Platelet/vascular pharmacology

Overview

-Platelet adhesion
-Warfarin/Pradaxa
-Clopidogrel/Ticagrelor
-Reopro
-Heparin
-Clot busters

LAST LECTURE

Classic Vascular pharmacology
-chronic
-systemic

Blood pressure control
Atherosclerosis
Endothelial Injury
Thrombus

Local Vascular pharmacology
-acute
-targeted

CABG → Patient burden
PTCA → Restenosis
Stent → In-sent restenosis
Drug eluting stents

Lipid lowering drugs
Platelet/SMC pharmacology

Thrombus and endothelium

-Platelet adhesion
-Warfarin/Pradaxa
-Clopidogrel/Ticagrelor
-Reopro
-Heparin
-Clot busters
Why are anti-coagulant agents so popular?
What is the most popular anti-coagulant agent?
- Odorless and tasteless

-Warfarin / Coumadin
-Anti-thrombotic by preventing coagulation
-Inhibits vitamin K reductase, causing an accumulation of oxidized vitamin K
-What does vitamin K do?
$650 Million to Settle Blood Thinner Lawsuits

By KATIE THOMAS

MAY 28, 2014

The German drug maker Boehringer Ingelheim has agreed to pay $650 million to settle thousands of lawsuits involving its blood thinner Pradaxa, the company said Wednesday.

The settlement will most likely resolve most of the 4,000 cases in state and federal courts filed by patients and their families who claimed that Boehringer failed to properly warn them that the drug, which is used to prevent blood clots, caused serious and sometimes fatal bleeding that could not easily be reversed. The first case was set to go to trial in September.

In a statement, the company said that it stood behind the safety and efficacy of Pradaxa and continued to believe that the lawsuits lacked merit, but that settling the case allowed the company to move on. "Time and again, the benefits and safety of Pradaxa have been confirmed," said Desiree Ralls-Morrison, senior vice president and general counsel of Boehringer Ingelheim USA.

Ned McWilliams, a lawyer in Pensacola, Fla., who represented some plaintiffs, said he was pleased with the agreement. "We believed from the very beginning that the company had no defense to the claims in this case," he said. "It is hard to believe that Boehringer Ingelheim can satisfy the claims of thousands of victims hundreds of millions of dollars." Pradaxa, which was approved in 2010, was the first in a new group of blood thinners intended to replace an older treatment, warfarin, that required patients to submit to frequent blood tests and adhere to a strict diet. One of

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-Prevents cardiac ischemic events in patients w/ symptomatic atherosclerosis (at risk of heart attacks).

-$6 billion annually growing 20% a year (marketing)

-2nd best selling drug annual basis

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-Inhibits platelet ADP receptor P2Y12 (irreversible)

-platelet activation/aggregation

-Prevention of ischemic events w/atherosclerosis

-Before or after MI
Advantage???

Inhibits platelet ADP receptor P2Y12 (Reversible)

Heart + Lung Institute
Providence
at St. Paul
Heart + Lung Institute
Providence

Results

ST-segment elevation.

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients who have an acute coronary syndrome with or without ST-segment elevation.

Background

The rate of death from vascular causes, myocardial infarction, or stroke without an intention, treatment with ticagrelor as compared with clopidogrel significantly reduced in patients who have an acute coronary syndrome with or without ST-segment elevation. (ClinicalTrials.gov number, NCT00391872.)

Conclusions

Most of the benefits of Plavix occurred in the first two months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 2).

Platelet adhesion vs coagulation

Table 4: Outcome Events in the CURE Primary Analysis

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>PLAVIX + ASPIRIN* (N=4235)</th>
<th>PLACEDOGREL + ASPIRIN* (N=4303)</th>
<th>RELATIVE RISK REDUCTION (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (Cardiovascular death, MI, stroke)</td>
<td>162 (9.3%)</td>
<td>170 (11.4%)</td>
<td>30% (10.3, 27.9) ( p &lt; 0.001 )</td>
</tr>
<tr>
<td>All Individual Outcome Events†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>318 (5.1%)</td>
<td>345 (5.5%)</td>
<td>7% (-7.7, 20.6)</td>
</tr>
<tr>
<td>MI</td>
<td>324 (0.3%)</td>
<td>419 (0.6%)</td>
<td>23% (11.0, 35.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>76 (1.2%)</td>
<td>87 (1.4%)</td>
<td>14% (-17.7, 36.6)</td>
</tr>
</tbody>
</table>

† Other standard therapies were used as appropriate.

* The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.
Reopro Providence Heart + Lung Institute at St. Paul's Hospital

Humanized Abs

Figure 34-1. Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) IIb receptor binding to collagen (IIIa GP IIb receptor binding, von Willebrand factor (VWF), and GP Ib-IXa, which binds fibronogen and other macromolecules. Antipatelet prostacyclin (PGI2) is released from the endothelium. Aggregating substances released from the degranulating platelet include ADP, TxA2, and 5-HT. Production of factor XIII is detailed in Figure 34-2. (Redrawn and reproduced, with permission, from Simoni ML, Decker JW: New directions in anticoagulant and antplatelet treatment. Editorial: Br Heart J 1993;4:371.)

- $C_{6462} H_{9964} N_{1660} O_{2049} S_{48} = ?$
- C₆₄H₉₉₆N₁₆₉₀O₂₀₄₉S₄₈ = ?
- mostly angioplasty. Why? Vasc. Damage in presence of little bleeding
  - short half-life but prolonged effect due to Ab. Unreversible.
- decreased restenosis
- decreased ischemic events
- inhibits chain reaction

Reopro

Platelet adhesion vs coagulation

Platelet Aggregation

Clotting

Reopro

Warfarin/pradaxa

Heparin

-Glycosylated and sulfated amino glycan
- Normally released by mast cells
- Used in ACS, fibrillation, angioplasty, thrombosis, ECC-pump

Heparin: mode of action

Indirect effect on Thrombin via AT. Acts like a catalyst in an enzymatic reaction.

- potentiates antithrombin III
- antithrombin III inactivates Factor X, IX XI and XII and thrombin.

Heparin

Platelet adhesion vs coagulation

Heparin
Platelet adhesion vs coagulation

Clot busters

- Heart attacks and strokes
- Given IV → issue?
- Within 3 hours of initial ischemic event
- In an overview of nine research studies, clot busting medications reduced the risk of a woman dying within 35 days after a heart attack by 12%
  - Its recombinant TPA

Tertiary hemostasis

TPA converts plasminogen into plasmin and degrades fibrin/fibrinogen - fibrinolysis