

## TEACHERS' TOPICS

### Teaching Pharmacodynamics: An Introductory Module On Learning Dose-Response Relationships

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The introductory pharmacodynamics course entitled, *Principles of Pharmacology*, was designed as an active-learning exercise to help students discover basic pharmacology principles associated with dose—response curves and drug-receptor interactions. Autonomic drugs were used to illustrate many of the principles. Rather than use pure lecture format, the instructor led students through a discovery process to understand the principles. During the learning process students were encouraged to develop both lower-order and higher-order learning processes. An example is presented here in which a simulated treatment of fever with an antipyretic demonstrates progressive development of a quantal distributional plot, a quantal cumulative dose-response curve, and a continuous cumulative dose-response curve, and the use of log dose to enhance data presentation.

**Keywords:** Pharmacodynamics, dose-response, drug-receptor interaction, Socratic teaching, pharmacology

#### INTRODUCTION

*Principles of Pharmacology* is a foundation course designed for first-professional-year pharmacy students. This introductory course was designed for the dual purpose of introducing basic pharmacological principles and giving an in-depth presentation of the autonomic nervous system, including drugs that affect autonomic function. These purposes were combined because many of the classical pharmacological principles were developed based on the actions of drugs affecting the autonomic nervous system. It therefore seemed like a natural fit to combine the principles and an understanding of this disparate class of drugs. The course has a prerequisite that students have a basic understanding of anatomy and physiology as well as biochemistry. The course is taught concurrently with the *Principles of Medicinal Chemistry* course, and the 2 courses are vertically integrated to complement each other.

Students successfully completing this course will demonstrate a thorough knowledge of autonomic pharmacology, as well as an understanding of basic principles of the mechanisms of action of drugs, especially with respect to drug-receptor interactions. This course is considered to be a foundation course, preparing students for a series of integrated therapeutic courses that combine basic science knowledge (pharmacology, medicinal

chemistry, anatomy, physiology, and pathophysiology) with clinical application (therapeutics, case studies, and decision-making). In demonstrating the understanding of the principles described above, students will use lower-order learning, such as knowledge and comprehension, as well as higher-order processes, such as analysis, synthesis, and evaluation.<sup>1</sup>

To enhance the learning experience, this course focuses on active-learning techniques. One of the goals of the instructor is to prepare students to be active participants in recitations and case studies that will be presented in advanced therapeutics courses. Many of the first-year students are unprepared to participate in discussions and to express their opinions. This course was developed to help them improve the self-learning process and to instill in them a desire to learn. It helps to build confidence in decision-making and even to challenge authority when appropriate.

#### DESIGN

To accomplish the course objectives, the instructor used a variety of teaching techniques inspired by various authors including Chickering and Gamson, Lubawy, and Novak.<sup>2-4</sup> The course is under constant revision based on the success or failure of various techniques. Students were well aware that grading in the course would be dependent on both knowledge learned and performance by application of the knowledge. The official philosophy of the instructor, clearly conveyed to students, was that participation in class discussion was required. Failure to participate in class discussion could result in a reduction

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Table 1. Rubric for Evaluating Student Participation in Class Discussions

Grade	Assessment
1 (F)	Has not read assigned material prior to class; asks questions only to appear to be participating; is not prepared to answer questions when called upon; is not prepared for active learning.
2 (D)	Has read assigned material in a cursory manner; tries to bluff an answer when called on; gives rambling answers; deflects a question to answer a different question.
3 (C)	Has read the assigned material and understands it; can answer questions when called on but rarely volunteers information; gives cursory or terse answers; does not "discuss" topics; provides minimum acceptable answers.
4 (B)	Has read assigned and optional material prior to class; volunteers answers but does not evaluate the importance of the answers; rationale may show flaws in reasoning.
5 (A)	Has read all assigned material and pursued independent reading; asks penetrating questions; exhibits thoughtful discussion but allows others to participate; willing to risk a rational guess.

