Heparin Formulation: New Standards of Units

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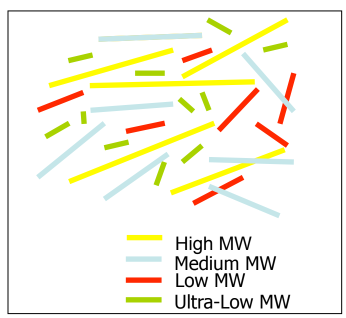
Heparin

- A naturally occurring anticoagulant found in tissues rich in mast cells (beef lung and porcine intestine).
- A heterogeneous mixture of highly charged sugar chains.
- Chains that vary in length from 15 to 50 units.
- Molecular weights vary from 2,000 to 40,000 Da.
- Exhibits multiple biological behaviors and interactions with blood vessels, cells, and proteins.



Heparin

- Clinically used as an anticoagulant for the immediate and acute:
  - Prevention of venous thrombosis
  - Treatment of venous thrombosis
  - Management of acute coronary syndrome
  - Prevention of blood clotting during interventional procedures and surgery
- Needs to be monitored to avoid over-dosing (bleeding) and under-dosing (thrombosis).

Current Events

- With the heparin contamination issue, the heparin monograph of the US Pharmacopeia (USP) was revised to include current state-of-the-art knowledge and assay techniques to enhance the identification of the heparin product and to detect impurities.
- In addition to the above improvements, the assays for biological activity were also ‘upgraded’.

Heparin Potency – Manufacturer's Assay

- **Past:** assayed in pooled citrated sheep plasma to which Ca^{+2} has been added; time to clot endpoint.
- **Present:** assayed in AT supplemented buffer for inhibitory activity against FXa and thrombin (FIIa); enzymatic assay with color endpoint. Determine ratio of AXa:AIIa activity.
- Assay results are compared to a USP heparin reference standard (RS).

Heparin Potency – Reference Standard

- In 1973 the USP established a heparin RS with unitage that differed from the European heparin standard (~10%).
- **In 2009** the current USP heparin RS was in short supply and a new RS needed to be established.
- **In 2009** the USP decided to conform with the unitage of the European heparin standard in the interest of globalization.

The Issue:
Change in Heparin Potency

- FDA notified healthcare professionals that effective **October 1, 2009** the USP has adopted a new potency assay for heparin and a new potency reference standard (RS).
- The new RS will harmonize the USP heparin unit with the International Standard (IS) for heparin issued by the WHO.
- The new USP unit definition for heparin will result in a 10% reduction in the potency for all heparins marketed in the US and Canada.

Evaluation of the New Heparin Potency

- **Objective:**
  To determine if there are significant differences in anticoagulant activity between the current lot of heparin used in the Loyola Health System (LUHS) and the new lot of heparin obtained February 2010.

- **Study Design:**
  – Two lots of heparin representing the old and new potency were evaluated.
  – Freshly collected human plasmas were supplemented *in vitro* with various concentrations of heparin, then evaluated by the **aPTT, Heptest, anti-FX, and anti-FIIa assays**.
  – Freshly collected human whole bloods were supplemented *in vitro* with various concentrations of heparin, then evaluated by the kaolin **ACT** (iSTAT).

Therapeutic Heparin Monitoring

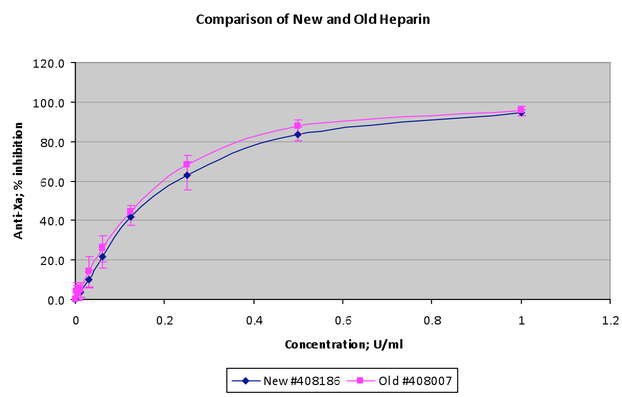
- Heparin is monitored on the basis of its activities within the coagulation cascade.
  - The activated partial thromboplastin time (aPTT) assay is used to monitor therapeutic heparin.
  - The primary actions of heparin are its ability to inhibit thrombin (FIIa) and FXa.

