Laboratory Monitoring of Anticoagulant Therapy

Session 4 of 4

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Session 4 Topics

Inhibitors of Platelet Function:
- Aspirin
- Plavix® and Prasugrel
- Ticlopidine
- ReoPro®

Drugs that are Currently Used to Inhibit Platelet Function
- Aspirin
- Clopidogrel
- Prasugrel
- Ticlopidine
- IIb/IIIa receptor blocking antibodies

Mechanism of Platelet Inhibition by Aspirin
- Aspirin acetylates cyclooxygenase 1 enzyme (COX-1)
- COX-1 needed to convert arachidonic acid to thromboxane
- Thromboxane is platelet aggregation potentiator and vasoconstrictor
- Aspirin also inhibits COX-2 enzyme to lesser degree

Need to Monitor Aspirin Therapy
- 15 – 45% patients are poor or non-responders
- Patients have suffered cardiovascular or neurovascular events while on aspirin

Methods of Monitoring Aspirin
- Platelet aggregometry, light transmission absent aggregation response with arachidonic acid
- AspirinWorks® - measurement of thromboxane metabolite in urine 11 dehydrothromboxane B2
- VerifyNow® Aspirin
Causes of Aspirin Failure

- Non-compliance
- Taking wrong drug
- Interference by other drugs – ibuprofen
- Polymorphisms of platelet binding sites
- Inadequate dose

AspirinWorks®

- ELISA assay measures 11dehydrothromboxane B2 in urine
- Metabolic breakdown product of thromboxane
- Reference levels
  - Patients not taking aspirin: >1500 pg/mg creatinine
  - Patients taking aspirin: <1500 pg/mg creatinine
- Identifies increased levels of thromboxane metabolite which is a risk factor for cardiovascular and neurovascular thrombotic disease

VerifyNow® Aspirin

- Measures aggregation response to arachidonic acid
- Reported in Aspirin Reactive Units, ARU
- Uses whole citrated bleed

Case History 60 Year Old Male on Aspirin

- 60-year-old male taking 81 mg aspirin per day because of history of neurovascular thrombosis
- Platelet aggregation with arachidonic acid – no response
- AspirinWorks® - 1900 pg/mg creatinine
- Aspirin dose increased to 325 mg per day
- Repeat AspirinWorks® - 900 pg/mg creatinine
Interpretation of VerifyNow® Aspirin

- Individuals not taking aspirin: >550 ARU
- Individuals taking aspirin: <550 ARU

Clopidogrel (Plavix®)

- Prodrug metabolized in liver by cytochrome P450 to active drug
- Active drug irreversibly blocks platelet ADP P2Y12 receptor – this inhibits activation of IIbIIIa receptor
- Inhibitory effect on platelets is irreversible, platelets inhibited for their life span

Clopidogrel Resistance or Drug Failure

- May be defined by thrombotic event while on drug
- May be defined by laboratory test of platelet inhibition
- Occurs in 4 – 30% of patients taking drug

Causes of Drug Failure

- Interference with P450 metabolism of clopidogrel, cytochrome P450 2C19 loss-of-function polymorphism
- Accelerated platelet turnover
- Polymorphism of the P2Y12 receptor (platelet)

Laboratory Tests for Drug Failure

- Platelet aggregation with ADP at 20 micromoles
- Expected result 40 – 60% inhibition of aggregation response
- VerifyNow® P2Y12
Adverse Effects of Clopidogrel
- Increased bleeding and/or bruising
- Thrombotic thrombocytopenic purpura, TTP-rare

Prasugrel (Effient®)
- Theinophyridine like clopidogrel
- Prodrug metabolized to active metabolite in the liver by cytochrome system
- Inhibits platelet function by irreversibly binding P2Y12 ADP platelet receptors
- Appears to be unaffected by cytochrome polymorphisms that inhibit clopidogrel

Adverse Effects of Prasugrel
- Increased bleeding and/or bruising
- Thrombotic thrombocytopenic purpura, TTP-rare

Monitoring Prasugrel
- Light transmission platelet aggregometry, ADP 20 micromoles
- Target range 50 – 70% inhibition of ADP induced aggregation
**Ticlopidine**
- Drug inhibits platelet aggregation and release of granule contents by inhibiting membrane function
- Inhibitory effect is irreversible for life of platelet

**Adverse Affects of Ticlopidine**
- Neutropenia
- Thrombotic thrombocytopenic purpura

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**Use of Ticlopidine**
- Rarely used due to adverse affects
- Used in patients that did not respond to clopidogrel
- Not monitored when used

**IlbIlia Blocking Agents**
- Abciximab (ReoPro®) – mouse antibody
- Eptifibatide (Integrilin®) – cyclic heptapeptide

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**Application of IlbIlia Blocking Agents**
- Used to treat patients with acute coronary syndromes
- Rarely monitored
- When monitored, platelet aggregation is almost completely inhibited in response to ADP at 20 micromoles
- Inhibitory effect on platelets is reversible

**Questions?**

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Thank You!