MAC Expanded:

AD50 and AD95 Values of Common Inhalation Anesthetics in Man

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Two important measures may be derived from patient responses to a range of anesthetic doses. The AD50, corresponding to MAC, estimates the median anesthetic concentration—that dose where half the patients are anesthetized and half are not. The AD95 approaches the theoretical "minimum" anesthetic concentration by estimating the dose that anesthetizes 95 per cent of a patient population. The AD50 and AD95 are logical extensions of the MAC concept and can be evaluated with current experimental methodology. Recomputed from available data, the AD50's of nine inhaled anesthetics proved to be numerically identical to their MAC values. The AD95's were 5 to 40 per cent greater than the AD50's. (Key words: Potency, anesthetic, MAC, AD50, AD95; Pharmacology, dose–response curves.)

ANESTHETIC POTENCY—how much drug anesthetizes the average patient—is as important to the clinician as it is to the scientist. As a result, MAC (minimum alveolar anesthetic concentration[1-7]) has become a household word to anesthesiologists. Over the years, however, certain semantic and statistical ambiguities of MAC have surfaced. For instance, the "minimum" in the definition of MAC is easily misinterpreted, and the fundamental nature of its median response properties overlooked. Further, confidence ranges of MAC estimates rarely were available, so hampering statistical evaluation.

Potency connotes different things to clinician and scientist. The scientist uses potency primarily to compare the actions of two drugs, or a change in action of a single drug, at a convenient equieffective level such as MAC. The clinician, on the other hand, uses potency to estimate the concentration that provides neither too light nor too deep an anesthetic plane—that is, a minimum anesthetic concentration.

In conducting a MAC assay, the subject's response (anesthetized or not-anesthetized) is plotted against the anesthetic concentration, with the midpoint of values representing MAC.[1] Without repeating work already done, newer computer techniques[8,9] can reconstruct the complete anesthetic dose–response curve from available MAC data. The statistical properties of this curve are such that the seemingly different requirements of clinician and scientist each can be satisfied by the same experimental approach. The purpose of this paper is to provide a framework for the concepts of median and minimum anesthetic concentration, and to furnish their newly computed values.

Theory

QUANTAL DOSE–RESPONSE CURVE

The notions of median and minimum anesthetic concentrations derive from the quantal dose–response relationship. As the name implies, quantal responses are counts of "yes" or "no" observations. For general anesthesia we ask whether a subject responds or does not respond to a standardized painful stimulus. Note that the subject can react in only one of two ways: it is a yes–no type of response.

To illustrate the process, we pooled data from three previously published halothane dose–response assays in man[1,3,7] (see

Methods, below). Table 1 condenses the observations obtained on 68 adult surgical patients anesthetized with halothane whose responses to skin incision—move or no-move—were observed. Subjects were assigned to one of five dose† groups, each spanning a 0.05 per cent alveolar halothane concentration range (first column). A subject was classed "anesthetized" if he didn't react to incision, "not anesthetized" if he moved. For example, the table's second row reveals that of 15 subjects with alveolar halothane levels between 0.70 and 0.74 per cent, three were anesthetized (*i.e.*, didn't move) and 12 were not anesthetized (*i.e.*, moved when the skin was incised).

These proportions next are converted to percentages (third column) to facilitate construction of the halothane dose–response curve. However, a plain graph of percentage response versus drug dose yields a skewed asymmetric curve that defies ready analysis. Fortunately, it has been found empirically that a dose–response plot based on the logarithm of the dose (instead of on the dose itself) forms a nicely symmetric curve that lends itself to statistical treatment.[10] The log dose–response curve constructed from the data in table 1 is shown in figure 1, where percentage anesthetized is plotted against logarithm of the corresponding halothane concentration, and the five points joined by a smoothly flowing curve.

Two key observations are immediately evident from the figure. First, the curve is symmetric around the 50% response midpoint (where half the subjects are, and half the subjects are not, anesthetized). This midpoint is the *median*. Second, while the central portion of the curve is steep, its lower and upper tails (near the 0 and 100 per cent response levels) are not. Thus, a relatively large change in anesthetic dose at the tails would only slightly change the percentage of subjects anesthetized. (In fact, the tails are asymptotic; that is, they never reach the 0 or 100 per cent response lines.)