of 1 letter grade. Exceptional participation could be rewarded by an increase of 1 letter grade. Students were presented with a rubric on the first day of class to help guide the quality of their participation (Table 1). The instructor used a modified Socratic method of instruction in which tiered questions were used to guide students in their own learning process. Of necessity, there were times when pure lecture format had to be used. However, there was usually opportunity, even during those lectures, to elicit answers from the class. Although the class usually consisted of about 65 students (has ranged as high as 90), students clearly understood the need to participate and generally made attempts to contribute. The instructor attempted to solicit comments and opinions from students, in addition to simple questions and answers. In particular, areas of controversy were explored with great interest. For instance, since autonomic drugs are an integral part of this course, there was ample opportunity to explore the topic of ephedrine use. This was particularly interesting since the University of Cincinnati draws students not only from Ohio, but from Northern Kentucky. These states have quite different regulations concerning the use of ephedrine products.

Although the course generally focused on autonomic drugs as examples, on occasion it was more instructive to use other drugs. For instance, the following was the introduction presented for the concept of dose-response relationships.

Today we are going to gain an understanding of drug-receptor interactions and how to evaluate those interactions. Let us assume that you all went to a Kappa Psi party over the weekend and now have all come down with the flu. You all have fevers of 104°F and belong home in bed, but know that you dare not miss one of Dr. Skau's lectures.

What a wonderful opportunity we have. We are going to use all of you as guinea pigs to determine some principles of drug action. We are going to begin by pretending to administer an antipyretic. Who can tell

me what an antipyretic is? [At this point there is an opportunity to discuss this particular class of drugs.] There are several drugs that could be used, common ones being aspirin and acetaminophen. Let us choose acetaminophen. Who can tell me the usual dose of acetaminophen? [Frequently the answers from students are 300 mg, 325 mg, or 350 mg. Eventually, the class is led into a discussion of the difference between a dosage form and a usual dose, agreeing that the usual dose is about 650 mg for adults. Although there are many other opportunities for asking questions in this lecture, for the sake of brevity those opportunities are omitted from this paper.] We will conduct this experiment by putting one of those digital thermometers on your foreheads and giving you 100 mg of acetaminophen. We have to set a target for what will be a response. For the purposes of this study we will say that, once your temperature has reached 99°F, we will designate you as having responded. This is an arbitrary target. You know that the average body temperature is 98.6°F, but that it may vary by as much as 1°F and still be normal. Consequently, we just decide that 99°F is our target for normal temperature. [This is a simulation. Since the students do not really have the flu, temperatures are not really taken and drugs are not really administered.]

We agree to administer 100 mg of the drug and evaluate after 15 minutes. If you have reached the target your role in the study ends and you get to go have a cup of coffee or take a nap. If you have not reached the target you get an additional 100 mg every 15 minutes until you reach the target temperature. After everyone has "responded," ie, your temperature has reached 99°F, we plot the dose of drug on the *abscissa* and the number of individuals responding at that dose on the *ordinate*. [The results look like Figure 1.] Some of you show great sensitivity to the drug so that you reach the target at low doses, and some are very resistant to the drug, only reaching the target at the high doses. The majority respond somewhere in the middle.

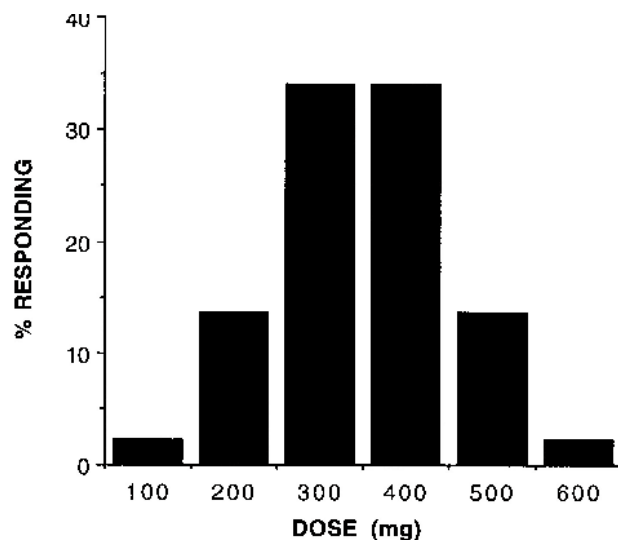


Figure 1. Noncumulative, quantal dose-response relationship.

