2014 CADTH Symposium
Policy Confirmed. Now What?

A Clinical Laboratory’s Perspective

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Background

The Ottawa Hospital is a large multi-site academic hospital, including the University of Ottawa, Heart Institute

TOH is the referral centre for 16 regional community hospitals
Background

• In 2009 the laboratory underwent a major change in methodology

• This change included a significant change in Troponin testing
  • Troponin is used as an aid in diagnosing heart attacks
  • Used predominantly by the ED and Heart Institute
  • Also used in ICU and various other locations throughout the hospital

• The laboratory undertook a targeted campaign to educate the clinical staff about the new Troponin assay
  • Change from Troponin T (TnT) to Troponin I (TnI)
History of Troponin Assays & The Evolution of Clinical Criteria

Specificity and Sensitivity of Troponin

1980's
- WHO MONICA MI Criteria
- Introduction of cTn assays: Roche cTnT®
- All others cTnI
- Limited sensitivity
- No standard
- Poor specificity
- No TnI standard

Early 1990's
- Introduction of cTnI assays: Roche cTnT®
- All others cTnI
- Poor specificity
- No TnI standard

1997
- TOH Civic Campus cTnT
- RI < 0.1 ug/L
- Improving Specificity

1997
- ESC/ACC defin. of MI cTn> 99th%
- TOH General Campus cTnT
- TnI assays improve correl. But no formal standardization

2000
- ESC/ACCF/AHA/WHF
- Redefine MI

2007
- “Troponinitis” complaints
- TOH switch to cTnI
- Cardiology Consults ↑↑↑

2009
- hscTn

2012
- Early publications
- US cTn

US cTn
Troponin 99\textsuperscript{th} percentile

Contemporary Assays

![Graph showing probability density and cumulative probability with LOD and 99\textsuperscript{th} percentile marker.]
The problem...

- Clinical staff has been using TnT for more than 10 years
- Very experienced with the correlation of TnT and clinical status
- Numerous publication available using TnT
- “Clinicians don’t like change” - our experience

- The new TnI assay has a lower limit of detection
- Increased sensitivity
- Can have decreased specificity for a heart attack, depending on use
- Numerical values are not similar to TnT and can not be compared
Initial communication with clinical groups

• Consulted the Heart Institute initially 3 mo prior to implementation

• Questions:
  • Why are you changing?
  • Can we just stay with TnT?
  • Can we adjust TnI to TnT values?
  • What about the decreased specificity?
  • Talk to ED first
  • ED said talk to Heart Institute first
  • Is there an MI (heart attack) specific cut-off?
Development of communication plan

• Points to consider:
  • Include why we are changing
  • Sensitivity and specificity of TnI
  • Numerical difference between assays
  • Discuss the use in diagnosis of MI
  • Need to speak with both ED and Heart Institute
  • Other groups?

• What is the best way to communicate?
  • Email
  • Information document
  • Oacis
Background

The Division of Biochemistry at The Ottawa Hospital is undergoing major restructuring of its analytical platforms. On Sunday, June 21, 2009, we will be implementing new Siemens Vista 8000 analyzers at the Civic, General and Riverside Campuses.

One of the significant changes that will be occurring at this time is a switch from Troponin I (cTnI) to Troponin I (cTnT). As with TnI, TnT is highly specific for cardiac tissue damage and provides similar diagnostic and prognostic information for cardiac patients and those suspected of having an acute coronary event. There are however a few differences between TnI and TnT. The table below is a brief comparison of the two assays.

<table>
<thead>
<tr>
<th>TnI (Siemens Vista)</th>
<th>TnI (Roche Pearnson)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Range</td>
<td>0.015-40 ng/ml (0.1-4)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.015 / 0.04 ng/ml (100% CV)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.015 / 0.04 ng/ml (100% CV)</td>
</tr>
<tr>
<td>Reference Interval</td>
<td>0.015-40 ng/ml (0.1-4)</td>
</tr>
<tr>
<td>Analysis Time</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Precision</td>
<td>0.015-40 ng/ml (0.1-4)</td>
</tr>
<tr>
<td>Known Interferences</td>
<td>HB &gt; 4 g/l (diluted values)</td>
</tr>
<tr>
<td>No interference</td>
<td>None</td>
</tr>
<tr>
<td>Inhibitory Substance</td>
<td>None</td>
</tr>
</tbody>
</table>

In an attempt to maximize the impact of clinical decision making, the two assays have performed extensive correlation studies between the two assays using various patient groups and troponin values. Instead these two assays provide very similar information regarding cardiac status and prognosis, however the numerical values cannot be directly compared.

