight loss, even modest (5%), results in improvement in insulin sensitivity.




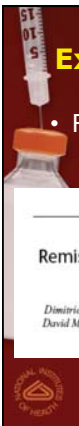
Excess energy intake...(cont.)

- Recent example:

ORIGINAL STUDY




Remission of Type 2 Diabetes After Gastric Bypass and Banding Mechanisms and 2 Year Outcomes

Dimitrios J. Pournaras, MRCSP¹, Alan Osborne, MRCSP², Simon C. Hawkins, MRCSP³, Royce P. Vincent, MSc¹, David Mahon, MD, FRCS⁴, Paul Ewings, PhD⁵, Mohammad A. Ghatei, PhD¹, Stephen R. Bloom, FRCP, DSc¹, Richard Wellbourn, MD, FRCS⁶, and Carel W. Le Roux, MRCP, PhD¹



Example from Pima Indians

- Median dose of insulin for a group of Pima Indians: 70 units/day.
- Average weight: 100 kg.
- Average HgbA1c: 9.4%
- High incidence of microvascular disease






Why?


- Principles behind insulin therapy
- Hyperglycemia over time will lead to microvascular/cardiovascular complications
- Insulin leads to weight gain and obesity, which also has co-morbidities
- Complications of weight gain vs. hyperglycemia






Answer

- Evidenced based medicine--treat diabetes
 - DCCT, EDIC, UKPDS, ADVANCE and other trials
- Evidence shows clear rationale for maintaining glucose levels as close to "target" as possible
- Yes, obesity is unhealthy, but hyperglycemia can lead to microvascular disease, cardiovascular disease.
- Looking back to "model patient populations": microvascular disease is rampant amongst the Pima Indian populations.






Efficacy of U-100 Insulin Delivery in High-Dose Requiring Patients

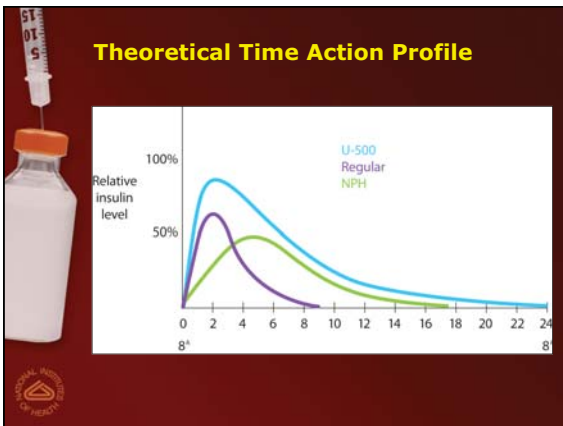
Practically:


- Syringes highest volume is 100 units.
- Pens highest volume is 60-80 units, with the total insulin pen cartridge only holding up to 300 units.
- Pump cartridges hold 180-300 units.
- Pump bolus rates and limits (25-30 units)
- Batteries for pumps need to be changed more frequently (every week as opposed to month)
- Insurance for supplies often at set levels/amounts (often based on Type 1 diabetes model)













Starting U-500

- *Verify* if and how patient is taking current U-100 regimen
 - Is delivery device optimal?
 - Can patient describe regimen well (since they supposedly do it every day)
- *Determine* daily insulin requirements



