THE NORTHERN HOSPITAL

CLOPIDOGREL

Gold Solidus of the Eastern Roman Emperor, Basiliscus 475 - 476 A.D, Constantinople mint.

He (Leo) made Basiliscus commander-in-chief, the brother of his wife Verina, a man who was extraordinarily desirous of the royal power….Basiliscus with his whole fleet put in at a town distant from Carthage no less than two hundred and eighty stades at a place named Mercurium…If he had not purposely played the coward and hesitated, but had undertaken to go straight for Carthage, he would have captured it at the first onset, and he would have reduced the Vandals to subjection without their even thinking of resistance…And Gaiseric, profiting by the negligence of Basiliscus, did as follows. Arming all his subjects in the best way he could, he filled his ships, but not all, for some he kept in readiness empty, and they were the ships which sailed most swiftly. And sending envoys to Basiliscus, he begged him to defer the war for the space of five days, in order that in the meantime he might take counsel and do those things which were especially desired by the emperor. They say too, that he sent also a great amount of gold without the knowledge of the army of Basiliscus and thus purchased this armistice…

Gaiseric thinking, as actually did happen, that a favouring wind would rise for him during this time…The Vandals, as soon as the wind had risen for them which they had been expecting…raised their sails and taking in tow the boats which they had made ready with no men in them, they sailed against the enemy. And when they came near they set fire to the boats

which they were towing, when their sails were bellied by the wind, and let them go against the Roman fleet. And since there were a great number of ships there, these boats easily spread fire wherever they struck, and were themselves readily destroyed with those with which they came in contact. And as the fire advanced in this way the Roman fleet was filled with tumult…and with a great din that rivaled the noise caused by the wind and the roaring of the flames, as the soldiers together with the sailors shouted orders to one another and pushed off with their oars the fire boats and their own ships as well, which were being destroyed by one another in complete disorder….Already the Vandals too were at hand ramming and sinking the ships, and making booty of such of the soldiers as attempted to escape…

Procopius, "The Histories", Sixth century A.D

History has not been kind to the memory of the Eastern Roman emperor Basiliscus who reigned for a brief period at Constantinople from 475 to 476 A.D. He is one of history's more spectacular examples of a mediocre talent rising by to a station far beyond his natural capabilities. The years of his reign saw the final collapse of the Western Roman empire, a collapse in which he himself had played an integral part in just seven years previously in a botched seaborne invasion of the Vandal homelands. With the West in complete chaos and amidst incompetence and scandal he was deposed by the very (eastern) emperor he himself had deposed, the emperor Zeno. Gibbon dismisses his reign, such as it was, in just a few lines:

"…but the palace of Constantinople was ruled by female influence, and agitated by female passions and Verina, the widow of Leo, claiming his empire as his own, pronounced a sentence of deposition against the worthless and ungrateful servant on who she alone had bestowed the sceptre of the east. As soon as she sounded a revolt in the ears of Zeno, he fled with precipitation into the mountains of Isuaria; and her brother Basiliscus, already infamous by his African expedition, was unanimously proclaimed by a servile senate. But the reign of the usurper was short and turbulent. Basiliscus presumed to assassinate the lover of his sister…by the conspiracy of the malcontents, Zeno was recalled from exile; the armies, the capital the person of Basiliscus were betrayed; and his whole family was condemned to the long agony of cold and hunger…"

In these lines Gibbon gives us the reason why a mediocre solider came to spearhead the last great military venture of the West before its ignominious demise, and then despite this unprecedented shame would become emperor in the East just seven years later! - Nepotism at the very highest level. Basiliscus's sister was none other than Verina the wife of the emperor Leo I. Verina splendidly continued the Roman centuries old leitmotif of "powerful woman behind the throne". She soon had Zeno (successor to her husband, after he had died)) deposed and then put up her own brother Basiliscus as the next emperor. This was not the first time that Basiliscus had been promoted via the agency of his sister. In 468 A.D the Western and Eastern empires had finally decided to join forces to invade and destroy the Vandal kingdom in North Africa.

