Dose-response relationships in clinical pharmacology.
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LOG DOSE-RESPONSE CURVES IN BASIC AND CLINICAL PHARMACOLOGY

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From a historical standpoint, the concept of a dose-response relationship has been known for at least several centuries. The idea that a small quantity of a drug might be useful and beneficial, whereas larger amounts might be toxic and deleterious, is an axiom that has been accepted by early biologists and physicians and has unfortunately permeated to the lay public, where the glib statement that "if one pill is good, two must be better" is commonly espoused.

The classical treatise on foxglove, published in 1775 by the English physician William Withering, entitled "The Account of the Foxglove and Some of Its Medical Uses," states that he was worried "that a medicine of so much efficacy should be condemned as dangerous and unmanageable," thus alluding to the dose-response relationship of digitalis (1). Likewise, the accounts of the isolation and purification of morphine from opium and the early depiction of its pharmacologic actions by Frederick Serturner (2) also give early acknowledgement to the concept of dose-response relationships. Serturner first studied morphine's effects in mice and dogs, and then did a clinical pharmacologic study on himself and three other volunteers. All took the drug in varying doses and thus, in this manner, he established morphine's dose-response relationship.

Pharmacologic responses are generally considered a) graded responses, i.e., the degree of response is functionally related to the dose of the drug administered, and each increasing dose produces a greater response, until the maximum effective dose is achieved. This latter dose is related to the biologic system under investigation. Thus, if a muscle strip can undergo contraction or relaxation, there is a limited degree to which this can be achieved. Similarly, if the heart is capable of contracting, this is not a limitless effect, and thus when a drug is administered, it can only produce an effect which is consistent with the ability of the tissue to respond. Seen less frequently, but also quite important, is another type of pharmacologic response--b) the quantal, or all-or-none response. Although less common, it does occur in certain pharmacologic situations, such as that involving the prevention of seizures by anticonvulsant medications (3). In

this case, the animal is either protected by the anticonvulsant, or it is not; thus it is termed an all-or-none response.

In pharmacology, the responses elicited, either graded or quantal, can be graphically expressed in what is termed a dose-response curve. Dose-response curves were originally depicted and graphed arithmetically. Now it is conventional practice in pharmacology, and in dealing with biologic responses in general, to utilize data which have been subjected to logarithmic conversion. A good example which makes this point comes from the work of Venning, et al. (4), who studied the biologic assay of the adrenal corticosteroids cortisone and 11-dehydrocorticosterone. A comparison of the arithmetic (or Cartesian) vs. logarithmic (or geometric) methods of presenting the data obtained from studying these two glucocorticoid drugs on the accumulation of liver glycogen in the mouse is illustrated in Figure 1. It is clear from the arithmetic presentation that cortisone is more potent than 11-dehydroxycorticosterone on liver glycogen accumulation. However, the degree of cortisone's potency is not as obvious from this presentation as it is from the logarithmic scale.

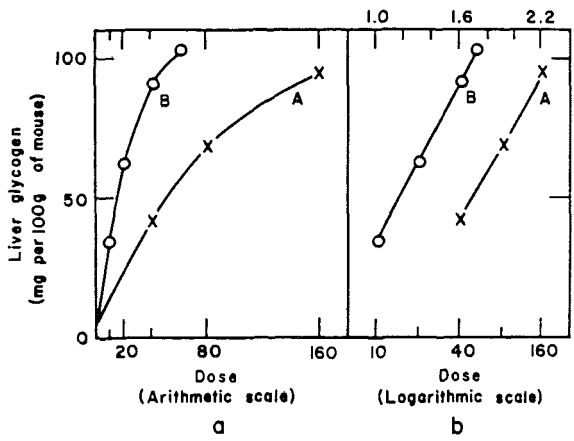

Fig. 1. Arithmetic and logarithmic dose-response curves. Effects of two steroids, 11-dehydrocorticosterone (A) and cortisone (B), on liver glycogen in mice. (From Venning, et al. Endocrinol. 38:79, 1946)

There are several distinct advantages to plotting dose-response data using semilogarithmic coordinates rather than using arithmetic coordinates. These have been summarized by Gaddum (5) in his textbook, and include:

a) The data points, when plotted on semilogarithmic paper, usually can be fitted to a straight line, whereas those plotted on arithmetic scales yield a curvolinear representation. Although every biologic response plotted as a semilogarithmic function is, for all intents and purposes, a sigmoid curve (Figure 2), i.e., there is always going to be some dose which is below the threshold dose and which will produce no effect, and there should be some dose, high as it may be, which will produce a maximal effect.