Point of Care Heparin Monitoring

- The Activated Clotting Time (ACT) test is used for heparin monitoring at the POC
  - Faster TAT than an assay performed in a laboratory
  - Heparin levels are higher than therapeutic levels
  - aPTT is too sensitive to the high doses
- POC sites
  - CV Surgery
  - ICU (cardiac assist device, balloon pump, sheath removal, etc)
  - Cardiology Cath Lab
  - Electrophysiology Lab
  - Interventional Radiology
  - Hemodialysis

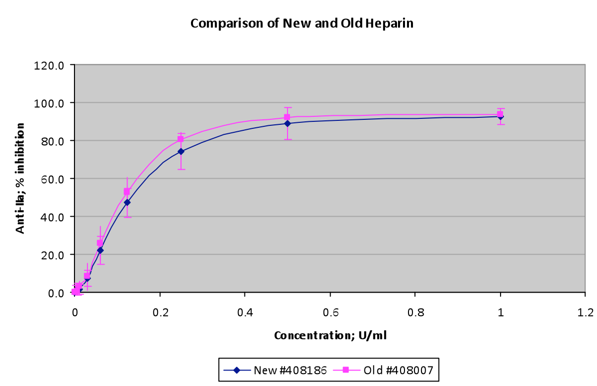
Potency Assay: Anti-FXa Test

This study was performed by testing freshly collected citrated human plasmas (3 male; 3 female; pool of each; n=7) supplemented *in vitro* with various concentrations of two lots of unfractionated heparin obtained from APP Pharmaceuticals. Results are mean +/- standard deviation.



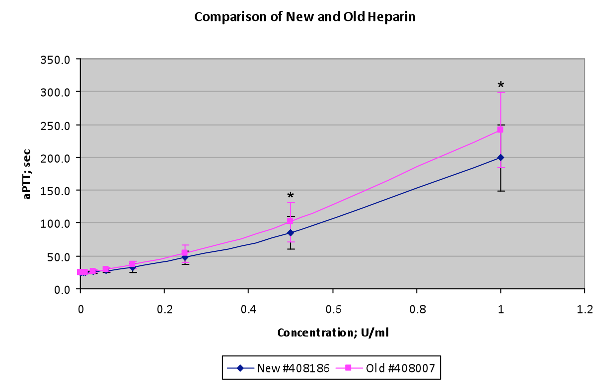
Potency Assay: Anti-FIIa (Anti-Thrombin) Test

This study was performed by testing freshly collected citrated human plasmas (3 male; 3 female; pool of each; n=7) supplemented *in vitro* with various concentrations of two lots of unfractionated heparin obtained from APP Pharmaceuticals. Results are mean +/- standard deviation.



Monitoring Assay: aPTT

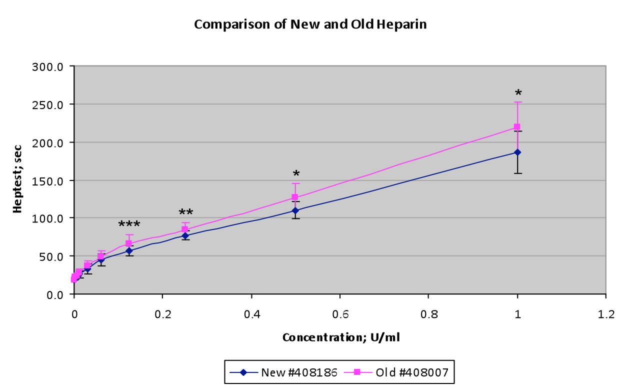
This study was performed by testing freshly collected citrated human plasmas (3 male; 3 female; pool of each; n=7) supplemented *in vitro* with various concentrations of two lots of unfractionated heparin obtained from APP Pharmaceuticals. Results are mean +/- standard deviation.



