Prescribing Medications: Complicating Factors I

Student Material: Reading Assignment

Introduction

You probably know that the liver and kidneys eliminate chemicals from the body. In this activity, we discuss other ways in which chemicals are eliminated from the body and distributed through the body. We use hypothetical numbers to help you understand the processes that are taking place because the correct numbers are sometimes impossible to determine since full information about the physiological process is often not known.

The primary method for elimination of drugs from the body is through filtration by the kidneys and liver metabolism. When the liver metabolizes a drug, it turns it into new chemical compounds. Sometimes these new chemicals are inactive in the body and are eliminated over time. Other times the new chemical also interacts with the body, causing other effects. For example, some of the asthma medication, theophyline, is metabolized into caffeine.

One interesting phenomenon is that the body can convert some of a chemical into a second chemical, then convert the second chemical back into the first chemical. This process is called **interconversion**. In this case, a person given one drug can end up being treated with two drugs. One goal of this activity is to help you understand the dynamics of drug interconversion.

One important chemical for which this happens is vitamin K, which is essential for the blood to coagulate. Without vitamin K in our system, we would continue bleeding from just a small injury. We would also be prone to hemorrhaging. Green leafy vegetables (e.g., spinach or cabbage), egg yolks, tomatoes, wheat germ, soybeans, and potatoes are all sources of Vitamin K.

The body metabolizes vitamin K into what is called **vitamin K-epoxide** which is inactive in the body, but the body converts some of it back into vitamin K. People who have had blood clots, pulmonary embolism and heart attacks are often treated with anticoagulants. One popular anticoagulant, Warfarin, works by preventing vitamin K-epoxide from converting back to vitamin K, resulting in a reduction in the amount of vitamin K in the blood, which then decreases the bloods ability to clot.

Another pair of chemicals for which interconversion occurs is Prednisone and Prednisolone. Prednisone is an adrenal corticosteroid used to treat an almost endless list disorders, such as skin rashes, asthma, arthritis, blood disorders, and ulcerative colitis. When chemicals convert to each other, over time the amounts of each of these chemicals in the body stabilize at a constant ratio. Because of this, physicians can prescribe either of these two medications and reach the same therapeutic level of Prednisone.

Interconversion occurs with the drug Clofibrate, which is used to help lower cholesterol and triglycerides. For this drug, interconversion can cause a problem. In people with reduced kidney function, there is often reduced elimination from the blood of

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the chemical paired with Clofibrate. This can cause Clofibrate to build up in the body if the prescribed amount is not reduced.

One more pair of chemicals that exhibit this behavior is Sulindac and Sulindac sulfide. Sulindac is prescribed to reduce inflammation and relieve pain from arthritis, bursitis and other inflammatory diseases. Sulindac is the chemical that is prescribed, but, in fact, Sulindac sulfide is the active drug. This interconversion helps moderate and sustain the concentration of Sulindac sulfide in the blood.

Drug interconversion is somewhat complicated to model. To begin, you will model a contrived and silly situation, but a situation that should be easy to follow. The drug model will be almost identical to this situation. Thus, once you master the contrived situation, you should be able to construct a model of drug interconversion.

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Simulating interconversion

You have a group of 3 or 4 people. Designate one person in your group to be person A and another to be person B. If there are 3 in your group, the third person will be person C and will also keep a table of the total of the amounts of money each person has at the beginning of each simulated "day" of this game. If there are 4 people in your group, the fourth person should keep the group totals, not person C.

You are going to play a "game" in which each of A, B and C have some amount of money. During each "day" or round of the game, each person will give some amount of money to each of the other two. The goal is to keep track of how much each person has after each day and to predict how much each person will eventually have if the game is played long enough. At the beginning of day 1, person A has $52, person B has $82 and person C has $20. Each person should write down their total in a "checkbook" like table 1 (below). Each person should also use this checkbook to keep track of how much they have given away, how much they have received, and how much they have at any point in time. There is a different set of rules for each player which describes how much money that person gives away and receives.

Rules for person A: Each day or round, you begin with a certain amount of money. Give 5% of that money to B and 40% of that money to C.

Rules for person B: Each day or round, you begin with a certain amount of money. Give 20% of that money to A and 10% of that money to C.

Rules for person C: Each day or round, you will give $7 of your money to A and $2 of your money to B.

Group rules: To begin each day, all three people simultaneously compute how much money they are going to give to each of the other people, using their individual rules. They each write "checks" to each of the other two people; that is, they write the amount they are giving each person on a slip of paper. After they have all completed their calculations and written their checks, each person gives their checks to the other two. Finally, each person tabulates how much money he or she has after giving this money away and collecting some money from the other two. This is the amount they begin the next day with. A fourth person records all three of these next day amounts in a table. (If your group has only three members, person C keeps the group table.)