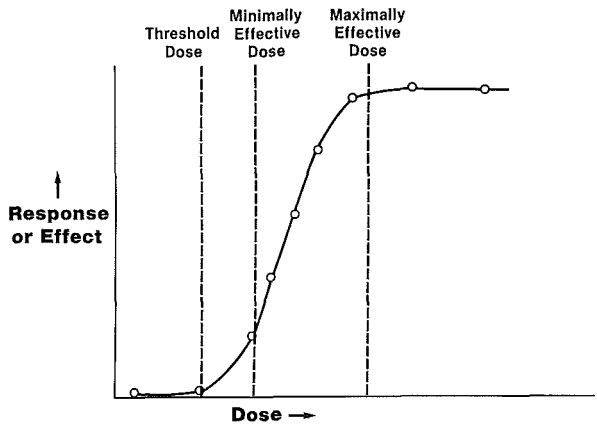

Fig. 2. Typical log dose-response curve.

b) In general, when comparing different drugs which have the same activity but varying potencies, the logarithmic presentation will result in dose-response curves yielding parallel lines. Thus, for any given effect, the dose of one drug which produces that effect, and the dose of the comparator drug, will always be the same percentage, i.e., their dose-response curves will be parallel.

c) On an arithmetic scale, the doses in the lower portion of the scale are plotted close to each other, whereas on a logarithmic scale, this is not the case, and the data are spread out more and thus much easier to interpret. Similarly, a wider range of doses can be graphed utilizing the logarithmic approach than can be accommodated with the arithmetic approach.

d) With arithmetic scales, the test error increases with increasing doses, whereas when logarithmic scales are used, the error is dose independent.

e) The generation of straight-line graphs, as opposed to hyperbolic curves, makes the data much easier to work with regarding statistical analysis and manipulation (6).

As stated earlier, the log dose-response curve is essentially represented by a sigmoid curve if the experimentalist determines a wide range of doses and identifies the threshold or the lowest active dose, as well as that dose which produces a maximal effect. Based on this, one can determine the linear portion of the sigmoid curve and thus that area in which responses can be used for comparing the effects of various other treatments (such as the effect of pH, the effect of antagonists, the effect of other agonists with similar structures, etc.).

The graded dose-response relationship lends itself ideally to an explanation by the receptor theory. A basic concept or assumption in biology, and especially in pharmacology, is that a macromolecular structure, termed a receptor, exists in biologic tissues and is capable of specifically and selectively reacting to a physiologic substance (such as a hormone or neurotransmitter), or to a drug which mimics, blocks, or modulates the effects of endogenous substances. Therefore, a drug's action is visualized as being the result of the combination of the drug with a specific receptor, thus forming a drug-receptor complex (Fig. 3). In the majority of cases, this is a reversible phenomenon. The degree of the response is thought to be directly proportional to the concentration of drug, i.e., the dose, and the number of receptors this drug combines with, to form the drug-receptor complex. This is also expressed as the number of receptors occupied (the occupancy theory). The assumption being made is that if the ideal drug is administered, it would occupy all of the receptors in the tissue, and thus will produce the maximum response to which that tissue is capable of responding. This theory becomes more complex when one considers that not all drugs interact with the receptor to the same degree to produce the pharmacologic effect inherent to that

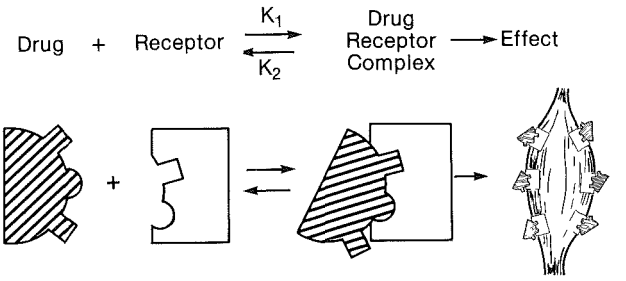

Fig. 3. The schematic interaction between a drug and its receptor.

