Bean Boozled! The Variability in Effects of The Clopidogrel metabolite pool
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Choose right and it could save your life, but choose wrong and you could be gone. Well maybe I’m exaggerating a tad, but still the repercussions of playing such a game could prove to be disastrous! What is this game you might ask? Well it is none other than the russian roulette of candy games! It is the age old family game Bean Boozled. 20 jelly beans in a can, half of them of course are exactly like one other jelly bean in the can with one exception, the taste. 10 jelly beans taste wonderful and magical, yet each possesses a duplicate that taste absolutely dreadful! You are hoping to experience something that taste good but in fact what you actually receive might be the worst thing you have ever tasted. The point I am trying to make here is that you never know what you are going to get, there is too much variability! Now trying to explain this exact same phenomenon to patients being treated for cardiovascular complications (number one killer of people in the USA by the way) with a drug that has variability in effects equivalent to that of a jelly bean game is no small task. Even as you read this now you might be asking, “is this guy serious?”. Yes I am serious, the differences in jelly beans in Bean Boozled mirror the variability in pharmacological properties that clopidogrel as an antiplatelet drug exhibits.
Clopidogrel, also known by its brand name Plavix is a popular agent designed to prevent platelets in your blood from accumulating at a site of injury on a blood vessel wall. Clopidogrel does this by inhibiting the interaction of a specific prothrombotic molecule called adenosine diphosphate (ADP), which mediates platelet aggregation by binding to a receptor on the surface of platelets known as $P2Y_{12}$. Clopidogrel is a prodrug, meaning that it is only active after being metabolized in your body by a family of enzymes called cytochrome p450 enzymes.
However as a result of clopidogrel’s dependence on cytochrome p450 enzymes for activation, the prodrug is subject to a complex activation process. This means that clopidogrel does not always metabolize in the same way and that can be problematic. In fact, studies have shown that clopidogrel can form numerous metabolites within the body. We have reason to believe that several of these metabolites are contributing to reports of unfavorable interactions with other drugs in the body and variability in response to clopidogrel amongst patients. To emphasize, 40% of patients respond poorly to clopidogrel. Furthermore, what is even more problematic is that little known research has been conducted to characterize the effects of clopidogrel metabolite family in order to confirm that all the drug is doing is inhibiting platelet aggregation. In light of this, the Lauver lab at Michigan State (my lab) is investigating what specific kinds of effects is clopidogrel having on the body.
In order to investigate clopidogrel’s effects, we are conducting a comparative study between the metabolite that is believed to be responsible for the inhibition of platelet accumulation (clop-AM) and the drug as a whole to see if there are differences in the effects that each has on the body. To test these effects, our research team has previously reported a drug known as DT-678 developed from the platelet inhibiting metabolite of clopidogrel. We also possess bleeding data that suggest clopidogrel causes more bleeding than DT-678 suggesting that it is doing something other than inhibiting platelets. We hypothesize in this study that, clopidogrel will display significant effects on blood vessels ability to constrict and dilate in the presence of molecules that promote vascular activity where DT-678 will not. We expect that clopidogrel will show effects on blood vessels in the absence of platelets, hinting that clopidogrel’s other metabolites may be affecting other receptors and biomolecules in the body. This project is contributing to important work by highlighting specific actions that clopidogrel is exhibiting in the body. This helps us to better understand the drugs that we are using to treat
people suffering from Acute Coronary Syndrome, Heart disease, atherosclerosis, heart attack, stroke, ischemia, and other platelet induced thrombosis related cardiovascular complications. Moreover, by investing clopidogrel metabolic pathways we can improve upon the antiplatelet therapeutic strategies that are currently in place. The more we can reduce the number of unknown actions of clopidogrel’s metabolites on the body the better because ultimately we do not want to play Bean Boozled with someone’s life.

Photos:
1. https://www.researchgate.net/figure/Pathways-of-clopidogrel-metabolism-Evidence-for-the-enzymes-involved-in-these-pathways_fig1_237076997
2. https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/high-blood-pressure/art-20045868