Applying these rules, person A's checkbook would look something like table 1 after the completion of the first day.

Table 1: Checkbook for person A			
Description	Debit	Deposit	Total
beginning of day 1			\$52.00
gave 5% to B	– \$2.60		\$49.40
gave 40% to C	– \$20.80		\$28.60
received from B		+\$16.40	\$45.00
received from C		+\$7.00	\$52.00
beginning of day 2			\$52.00
. . .			

1. Each person already knows his or her first day amount.

a. Each person computes his or her amount at the beginning of day 2 and completes that portion of the checkbook (as has already been done for person A in Table 1). Each person should share these results with the rest of the group and one person should record the final results in a table.

b. Each person computes his or her amount at the beginning of day 3, completes that portion of the checkbook, and shares these results with the group.

c. Each person computes his or her amount at the beginning of day 4, completes that portion of the checkbook, and shares these results with the group.

2. Let a represent the amount of money that person A has at the beginning of some day. Let b represent the amount of money that person B has at the beginning of that same day.

a. Write a simple expression in terms of a for how much money person A has after removing the money he or she is going to give to persons B and C.

b. Write a simple expression in terms of b for how much money person A is receiving from persons B and C.

c. Use your answers to parts a and b to write an expression for a_{next}, the amount that person A has at the beginning of the next day. This expression should be in terms of a and b.

d. Write an expression for b_{next}, the amount that person B has at the beginning of the next day. This expression should be in terms of a and b.

e. Check the equations you developed in parts c and d by substituting A and B's day 1 results into these equations for the letters a and b, and by substituting A and B's day 2 results for a_{next} and b_{next}. Check one more time using the day 2 results for a and b and the day 3 results for a_{next} and b_{next}.

f. As you will see if you work part g, after a large number of days, person A will have about the same amount of money at the beginning of each day. This means that the amount A has at the beginning of one day, a, and the amount person A has at the beginning of the next day, a_{next}, will be about the same. This means that $a \approx a_{\text{next}}$. To help find out what this value is, you can substitute a for a_{next} in the expression you developed in part c. Similarly, after some amount of time, $b \approx b_{\text{next}}$, so you can substitute b for b_{next} in the expression you developed in part d. Solve this sysyem of two equations.

g. (Optional) Use a calculator or spreadsheet program to compute the amounts of money A and B have at the beginning of the 5th, 10th, and 20th days, using full accuracy of your calculator, even though you can't have a fraction of a cent in real life. Compare your results to the answer to part f.

h. (Optional) Let person A begin with $20, let person B begin with $30, and let person C begin with $94. Repeat the same rules and determine the amounts of money A and B have at the beginning of the 5th, 10th and 20th days, again using full accuracy of your calculator. Do these answers make sense to you?

3. Play the game again using the same rules for A, B and C. But this time, let person A begin with the amount you got for a in problem 2f, let person B begin with the amount you got for b in problem 2f, and let person C begin with $124.

a. Complete a table similar to table 2:

Table 2: Totals at beginning of day

	Day 1	Day 2	Day 3
A			
B			
C			

b. Explain your results. How does your work in problem 2 connect to these results?

When the game has reached the point in which the amount of money that A, B and C have doesn't change from one day to the next, the game is said to be in **equilibrium**. In the homework, you will develop a model of interconversion of two chemicals in the body which will be similar to the money model you just developed. Like the money model, the chemical model will reach a point in which the amount of each of the two chemicals in the body doesn't change from the beginning of one time period to the beginning of the next. As with the game, at this point we would say these two chemicals are in equilibrium in the body. The purpose of problem 2h was to see that, often, the equilibrium does not depend on the starting amounts. To convince yourself of this fact, try starting A, B and C with other amounts, keeping the total amount at $154.

There are two reasons we didn't ask you to develop an equation for person C. The first is that the total amount of money the 3 people have remains constant. Thus, once

you know how much money A and B have, you can easily figure how much money C has. The second is that when you develop a model for the interconversion in the homework, there will be two chemicals that will take the place of person A and person B. Person C represents the amounts of the two chemicals that are added to the body and removed from the body each day. Our main concern is the amount of the two chemicals in the body, so like our money problem, we only develop equations for the two chemicals, A and B.

