Does a One-Size Drug Dose Fit All?

or

Why All the Variability in the Theophylline Blood Concentrations?

by
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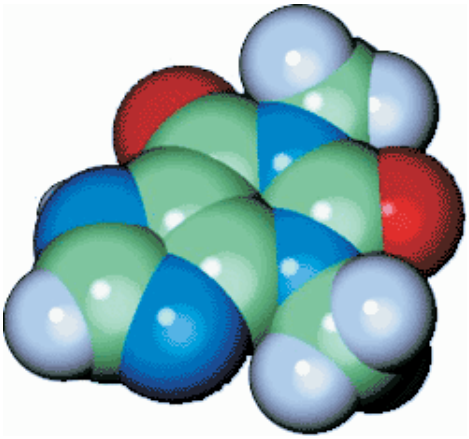

Dr. Chris Brason had just returned from teaching her drug therapeutics class, when she noticed that there were several voice mail messages for her. She sat down at her desk to draw a deep breath and relax for a moment. While she found teaching to be personally rewarding, it was also mentally exhausting. Her students expected a lot from her and she did her best not to disappoint them. She picked up the phone, opened her voice mailbox, and patiently listened to the messages. One of the messages was from her husband, informing her that his root canal at the dentist's went as well as could be expected. Another message was from a departmental administrative assistant, asking if she could attend a department meeting next Thursday afternoon. The last message was from an old friend from graduate school.

"Hey Chris, long time, no talk!" bellowed the recorded voice. "Seems like it's been a few years since we last saw each other at the Experimental Therapeutics conference. Hope all is well with you. Hey, the reason I'm calling is I need some help with a clinical trials drug study I'm conducting. Since you're the expert in drug therapeutics, I'd thought I'd call you and see if you'd be interested in collaborating on the study. I really need your help. I'll be in until 5:30 today, so if you can, please give me a call back and let's talk. Walther, at area code two-three-four, 567-8901."

Chris smiled. "What's Roger up to now?" she thought to herself. "It has been a while since we've crossed paths." Chris quickly dialed Roger's number. The phone rang once. Twice. A third time. Then,

"Hello, Dr. Roger Walther, Department of Clinical Pharmacology, speaking!"

"Hi Roger! How are you? How's the family? It's been a while since we've talked!"

"Chris, it's so great to hear from you! I'm glad that you returned my phone call!"

And with that, Chris and Roger chatted like old friends—about family, the "good old days," and their research interests. The conversation eventually turned to Roger's clinical drug study.

"Chris, here's the story. I'm conducting a study of theophylline in patients with asthma. Basically, the problem is that clinicians have a difficult time dosing patients with theophylline. Different patients respond differently to the same theophylline dose—some patients respond well and their asthma is controlled. Other patients do not respond well and their asthma is uncontrolled or, just as worrisome, they experience toxic side effects. The question is why do different people respond so differently to theophylline? My clinical colleagues and I think that there are certain patient characteristics that may predict how a patient may respond to theophylline. So we're doing a clinical trial on the dosing of theophylline and trying to identify predictive factors. Basically, when a patient is admitted to the hospital

with uncontrolled asthma, we take a detailed history from the patient, and start the administration of theophylline by intravenous infusion at a rate of 0.5 mg per kg body weight per hour for 24 hours. We closely monitor each patient during this time to see if his or her asthmatic condition improves. Then we draw a 5 ml blood sample at 24 hours to determine what the theophylline blood concentrations are after the drug infusion period. This study has been on-going for about 13 months, and so far we've collected data on 144 patients of all types from all walks of life."

"Sounds like a terrific study, Roger, and it certainly addresses an important drug therapy issue," interjected Chris. "But in your voice mail, you said that you might be able to use my help."

"Yes, I was getting to that part," said Roger. "We have a lot of data, and we're having a difficult time sorting it all out. For the same intravenous dose, we're observing blood concentrations that range from 8 to 31 micrograms per ml. Some patients respond well and others don't. We've tried to identify which patient factors might be related to the blood concentrations, but we're just overwhelmed by all the data. We need your help. Would you be willing to look at the data and help sort it all out?"

"Certainly!" said Chris. "Just send the data to me and I'll see what I can do."

"Great! I'll send the data to you by Fed Ex."

Thinking Questions:

1. What is the scientific problem? How might the problem be stated as a scientific hypothesis?
2. Describe each step of the clinical trial. What information might be obtained from each step? (Hint: You may need to do a web search for information on clinical trials. A good starting point is the Food and Drug Administration's (FDA) website on clinical trials at: http://www.fda.gov/cder/learn/CDERLearn/default.htm. This web site is free, but you will need to register for it and requires 90 minutes to complete. Another alternative FDA website on the drug development process and clinical trials is: http://www.fda.gov/cder/handbook/develop.htm. This site has an interactive chart that offers detailed information on the clinical trials process.)

Group Activity:

1. You are to assume the role of Dr. Chris Brason, an expert in drug therapeutics. In class you will receive the patient data cards to identify
    a. those patient factors which influence theophylline blood concentrations, and
    b. the therapeutic range of theophylline blood concentrations.
2. What results would you report back to Dr. Roger Walther?
3. How would the results guide the development of an individualized dosing regimen?

Image Credit: A ray-traced, space-filling model of theophylline generated by Sam Mikes (http://www.cs.hmc.edu/~smikes/). Used with permission.

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