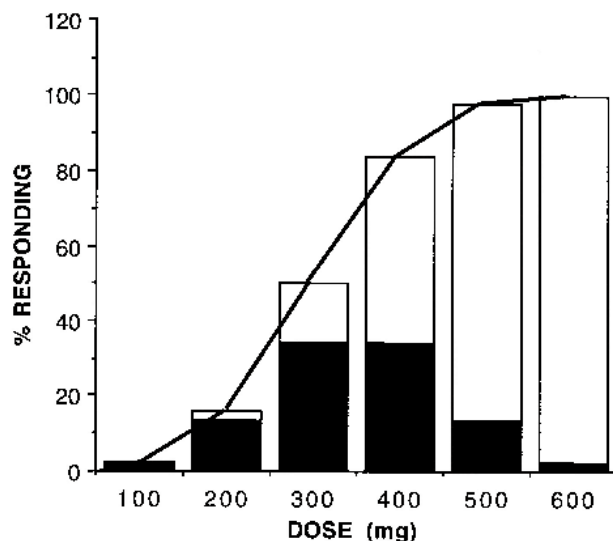


Figure 2. Cumulative, quantal dose-response relationship.

We have now generated a *dose-response (D-R) curve*. D-R curves are a major tool that pharmacologists use to quantify drug responses. In this case we have generated a *quantal* D-R curve. It is called *quantal* (much like quantum mechanics of chemistry) because it involves a single or quantal response. We set a target and record whether or not you reach the target at the given dose. It should be evident to you that this curve resembles a normal distribution. In fact, with a more extensive population we would see a slight skew, but it is very close to the normal distribution. This particular plot is of little use to us. We usually do not care to see results detailing at what particular dose an individual responds. We are more interested in the total number of individuals that respond at that dose. For this we assume that if you respond to a given dose, you would also respond to all greater doses. There are rare occasions when this is not true, but for our gener-

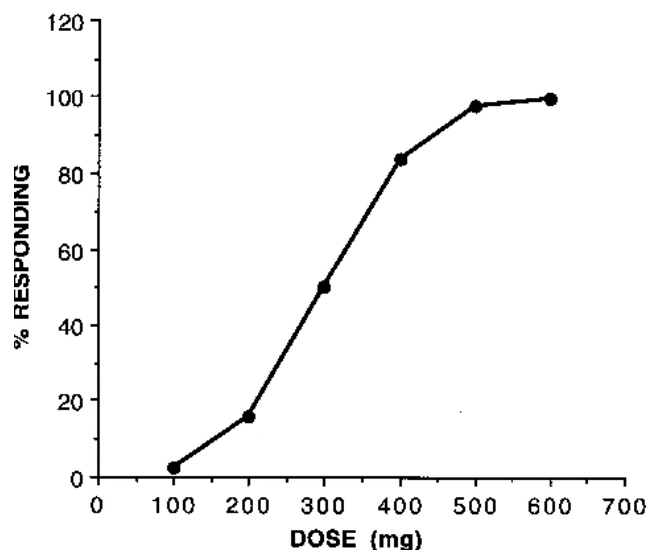


Figure 3. Typical sigmoidal dose-response curve.