† In keeping with general pharmacologic practice, and for convenience's sake as well, "dose" is used here, even though "concentration" and "tension" would be more apt terms for inhaled anesthetics.

TABLE 1. Halothane Dose–Response Assay in Man*

Halothane Concentration (Per Cent Atm)	Subjects Anesthetized†	
	Count	Per Cent
0.67 ± 0.02	0/10	0.0
0.72 ± 0.02	3/15	20.0
0.77 ± 0.02	16/28	57.1
0.82 ± 0.02	7/8	87.5
0.87 ± 0.02	7/7	100.0

* Pooled data from three halothane MAC studies[1,3,7] of 68 adult subjects, covering the alveolar concentration range of 0.65–0.89 per cent (outrider values deleted for illustration's sake only).

† Subjects not responding to skin incision.

TAMING THE CURVE

Less immediately evident from the figure is the difficulty of joining the individual dose–response points by a curve. While ways of directly fitting yes–no observations to a curve exist, it is graphically easier, and conceptually simpler, to deal with a straight line. Inspection, aided by a dash of imagination, shows that the dose–response curve might be straightened by stretching it a little at the center (where it is already nearly linear) and a lot at the tails. Such variable stretching is accomplished by substituting units called *probits*[11] or *logits*[12] for the more familiar percentages—just as earlier we substituted log dose for dose.

[The cumulative normal probability function and the logistic function are near-perfect matches of the log dose–response curve. Probits are percentages of area under the normal distribution curve expressed in multiples of standard deviation (with 5 added to avoid negative units). Logits are natural logarithms of the sample percentage responding, divided by the sample percentage not responding. For instance, an 84 per cent response frequency, corresponding to the cumulative probability of one standard deviation from the mean, is represented by a probit value of 6 (1 + 5). The logit of the 84 per cent response simply is ln (84/16) or 1.66 units.]

The log dose–response probit line of halothane, corresponding to the curve in figure 1, is shown in figure 2. The "stretching" of the parent curve is evident from the
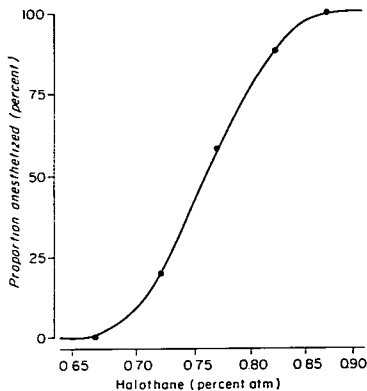
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FIG. 1. Halothane log dose–response curve derived from data in table 1. Percentage of subjects anesthetized (*i.e.*, not responding to skin incision) within each of five halothane dose ranges is on the vertical axis. Horizontal axis is scaled to the logarithm of the alveolar halothane concentration. Note the curve's symmetry around the median (50 per cent response) point.

corresponding percentage scale on the right-hand side. The farther away from the central (50 per cent) response, the farther apart are the percentages. Note too that the 0 and 100 per cent response probits cannot be shown because they are infinitely far away. Linearization with probits or logits thus has the drawback that 0 and 100 per cent responses yield minus and plus infinity values, respectively. Since single quantal observations are either 100 per cent (yes) or 0 (no) responses, they cannot be plotted on probit or logit coordinates. To overcome this hurdle, subjects must be grouped so as to obtain non-extreme values (*e.g.*, two of five responding). Should a group response still fall at 0 and 100 per cent (as it did in the first and fifth rows of table 1) special correction factors must be applied.[11,12]

The need for grouping, and the inability to use grouped extreme responses directly, are major flaws of probit and logit analysis. To avoid these drawbacks, we must turn to statistical techniques that construct the curve directly from individual observations.[8,9] The advantage here, particularly in clinical studies where anesthetic concentration is less readily controlled than in the laboratory, is that the investigator need not bunch his subjects into equi-dose groups. A disadvantage of curve-fitting is that it approaches the "ideal" curve by repeated approximations, making a computer, and programs to input and process the data, essential.