Key points to keep in mind when interpreting the new TnT assay are listed below:

- The 99th percentile reference cut-off is 0.015 ng/ml, and the lower limit of detection is 0.005 ng/ml.
- TnT and TnI values are not interchangeable.
- The numerical values are significantly higher than TnI values.
- The diagnostic accuracy (for detection of cardiac necrosis) of both TnT and TnI are similar regardless of the numeric value.
- Although the TnI values are much higher than TnT, in general similar information is provided by the relative numeric value.

If you require and further information regarding Troponin I measurement of interpretation, please do not hesitate to contact my office or one of the Biochemists.

Comparison of 99th % Cut-offs:

TnI results (0.015 ng/ml) and TnT results (0.015 ng/ml) were analyzed by the Siemens Vista Troponin assay, 97% of patients specimens were below the 99th percentile cut-off values and 10% were below the lower detectable limit of 0.015 ng/ml and 8% had levels above the 99th percentile. The details of the patients with TnT results below the 99th percentile are presented in the table below. In addition, information from data, patients with undetectable cTnT and cTnI above the 99th percentile of all three forms of cardiac pathology, suggesting that cTnT may have increased sensitivity compared to cTnI, however more extensive controlled studies would be required to validate this finding.
Communication

- The documents were sent to the Heart Institute and ED Division Heads for distribution to their members
- Email to other Division and Department Heads
- Notice place on the clinical information system (Oacis)
- Met with heads of ED and Heart Institute

- Wait...
Complaints & questions

- We did not have a formal audit and feed-back mechanism.
- Waited for issues and questions regarding the change
- Assumed, “no news is good news”

- Received a number of questions and concerns:
  - When did this change occur?
  - Why was it happening?
  - Why did you not consult the clinical staff?
  - We heard nothing until we saw the different results!

- Also received questions from ICU, general medicine and nursing

- Clearly our communication plan was not effective!
Revised plan

- Re-send documents to ALL Division and Department Heads and follow-up that they have been distributed to all members of the department

- Arranged for presentation at various rounds
  - Medical Grand Rounds
  - ED Rounds
  - Cardiology Rounds
  - ICU Rounds

- Communication with Nursing
TPMT Analysis

A not so successful example.
Thiopurines

Azathioprine, 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) are a class of immunosuppressive drugs.

Commonly used as second-line treatments of autoimmune disorders including pemphigoid and inflammatory bowel disease.

AZA and 6-MP are effective in inducing remission in 50-60% of IBD patients.

Thiopurines have no intrinsic biological activity and require extensive metabolism for activity.
Thiopurine metabolism

Inhibition of de novo purine synthesis

- 6-MethylIMP (inactive)
- 6-MethylIMP
- 6-MethylGMP (inactive)
- 6-MethylTG (inactive)

AZA → 6-MP → 6-IMP → 6-tIMP → 6-tXIMP → 6-tGN

HGPRT
IMPDH

6-thiouric acid (inactive)

XO

Decreased expression:
- TRAIL
- TNFRSF7
- α4-integrin

Decreased inflammation

Rac1 inhibition
Incorporation into DNA

Increased apoptosis

GD or AO

6-thiouric acid (inactive)

XO
Experience with TPMT testing

DSM Experience

Since Feb 2008
N = 400 patients

Agreement with previous studies and other labs offering test
Thiopurine toxicity

Thiopurine-based drugs have been associated with various toxic adverse events, including myelosuppression, hepatotoxicity, pancreatitis, and flu-like symptoms, among others.

One of the most serious dose-dependent reactions is myelosuppression either due to overdosing or a low rate of thiopurine metabolism.

The most extensively characterized enzyme in the metabolism of thiopurines is TPMT.

