Modern Anticoagulant Drugs

Lab Monitoring in a No Monitoring Age.

(A.K.A How do you Correct the Uncorrectable ?)

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Background

- For almost 50 + years only 2 kinds of anticoagulants drugs were available in the US.
- Unfractionated heparin since the late 1930's
- Coumadin since the late 1950's.
- Aspirin has been available for 100 years but nobody knew of it's antiplatet effect till the 1970's

More Background

- In the 1980's the onset of LMW Heparins brought in the idea of not requiring monitoring. (FDA)
- The need to monitor was dependent on having an effective assay and was limited to "special" populations.
- The pharmaceutical industry has championed the need for no monitoring.

Even More Background

- Monitoring when required used only 2 lab tests.
- PT initially as a ratio and then as INR to monitor Coumadin therapy.
- APTT to monitor UFH therapy.
- Anti Xa assays were introduced later to monitor LMWH in ”special” groups and recently for both UFH and LMWH.

Concerns and Challenges

- All anticoagulants have one major complication – "bleeding"
- Therapy is therefore a constant challenge between efficacy and safety.
- The "gold " standard tests both PT/INR and APTT have major limitations.
- They became the "gold" standard by default. (no alternatives)
- Transfusion therapy was predictable !

More Concerns

- About 10% of patients who are treated with UFH have a prolonged APTT before starting therapy.
- How do you assess efficacy in this situation ?
- People still quote the original 1.5 x 2.5 times "something" as acceptable UFH therapy. **(the "Actin" effect)**

Even More Concerns

- The use of Anti-Xa assays is still considered "heretical" and unproven by some people.
- We have used this for 4 years at Emory and done >100K tests without any incidents. (no suits so far)
- If you don't check a level how do you know the drug is effective ?

Still More Concerns

- For many years despite the improvement in the control of OACs using the INR method some patients still had bleeds and others had very variable INRs and were considered OAC "failures" or non compliant
- The identification of the genetic impact of the CYP2C9 and VKORC-1 gene mutations has helped improve OAC control.
- This has even been shown to be cost effective.

Safety versus Efficacy

- The PT/INR and APTT/anti Xa are used to quantify drug efficacy to make sure the therapy is working.
- Levels of any of these lab values if high or low usually lead to adjustments of doses to minimise complications of bleeding or clots.
- In modern medical practice safety considerations are important QC metrics.
- Would you ever treat a ICH with an OAC "overdose" without an INR to help guide therapy and FFP to transfuse?

More Safety versus Efficacy

- If the drug has is so safe that no monitoring is needed, how do you assess efficacy ?
- Trust me it works!! The FDA says so !
- What if the patient is bleeding and we no nothing about any impact of the drug.
- How do I treat the bleeding ?

The "Excrement" Concept

- Even drugs that have been used for 50+ years still have major issues for safe use.
- Pharmacogenomics have important roles in predicting or monitoring therapies for Coumadin/ Aspirin/Plavix.
- Are we naïve enough to think any anticoagulant drug is inherently safe !

More "Excrement"

- Sometimes complications are small !

Even More "Excrement"

- Excrement happens, but why did I have to get diarrhea?

Ultimate "Excrement"

- Some times you just get buried in "excrement" !!

Avoiding the "Excrement"

- Don't approve Melagatran !!
- One of the most anticipated drugs in history.
- Pharmaceutical company and Wall Street salivated over it's potential sales. (> $ 1 billion)
- Approved in several European countries.
- Major serious side effects (liver failure) – withdrawn from market.

New Anticoagulant Drugs.

- In the past 15 years a slew of new drugs.
- LMW heparins (3) [anti-Xa]
- Fondaparinux (Pentasaccharide) [anti-Xa]
- Hirudin, Leparudin,Bivalarudin [anti IIa]
- Argatroban [anti IIa]
- Dabigatran [oral anti IIa]
- Rivaroxaban [oral anti Xa]
- Apixaban [oral anti Xa]
- More Bans & Trans coming !

Very New Drugs

- Dabigatran is an oral anti IIa inhibitor very heavily advertised in TV.
- Available in US for just over 1 year.
- Short Half Life.
- Pro-drug needs converting to active drug in vivo.
- Twice a day dosage, renal excretion
- Heavily promoted for Atrial Fib.