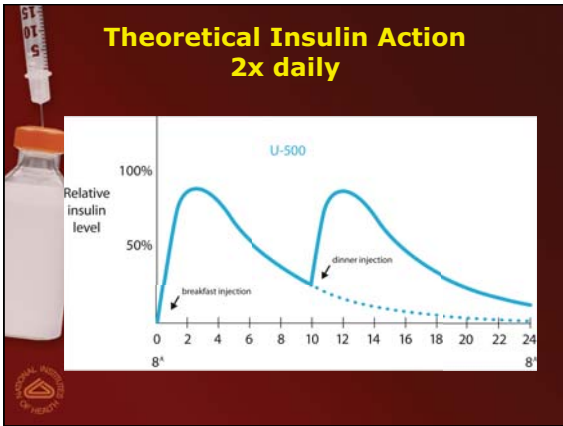
Dosing of U-500

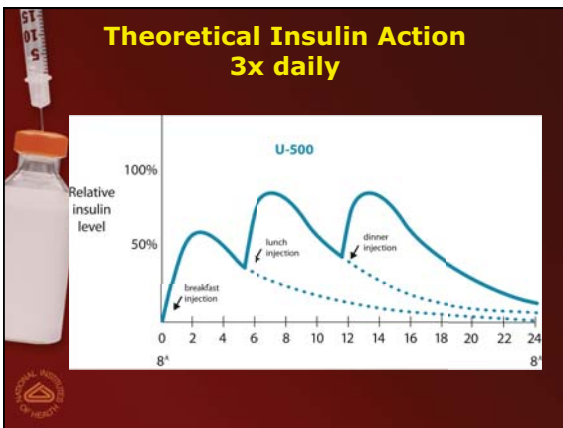
- 1) *Stop* all forms of insulin U-100
- 2) HgbA1c <8%, reduce 10-20%
HgbA1c >10%, increase 10-20%
- 3) U-500 "Basal/Bolus Therapy"
 - A. twice daily
 - B. three times daily
 - C. four times daily, for over 600U/day
- 4) Determine best delivery method



Algorithm for the Administration and Dosing of U-500 Insulin

INSULIN DAILY DOSE	INJECTION FREQUENCY/SCHEDULE/DELIVERY	GUIDE FOR HOW DOSES ARE DIVIDED DAILY VIA PERCENTAGE (%) OF THE TOTAL DAILY DOSE
100-300 units/day	Twice daily (i.e. 8A, 6PM) -- Basal Insulin	60/40
	Three times daily (i.e. 8A, 12noon, 6PM) -- Basal Insulin	40/30/30
	Via insulin pump (unit = 0.01 mLs, 0.01 mLs of U-500 insulin = 5 units)	Three mealtime boluses (30/25/25) In addition a set basal rate of 20% of the total daily dose (minimum basal rate changes per day) Or basal at 50% of total daily dose, and divide up boluses (20/20/10). Nighttime basal may need to be hormonally adjusted.
300-600 units/day	Three times daily	40/30/30
	Four times daily (i.e. 8A, 12noon, 5PM, 10PM)	30/30/30/10
	Via insulin pump (unit = 0.01 mLs, 0.01 mLs of U-500 insulin = 5 units)	Three-four mealtime boluses For basal rate 20% of daily dose, boluses are (30/30/20 or 30/25/20%). For basal at 50% of total daily dose, and divide up boluses (20/20/10 or 20/15/10-5). Bedtime snack bolus should be 10% or less of total daily dose.
> 600 units/day	Four times daily ** do not inject more than 2 mLs in any one injection site	30/30/30/10





Appropriate Prescription Example


- **TB syringe**
 - Insulin Human Regular U-500, inject 150 units, **0.3 mLs subcutaneously**, 3 times daily before meals. Dispense 2 vials.
- **Insulin syringe**
 - Insulin Human Regular U-500, inject 150 units, **30 unit markings subcutaneously**, 3 times daily before meals. Dispense 2 vials.

Dosage Conversion Chart

Volume - Tuberculin Syringe (mLs)	U-100 Syringe (unit markings)	U-500 Insulin Dose (actual units)
0.1	10	50
0.2	20	100
0.3	30	150
0.4	40	200
0.5	50	250
0.6	60	300
0.7	70	350
0.8	80	400
0.9	90	450
1.0	100	500

Insulin Pump Use

- Technically "off-label" use through pump
- Doses 100-600 units/day
- Not recommended for >600U/day
- Not in volume, use "pump units"
 - 1 "pump unit" = 0.01mLs
 - 0.01mLs = 5U of U500
 - 1 "pump unit" = 5 actual units of U-500




Insulin Pump Use (cont.)...

