Sriya Avadhanam
Mentor: Dr. Rashid

Introduction

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a prominent pharmacotherapy in the treatment of Type 2 diabetes (T2DM). Glucagon-like peptide 1 (GLP-1) is a hormone produced endogenously that stimulates insulin secretion, inhibits glucagon secretion, and delays gastric emptying. Together these effects help reduce the postprandial glucose excursion and may reduce the incidence of hyperglycemia. GLP1 RAs mimic these effects but are able to exert their effects over a much longer period than GLP1, which is quickly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4).

Determining which patients GLP-1RAs work best for is an open problem in personalized medicine. The models will be useful in generating a diverse population of virtual patients and simulating the pharmacological effects of the GLP-1RAs class of anti-diabetic pharmacotherapy. Towards this goal, this project focuses on developing mathematical models of GLP-1RAs and comparing the model results with data reported in literature and other pharmacological studies. In this project, we focused primarily on developing and refining the pharmacokinetic model of GLP-1RAs class of anti-diabetic drugs.

We focused on the GLP-1RA drug liraglutide, and studied how the drug concentration in the blood changed over time after subcutaneous administration. Our focus was to simulate a study and its conditions in order to generate synthetic population data that could be used to estimate model parameters and validate simulation results. Lastly, we utilized t-tests to compare our simulated group with the group from the research paper and validate that both groups had the same mean drug concentration level.
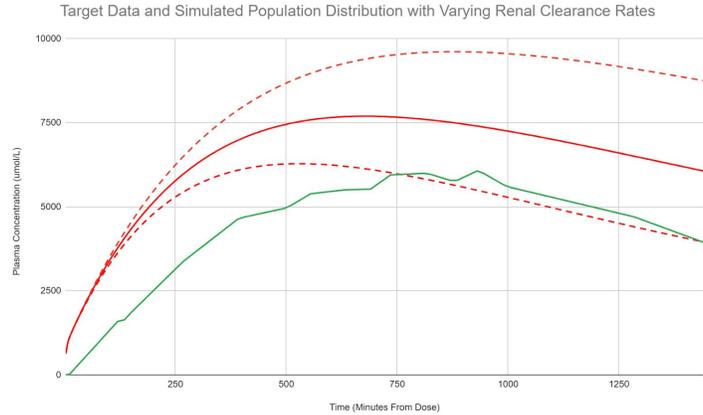
Methods

We looked at a study that was conducted by the British Journal of Clinical Pharmacology to study the influence of hepatic impairment on the pharmacokinetics of liraglutide. We decided to simulate their healthy group, which had patients with no hepatic impairment, using the software PK Sim. We simulated virtual patients on PK Sim using the same sample size, ratio of men to women, age group, BMI range, race, and method of administration. The PK Sim software asked for additional information including the lipophilicity of the drug as well as the solubility of the drug at a reference pH. This was not provided by the research study so we had to look to other sources to find this information. We simulated a 24 hour interval of the post administration drug concentration.

Using the graph of the research study's findings, we compared our simulated group's drug concentration over time with the curve of their healthy treatment group. Each time we changed the clearance rate of the drug we simulated the group. Therefore we had many different simulations that differed in only the clearance rate of the drug. PK Sim allowed us to find data points for every 3 minutes, which usually can't be done by clinical research studies done on human subjects. We interpolated the data from the study to have the same amount of data points from both groups. Next, we ran t-tests between each of our simulated groups and the study group in order to see if we could find a p-value greater than 0.05.

Results

Target Data and Simulated Population Distribution with Varying Renal Clearance Rates

GROUP	PVALUE
0.001	1.79E-17
0.002	6.24E-16
0.003	2.86E-14
0.005	7.44E-11
0.006	3.19E-09
0.007	1.06E-07
0.008	2.53E-06
0.01	4.73E-04

As we increased the renal clearance rate of the drug, the p-value that resulted from the t-tests increased, indicating that the difference in the mean drug concentrations between the simulated groups and the group from the study is becoming narrower. A p-value greater than 0.05 would mean we could accept our null hypothesis and agree that both groups have the same mean drug concentration. However, all of our PK Sim groups generated p-values less than 0.05. As shown by the graph, the mean of the simulated studies (solid red line) was higher than the mean of the research study group (green line).

Discussion
Although we didn't get the expected results, we observed a relationship between the rate of renal clearance and the Cmax, maximum concentration of the drug on the graph. As we increased the rate of clearance, the Cmax value decreased. Additionally, we observed that PK Sim can be efficiently used to get much more precise and detailed results of how a drug is eliminated over time. It can overcome the limitations of clinical trials and provides instantaneous data points that make it easier to model and define the relationship between the variables. Ultimately these models can help researchers and clinicians optimize drug treatment for type 2 diabetes.