MEDIAN

All the above analytical procedures yield the 50 per cent response or *median* value as a first step. As the median lies on the steepest absolute part of the curve *it is defined more accurately than any other point*. This property holds regardless of the location and slope of the curve, hence the median is a natural candidate for comparing anesthetic potencies. To distinguish the median (50 per cent response) from other points, pharmacologists identify it with a mnemonic such as ED (effective dose), LD (lethal dose), etc., and the subscript 50. The ED_{50} then is the median effective drug dose.

AD_{50}

MAC, the minimum alveolar anesthetic concentration that prevents movement in 50 per cent of patients, corresponds to the median value of an anesthetic dose–response curve. We can simplify this description, and at the same time use conventional statistical notation, by calling MAC an anesthetic ED_{50} or, shorter yet, the AD_{50}.

Bear in mind that the AD_{50} (equals MAC) is a *median* value. So that a patient given an AD_{50} of halothane has a 50–50 chance of moving when the incision is made. For half of our patients, the AD_{50} (or MAC) thus is *not* a minimum concentration. Plainly, for the clinician, who must prevent his patients from rearing up from the operating table, a *minimum* anesthetic concentration would provide much more useful information. That way, he has at least a guideline to the lowest anesthetic dose that will keep *all* his patients still.

FIG. 2. Log dose–probit response line constructed from data in table 1 by weighted probit analysis.[11] Logarithmically scaled horizontal axis as in figure 1. The left vertical axis illustrates probit units, with 5 representing the median (50 per cent) response. Equivalent percentages are on the right vertical axis. Note how probit linearization compresses the percentage scale near the central median, and expands it increasingly towards the upper and lower tails. The 0 and 100 per cent responses do not appear on this graph because they are infinitely far away.
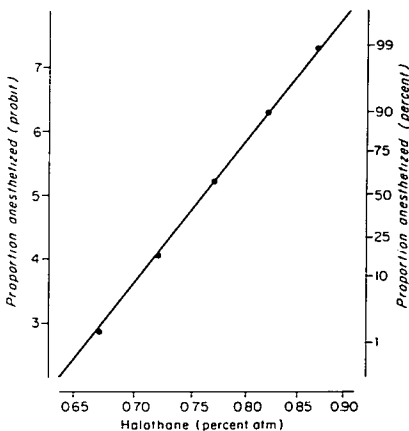
AD₉₅

Regrettably, a minimum concentration applicable to 100 per cent of patients (*i.e.*, an AD_{100}) cannot be computed from the anesthetic dose–response assay. The reason for this is the aforementioned asymptotic behavior of the curve at the extreme (0 and 100 per cent) points. As a compromise, however, we could pick a point close to the 100 per cent response level of complete anesthesia, and so arrive at a value of greater clinical utility than the AD_{50}. We propose the AD_{95} value, the dose that anesthetizes 95 per cent of the patient population.

The AD_{95} value is readily computed. Either the linearization or the curve-fitting method of dose–response analysis yields, in addition to the median value, an expression for the log dose–response relationship. Appropriate substitution into this expression provides values for all points (except 0 and 100 per cent), including that for a 95 per cent response. While a number can now be attached to the AD_{95}, we should keep in mind that the 95 per cent response falls on an almost horizontal portion of the curve; hence the precision with which we can express the AD_{95} is considerably less than that of the AD_{50}.

Methods

Consenting surgical patients were anesthetized with the anesthetic in oxygen.[1–6] End-tidal anesthetic concentrations were held constant for 10 minutes or more prior to incision. The subject's response to incision—movement or no-movement—was recorded. The resulting quantal (yes–no) observations were analyzed by a procedure specially tailored for dose–response assays.[8] Briefly, individual observations were fitted recursively to a logistic curve with a first-order Taylor approximation.[9] Analyses were performed with a FORTRAN program that furnished median and slope values, along with their standard errors, as well as an expression for the best-fitting logistic curve. The AD_{95} estimator was calculated directly from the latter.