Table 2. Data for Log Dose-Response Curve

Histamine, mM	Response, %
0.0001	0.5
0.0003	2.25
0.001	18.5
0.003	32.0
0.01	78.0
0.03	91.0
0.1	96.0
0.3	100.0

al principles we can assume that if you responded at 100 mg, you would also respond at 200 mg, 300 mg, and all higher doses. So we can now sum all responses at lower doses to produce a cumulative D-R curve (Figure 2). This is much more useful as it allows us to see why a dose of 650 mg of acetaminophen is used. At this dose, essentially all participants will show a response. This is still a quantal D-R curve, but is called a *quantal, cumulative D-R curve*. In Figure 3 we remove the bars to make it easier to study. It should also be noted, at this time, that this particular example is a bit fortuitous in that the responses are all within a narrow dose range. For many drugs the dose range may be quite extensive. To be able to conveniently plot such relationships it is often necessary to use the log of the dose. This would then be called a *log D-R curve* and would still have the sigmoidal shape. Examine the data in Table 2, which are actual data from an experiment of mine. The dose ranges from  $1 \times 10^{-7} \text{M}$  to  $3 \times 10^{-4} \text{M}$ : a range of 3000 fold. Plotting such data on a linear scale (Figure 4a) results in undue emphasis on the higher doses. However, by using a log scale for the dose axis we get a nice sigmoidal D-R curve as in Figure 4b.

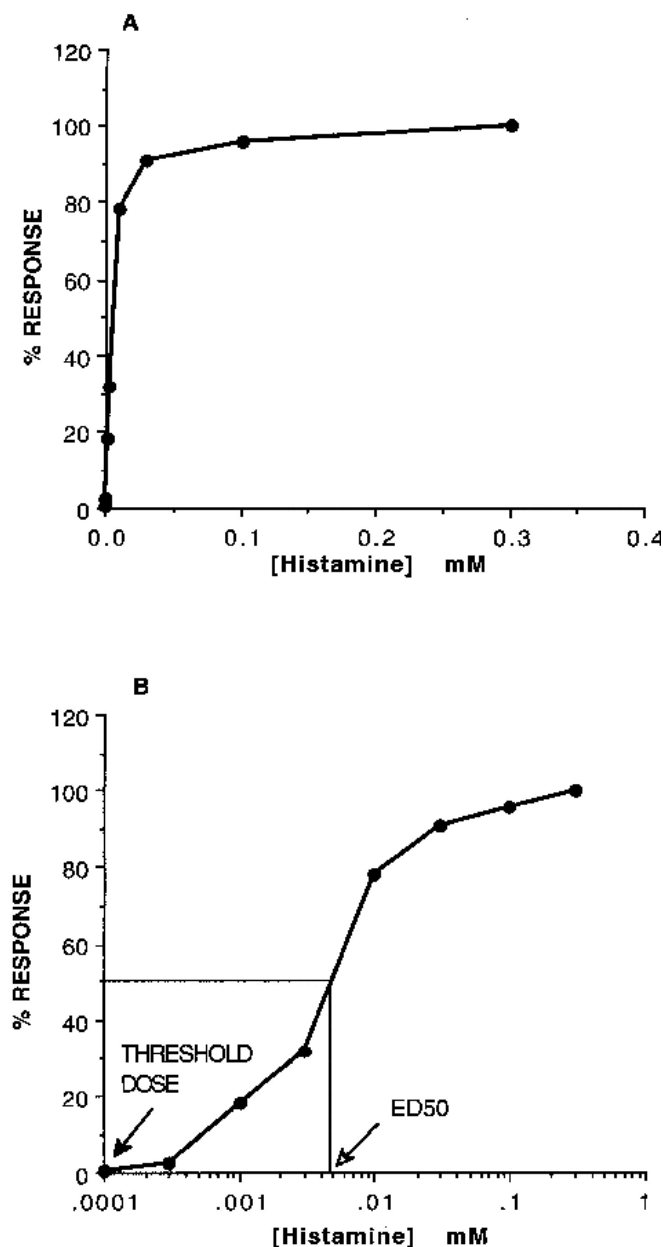


Figure 4. Continuous dose-response curves. (a) Plot of drug concentration on linear scale. (b) Plot of drug concentration on log scale.

