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Editorial Views

On Dose–Response Curves and Anesthetics

BEGINNING with treatises by Gaddum [1] and Clark [2] in the twenties and culminating in the presentation of a satisfactory approach by Stephenson in the fifties,[3] pharmacologists have spent about three decades wrestling with the problem of interpretation of dose–response curves. Anesthesiologists seem to be retracing the same path. Thus, it is probably a good time to take a close look at the nature of dose–response curves of anesthetics before too much effort is wasted on measurements already known to be ambiguous.

We may start by classifying responses as graded, quantal and ordered, where we introduce the last term with special reference to anesthesia. Graded responses are those which, like arterial pressure, can be measured on a continuous scale. Depth of anesthesia cannot be treated as a graded response because no natural scale is available. Quantal responses, like awake or asleep, are all-or-none responses. To illustrate a quantal dose–response curve, loss of response to pain could be chosen as an end-point and an anesthetic administered in a series of fixed concentrations. The number of subjects reaching the end-point at each concentration would be plotted against that concentration. This number would run from zero at low concentrations up to all of the subjects at high concentrations to give a typical dose–response curve. In this way, depth can be handled by the quantal approach if any given end-point is considered, but then the idea of a passage through ordered stages or planes is lost. To retain the useful notion of depth as a graded process, anesthesiologists have created empirical scales such as Guedel's classification or, more recently, a scale of electroencephalographic end-points.[4] Responses of this nature can be called ordered responses to emphasize that all we can say is whether one end-point comes before or after another. For convenience or appearance, such end-points are often plotted at evenly-spaced intervals along a scale of ordinates, but one must constantly be on guard against subsequently trying to draw a conclusion that would change if some other spacing had been used. That is, "distance" between end-points can have no meaning. For example, the observation that "almost a straight line correlation" obtained between electroencephalographic levels and concentrations of ether in the blood [4] can be no more than fortuitous.

To illustrate further problems that arise in interpretation of dose–response curves, we may return for a moment to graded responses. Even here, it is rarely possible to attach any significance to the shape of the dose–response curve.[3, 5] More specifically, we have just not reached the stage where we can predict *a priori* the relation between the number of receptors activated by a drug and the response that will result. The situation is even less clear with anesthetics; we don't know if a receptor is involved. Therefore, if we are to benefit from the experience of pharmacologists (Stephenson [3] and Schild,[6, 7] in particular) we must draw from dose–response curves only those conclusions that do not depend on assumptions as to the shapes of the curves.

What does this leave us? We have essentially the class of potency comparisons. That is, we can pick some constant depth of anesthesia as end-point, compare concentrations of agents that produce it and hence get ratios of potency or "dose ratios."[8] What responses can we use? Any measure is acceptable, but the most attractive will be one which can be repeated with minimal random error. A currently popular index is the end-point of just barely responding to a painful stimulus.[9]

Another problem familiar to pharmacologists is relevant. If you have two drugs which act by a similar mechanism, for example, acetylcholine and methacholine, you can expect dose–response curves to be parallel, and the comparison of the two agents by a single figure—a potency ratio—is reasonable. Since the dose–response curves are parallel, you will get the same ratio regardless of the height of the response chosen for the end-point. If, on the other hand, you compare two drugs that do not have parallel dose–response curves, a potency ratio is meaningless; the value will depend on what level of response you choose as the end-point.

Next, let us turn to the dose part of a dose–response curve. First, it should be stated that the term "dose" is meaningful only in the sense that a certain (constant) volume of distribution is implied, so that administration of a given dose would lead to a specific concentration at the site of action. Strictly speaking, we should refer to *concentration*–response curves, but "dose" is a shorter word. In any case, the appropriate concentration we should consider is that at the site of action. Rarely is this measured directly; usually an indirect but more convenient index is used. Blood concentration is often chosen with the assumption of a constant blood–tissue concentration ratio. Currently, the alveolar concentration reached after a reasonable equilibration period is being used.[9] Use of alveolar concentration as an index of cerebral concentration involves what the engineers would call a "trade-off" between convenience of sampling and indirectness of the measurement. However, the brain is perfused well enough that alveolar concentration can be expected to mirror cerebral concentration well.[10]

If we now put together the particular end-point of marginal response to a painful stimulus and the associated alveolar concentration, we have a point on an anesthetic dose–response curve. The abscissa of this point has been called MAC[9] (the M means "minimal," implying barely enough to block the response to the stimulus, and the AC, alveolar concentration, indicates explicitly what measure of concentration is being used). This point on a dose–response curve has been examined in great detail. It was chosen both for convenience of observation and because it produced results with a manageable variance. It represents a considerable improvement over other approaches in which less care has been applied to making sure that both ordinates and abscissae of points on the dose–response curve are obtained as precisely as possible. In fact, if the introduction of MAC had done nothing but shift attention from inspired to alveolar anesthetic concentrations, the notion would have been well worthwhile.