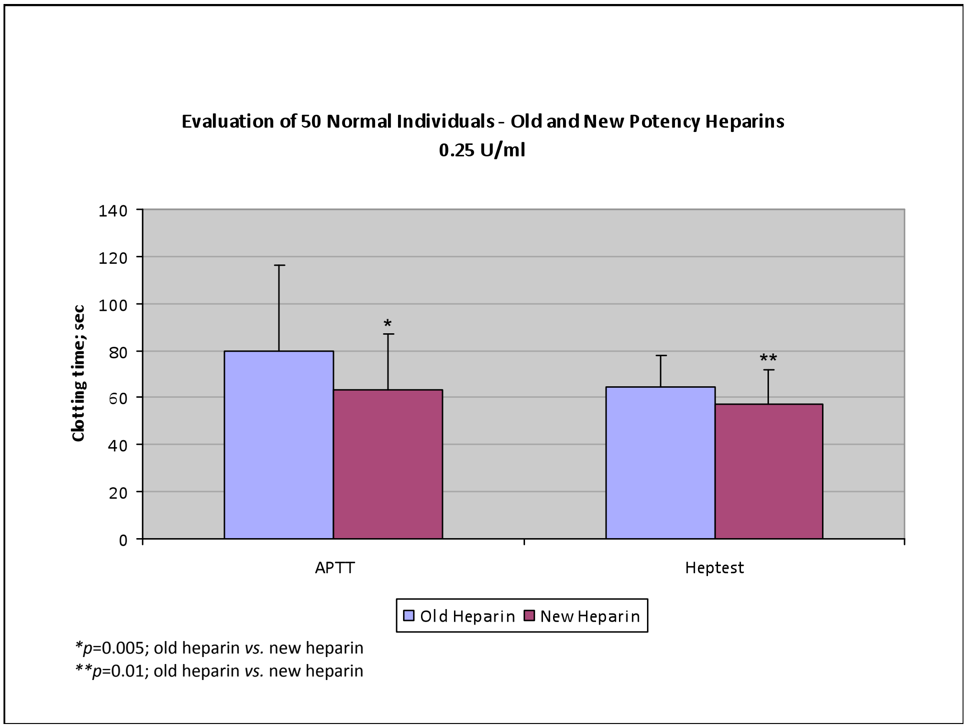
p<0.001 New *vs.* Old

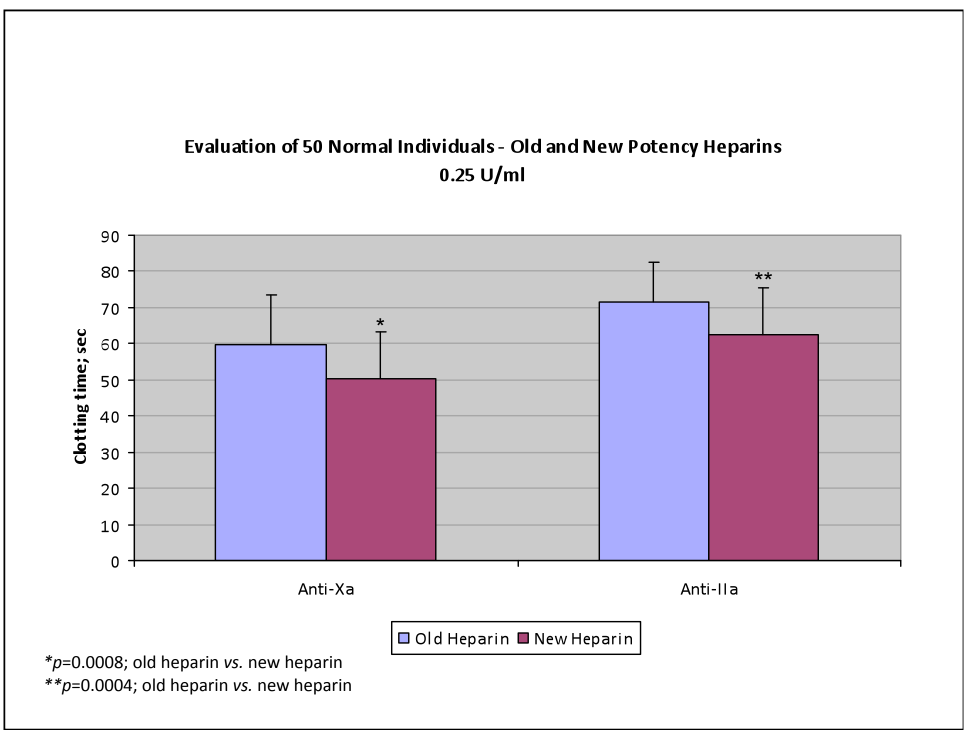
Clot-Based Heptest Assay

This study was performed by testing freshly collected citrated human plasmas (3 male; 3 female; pool of each; n=7) supplemented *in vitro* with various concentrations of two lots of unfractionated heparin obtained from APP Pharmaceuticals. Results are mean +/- standard deviation.

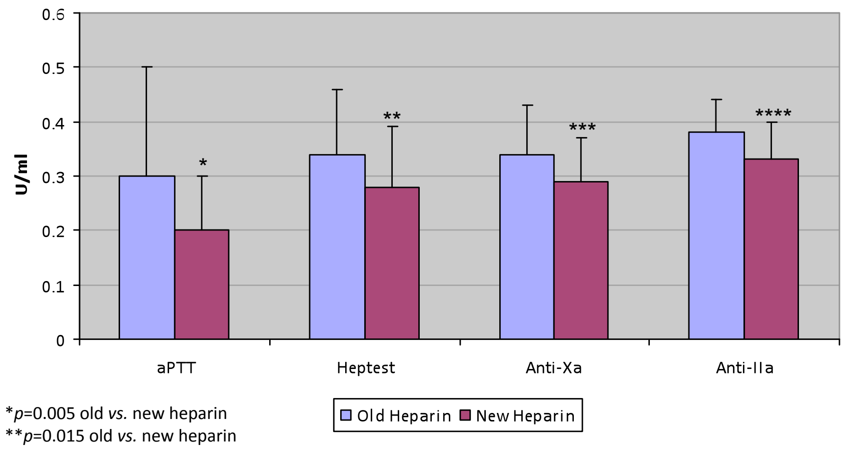


**p*<0.001; New *vs.* Old
***p*=0.049; New *vs.* Old
****p*=0.013; New *vs.* Old


Evaluation of 50 Normal Individuals - Old and New Potency Heparins
0.25 U/ml
Clotting time; sec
140
120
100
80
60
40
20
0
*
**
APTT
Heptest
