

Does a One-Size Drug Dose Fit All? Or, Why All the Variability in the Theophylline Blood Concentrations?

Dr. Patricia Todebush had just returned from teaching her Medicinal Chemistry 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 appointment at the dentist's went as well as could be expected. Another message was from a Dr. Clower, asking if she could attend a department meeting next Thursday afternoon. The last message was from an old friend from graduate school.

"Hey Patricia, 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 this type of thing, 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. My number is 481-567-8901."

Dr. Todebush smiled. "What's Roger up to now?" she thought to herself. "It has been a while since we've crossed paths." Dr. Todebush 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!"

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

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

"Patricia, 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 Dr. Todebush. "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 (the data he is referring to are the cards with the patients info. The blood concentration is listed on the top right). We need your help. Would you be willing to look at the data and help sort it all out?"

"Certainly!" said Dr. Todebush. "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."

Answer the following questions before you are given the patient data cards. You are welcome to work in groups. Feel free to have inter- or intra-group discussions.

- What is the scientific problem? How might the problem be stated as a scientific hypothesis?
- List 5 factors that you think can affect the responsiveness of a patient to any drug.
- Describe the pharmacokinetics of theophylline. Make sure you include the following three terms in your response: Absorption, Distribution, Metabolism and Elimination
- How long has Theophylline been on the market? State the side effects associated with low blood concentration of Theophylline and the side effects associated with high blood concentration of Theophylline.

Ask for your patient data cards now. Your patients will NOT be the same as your neighboring group. Combine your data with the other group to answer the questions below.

- From the patients' cards, what is the therapeutic range of theophylline blood concentrations? What is the concentration at which it starts causing side effect and what is the concentration at which it has no significant therapeutic effect?