- Patients on U-500 MDI, 50% of TDD ÷ 24, single basal hourly rate. Remaining 50% distributed as pre-meal boluses
- Patients on U-100, 50% of TDD ÷ 5 then ÷ 24 to determine basal.
- Insulin on board: Set at 6 hours
- Important info: 1) fasting basal, 2) endogenous insulin production



Insulin Pump Conversion Example

- Lane et. al. (2009) Endocrine Practice— section “Implementation of U-500 Regular Insulin Therapy”, p. 75
- Brief case example



Practical Administration: Inpatient Setting

- Patients on U-500 Insulin
 - Clinicians understand and think in terms of dose. Patients think in terms of practical administration. VERY IMPORTANT!
 - *Have them demonstrate measuring dose.

Dose Verification Tool




*** THIS IS NOT AN ORDER *** **INSULIN HOME DOSE VERIFICATION:**
DOSE & SYRINGE MUST BE VERIFIED PRIOR TO DISPENSING MEDICATION.

Patient or care provider verbalized and demonstrated measuring to the marks described for each dose below:

Patient uses INSULIN SYRINGE at home - dose is reported as Unit markings measured on an INSULIN syringe	Patient uses a TUBERCULIN SYRINGE at home - dose is reported in volume (mL)
<input type="checkbox"/> Breakfast Dose: 5 X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Breakfast Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Lunch Dose: 5 X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Lunch Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Dinner Dose: 5 X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Dinner Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Bedtime Dose: 5 X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Bedtime Dose: 500 X _____ mL = _____ units U-500 insulin administered.

Inpatient Setting (cont.)

- Policy for prescribing and administering
 - Write the prescription in terms of volume
 - Use TB syringes when inpatient
- Possibly use insulin drip until hospital pharmacy acquires U-500 and/or use of patient's home medication



Inpatient Setting: Syringe Selection




TB Syringe

- Recommended for volume measurement
- 0.5 mLs, 1.0 mLs
- Available in safety needle form

Insulin syringe



- "unit markings"

*Prescription must match syringe



Inpatient Setting:

- Resources such as the American Journal of Health-System Pharmacy
- Standing order insulin vs. Corrective Regimens
- Pharmacy prepare dose vs. Nurses drawing up dose
- IMPACT OF DIET
 - Patient may only require U-100 insulin in the hospital, as they are eating less
 - Examples of diet (energy intake) on insulin doses



Inpatient Setting (cont.)

Volume - Tuberculin Syringe (mLs)	U-100 Syringe (unit markings)	U-500 Insulin Dose (actual units)
0.1	10	50
0.2	20	100
0.3	30	150
0.4	40	200
0.5	50	250
0.6	60	300
0.7	70	350
0.8	80	400
0.9	90	450
1.0	100	500

Outpatient Setting

- Health insurance coverage issues of insulin and supplies
- Specialized teaching:
 - Transcribing dose such that patient understands
 - Reinforcing proper regimen communication



Outpatient Setting (cont.)

Before Breakfast (Between 7A-10A) and Lunch (11A-1P):

Blood sugar	Insulin U-500 to inject	Actual units of insulin
80-124	0.15 mL (15 unit markings)	=75 units
125-249	0.2 mL (20 unit markings)	=100 units
250-299	0.3 mL (30 unit markings)	=150 units
300-349	0.5 mL (50 unit markings)	=250 units
350-449	0.6 mL (60 unit markings)	=300 units
>449	0.8 mL (80 unit markings) and Call MD for >449	=400 units

Before Dinner (Between 5P-8P):

Blood sugar	Insulin U-500 to give	Actual units of insulin
80-124	0.08 mL (8 unit markings)	=40 units
125-199	0.12 mL (12 unit markings)	=60 units
200-299	0.2 mL (20 unit markings)	=100 units
300-349	0.3 mL (30 unit markings)	=150 units
350-449	0.4 mL (40 unit markings)	=200 units
>449	0.5 mL (50 unit markings) and Call MD for >449	=250 units



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 - Karen Samaan, PharmD

...and my courageous patients





Questions?

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