Results

These computations of the AD_{50} agree almost exactly with the previously published MAC values (table 2). Confidence limits on the AD_{50} and slope of the logistic function can be calculated from the respective standard errors and the appropriate t-factor for (n − 2) degrees of freedom. (See Appendix

TABLE 2. Inhalation Anesthetics (Oxygen Carrier; Adult Subjects)

Agent	$AD_{50}{}^*$ $\pm$ SE	MAC†	AD_{95}‡	Slope§ $\pm$ SE	n¶
Methoxyflurane	0.16 ± 0.01	0.16	0.22	9.0 ± 4.4	17
Halothane	0.74 ± 0.03	0.74	0.90	15.2 ± 6.7	24
Isoflurane	1.16 ± 0.05	1.15	1.63	8.6 ± 3.8	34
Enflurane	1.69 ± 0.04	1.68	1.88	27.3 ± 14.0	19
Diethyl ether	1.92 ± 0.07	1.92	2.22	20.6 ± 10.0	17
Fluroxene	3.40 ± 0.05	3.4	3.57	60.1 ± 36.5	15
Cyclopropane	9.14 ± 0.23	9.2	10.1	30.4 ± 16.0	18
Ethylene	67.21 ± 1.44	67.0	74.5	28.7 ± 11.8	20
Xenon	69.44 ± 2.50	71.0	87.2	13.0 ± 4.8	28

* Median dose computed from best-fitting logistic curve.
† MAC as reported originally (see Methods).
‡ Dose corresponding to 95 per cent anesthesia.
§ Slope of the logistic curve.
¶ Number of subjects; degrees of freedom = (n − 2).
See Appendix for comments on instability in the error estimates.

for instability introduced by sequencing.) The AD_{95} values are 5 to 40 per cent greater than the corresponding medians.

Discussion

Several advantages derive from the above-described statistical approaches to anesthetic dose–response assays. First, they can be applied as readily to tissue or blood assays of potency as to alveolar gas samples. Second, they introduce conventional terminology for potency; these more familiar terms should facilitate the interchange of ideas with scientists not familiar with our speciality jargon. A third consideration is the ease and clarity with which other points on the dose–response curve (*viz.* AD_{95}) can be defined without having to coin new acronyms.

One of the advantages of the AD_{95} over the AD_{50} is its clinical utility. The AD_{50} represents the dose that anesthetizes half the patients, a value that, though of great importance in potency studies, is not terribly handy in clinical practice. The AD_{95}, on the other hand, by estimating the concentration that anesthetizes 19 of 20 patients, is a convenient clinical reference point—even though its uncertainty range is quite large. The AD_{95} also has theoretical utility in that it permits comparison of anesthetic actions at an equieffective level other than the median.

Though the move-no-move endpoint may seem somewhat crude in this electronic age, no better alternative for defining anesthesia is on hand. Neither electroencephalogram[13] nor evoked neural or cortical response characterizes the transition from no-anesthesia to anesthesia as uniformly and consistently as does the human withdrawal response to noxious stimulation. While the withdrawal response itself is a complex neural mosaic,[14] and while it can be modified by neuromuscular blocking agents, it possesses the virtues of simplicity, consistency and generality that other methods regrettably lack. The appeal of the statistical approach described here is that it will remain applicable if and when more elegant ways of identifying the anesthetic state come along.

APPENDIX

A fundamental assumption of the curve-fitting procedure is random dose assignment. In the original MAC studies an attempt was made to bracket anesthetic concentrations around the anticipated MAC, as estimated from preceding determinations. A degree of sequential dose estimation that might tend to underestimate the error of the median[15] was introduced thereby. While methods for rigorous evaluation of the error are not available at present, randomized grouping experiments[6] yielded an empirical approxima-

tion of 50 to 100 per cent slippage in the error estimates. Doubling the errors shown in the table thus should provide satisfactorily conservative fiducial ranges. (We are indebted to Professor Robert M. Elashoff, UCSF, for pointing out this instability and estimating its magnitude.)

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