Sometimes we may not want to measure a quantal response. We could alter our experiment to say that we will administer the drug and record the temperature 15 minutes later. Here we are not setting a target; we are observing a continuous change. As it happens, there is a maximal response that can occur (from 104°F-99°F) that we can call our 100% response. This graded or continuous cumulative D-R curve has the same shape as a quantal response.

Let us now look at the sigmoidal shape of the D-R curve, as we can learn something about drug responses from this shape. First, notice that there is a dosage

below which there is no measurable response. Thus, there is a threshold dose (solid arrow in Figure 4b). This is true for both quantal and continuous D-R curves. At doses lower than this threshold dose we have no individuals responding (quantal) or no measurable response (continuous). Likewise, there is a dose that produces a maximal response. Beyond this dose there is no increased response. This important point may not be evident to your patients. Some may think that if 2 tablets are good then 4, 6, or 8 are better. As we can see, this is not true.

The middle portion of the sigmoidal D-R curve is very important. This is where we have the most rapidly changing responses to small dosage adjustments. This is a linear portion of the curve and is the most appropriate region for comparing 2 D-R curves. The very center of the D-R curve, at the 50% response, can be considered to be an inflection point. On either side of this 50% response point, the arcs of the curve are inverted mirror images. The dose that produces this inflection point is called the  $ED_{50}$  for *effective dose 50%* (open arrow in Figure 4b). This is a common comparison dose as it is in the middle of the linear portion of the curve.

The therapeutic range for a drug may encompass a wide range of doses on the D-R curve. We do not always want to give the dose that produces a maximum effect. Consider, for example, a case where a hospitalized patient is exhibiting a very slow heart rate. We may want to treat him/her with epinephrine to increase the heart rate, but we do not want to induce a maximal heart rate. We only want to increase the rate to be compatible with an acceptable homeostasis. The dose to produce this may be quite low on the D-R curve.

Let us now consider the mathematical basis for the dose response curve. In the 1920s and 1930s, A.J. Clark began a series of experiments that led him to develop a mathematical model for drug receptor interactions. Clark built on theories of Paul Ehrlich and John Langley that proposed that drugs bind to some part of a cell. Although it was unknown what the drugs bound to, these researchers suggested that there was a receptive substance, or receptor, that was specific for a particular drug. Clark suggested that the drug receptor interaction would follow the law of mass action such that the following equation could be described:



You should remember this equation, and the law of mass action, from freshman chemistry. In this equation, D represents the concentration of drug, R is the concentration of receptors and DR is the reversibly



produced complex of drug bound to receptor. For all of the following discussion it is important to recognize that this is a reversible reaction. Binding of most drugs to receptors represent relatively weak binding forces, such as ionic, van der Waals, and hydrophobic bonds. When a drug binds selectively to a particular receptor we say there is an *affinity* between the drug and the receptor. The drug has an affinity for the receptor and the receptor has an affinity for the drug. Initially, this equation was adequate to describe binding, but not really acceptable to describe an effect. An additional term had to be added:



When we can measure an effect produced by a drug-receptor interaction, we say that the drug possesses *intrinsic activity*. A drug that has both affinity and intrinsic activity is called an *agonist*. Clark used principles derived for enzyme kinetics to describe the effect of the agonist in the following terms:

$$E = \frac{E_{\max}[D]}{[D] + K_d}$$

In this equation,  $E$  is the effect produced by a particular agonist concentration  $[D]$ .  $E_{\max}$  is the maximum effect produced when all receptors are occupied by agonist, and  $K_d$  is the dissociation constant for the agonist on the particular receptor system being studied. Clark made some assumptions in deriving this equation. It is now clear that some of these assumptions are valid and some of them pertain only to certain situations. His assumptions included: (1) there is a one-to-one relationship of binding of agonist to receptor; (2) agonist concentration is generally much greater than receptor concentration and therefore not limiting; (3) each binding of an agonist to a receptor produces an all or none response; (4) receptor numbers are relatively constant for a given tissue within the time frame of an agonist interaction. As we shall see later, some of these assumptions do not always hold true for all drug-receptor interactions.