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student materials: Homework

4. Play the same "game" with the following new rules.
A's rules: Person A gives 20% of his or her money to B and 20% to C each day.
B's rules: Person B gives 30% of his or her money to A and 30% to C each day.
C's rules: Person C gives $8 to A and $3 to B each day.
Person A begins with $10, B begins with $170, and C begins with $30.
a. Find each person's day 2 amount.
b. Find each person's day 3 amount.
c. Find equations for a_{next} and b_{next} in terms of a and b.
d. Check your equations using your day 1 results for a and b and your day 2 results for a_{next} and b_{next}.
e. Substitute a for a_{next} and b for b_{next} in the equations you developed in part c and solve for a and b. Here, you are assuming the game reaches an equilibrium. You can check this assumption in part g.
f. Write a sentence or two explaining what you are doing when you substitute a for a_{next} and b for b_{next}.
g. (Optional) Find the day 5, 10, and 20 amounts for A and B and compare to the answer to part e. Here, you are verifying that the game approaches its equilibrium.

Modeling Interconversion with Mathematics

Suppose there are two chemicals in the body, which we call X and Y. Suppose the body eliminates 10% of X and 15% of Y each day through the kidneys. Suppose in addition, liver enzymes metabolize 40% of the X into Y and 30% of the Y into X each day. Let us assume the body absorbs 30 mg of X and 50 mg of Y each day from its diet. The question we wish to answer is, over time, how much X and Y will be in the body at the beginning of each day?

To answer this question, we let x and y represent the amount of X and Y, respectively, in the body at the beginning of some day. We wish to compute x_{next} and y_{next}, the amount of X and Y, respectively, in the body at the beginning of the next day. You are now going to develop a model that is quite similar to the model you developed for our contrived game.

5. In this question, you are going to find an equation for x_{next} in terms of x and y. It may help to use the following steps. 1) Find an expression in x for the amount of X left in the body after 10% is filtered and 40% is metabolized into Y. 2) Find an expression for the additional amount of X in the body, after 30% of the Y is metabolized into X and 30 mg of X is consumed. 3) Find an expression for x_{next} in terms of x and y, using the answers to parts a and b.

6. Find an equation for y_{next}.

7. Substitute x for x_{next} and y for y_{next} into the equations you developed in problems 5 and 6. Then solve the two equations to find the equilibrium amount of the two vitamins in your system. In the next part, you will verify that the body reaches equilibrium.

8. (Optional) Pick your own values for the beginning amounts of X and Y in your body. Use the equations you developed in problems 5 and 6 to find the amount of X and Y in your body after 10, 20, and 30 days. How do these amounts compare with the answers to problem 7?

Summary

In real situations, it is difficult to compute the percent of each chemical that is converted to the other. It is easier to compute the amount of each chemical that is eliminated in the urine. By actually observing the equilibrium of the drugs in your blood and the amounts eliminated in the urine, scientists can make inferences about the conversion rates.

One point behind this activity is to help you understand how interconversion can affect the amounts of chemicals in your body and also affect the elimination rates. In studying the urine to determine how much of chemical A is being eliminated, a physician would come to an incorrect conclusion if she did not know about interconversion. One way she could make an error is that some of drug A may be converted to drug B, which is then eliminated. This would mean that more A is eliminated than the urine test seems to indicate. On the other hand, it could be that some of drug B is being converted into drug A, which is then eliminated. This would lead the physician to think that more A is being eliminated than actually is eliminated. Either result could lead to the physician prescribing an incorrect dosage for the patient.

Another point is to see that interconversion, combined with constant dosage of one or the other or both chemicals, leads to an equilibrium amount in our bodies. If you did the optional problems, you saw how over time the total amount of each chemical stabilized at the same amount, no matter what the starting amount. The equilibrium amounts correspond to a physician's target goal for one or both of the medicines.

Prescribing Medications: Complicating Factors II

Student Classroom Materials with a follow-up Reading Assignment

There are other factors that complicate the elimination of chemicals from our bodies. One of these factors is that usually a chemical is deposited in several places in the body. Lead is one chemical where this is of concern. The percents in problem 1 are not accurate. It is difficult to compute the correct values for lead, and they vary from child to child; but the general process described in the problem, which leads to a large amount of lead being deposited in the bones, is accurate.

1. Suppose a child absorbs 6 μg (micrograms) of lead into his blood each day. Suppose that each day, 1.5% of the lead in the blood is filtered out by the kidneys, 3.8% of the lead in the blood is absorbed into the bones, and 0.2% of the lead in the bones is released back into the blood.

a. Let x represent the amount of lead in the child's blood today and let y represent the amount of lead in his bones today. Let x_{next} and y_{next} represent the amount of lead in the child's blood and bones, respectively, tomorrow.

i. Develop one equation for x_{next} and another for y_{next}, both in terms of x and y.

ii. Substitute x for x_{next} and substitute y for y_{next} into the equations. Solve for the equilibrium values x and y. This gives the amount of lead that would eventually be in this child's blood and bones over a period of time.