receptor system. Therefore, an agonist drug and an antagonist drug may have the same affinity for a receptor, and while one of the drugs (the agonist) produces the effect, the other (the antagonist) is inactive. Furthermore, if the antagonist is given prior to the agonist, it can block the agonist's action (fig. 4).

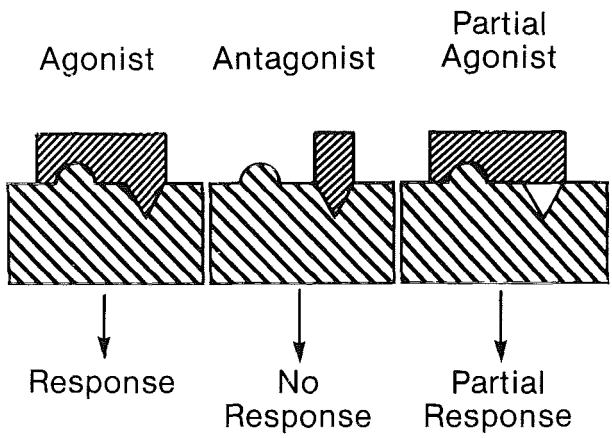

Fig. 4. The schematic interaction between an agonist, an antagonist, and a partial agonist with a receptor.

This has lead to the concept of intrinsic activity (or efficacy) of a drug at its respective receptor. A drug with a high intrinsic activity will combine with the receptor and stimulate it to produce the response for which it is programmed. An antagonist may also have an affinity for that receptor, but lacks any intrinsic activity, and thus no response would be expected. A partial agonist (7) is a drug which exhibits an affinity towards the receptor, but has a lesser degree of intrinsic activity, and thus it may serve as an agonist when administered alone, or as an antagonist when given prior to or when coadministered with a potent agonist. Examples of these are dichloroisoproterinol (8) and nalorphine (9). Thus, a drug's biologic effect is the overall effect of the dose of that drug, the degree of receptor occupancy (i.e., the affinity of the drug for the receptor), and its intrinsic activity (or its efficacy). As a result of all these factors, the utilization of different doses of the drug will generate a dose-response curve specific for the drug and the receptor system involved.

The log dose-response curve has been widely employed in all aspects of pharmacology, including the central nervous system, the cardiovascular system, the gastrointestinal system, intermediary metabolism, chemotherapy, endocrine pharmacology, and clinical pharmacology. In addition, it has been utilized in all types of experimental situations, including in vitro, in vivo and in situ situations, and at all levels including isolated cells, intracellular organelles, isolated tissues and organs, and ultimately in the whole animal or man. To illustrate the widespread implication of the log dose-response curve running the gamut from the cell to the whole organism, several representative examples have been chosen using biogenic amines, including histamine, serotonin, and the catecholamines or their related substances. The following examples are given.

Certain drugs can inhibit the activity of purified enzyme preparations or crystalline enzymes. An example is the inhibition of the enzyme monoamine oxidase by the MAO inhibitors employed as antidepressants (10). Another example involves the microsomal enzyme capable of converting tyramine to dopamine (11,12). BW392C60, a close congener of the antihypertensive bethanidine, SKF-525 and desmethylimipramine (DMI) inhibit the conversion of the monophenol tyramine to the catecholamine dopamine in a dose-related manner (Fig. 5). This inhibition can be expressed in a log dose-response curve. In contrast, BW392C60 has no effect on a typical microsomal drug-oxidation system which metabolizes the barbiturate hexobarbital, whereby SKF-525A and DMI also inhibit this enzyme.

