THE STORY OF WARFARIN: FROM RAT POISON TO CLINICAL USE

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ABSTRACT

- We narrate a very interesting story of warfarin: a rat poison that eventually became one of the most widely used anticoagulants.
- Discovered as a compound in the mold of Melilotus alba, warfarin caused internal bleeding in farm cattle who consumed the mold.
- Warfarin inhibits the liver enzyme epoxide reductase, which activates the vitamin K dependent clotting factors II, VII, IX, and X.
- New drug advancements aim to improve reduction of thrombotic events, minimize bleeding risks, and offer more selectivity and speed in anticoagulation.

HISTORY/BACKGROUND

- 1920's: Dairy farmers became perplexed when they started noticing their cattle begin to bleed internally without any cause, and die.
- The cattle and sheep had grazed on sweet clover hay (Melilotsus alba and Melilotus officinalis)
- Hemorrhaging occurred most commonly when the climate was damp and the hay had become infected with mold.
- The hemorrhagic disease became known as 'sweet clover disease'.
- Rates of fatal bleeding were highest during humid months, when a certain type of mold could easily grow on the crop.
- Wisconsin farmer Ed Carlson loaded a dead cow on his truck and approached biochemist Karl Link to ask for help.
- Link and his colleagues isolated a compound from the hay that inhibits the clotting of rabbit blood in a test tube. They assigned it the name dicoumarol.
- Link considered using dicoumarol as a poison against rats who were becoming shy of consuming fast-acting poisons.
- The research was sponsored by the Wisconsin Alumni Research Foundation (WARF), whose name was eventually incorporated in the drug we know today as warfarin.
- In 1954 it was approved for use in humans, initially for the prevention of stroke in patients with atrial fibrillation.

INDICATIONS AND CONTRAINDICATIONS

Warfarin is indicated for diseases that confer a hypercoagulable state:

1. Deep vein thrombosis,
2. Venous thromboembolism
3. Atrial fibrillation
4. Prosthetic heart valves

The clot has either already formed or is likely to form because of abnormalities in blood flow through vessels.

PROCESS OF COAGULATION

The process of clotting relies on two main pathways:
A) Formation of the platelet plug AND
B) Cascade response of coagulation factors that form a fibrin meshwork to strengthen platelet plug
Platelets are made primarily in the bone marrow while clotting factors are made in the liver.

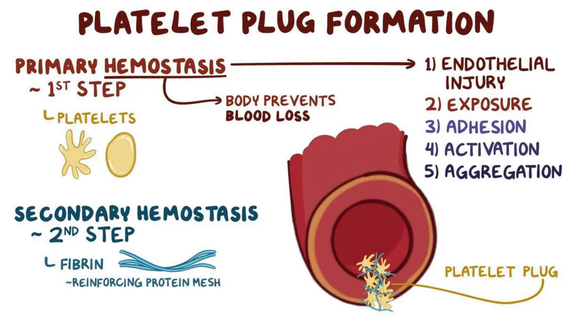

Figure 1: Platelet Plug Formation

COAGULATION CASCADE

- Within the coagulation cascade, there are two pathways that respond depending on the type of injury:
- The extrinsic pathway is activated if there is external tissue injury, such as a cut or wound.
- The intrinsic pathway is activated if the chemical balance inside the blood vessel tips in favor of clotting or if there is internal injury to the lumen of the blood vessel.