Old Heparin
New Heparin
*p=0.005; old heparin vs. new heparin
**p=0.01; old heparin vs. new heparin

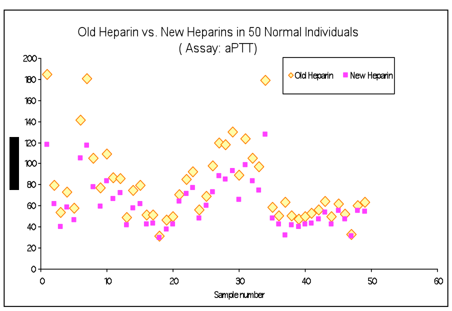

Evaluation of 50 Normal Individuals - Old and New Potency Heparins
0.25 U/ml
Clotting time; sec
90
80
70
60
50
40
30
20
10
0
*
**
Anti-Xa
Anti-IIa
Old Heparin
New Heparin
*p=0.0008; old heparin vs. new heparin
**p=0.0004; old heparin vs. new heparin

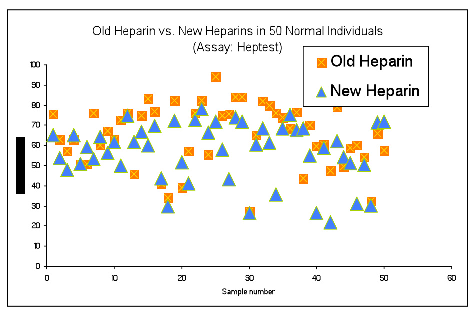
Evaluation of 50 Normal Individuals - Old and New Potency Heparins Cross-references Against USP-K1 Standard 0.25 U/ml



*p=0.005 old *vs.* new heparin
**p=0.015 old *vs.* new heparin
*** p=0.0008 old *vs.* new heparin
**** p=0.0004 old *vs.* new heparin