FDA Monitoring for Pradaxa

Pradaxa Issues

- Already higher rates of bleeding complications are occurring in older patients. (250+ fatalities)
- The FDA, European , Japanese and Australian medicine safety groups are recommending frequent monitoring of renal function (why not drug levels ?)
- Drug is coming under a cloud !!

Emory Case.

- 83 yo. man was admitted to EUH with ICH.
- Was taking "Coumadin" for his A-Fib.
- Nobody could tell when he last took it, or even if he had taken to many.
- Creatinine was elevated (3.5mg/dL)
- PT and APTT were both very prolonged.

More Emory Case

- Challenge of how to assess ongoing bleeding risk and how to treat and what to monitor. Patient not on Coumadin ?
- Our lab was setting up a Dabigatran assay and we tested his plasma.
- His level was 1.36µg/mL(Oh excrement!)
- Upper limit of therapeutic range is 0.44µg/mL
- Confirmed by HPLC by drug company

Safety is Paramount

- If we have learned nothing during the past 50 years it's that the idea of anticoagulant drugs never requiring monitoring is flawed, no matter what the FDA says.
- Drug company studies are carefully chosen so that there tends to be Monopathology in patients and control groups.

More Safety

- In the trials of Dabigatran v Warfarin, Pradaxa was safer and more effective.
- Why are we seeing so many bleeds ?
- Real world older patients are not the same as a drug study population.
- They take multiple drugs, often skipping or doubling doses. They have multiple pathologies.

Even More Safety

- " A lot of people think that when you don't need to monitor a drug, you don't' need to test for the drug"

Dr. Michael Laposata MD, Ph.D quoted in CAP today, January 2012.

Drug Safety & Lab Support

- If we accept that the efficacy of these new oral anticoagulants is established, then the safety issue becomes paramount
- Needs support from lab.
- How do you set up a test for a drug not requiring monitoring ?
- Is there any test even available ?
- Can we modify what we currently do.

Testing New Oral Drugs.

- In the phramaceutical industry many drugs are now tested by sophisticated techniques such as HPLC or Tandem Mass Spectroscopy.
- Not exactly available in your average coag lab.
- What can we do. How to validate ?
- Hopefully use our brains !

