Genetic Factors: Effects on Medication

Student Materials: Reading Assignment

Introduction

In this unit you will learn how to determine the proper dosage of a medication that is metabolized differently by people with certain genetic variations, and what the consequences would be if those patients weren't treated individually.

Most medicines act fairly consistently from one person to the next. This is why many medicines, including most over-the-counter medications, are prescribed using one standard dose for all adults. But we all know that some people can be more sensitive to a particular medication than other people. This variation might be due to different weights; the same size dose would produce a smaller concentration of the medicine in larger people than in smaller people . Another reason for different responses to a medicine is due to variations in genetic make-up that cause some people to metabolize a certain medicine differently than others do. Most of these genetic differences are complex and are difficult to determine with any degree of certainty; but a few genetic differences are well documented.

One genetic trait that has been well documented is the difference between what are called **slow** and **fast** acetylators. Slow acetylators break down certain medicines at a very slow rate while fast acetylators break down the same medicines much more quickly. Among the drugs that are metabolized differently by these two groups are an anti-tubercular drug, many sulfa drugs used to treat bacterial infections, and a drug that helps control the heart-rate. Slow acetylators are at risk of toxic affects from these medications because more of the drug reaches their plasma than for fast acetylators. Fast acetylators are at risk of having too little of the drug in their plasma to have the desired beneficial affect.

Different proportions of the population of different ethnic groups are slow and fast acetylators. The following table lists some populations and the approximate percents that are slow acetylators.

Ethnic group	slow acetylators
Koreans	10%
Thai	25%
Chinese	20%
Japanese	10%
Indians (India)	60%
Germans	50%
Italians and Spanish	55%
Athabascan Indians	40%
Yellowknife, Dogrib, and Chippewyan Indians (Canada)	10%

Generally, about 60% of people of European and African ancestry are **slow** acetylators with the remaining 40% being **fast** acetylators. However, the percents can vary

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somewhat by country and latitude. For example in Africa, a study of Ugandans indicated that between 49% and 61% are slow acetylators, while a study of Egyptians indicated that between 72% and 94% are slow acetylators.

Slow acetylators are homozygous, meaning that they have two copies of the allele that causes slow acetylation. Fast acetylators include both homozygous individuals, those with two copies of the fast acetylation allele, and heterozygous individuals, those with one copy of each allele. There is some evidence that the heterozygous individuals have a slightly slower acetylation rate than the homozygous fast acetylators. For the purposes of this unit, we group the intermediate and fast acetylators into one group.

Unfortunately, the only realistic way to know whether a person is a slow or fast (or intermediate) acetylator is to monitor the drug concentrations in that person or to monitor the actual affects of the medicine.

Hydralazine and Hypertension

In this unit, you will study a drug called Hydralazine that is used in the treatment of hypertension or high blood pressure (including severe hypertension during pregnancy), congestive heart failure, and other diseases and conditions. This medicine reduces blood pressure rapidly, and so it must be used with extreme caution so that the patient's blood pressure does not drop too low.

An additional risk in prescribing Hydralazine is that only 10-20% of an oral dose of Hydralazine reaches the blood in a patient who is a fast acetylator, while 30-40% of the oral dose reaches the blood in a patient who is a slow acetylator. The reason for the differences is that fast acetylators break down more of the drug before it reaches the blood than do slow acetylators.

Normally, a patient takes one tablet of Hydralazine twice daily. A typical 150 pound patient would respond to treatment if 10.5 mg of the Hydralazine in this tablet reached his or her blood. Essentially all of the Hydralazine taken in one tablet is eliminated from the blood when the next dose is taken, so the physician doesn't have to worry about the medicine building up in the patient. The physician just has to find the correct dose to get the 10.5 mg of medicine into the patient's blood.

1. Suppose a patient is given a 50 mg tablet of Hydralazine. Find the range of amounts of the Hydralazine which reaches the bloodstream of a slow acetylator. Then find the range of amounts of the Hydralazine which reaches the bloodstream of a fast acetylator.

2. Suppose that a certain patient absorbs 15% of the Hydralazine. Find the dose that would result in 10.5 mg being absorbed.

3. Suppose a patient is given 60 mg of Hydralazine. If this is exactly the proper dose, what fraction of the Hydralazine must be absorbed.

Prescribing Hydralazine Safely
Classroom materials

Recall that 1) fast acetylators absorb 10-20% of an oral dose of Hydralazine into the blood, and slow acetylators absorb 30-40%. There are two quantities that vary: the size of a dose of Hydralazine varies from patient to patient, and so does the percent of the Hydralazine that is absorbed into the patient's blood. The one constant is that 10.5 mg of Hydralazine should be in the blood after taking a dose.

Let x represent the fraction of Hydralazine that reaches the blood in a patient. For a fast acetylator, x would normally be between 0.1 and 0.2, but for a slow acetylator, $0.3 < x < 0.4$ is typical. Let y represent the number of milligrams of Hydralazine that needs to be prescribed so that 10.5 mg of Hydralazine reaches the patient's blood. Normally this dose of y mg is given every 12 hours, although elderly patients may require smaller doses given 4 times per day.

4. Develop an expression relating y, the number of milligrams of Hydralazine being prescribed, and $x,$ the fraction of that amount which is absorbed into the blood, remembering that the goal is to have 10.5 mg reach the blood.

5. Write y in terms of x. Graph this equation on a calculator, using a realistic window for x.

6. Find the normal range of medication that slow acetylators receive, remembering that they absorb between 30% and 40% of the medicine. Pills come in 10, 25, 50, and 100 mg sizes, and they can easily be broken in half. Determine what might be a proper dose for a slow acetylator.

7. Find the normal range of medication that fast acetylators receive, remembering that they absorb between 10% and 20% of the medicine. What might be the proper dose for a fast acetylator?

8. Explain, using the graph of y in terms of x, why there is a greater range for prescribing Hydralazine to fast acetylators than to slow acetylators. (The graphs of functions of this form are called *hyperbolas.)*

Because of the difficulty in determining the genetic type of a patient, Hydralazine is initially given in small doses which are increased in size until the optimum effect is seen.

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