A massive simultaneous three pronged attack would be led by three eastern generals, Marcellinus would attack the Vandal stronghold of Sicily. Heraclius would invade the Vandal homeland centered at Carthage, from Egypt. The third prong of the attack was to be the main game - an astonishing seaborne attack directly on Carthage itself. Nothing on this scale had been attempted since the days of the Punic Wars. But the latter Roman Empire was a very

different entity to the old Republic. Both east and west were rife with internal decay and political rivalry and corruption. The best generals could not be given such important commands - partly out of fear of the success that would make these men rivals to the emperors themselves. As the Western emperor Anthemius feared his best general Ricimer, so the eastern Emperor, Leo feared his best general Aspar. Both emperors desperately sought to bring down the Vandal kingdom, but not at the expense of their own thrones! Another great general would have to be found. Verina had just the person - her brother Basiliscus, and such was the power of her forceful personality, Leo dutifully accepted his wife's nomination.

The scene was therefore set for the Roman world to once more unite and defeat a great barbarian kingdom, and thereby regain a great part of the lost western empire, that if achieved could have drastically altered the course of history. But two factors combined that would see catastrophic defeat, that led to the final and total collapse of the West just seven years later. The first was that the Vandal king, Gaiseric was one of the greatest barbarian generals in history. Even if Rome enjoyed superiority of force, it had a very difficult task in the form of the extremely rare for the time, seaborne invasion. An exceptional leader would be required to lead such an expedition and to do battle with Gaiseric. And herein lay the second reason for the disastrous defeat - Basiliscus was completely unequal to the task. Details are obscure and fragmentary, as is most of the history of the latter western empire, but it seems that Gaiseric played Basiliscus a clever ruse. He stalled Basiliscus after he had landed by feigning to "negotiate" with him. While these "negotiations" were going on, Gaiseric hoped for favourable winds for his own fleet. It should also be noted that at this time the Vandals were unsurpassed in the Mediterranean world as seafarers. As fortune would have it, the winds did became favourable and Gaiseric immediately launched a massive seaborne counterattack against the Roman fleet. The lightly defended fleet was practically annihilated by the ingenious use of "fireboats". Although Marcellinus and Heraclius had successfully completed their invasions, Basiliscus in charge of the main Roman force was now completely cut off from all communication and supply - stranded on the beaches outside of Carthage. Gaiseric had won. His brilliant strategies would be noted and copied by commanders and generals for the next millennia and a half. Fire boats would play a role in the defeat of the Spanish Armada in 1588 and Nelson would repeat Gaiseric's trick at the Battle of the Nile to defeat Napoleon in Egypt.

After the sea battle Basiliscus fled back to Sicily and thence to Constantinople. His sister Verina saved him from execution, and he was exiled. Just Seven years later in 476 A.D the Western empire finally collapsed. The same year the unpopular eastern emperor Zeno was deposed, and stunningly was replaced by the exiled Basiliscus on the recommendation of Verina. Clearly the Roman senate did not look too closely at his "referees"! More to the point, it says oceans about the power and prestige still wielded by Verina, the old Empress and consort to the revered memory of Leo I. Basiliscus's reign lasted less than two years. He was no leader of men, and his reign proved just as disastrous as his African campaign. He showed astonishing disrespect and extraordinary ungratefulness to his sister by having her lover executed. Basiliscus proved so unpopular at court and amoung the people, that supporters of the disposed emperor Zeno deposed him. Zeno was recalled and given a second chance and would reign successfully for the next sixteen years.

Clopidogrel was once the supreme agent amoung all the cardiovascular drugs, heavily promoted by powerful allies in the form of Big Pharma. With time however, its abilities like the ill fated emperor Basiliscus proved unequal to the important tasks required of it.

CLOPIDOGREL

Introduction

Clopidogrel (trade name in Australia, "**Plavix**" amoung others) is an oral antiplatelet agent used in the ED for the treatment of acute coronary syndromes.

Outside of the ED it is used for the prevention of stroke/ TIA/ ACS.

Clopidogrel was the archetype **$P2Y_{12}$ - ADP-receptor** antiplatelet agent.

Its principle drawback is that it is a **prodrug**. Inhibition of platelet aggregation by clopidogrel is due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by **genetic variations** in CYP2C19 and by concomitant medications that interfere with CYP2C19.

It is still widely used, for secondary prevention treatments, but in the setting of ACS in the **ED** and the **Cardiac catheter Laboratory**, it has been being replaced by better agents such as **ticagrelor.**

It still however used in ACS settings in situations where **ticagrelor** is **contraindicated**.