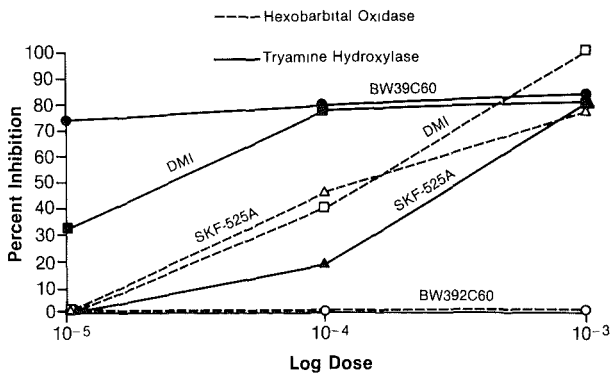

Fig. 5. The effect of BW392C60, SKF-525A and desmethylimipramine (DMI) on hexobarbital oxidase and tyramine oxidase in rabbit liver microsomes.

Log dose-response curves can also be used for studying the effects of drugs on isolated cells. The platelet, a non-nucleated cellular component of the blood, is capable of accumulating biogenic amines, including serotonin. Nisoxetine, an antidepressant, was shown to selectively block norepinephrine uptake in man at clinical doses without affecting serotonin reuptake (13). The uptake of tritiated serotonin into human platelets studied in vitro is shown in figure 6 . The data indicate that to affect serotonin reuptake into platelets in man, nisoxetine plasma concentrations many times higher than are obtainable under normal clinical circumstances would be required.

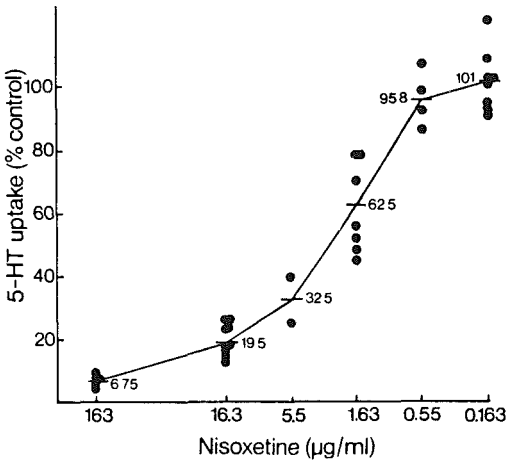

Fig. 6. The effect of nisoxetine on the uptake of (^{3}H)-5-HT by human platelets. (From Lemberger, et al. (13))

Isolated tissue preparations have also been extensively utilized to study log dose-response relationships. For example, Paton et al. (14) studied the various doses of histamine (ranging from 25 mg to 56 mg) on contraction of the guinea pig ileum and demonstrated that the effective dose was about 600 mg. Others have shown that typical antihistamines (antagonists) causes a shift in the dose-response curve to the right.

Log dose-response curves have also been used to study the effects of drugs on whole organs. For example, Carlsson et al. (15) administered various doses of reserpine, and 16 hours later removed the brains, hearts and adrenal glands and measured the depletion of catecholamines from these organs. The results are shown in Figure 7.

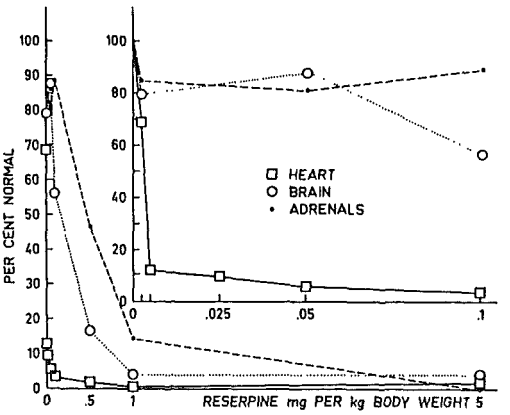

Fig. 7. Effect of various doses of reserpine on tissue catechol amines. Reserpine was given intravenously. Time interval 16 hours. (from Carlsson, et al. (15))

There are numerous examples in basic pharmacology where pharmacologic effects in whole animals can be expressed using log dose-response curves such as the blood pressure response to a drug and the modification of that response by specific antagonists. Studies in humans also lend themselves to utilization of log dose-response relationships. In 1918 Sollmann et al. (16) reported that the local anesthetic effect of cocaine could be presented as a log dose-response curve. Similarly, Bain (17) studied the effect of the systemic administration of various doses of six antihistamines on the blockade of the histamine wheal size in humans. These data were also best presented as a log dose-response curve and thus allowed for the assessment of the potency of these particular drugs.