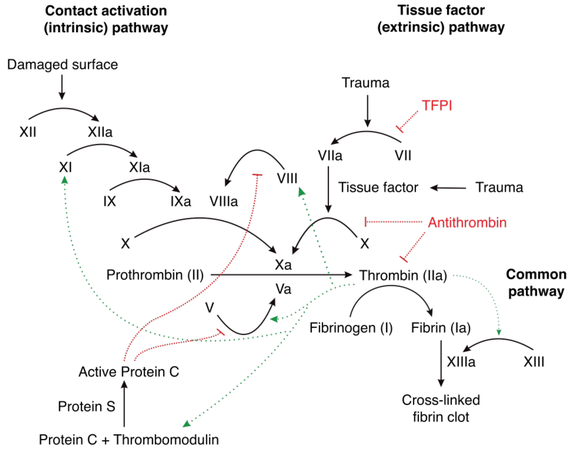

Figure 2: Coagulation Cascade

MECHANISM OF ACTION OF WARFARIN

- Vitamin K is necessary for the biochemical activation of clotting factors II, VII, IX, and X.
- Acting primarily in the liver, warfarin inhibits the enzyme epoxide reductase, which normally restores vitamin K to its active form. As a consequence, factors II, VII, IX, and X are not able to participate in the coagulation cascade.

THERAPEUTIC DRUG MONITORING

1. The half-life of warfarin in the plasma ranges from 20-60 hours and the duration of effect is 2-5 days.
2. The maximum effect of a dose occurs around 48-72 hours after administration.
3. Due to delayed response, careful monitoring of drug levels in the body is warranted to maintain a therapeutic window.
4. The effects of warfarin can be followed by a laboratory test known as the prothrombin time (PT).
5. To standardize measurements, the patient's PT is compared to a control PT by calculating the International Normalized Ratio (INR).

$$\text{INR} = \frac{\text{Patient PT}}{\text{Control PT}}$$

6. The INR must be measured routinely while the patient is on warfarin to confirm appropriate drug levels. An INR range of 2.0-3.0 is a generally acceptable therapeutic range.

DOSING OF WARFARIN

- A typical loading dose of 5 mg is given and adjustments are made a few days later after calculating the INR and considering the patient's history and risk factors.

ADVERSE DRUG EFFECTS AND INTERACTIONS

- Major bleeding, easy bruising, blood in urine or stool, coughing up blood, or neurological disturbances.
- These can be treated by oral Vitamin K, injectable Vitamin K and fresh frozen plasma that repletes coagulation factors.
- Warfarin inhibits liver cytochrome p450s (CYP450) that normally break down and maintain healthy levels of other drugs and substances in the body.
- A number of other drugs act as inhibitors of CYP450:
  1. trimethoprim/sulfamethoxazole (antibiotic)
  2. amiodarone (anti-arrhythmic)
  3. fluconazole (anti-fungal)

SUMMARY & CONCLUSIONS

- We hope you enjoyed this interesting story of how a rat poison turned into one of the most widely therapeutic drugs in the world with the help of a chemist and later on clinicians.
- Warfarin has several disadvantages: need for constant monitoring of INR, drug interactions, and side effects.
- Although DOAC's have been introduced, warfarin still continues to hold therapeutic value due to being relatively inexpensive.

FUTURE DIRECTIONS

- New drugs on the market aim to achieve similar outcomes as warfarin while minimizing drug interactions and risk of bleeding.
- These drugs (DOAC's) require less monitoring and are well tolerated.
- DOAC's significantly reduce the rate of risk of bleeding events.
- We will study DOAC's that may replace warfarin as the standard of care in anticoagulation therapy.

ACKNOWLEDGEMENTS

- We give special thanks to Aditya Sathe, our mentor, the GTF board, and Dr. Atul Laddu for their encouragement and help with the preparation of this project.

REFERENCES

- Granger CB, Alexander JH, McMurray JJ V, et al: Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med, 365, 981-92, 2011.
- Hirota Y, Suhara Y. New Aspects of Vitamin K Research with Synthetic Ligands: Transcriptional Activity via SXR and Neural Differentiation Activity. International Journal of Molecular Sciences. 20, 3006, 2019.
- Lane DA, Lip GYP. Maintaining therapeutic anticoagulation: The importance of keeping "within range". Chest, 131,1277-1279, 2007.
- Lim, Gregory B. "Warfarin: From Rat Poison to Clinical Use." Nature News, Nature Publishing Group, 14 Dec. 2017, www.nature.com/articles/nrcardio .2017.172.
- Wigle P, Hein B, Bloomfield HE, Tubb M, et al: Updated guidelines on outpatient anticoagulation. Am Fam Physician, 15, 87, 556-66, 2013

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