Using Oral Delivery of Tenecteplase for Treatment of Plaque Buildup Resulting from Atherosclerosis in Coronary Artery Disease

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PROBLEM & SOLUTION

Coronary Artery Disease is the 3rd leading cause of mortality globally, with approximately 18 million deaths annually, and is the most common form of heart disease in the United States. Coronary Artery Disease is deadly due to its "silent but deadly" progression, its common occurrence along with high blood pressure, and the lack of access to treatments.

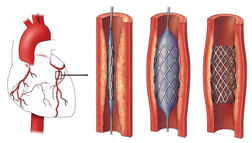
Our solution

Our solution to create a more effective, safe, and accessible treatment is to engineer an oral version of Tenecteplase. Currently, Tenecteplase is the most effective fibrotic blood clot-dissolving agent that is administered through IV. The oral medication would have an enteric coating to ensure that the intestinal tract does not disintegrate the medication. Furthermore, an enzymatic inhibitor extends the half-life and prevents unnecessary bleeding.

HISTORY & ALTERNATIVES

There have been many iterations of a similar medication. Most of which are versions of tissue plasminogen activators(tPA) which utilize amino acid substitutions from sites T, N, and K enhance their stability, specificity, and pharmacokinetic properties thereby dissolving blood clots. These medications clear blood clots by attaching to the fibrin at the surface of the clot and activating the plasminogen, converting it into plasmin. The plasmin then breaks up the fibrin molecules to dissolve the blood clot. Some side effects include surplus bleeding due to thinning of the blood and the breaking up of productive blood clots elsewhere in the body. The three most common fibrinolytic agents are Alteplase, Reteplase, and Tenecteplase, with Tenecteplase being the safest, cheapest, and most effective. For comparison, currently, Alteplase costs around $3600 while Tenecteplase costs around $1600 per dose. Other fibrinolytic agents are: Streptokinase, which binds with free circulating plasminogen to form a complex that converts plasminogen to plasmin, and Anistreplase which is a version of Streptokinase with plasminogen included so that it does not rely of free circulating plasminogen. However both Streptokinase and Anistreplase can lead to severe allergic reactions which could result in death, making is riskier than Alteplase, Reteplase, and Tenecteplase.

Another treatment for Coronary Artery Disease uses balloons to unclog the artery and then Stents to keep the arteries open. Stents are tubes made of wire mesh that is surgically inserted into the bloodstream and inflated using a balloon. These are relatively effective but can only be inserted invasively, and can result in an allergic reaction and rejection of the foreign Stent. Lastly, Stents are also costly and inaccessible.

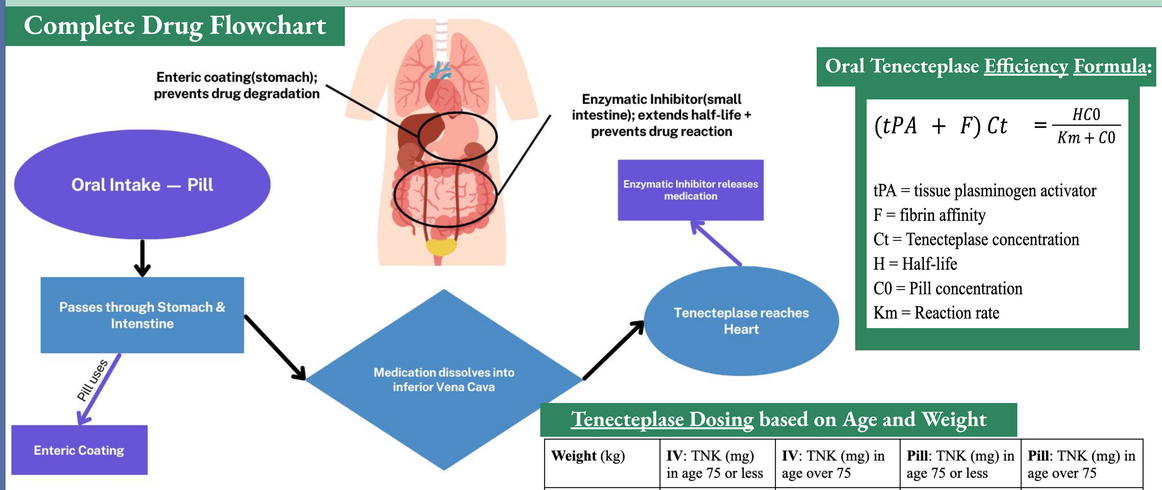


SELECTION MATRIX

	Stent Idea	Nano Medication Idea	**OUR SOLUTION:**
Solution:	Oral intake of **drug-eluted stent** (deflated/small) with entric coating & targeting fibrin	**Nano-Medication** in oral form with enteric coating which administers proper dosage of tenecteplase (or other chosen drug)	Oral medication of **tenecteplase** encased within inhibitors to stop early release & enteric coating
Efficacy(1-5)	4, Stents known to work well	3 or 4, Quite successful & used in multiple drugs already, but tissue response could be risky	5, Tenecteplase is known to work especially well
Accessibility(1-5)	3, Manufacturing Stents can be difficult	2, expensive	4, oral medication significantly more accesible than IV
Durability(how long does one dose last)(1-3)	2, Stent can last a lifetime, but may need to be replaced if an allergic reaction occurs	2, self administering	2, one dose required depending on bodyweight
Comfort(usability, pain level, administration)(1-4)	2, Difficult to infuse into bloodstream	4	4
Risk(side effects, safety, risk factors)(1-3)	1, Risky because of potential allergic reaction	1, body response to foreign body could be deadly	2, excess bleeding
Ethical & Waste(1-2)	1	1, expensive	2, no waste and cheaper than Alteplase

