While many different microorganisms can cause endocarditis, the agent that the microbe is susceptible to. One option for antimicrobial cases need to be treated as quickly as possible with an antimicrobial drug-drug interaction. INR is a standardized measure of how long it patient's International Normalized Ratio (INR) due to the indirect action of warfarin (an oral anticoagulant) for a previous condition and person fails to use sterile technique when using a needle to inject themselves, the bacteria on the skin goes straight into the bloodstream and to the right side of the heart. The physician ordered penicillin G potassium, 4 million units IV every 4 hours. Penicillin kills S. aureus among other bacteria, such as Escherichio coli and Bacteroides fragilis. The pharmacist noticed the patient was also taking warfarin (an oral anticoagulant) for a previous condition and knew that penicillin G can enhance the effect of warfarin. However, the antibiotic was needed to save the man’s life, so the medication order was approved, along with a note to closely monitor the patient’s International Normalized Ratio (INR) due to the indirect drug-drug interaction. INR is a standardized measure of how long it takes a patient’s plasma to clot. Infective endocarditis is an infection and inflammation of the heart. While many different microorganisms can cause endocarditis, the most common cause is bacterial, specifically members of the Staphylococcus genus. Endocarditis can lead to several complications, the most dangerous and lethal of which is congestive heart failure. All cases need to be treated as quickly as possible with an antimicrobial agent that the microbe is susceptible to. One option for antimicrobial therapy is penicillin G, which binds to penicillin binding proteins and will be discussed in more detail.

Penicillin G and Penicillin Binding Protein 4: A Patient Case Related to Medicinal Chemistry and Drug Design
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Penicillin G (Figure 1) can enhance the effect of warfarin indirectly, leading to possible bleeding problems. Penicillin G binds to and destroys bacteria in the intestines that produce vitamin K. Vitamin K is used in body to create clots in bleeding episodes. Warfarin is used as a blood thinner and makes our blood less likely to clot. When penicillin G and warfarin are used in combination, a dangerous decrease in blood clotting occurs, making for an increased risk for life threatening bleeds. The following poster is a review of the indirect drug interaction between penicillin G and warfarin and will discuss a patient case dealing with this drug-drug interaction.

Penicillin Binding Protein 4 (PBP4) Structure:
- Consists of three domains (Figure 2)
  - Domain I consists of residues 1-80 and 294-477
  - Domain II consists of residues 81-172 and 248-292
  - Domain III consists of residues 173-247
- Enzymatic activity is found in Domain II
- C-terminus contains transpeptidase activity (Figure 3)
  - Consists of five stranded antiparallel β-sheet between two helical clusters
  - One cluster has seven helices and the other has two helices
- Active serine residue (serine-X-lysine) located in the larger α-helix cluster
- C-terminus contains carboxypeptidase activity (Figure 3)
  - Consists of two antiparallel β-sheets
  - Contains conserved sequences
  - serine-X-aspartagine
  - lysine-threonine-glycine
- Binding site for penicillin
- Penicillin binding site (Figures 4 and 5)
  - Pocket consists of three main residues, each in the context of a conserved sequence
  - Ser-X-Lys ➔ catalytic residue
  - PBP4: Pro-Ala Ser62-Thr-Gln-Lys-Val-Ile-Thr-Ala-Leu
  - Ser-X-Asn ➔ Beta-lactam antibiotic target
  - PBP4: Lys-Ile-Met-Leu-Lys-Ser306-Asp-Asn-Met-Ile
  - Lys-Thr-Gly ➔ Beta-lactam antibiotic target
  - PBP4: Val-Asp-Gly-Lys-Val-Ser-Ala-Lys-Thr418-Gly-Ser

Penicillin G
- Beta-lactam antibiotic
- Inhibits bacterial wall synthesis in gram positive and gram negative organisms
- Forms an irreversible covalent bond with PBP4 at the C-terminal end initiated by acylation involving a nucleophilic attack by serine5
  - Permanently inactivates PBP4, which inhibits its functions associated with cell wall formation5
  - Cell wall is weakened to the point of autoysis ➔ bacterial cell death ➔ fewer microbes and less vitamin K synthesis

The direct interaction between warfarin and penicillin G is due to penicillin binding to and killing microbes, decreasing the synthesis of vitamin K. The vitamin K reduction leads to warfarin toxicity and increases the risk of bleeding. Penicillin G could be modified to improve selectivity to a specific microbe, such as S. aureus. Through increasing specificity to S. aureus, other normal flora, such as E. coli and B. fragilis, would not interact with penicillin. Thus, normal flora would not be killed and vitamin K and clotting factors would still be produced without decreasing the effectiveness of the antibiotic. This would lead to less warfarin toxicity and less bleeding risks when taking penicillin.

Summary
As previously discussed, penicillin covalently binds to PBPs receptors within various microbes, including S. aureus and E. coli, which leads to weakened cell walls and, ultimately, autolysis. The penicillin kills the bacteria that produce vitamin K. Since there is less vitamin K present after taking penicillin, there is an increased risk of bleeding when concurrently taking warfarin. Modification of the penicillin molecular structure is the next step to producing a drug that binds more specifically with the microorganism resulting in fewer drug interactions.

References