Wide Range of Individual Responses Between the Old and New Potency Heparins

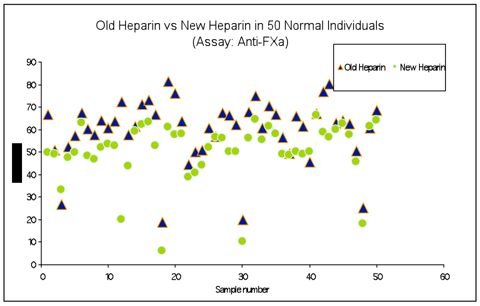


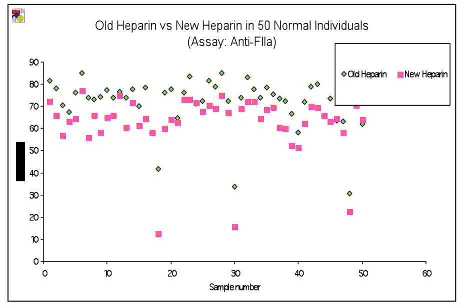


Clot-based Assays

Paired t-test analysis revealed **intra-individual** differences between heparins.
Heptest: p=0.00028
aPTT: p<0.00001

Wide Range of Individual Responses Between the Old and New Potency Heparins





Chromogenic Assays

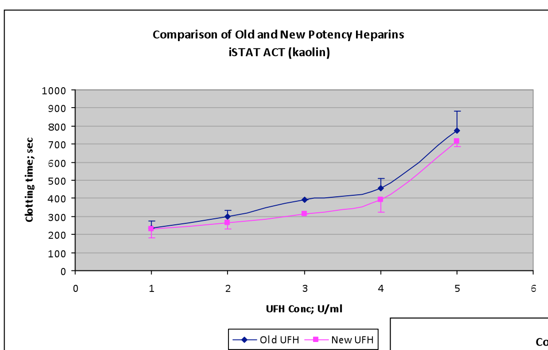
Paired t-test analysis revealed **intra-individual** differences between heparins.

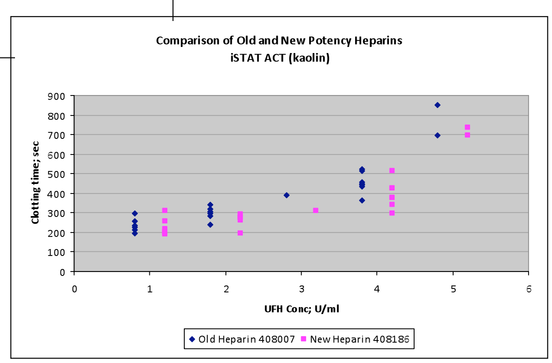
anti-FIIa: p<0.00001

anti-FXa: p<0.00001

Comparison of Old and New Potency Heparins

iSTAT ACT-kaolin





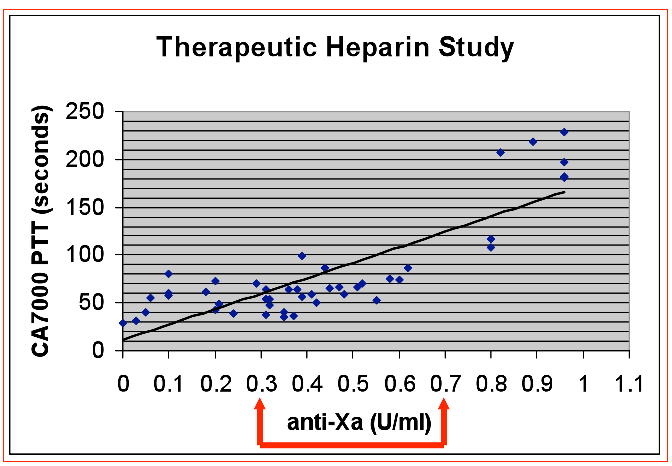
Paired t-test analysis revealed **intra-individual** differences between the heparins (p<0.002).