DIAGRAM

Complete Drug Flowchart



Oral Tenecteplase Efficiency Formula:

$$(tPA + F)\,Ct = \frac{HC0}{Km + C0}$$

tPA = tissue plasminogen activator
F = fibrin affinity
Ct = Tenecteplase concentration
H = Half-life
C0 = Pill concentration
Km = Reaction rate

Tenecteplase Dosing based on Age and Weight

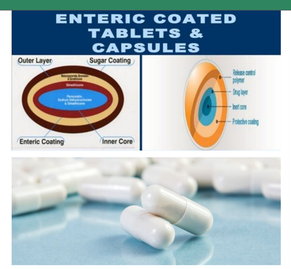
Weight (kg)	**IV**: TNK (mg) in age 75 or less	**IV**: TNK (mg) in age over 75	**Pill**: TNK (mg) in age 75 or less	**Pill**: TNK (mg) in age over 75
<60	30 mg (6 mL)	15 mg (3 mL)	3 mg	1.5 mg
60 to <70	35 mg (7 mL)	17.5 mg (3.5 mL)	3.5 mg	1.75 mg
70 to <80	40 mg (8 mL)	20 mg (4 mL)	4 mg	2 mg
80 to <90	45 mg (9 mL)	22.5 mg (4.5 mL)	4.5 mg	2.25 mg
≥90	50 mg (10 mL)	25 mg (4 mL)	5 mg	2.5 mg

Detailed Solution

To provide widely administered availability, especially for lower income communities, we propose using an oral intake method to administer tenecteplase. In our pill, it will be lyophilized (freeze dried), but kept in that powder form. Additionally, it is standard for oral intake of a drug to be 90% less concentrated than if in IV, so we will have a maximum concentration of 5mg. The Tenecteplase dosage within the pill will still vary based on body weight similar to conventional Tenecteplase.

Two of the primary design methods involved in creating a suitable pill for Tenecteplase are the use of enteric coating and two enzymatic inhibitors:

First, because the digestive system would typically cause a pill to dissolve from acid and enzymes once it reaches the stomach, and subsequently the drug to be circulated in the bloodstream. Our solution uses enteric coating to help keep the drug intact until it bypasses the stomach and reaches the intestine; thus dissolving the drug with a pathway to the heart.



Second, are the active enzymatic inhibitors which block the active substrate site of the drug with reacting to bodily enzymes. We chose reversible competitive inhibitors for easier engineering. The first inhibitor occurs in the stomach and beginning of the intestine, similar to the enteric coating, provides a secondary prevention of stomach and intestinal enzymes from denaturing the Tenecteplase drug. The second enzymatic inhibitor prevents Tenecteplase from decaying within its normal half-life of 20 minutes. Instead, the inhibitor extends the half life to 4-6 hours of Tenecteplase by blocking the 3 active sites: T, N, and K. Therefore, the drug will only active upon reaching the heart. Lastly, extending Tenecteplase half-life also prevents unnecessary bleeding since the drug is inhibited from dissolving in the bloodstream.

TESTING & BENCHMARKING

Testing will be done in 2 phases to ensure our drug is safe and effective for patients. First there is a computational simulation of drug efficacy, which was already completed by using Machine Learning to account for our drug's extended half-life and enzymatic inhibitor. Second, is animal clinical trials.

Simulating Drug Delivery

1. Quantifying and simulating how oral Tenecteplase moves through the bloodstream to ensure safety and efficacy
2. Using Machine Learning and data analysis, our solution already quantifies our drug efficiency. Shown in the efficiency formula above and uses the Michaelis–Menten model of enzyme kinetic to account for half-life enzymatic inhibitor

Animal Clinical Trials

1. For clinical trials, we would use a wide variety of mice with different heredity traits but with diagnosed or simulated Coronary Artery Disease.
2. One control group would take Alteplase and another with Tenecteplase, both administered through IV.
3. Then the test group will take a modified and sized-down dose of our oral Tenecteplase.

TECHNICAL CHALLENGES

There are 2 major technical challenges to account for:

1. First, if the enzymatic inhibitor is released too early or does not work properly, the Tenecteplase could no longer be active once it reaches the heart, it could be partially dissolved. Because Tenecteplase is a blood thinning and clot dissolving agent, its early release could also result in excess bleeding, as other parts of the body are unable to clot cuts. However these side effects are similar to that of conventional Tenecteplase. Our solution overcomes this challenge by opting for a longer half-life—by administering the drug with an inhibitor—to ensure the drug has reached the heart before activating.
2. Second, similar to the enzymatic inhibitor, if the enteric coating is too weak, the drug may be partially dissolved because of the stomach intestine's harsh conditions. Ultimately the effects of a weak enteric coating could also result in excess bleeding and and ineffective drug. There is not a real solution to this, but to standardize manufacturing with prudence.

ETHICAL & SOCIAL CONCERNS

Coronary Artery Disease is the most common heart disease in the United States. The high prevalence implies that the drug must be widely accessible to many people. Tenecteplase, being an improved version of Alteplase, is much cheaper. The maximum cost of alteplase through IV injection is $3600, while the maximum cost of tenecteplase through IV injection is $1600. Tenecteplase is covered by insurance, thus making it more accessible to a wider range of people

The oral delivery of Tenecteplase makes the cost further reduced, and therefore more accessible. Some ethical concerns of Tenecteplase include possible failure while being delivered. If tenecteplase is released from the pill early, there may be multiple consequences. The first involves the medication failing to be administered, and the blood clot still remaining. This scenario will lead to further issues stemming from the blood clot not clearing. The second involves excess bleeding in other parts of the body, including intracranial hemorrhage, systemic hemorrhage, immunologic complications, hypotension, and myocardial rupture. These can be incredibly dangerous towards the patient receiving the medication.

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