See also separate document on Ticagrelor (in Drugs folder).

History

Clopidogrel was introduced into clinical practice in 1998.

Before the expiry of its patent, clopidogrel had become the second biggest selling drug in the world.

Chemistry

Clopidogrel belongs to the **thienopyridines** class of selective, irreversible ADP receptor/P2Y12 inhibitors used for their anti-platelet activity.

Drugs in this class include prasugrel, ticlopidine and clopidogrel.

Physiology

Extracellular adenosine has a half-life of just several seconds due to rapid cellular uptake via:

1. Sodium independent equilibrative nucleoside transporters (ENTs)

    - ENTs are ubiquitous, present on erythrocytes as well as the liver, heart, spleen, kidneys, lungs, intestines, and brain

And

2. Sodium dependent concentrative nucleoside transporters (CNTs).

    - CNTs are found primarily in the liver, kidneys, and small intestine.

The adenosine receptors (or P1 receptors) are a class of purinergic G protein-coupled receptors with adenosine as endogenous ligand. There are four known types of adenosine receptors in humans: A1, $A2_A$, $A2_B$ and A3.

Three adenosine receptor subtypes A1, $A2_A$, and A3 have cardiac expression with agonism resulting in bradycardia, coronary vasodilatation, and activation of multifaceted cardio-protective mechanisms, respectively.

Classification

The classes of antiplatelet drugs include:

1. Irreversible cyclooxygenase inhibitors:

    Aspirin acts by irreversibly acetylating COX-1, whereas other NSAIDs reversibly acetylate both COX-1 and COX-2, which prevents synthesis of TXA_2, a key factor in the platelet aggregation process.

    - Aspirin
    - Triflusal (Disgren)

2. Adenosine diphosphate (ADP) receptor inhibitors:

    Thienopyridines impair platelet aggregation by blocking the interaction of ADP with its receptor.

    - **Clopidogrel** (Plavix)
    - Prasugrel (Effient)
    - Ticagrelor (Brilinta)
    - Ticlopidine (Ticlid)

3. Phosphodiesterase inhibitors:

    Phosphodiesterase inhibitors (PI) are thought to act by blocking the decomposition of cAMP, which inhibits calcium release during platelet activation.

    - Cilostazol (Pletal)

4. Glycoprotein IIB/IIIA inhibitors (intravenous use only):

Glycoprotein IIb–IIIa antagonists block the IIb–IIIa fibrinogen receptors, which are involved in the final step of the platelet aggregation pathway.

- Abciximab (ReoPro)
- Eptifibatide (Integrilin)
- Tirofiban (Aggrastat)

5. Adenosine reuptake inhibitors:

- Dipyridamole (Persantine)

6. Thromboxane inhibitors:

- Thromboxane synthase inhibitors
- Thromboxane receptor antagonists
  - ♥ Terutroban

Preparation

Preparations include:

Clopidogrel as:

Tablets:

- 75 mg
- 300 mg.

A fixed dose preparation with aspirin:

- Clopidogrel 75 mg + aspirin 100 mg.

Mechanism of Action

Clopidogrel, (like prasugrel and ticagrelor) inhibits platelet aggregation by blocking the platelet P2Y12 receptor.

$P2Y_{12}$ belongs to the Gi class of a group of G protein-coupled (GPCR) purinergic receptors and is a chemoreceptor for adenosine diphosphate (ADP).

The P2Y family has several receptor subtypes with different pharmacological selectivity, which overlaps in some cases, for various adenosine and uridine nucleotides. This receptor is involved in platelet aggregation.

Clopidogrel (and prasugrel) lead to **irreversible** platelet inhibition and are given **once daily.**

Pharmacodynamics

Acutely dose dependent inhibition of platelet aggregation occurs 2 hours after single oral dose of clopidogrel.

Higher doses provide a quicker response.

Long-term use of antiplatelet drugs has shown consistent benefit in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

Pharmacokinetics

Absorption:

- Clopidogrel is administered orally.

  Clopidogrel is a **prodrug** and inhibition of platelet aggregation by clopidogrel is due to an active metabolite.

  The active metabolite is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis.

Distribution:

- Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively).

- It is unknown if clopidogrel crosses the human placenta.

- It is unknown if clopidogrel is excreted into human breast milk.