In summary, the log dose-response curve has been in use in basic and clinical pharmacology for centuries, as exemplified by the early studies of William Withering and Frederick Serturner. The log dose-response curve can be employed when dealing with quantal-type responses and with graded responses. The advantages of log dose-response curves over arithmetic dose-response curves have resulted in their widespread usage and acceptance. They are ideal for demonstrating the interactions between agonists and antagonists on biological preparations, running the gamut from intracellular structures, such as isolated enzymes and isolated organelles, to actions at the cellular, the tissue, and the organ level, and all the way to the whole

animal and man. This use of log dose-response curves has enabled researchers to achieve a clearer interpretation of biologic data.

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Discussion - The log dose-response curve in basic and clinical pharmacology

D.G. Grahame-Smith

One of the things that is exercising people in neuropharmacology is this situation where may be the action of a neurotransmitter's partial agonist, and therefore partial antagonists, is actually dependent to some extend on the amount of natural neurotransmitter in the synaptic cleft. In other words, how much partial agonist activity or how much partial antagonist activity a drug will actually produce at a post-synaptic receptor site will, in fact, depend on how much of the neurotramitter it is competing with. I just wonder whether you have any thoughts on what could be a very difficult and important problem to interpret in the therapeutic situation.

L. Lemberger

Your question is clearly very important, and very difficult to answer. To make things even more complicated, one should also remember that there are also drugs that require the presence of the neurotransmitter to exert their activity. Thus, when the dopamine agonists used in the treatment of parkinsonism are given in conjunction with L-dopa one generally obtains good results, but if parlodel or pergolide are given alone their effects appear to be less beneficial.

B.P. du Souich

We have been speaking about log dose-response curves, but I wonder whether these are truly appropriate to characterise effects. In log dose-response curves one focuses on the straight line segment, which can be described by a very simple equation. However, these equations ignore zero effects and, at the other end, if it is not possible to evaluate a wide range of doses, one will have difficulties in characterizing E_{max}.

R.L. Galeazzi

For clinical practice, and also for teaching, I don't like the log dose-response curve. I think the log dose response curve may induce errors. People like it because in the lower doses it

spreads the dose, but I don't like it because at higher doses it brings the doses together. So, the practicing physician and the student may be led to think the log dose-response curve is linear, which is completely wrong. Many years ago, a paper was published showing that the log dose-response curve for theophylline is linear. And from that day on the rate of theophilline toxicity increased because many physicians thought that increasing the dose would increase the efficacy. However, if one draws the same data on a cartesian plot, one sees that between 10 and 20 µg/ml there is almost no increase in efficacy.

L. Lemberger

As it has been mentioned before, dose ranges may be rather limited in clinical situations, but from a basic pharmacological standpoint, when one is trying to uncover mechanisms and compare different drugs the log dose-response curve does have a useful function.

D.S. Davies

I would like to comment on the term 'dose-response'. In the organ bath, there is a relationship between the dose one puts in and the concentration at the target. In man or in animal, particularly for drugs which are metabolized, the relationship between dose and concentration at the target site is very complicated.

L. Lemberger

You are right. When one gets into the clinical situation, or even the whole experimental animal, the situation becomes much more complex, but it is still worth trying to relate dose or plasma levels to response, at least to obtain some sort of leads about active metabolites, duration of activity, etc.

R.J. Temple

Even if the dose-response curve that you observe is complicated by metabolism and multiple active metabolites, it is still essential to have some idea of what happens to people when you give more of a drug and if you don't see any change that may be a clue that you need to look at blood levels, figure out how many

active metabolites there are, and things like that. In fact, one problem with drugs that are highly metabolized is that it may well be that a large number of patients who get them don't get enough drug at the receptor site to respond at all. If this were known earlier, it might lead a company to develop not the initial drug, but one of the metabolites as a more practical product.