This equation defines a rectangular hyperbola. If we plot the effect against agonist concentration or dose on a semilog graph, we get a sigmoid-shaped D-R curve. The law of mass action and the above equation clearly show why there is a maximum dose beyond which no further increase in dose produces an effect. When all of the receptors are occupied by agonist, we will produce the maximum effect. Adding more agonist cannot produce additional effects because there are no more receptors to occupy. The emphasis on occupancy of receptors has resulted in this being called *occupation theory*.

The above discussion is the introduction to drug-receptor theory. From here we can define potency and efficacy; determine therapeutic, toxic, and lethal D-R curves; compare multiple agonists by their D-R curves,  $ED_{50}$ s or  $K_d$ s. We then discuss such topics as therapeutic index, partial agonists, and spare receptors. For the purposes of this paper, the principles are presented as if in lecture format. However, in the classroom, students are led through the process by a modified Socratic method in which they are asked questions that lead them to discover and articulate the principles.

## OUTCOMES

Determination of outcomes is particularly important in this course and requires several attributes including patience and a critical sense of fairplay. Early in the course, students are somewhat hesitant to answer questions. It is my opinion that in the basic science prepharmacy courses students are rarely called upon to answer questions in class. Basic science courses tend to be heavily weighted toward lecture-based transmission of knowledge. I have found that, initially, students do not readily volunteer to answer questions, especially when they must raise their hand to be called on. However, questions early in the course are somewhat easy to answer and can be used to enhance the confidence of those willing to risk an answer. When no one will answer, I wait. Students become very uncomfortable when there are periods of a minute or 2 when nothing is happening while I wait for an answer. Eventually, someone will be willing to hazard a guess. It is crucial at this stage to find something positive in any answer, even if the answer was mostly wrong. Students need to gain confidence that they will not be ridiculed for wrong answers. I have found that, even though I am extremely careful not to ridicule students, there are often highly sensitive students who interpret any negative response as being critical. While I decry modern attempts to be extraordinarily sensitive to students' self-esteem, there is never a good reason to humiliate students in front of their peers. As the course progresses, it becomes easier for students to understand how they may be exhibiting flawed thinking processes. Once the students understand that they can be wrong without being ridiculed, they become more responsive to questions. There are always students who claim that they are too shy to participate. I attempt to counsel these students (outside of class), explaining that pharmacy is a profession that requires communication and that they will be required to communicate in their therapeutics courses and professional practice experiences. Most students will develop some degree of communication, although some are always quite hesitant.

An especially gratifying result of this course occurs when I teach in the *Therapeutics* course, which is taken 1 year after the *Principles of Pharmacology* course. I find that the students have matured with respect to their learning abilities and have retained a good understanding of the principles that we discussed in the earlier course. In addition, although the College of Pharmacy has no formal means of identifying adequate preparation, anecdotal reports from faculty members in other therapeutics courses suggest that the *Principles of Pharmacology* course prepares the students to participate in recitations and case studies in the advanced courses. Students have ranked this as the top winter quarter course in 5 of the last 6 years. Student comments on formal evaluations typically state that it is one of the hardest courses that they have ever taken, but that they feel it is one of the most relevant courses. They frequently state that they feel prepared to proceed in the therapeutics courses. There are frequent comments that they have never had a course like this before, but that it has enhanced their confidence in their decision-making abilities. Finally, of much gratification to the instructor is when students tell him that their preceptors, who took the course years ago,

warn them that it is a very difficult course but one of the most important courses that they will take in the College.

## SUMMARY

One professor's/instructor's approach to facilitating learning in an introductory pharmacology course has been described. The course helps students discover basic principles of pharmacodynamics and how they will apply those principles to modern drug therapeutics and patient care. The course requires class participation during lectures and focuses on active-learning techniques.

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