Metabolism and excretion:

- Clopidogrel is a **prodrug** and inhibition of platelet aggregation by clopidogrel is due to an active metabolite via the enzymes CYP2C19.

  There is **genetic variability** in the population in the activity of the CYP2C19. Up to 30% (by some reports) [6] of people are not able to effectively metabolize clopidogrel to the active form. This is clopidogrel's principle drawback.

Indications

Principle indications in the **ED** include:

1. ACS (with or without ST-segment elevation), (given *together with aspirin*)

    - Note however careful assessment of bleeding risk should be undertaken before using these agents. Avoid if **emergency coronary artery bypass grafting** is likely to be required.

    In the setting of ACS in the **ED** and the **Cardiac catheter Laboratory**, it has been replaced by better agents such as **ticagrelor.**

    It still however is used in ACS settings in situations where **ticagrelor** is **contraindicated**.

    If the patient is considered to be a **high probability for needing CAGS** then clopidogrel should be withheld - ideally CAGS is not undertaken until > **5 days** after ceasing clopidogrel.

    Where uncertainty exists - clopidogrel may be withheld until the **coronary angiogram has been done** and the need for CAGS has been definitively determined.

Indications outside the ED:

2. Secondary prevention of ischaemic stroke/ TIA,

3. Secondary prevention of MI or unstable angina

Contraindications/ Precautions

1. Hypersensitivity to clopidogrel, prasugrel or ticlopidine contraindicated

    - These is a risk of cross reactivity within the **thienopyridines.**

2. Severe active bleeding or disease states with an increased risk of severe bleeding:

    - e.g. bleeding disorders, severe hepatic disease.

3. Other drugs that can affect the clotting process may increase the risk of bleeding

    - Avoid combinations where possible or monitor closely.

4. Drug interactions:

    - The enzyme CYP2C19 metabolises clopidogrel to its active metabolite, consequently combining clopidogrel with other drugs that inhibitor CYP2C19 will reduce its effectiveness.

5. A genetic lack of CYP2C19 activity may reduce clopidogrel's effectiveness in reducing the risk of cardiovascular events

6. Surgery:

   The risk must be weighed between cardiovascular events (including stent thrombosis) from stopping antiplatelet agents against bleeding risk if continued.

   It may be safe to continue antiplatelet agents before **minor** surgery with low risk of bleeding, e.g. dental procedures, cataract surgery or some dermatological procedures.

   It may be necessary to reduce the antiplatelet effect before **surgery with a high bleeding risk**, e.g. CABG

   For patients with coronary stents, consider delaying elective surgery until dual antiplatelet treatment is no longer required; consult patient's cardiologist before stopping antiplatelet agents.

   If antiplatelet effect is **not wanted,** stop **clopidogrel > 5 days** before, prasugrel > 7 days before and ticagrelor 5 days before planned surgery.

Pregnancy

Clopidogrel is classified as a category B1 drug with respect to pregnancy.

Category B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage

A few case reports have described healthy pregnancy outcomes following maternal use of clopidogrel. However, consider an alternative medicine with more safety information in women who are planning to become pregnant and during pregnancy.

If clopidogrel is the medicine of choice, monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended.

Breast feeding

Published reports describing the use of clopidogrel during breastfeeding have not been located.

In circumstances where clopidogrel is the treatment of choice, women who choose to breastfeed their healthy full-term infant while using clopidogrel should observe the breastfed infant for signs of bleeding, unusual bruising, rash and diarrhoea.

Adverse Effects

1. Allergic reactions.
2. **Bleeding** is the principle adverse reaction.
3. Dermatological hypersensitivity reactions
    - Rarely, Stevens-Johnson syndrome / exfoliative dermatitis.

Dosing [2]

ACS:

- Loading dose 300 mg

Then:

- 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.

Placement of a coronary stent:

- Loading dose 300 - 600 mg at least 6 hours before the procedure

Then:

- 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.

Prevention of vascular ischaemic events

- 75 mg once daily.

"A Roman Lady", oil on canvas, 1858, Lord Frederick Leighton

Women were (with only two exceptions in the East) excluded from the Imperial throne of Rome. But this didn't stop many of them wielding great power behind the scenes, or indeed over the emperor himself. The Fifth century Empress Verina was but one in a long line of powerful women who both made and broke emperors.

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Reviewed 2 July 2019.