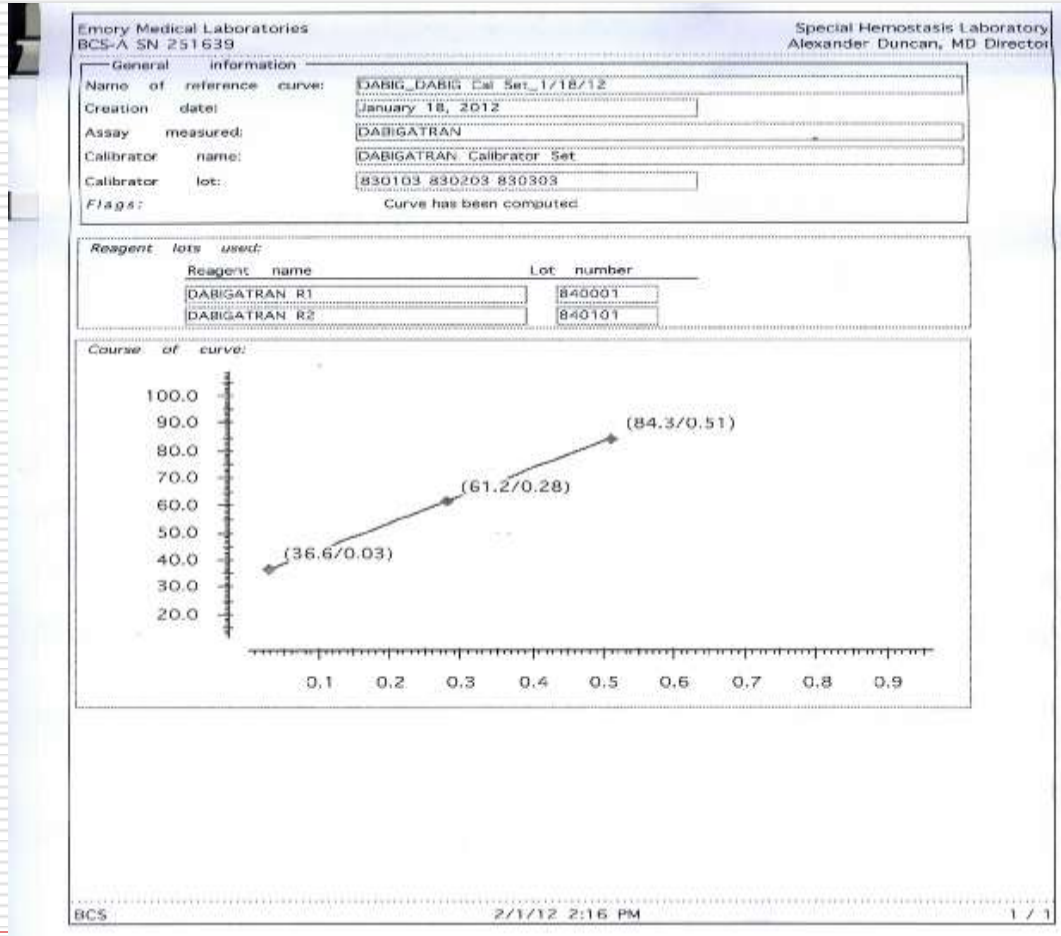
Monitoring anti IIa activity

- Several techniques exist to detect DTI drugs.
  - Thrombin clotting time based tests.
  - Echarin clotting time tests.
  - Chromogenic assay based tests.

EML Assay

- We use a thrombin time based clotting test using specific calibrators for Dabigatran.
- We have controls for both high and low levels.
- We have validated the assay using patient plasmas & comparing them to the original HPLC assay used by Boerhinger Ingelheim.

Dabigatran TT based assay



DABIGATRAN CONTROL PLASMA
224701-RUO

For Research Use Only. Not for Use in Diagnostic Procedures

ENGLISH

Lot : 13602 - Exp. : 2014-03

C1 (Control 1)	**Lot : 13602-1**	
[C]:	0.11	µg/mL
Acceptance range:	0.06 – 0.16	µg/mL
C2 (Control 2)	**Lot : 13602-2**	
[C]:	0.31	µg/mL
Acceptance range:	0.23 – 0.39	µg/mL

DABIGATRAN PLASMA CALIBRATOR
Référence 222801-RUO

Pour recherche à titre exclusivement

FRANÇAIS

Lot : 13603 - Exp. : 2014-03

Concentration [C] en DABIGATRAN dans les calibrateurs

Cal 1	Lot : 13603-1		
	[C] :	0.03	µg/mL
Cal 2	Lot : 13603-2		
	[C] :	0.28	µg/mL
Cal 3	Lot : 13603-3		
	[C]	0.51	µg/mL

What about Anti Xa drugs ?

- Based on past experiences, anti Xa drugs have been "safer" than anti IIa.
- Can we use our existing anti Xa assays.
- If not, what should we use ?
- Any specific tests available?
- There are calibrators and controls available for a specific test also.

More Anti Xa testing.

- Since intellectually our anti Xa assay should work we intend to use the "Rox" specific calibrators and our current anti Xa assay.
- How do we validate this?
- Who do we exchange samples with ?
- Coag testing can be "excrement " rich

Conclusions

- Despite the FDA mandate for no monitoring, past experience tells us that is not going to be true.
- The same rationale for testing children, the obese, pregnant woman, acutely ill patients & other "special" populations will likely force safety testing.

More Conclusions

- The lack of FDA approved tests will be an impediment.
- Need for validation testing will not be easy.
- Impact of the FDA position needs to be clarified (risks of LDTs)
- These drugs are used in an older higher risk population. Increasing age & bleeding go together.

Even More Conclusions

- If I get a high level of drug what do I do ?
- In the bleeding patient what are my therapeutic options?
- Tincture of time?
- Is the drug the cause of the bleeding or just a confounder ?
- What to transfuse ?

Even More Conclusions Still

- Are there any specific transfusion therapies or is "stuff " enough
- What "stuff" is indicated ?
- PCCs appear to work for Rivaroxaban not Dabigatran.
- Role for NovoSeven (rec. F VIIa)
- **"Excrement" never goes away !**

Ultimate Conclusions

- More oral drugs are on the horizen.
- Big Pharma is not going to suggest monitoring for any of these.
- Certain defined population will be at higher risk for bleeding or maybe clotting.
- Specific antidotes are " pending" but there will still be a role for Txs.

Excrement is Everywhere !