b. In addition to being deposited in the blood and bones, some lead is also absorbed into the kidneys and liver. Let z represent the total amount of lead in the kidneys and liver, as a unit, today and let z_{next} represent the total amount of lead in the kidneys and liver tomorrow. In addition to our previous assumptions about lead, assume that 1% of the lead in the blood today is absorbed into the kidneys and liver tomorrow, and that 2% of the lead in the kidneys and liver today are absorbed into the blood tomorrow. Develop 3 equations, one each for x_{next}, y_{next}, and z_{next}. Then substitute x, y, and z for the appropriate inputs and outputs and solve for the equilibrium amounts of lead in the blood, the bones, and the kidneys and liver.

2. Vitamin A is stored primarily in our plasma and our liver. Suppose that 40% of the vitamin A in the plasma is filtered out by the kidneys each day and that 30% of the vitamin A in the plasma is absorbed into the liver each day. Also assume that 1% of the vitamin A in the liver is absorbed back into the plasma each day. Suppose you have a daily intake of 1 mg of vitamin A each day, which goes directly into the plasma. Determine equations for x_{next} and y_{next}, the number of milligrams of vitamin A in the plasma and liver, respectively, tomorrow in terms of x and y, the amount of vitamin A in the plasma and liver, respectively, today. Find the equilibrium amounts of vitamin A in the plasma and liver.

Sources of Vitamin A include dark green and deep yellow vegetables, eggs, fish liver oils and animal organ meats. Vitamin A contributes to bone growth and healthy skin. One of its major tasks in our bodies is to synthesize protein. Vitamin A deficiency and protein deficiency are the human race's two most serious nutritional problems. Deficiency of Vitamin A is common in Southeast Asia, the Middle East, Africa, Central America, and South America; it is particularly common among children. Vitamin A deficiency can result in night blindness (inability to see well in medium-dim light), increased respiratory infections, skin lesions, and diarrhea.

While the numbers we use for the transfer of vitamin A between the liver and plasma are not quite right, they give a good sense of what actually happens; that is, the amount of vitamin A in your liver is much greater than the amount in your plasma. This is true for many animals. The vitamin A concentration in polar bears' livers is so high that people have had toxic reactions to vitamin A from eating them.

Using the same numbers as in problem 2, assume that you stop taking in vitamin A; that is, the amount of vitamin A ingested each day is 0, not 1 mg. Then if you use your new equations for x_{next} and y_{next} recursively, starting with x and y at the equilibrium you computed in problem 2, you would see that the amount of vitamin A in your plasma remained at or near 1 mg, whether you stopped taking vitamin A for 2 days or 2 months. The reason this happens is that most of the vitamin A is in the liver but most of the elimination is from the plasma. Thus, if your body is not supplied with vitamin A, your liver's reserves of A drop gradually. Thus, the good news is that it takes several months for a vitamin A deficiency to become a problem. The bad news is that vitamin A deficiency cannot be easily diagnosed with a blood test, since normal concentrations of vitamin A in the plasma could be a result of adequate supplies or a recent, temporary, addition of vitamin A to the diet.

Interconversion also occurs with vitamin A. For a more complete understanding of vitamin A in our bodies, we could develop a model that includes both interconversion and the storage of vitamin A in both our plasma and our liver.

Prescribing Medications: Complicating Factors I and II may have helped you understand some of the intricate interactions that occur between chemicals in your body that can make it difficult for physicians to prescribe the correct dosage of a medicine. When we consider the fact that interconversion may occur simultaneously with the two chemicals being absorbed into several different parts of the body, as with vitamin A, it is clear that much work is required to totally understand the dynamics of any chemical being studied. Another complicating factor is that it is often impossible to measure directly how much of a chemical is changing or moving from one part of the body to another. Much of the evidence being gathered about chemicals is circumstantial and the conclusions made are through inference. But good use of mathematics can help researchers make better deductions.

Acknowledgment: Some material for this lesson came from 1) *Fat-Soluble Vitamins: Vitamins A, K, and E* by H. George Mandel and Victor H. Cohn in **Goodman and Gilman's The Pharmacological Basis of Therapeutics**, edited by A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, Pergamon Press, Elmsford, N.Y., 1990; 2) **Clinical Pharmacokinetics: Concepts and Applications** by Malcolm Rowland and Thomas Tozer, 1989, Lea & Febiger, Philadelphia; and 3) The **Pill Book, 4th Edition**, by Gilbert Simon and Harold Silverman, 1990, Bantam Books, New York. We also thank Dr. Carl Peck, Professor of Pharmacology and Medicine, Georgetown University, for helpful comments and suggestions.