Work Still to be Done

When Patients are Exposed to the New Heparin

- Validate the therapeutic range for heparin monitoring.
- The current recommendation is that therapeutic heparin is achieved in the aPTT range that corresponds to <u>0.3 – 0.7 IU/mL heparin:</u>
  - Hirsh J and Raschke R. *Chest* 2004;126(3):188S
  - IU/mL heparin is determined with a chromogenic substrate anti-FXa assay

Establishing the Therapeutic Range for Treatment of VTE with Heparin



Patient samples were tested to determine the aPTT range that corresponds to 0.3 – 0.7 IU/mL.

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Heparin Nomograms Currently Utilized at LUHS

Nomogram Name	Therapeutic aPTT Range
Heparin High Range Nomogram	60 to 110 seconds
Heparin Intermediate Range Nomogram	60 to 80 seconds
Heparin Low Dose Infusion	Same

Heparin Nomogram: High Range: for treatment of Acute DVT and/ or Acute PE, for anticoagulation of patients with Mechanical Heart Valves, and other indications as determined to be clinically necessary. Equivalent to 0.3 to 0.7 IU/mL by FXa inhibition.
Intermediate Range Heparin Nomogram: for treatment of Acute Coronary Syndromes, for patients with Atrial Fibrillation, and other indications as determined to be clinically necessary. Equivalent to 0.3 to 0.5 IU/mL by FXa inhibition.
Heparin Low Dose Infusion: for prophylaxis of thrombus formation in patients on intra-aortic balloon counter-pulsation devices and other indications as determined to be clinically necessary.

FDA Recommendations for Clinicians (Oct. 15, 2009)

- Clinicians should NOT routinely increase a patient's heparin dose to compensate for the reduced potency of heparin.
- Heparin dosing is individualized based on patient-specific conditions.
- The 10% change in potency should be an additional consideration when determining the heparin dose.

Potential Clinical Consequences

Fixed bolus dose	Prophylaxis	Potential problem
Dose on weight basis	Dialysis, other	Potential problem
Dose by ACT	PCI CPB	Not a problem
Protamine neutralization	CPB	Potential problem
Dose by aPTT	Therapeutic use	Not a problem if nomogram re-validated
Special populations: Liver disease Renal disease Hypercoagulable state Abnormal metabolism High risk (e.g., IVC filter to prevent PE)	Very sick patients where a 10% difference could be 'huge'	Potential problem
Heparin coated medical devices	Procedures, surgery	Potential problem
Blood collection tubes Reagents/kit standards	Clinical Labs	Potential problem

FDA Recommendations for Manufacturers (Oct. 9, 2009)

- "The new USP reference standard may require modifications of procedures, specifications, formulations, in-process tests, quality control criteria, or other critical aspects of the manufacturing process for your device, or modification of the device itself."
- " You are required …. to document the assessment of the impact on your products or processes of the new USP heparin reference standard and any resulting changes …."

Summary

1. All anticoagulant assays revealed a **10% weaker potency** of the newly standardized heparin.
2. There were obvious **inter-individual responses** between the two heparins with some reaching significant differences.
3. In particular, the anticoagulant potency of the new potency heparin was **significantly *lower* at higher concentrations**:
   - In the aPTT (used to monitor therapeutic heparin) significant differences were identified at concentrations ≥0.25 U/mL.
   - In the ACT (used to monitor heparin during interventional procedures and surgery) differences were identified at concentrations ≥2.0 U/mL.
4. During the period of change from the old potency heparin to the new potency heparin, ***more frequent or intensive patient monitoring*** and ***more heparin*** may be needed to achieve desired anticoagulation.

Conclusion

- From the FDA Medwatch letter:

"*This may have clinical significance in some situations, such as when heparin is administered as a bolus intravenous dose and an immediate anticoagulant effect is clinically important.*

Healthcare providers should be aware of the decrease in heparin potency as they monitor the anticoagulant effect of the drug; more heparin may be required to achieve and maintain the desired level of anticoagulation in some patients."

Clinical judgment is essential in determining the dose of heparin.

Take Home Message

- The reduced potency of the new heparin may result in under-heparinization in some patients.
- Proper monitoring (signs/symptoms of patient; assay monitoring) and re-validation of the therapeutic heparin nomogram may avoid potential efficacy problems.