Patients on azathioprine drugs should be monitored regularly to avoid myelosuppression.
Thiopurine toxicity

Various clinical guidelines suggest measuring TPMT enzymatic activity or screening for TPMT alleles associated with reduced enzymatic activity before starting patients on thiopurine drugs.

However, measuring TPMT activity may not lead to reduced drug-related toxicity since regular monitoring is recommended.

Complete blood counts, including platelet counts are recommended to be done weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary.
Should we screen?

Should all patients prescribed thiopurine therapy (AZA and 6-MP) be screened for TPMT activity prior to receiving the drug?

Yes
No
Assessment of Thiopurine Methyltransferase Activity in Patients Prescribed Azathioprine or Other Thiopurine-based Drugs

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KQ1. In terms of the analytical performance characteristics of enzymatic measurement of TPMT activity and determination of TPMT allelic polymorphisms:

a) What are the preanalytical requirements for enzymatic measurement of TPMT and determination of TPMT allelic polymorphisms?
b) What are the within and between laboratory precision and reproducibility of the available methods of enzymatic measurement of TPMT and determination of TPMT allelic polymorphisms?
c) What is the diagnostic sensitivity and specificity of TPMT allelic polymorphism measurement compared to the measurement of TPMT enzymatic activity in correctly identifying chronic autoimmune disease patients eligible for thiopurine therapy with low or absent TPMT enzymatic activity? How do effect modifiers explain any observed heterogeneity in sensitivity and specificity?
d) Are there any postanalytical requirements specific to measurement of TPMT enzymatic activity or TPMT allelic polymorphism measurement?

KQ2. Does the measurement of TPMT enzymatic activity or determination of TPMT allelic polymorphisms change the management of patients with chronic autoimmune disease when compared with no determination of TPMT status?

KQ3. In chronic autoimmune disease patients prescribed thiopurine-based drugs (AZA or 6-MP), does the assessment of TPMT status to guide therapy, when compared with no pretreatment assessment, lead to:

a) reduction in rates of mortality, infection, hospitalization, withdrawal due to adverse events (WDAE), serious adverse events (SAE) and improvement in health-related quality of life?
b) reduction in rates of myelotoxicity, liver toxicity, and pancreatitis?
c) In the absence or inconclusiveness of evidence answering key question 3a and/or 3b above, is there an association between TPMT status and/or the following amongst chronic autoimmune disease patients treated with thiopurines?
   i. the clinical outcomes of mortality, infections, hospitalization, WDAE, SAE and health-related quality of life?
   ii. surrogate outcomes of myelotoxicity, liver toxicity, and pancreatitis?

KQ4. What are the costs of determining TPMT enzyme activity and/or genotyping for patients with chronic autoimmune disease being considered for thiopurine-based therapy (e.g., costs of testing, costs of care, and costs of treating drug-associated complications)?
KQ2. TPMT guided therapy

Only a single (unpublished at the time) article was identified that addressed this question.

Fair quality randomized control trial with 333 chronic inflammatory disease patients.

Patients were randomized to either with or without genetic TPMT pre-testing (*2, *3A, B & C).

Therapy was to be guided by the TPMT results, however ultimate treatment decisions were left to the Dr.

No significant dosage differences between those that were genotyped and those that were not.

However, only 1 homozygous individual was identified.
KQ3(b). Reduction of myelotoxicity, liver toxicity, and pancreatitis

Two trials addressed this question, the previously mentioned study and a retrospective cohort study, both had 4 months of follow-up.

64 pediatric patients on AZA who’s initial dosing was based on TPMT enzymatic analysis.

Control group was 37 historical patients who’s AZA was adjusted based on clinical assessment.

14% had intermediate TPMT activity, none had low/absent activity.

On average, the study group received slightly more AZA than the control group.

*In both studies there was no difference between the groups for myelotoxicity, liver toxicity or pancreatitis.*
KQ3(c) Myelotoxicity
Implementation

• Discussions with Gastroenterology and Dermatology
  • Rheumatology does not order

• Feedback through patient reporting

• Physicians insist on ordering
  • Recommended by various guidelines
  • “Other” centers allow ordering
  • Fear of litigation

• More definitive trials are required
Questions?