On the other hand, one must constantly remember that attention is being focused on just one point of a dose–response curve or, if two agents are being compared, on one point on each of two such curves. To put it another way, draw two dose–response curves (as A and B in figure 1) and on each curve mark a point corresponding to the same distance up the response axis. Now look only at the horizontal strip, about a millimeter wide, that includes the two points (the unshaded area in the figure). Throw away the rest of the graph. You are left with what you see if you stick to one end-point. Specifically, you cannot tell if the two dose–response curves are parallel (compare curves B and B′). As indicated earlier, this means that a potency ratio obtained just from a ratio of MAC's is unreliable. It may be correct, but you can't tell! Note that invoking multiples of MAC ("MAC 2," "MAC 3," etc.[9]) does not alter the situation; these are all derived from the single original response end-point.

MAC may be useful as a rough measure of potency, but unfortunately, human nature is such that one can easily forget that extrapolation to other response levels without direct experimental confirmation is hazardous. A re-

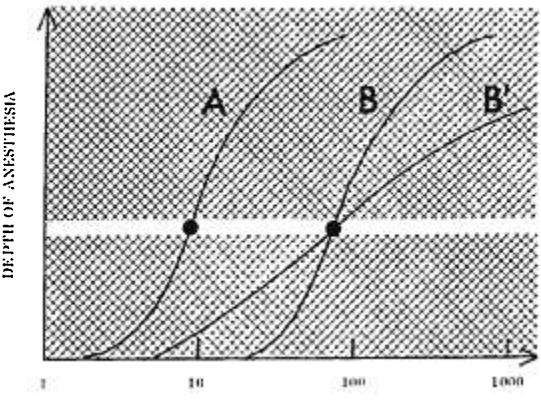

FIG. 1. Diagram to illustrate a form of tunnel vision that can result if measurements are restricted to just one level of response. *Ordinates:* depth of anesthesia (arbitrary scale). *Abscissae:* concentrations (arbitrary units). Curves A and B represent dose–response curves to two agents that might be under comparison. Curve B' represents an alternative situation in which the curve to the second drug is not parallel to that of the first. The unshaded area represents the small window through which one looks when only one level of response is examined. From looking only through this window, it is impossible to tell whether the curves are parallel.

cent discussion in the Journal [11] illustrates the confusion that can result. (In that particular case, direct measurement of alveolar or blood concentrations at the relevant depth of anesthesia would have given the appropriate frame of reference.)

In this issue of the Journal, an article focuses on another point on the dose–response curve.[12] And we suspect that many similar studies may follow. Before this proceeds much further, we should like to suggest restraint. There is an almost inexhaustible supply of possible candidates for new end-points. But are we going to learn anything from charting a lot of these individually? For example, it is hard to see how the introduction of even the second "MAC" is going to alter either the way one will administer anesthesia or the way one will picture underlying processes. Even the authors have mentioned nothing of this nature. In general, it is inadvisable to measure something just because it is there to be measured. If estimates of relative potency are to be made, it would be advisable to make comparisons at several depths of anesthesia, and to do this in the same group of subjects to minimize experimental error.

As a final point, we shall once again refer to experience in more accessible systems,[3, 5] and note that it is unlikely that examination of anesthetic dose–response curves *per se* will shed much light on mechanism of action.

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Drugs

CLONIDINE The acute circulatory effects of 2-(2,-dichloroanilino)-2-imidazoline (Clonidine) were studied in eight hypertensive patients at rest and exercise. Imidazoline compounds, such as phentolamine and tolazoline, have been used as hypotensive and peripheral vasodilating drugs, respectively, but gastrointestinal symptoms and development of resistance to its hypotensive action have limited the use of phentolamine. Clonidine decreased the blood pressure by variable reductions in cardiac output and systemic vascular resistance. In its hypotensive action, clonidine is neither an alpha nor a beta blocker, nor has a ganglionic blocking action been demonstrated. The mechanism of action is probably a centrally-mediated reduction in sympathetic tone. The circulatory responses to exercise in the supine and erect positions were unimpaired. Since all current hypotensive agents cause decreases in blood pressure with exercise, Clonidine would seem to be an important addition to the therapy of hypertension. (*Muir, A. L., Burton, J. L., and Lawrie, D. M.: Circulatory Effects at Rest and Exercise of Clonidine, an Imidazoline Derivative with Hypotensive Properties, Lancet 2: 181 (July) 1969.*)

TETANUS Patients with severe tetanus are routinely treated by a regime of tracheostomy, curarization, adequate sedation and intermittent positive-pressure ventilation (IPPV). The form of therapy used derives from the suggestion that the clinical and physiologic syndrome already described may be due to sympathetic overactivity. The aim has been to suppress such overactivity, where it exists, by three pharmacologic methods: 1) the use of drugs having nonspecific antiadrenergic activity, *i.e.*, phenothiazine derivatives; 2) nonspecific suppression of neuronal activity using general anesthetic agents; 3) specific suppression of adrenergic transmission at nerve endings and receptors. (*Prys-Roberts, C.: Treatment of Cardiovascular Disturbances in Severe Tetanus, Proc. Roy. Soc. Med. 62: 662 (July) 1969.*)