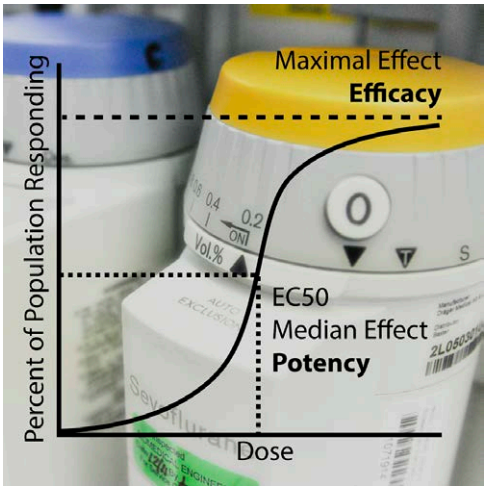
Anesthetic MAC: Origin, Utility, and Nomenclature Revisited

Evan D. Kharasch, M.D., Ph.D.

Anesthesiology is a specialty grounded in basic and clinical pharmacology. These domains have concepts and vocabularies that are useful to scientists and clinicians, in their understanding and application of pharmacology. Potency (drug dose or concentration producing a given effect) and efficacy (maximum drug effect) are two concepts that ground pharmacology. One of the venerated concepts and terms in anesthesiology is "MAC." MAC is a *nom de plume* for potency and EC50 (*vide infra*). Among the entire pharmacologic armamentarium, inhaled anesthetics are the only drugs for which potency has a special name, and inhaled anesthetics are the only ones in anesthesiology—indeed in all of medicine—that are dosed as a fraction of their EC50. As we celebrate the 60th anniversary of MAC, it is useful to examine what it means and what it stands for.



"It is time to call a MAC (minimum alveolar concentration) a MAC (median alveolar concentration)."

Last month in Anesthesiology, Dr. Larry Saidman, former Editor-in-Chief of Anesthesiology, recounted in a Classic Papers Revisited article[1] his role in the first study to determine MAC in humans.[2] He and Dr. Edmond "Ted" Eger II anesthetized 68 surgical patients with halothane to produce a light plane of surgical anesthesia, recorded the end-tidal halothane concentration, and observed whether the patients showed a muscular response to surgical incision. The halothane concentration at which half the patients responded with movement and half did not (the "transition point") was termed the MAC.[1,2] As described by Dr. Saidman, "The discovery of MAC in humans was revolutionary for clinical and research purposes in that it allowed the pharmacologic effects of inhaled anesthetics to be compared against each other at a similar anesthetic depth." Classic pharmacology.

This month in Anesthesiology, Drs. Jan F. A. Hendrickx and Andre M. De Wolf explicate the foundations of MAC, the underlying physiology and pharmacology, the clinical application, and the terminology in a Clinical Focus Review.[3] They explore definitions and determination of MAC, types of MAC (MAC_{awake}, $MAC_{unconsciousness}$, $MAC_{immobility}$, MAC_{BAR}), factors affecting MAC, fraction of a MAC delivered to a patient (fMAC), relationship between fMAC and clinical effect, and drug interactions or other factors affecting fMAC. They also present pragmatic approaches to using MAC and fMAC in clinical care. This comprehensive and lucidly written review provides both text and illustrations to visualize and reinforce the concepts. It is recommended to trainees as well as experienced clinicians.

Astute readers will detect that while this essay has described MAC, it has not yet defined it. For this, we need a bit of pharmacologic grounding (fig. 1). There are two types of dose (or concentration)–response curves. Graded dose-response curves describe drug response along a continuous scale (0 to 100% of maximal response—termed efficacy) in a single unit (*e.g.*, cell, organ, animal, or human). Quantal or population dose-response curves describe the fraction of a population of units responding with an all-or-none response (*e.g.*, awake or not). The amount of drug needed to produce 50% of a maximum effect in one unit is the ED_{50} or EC_{50}. The amount of drug needed to produce a quantal response in 50% of a population is the ED50 or EC50 (also known as the median dose or concentration). Both EC_{50} and EC50 describe drug potency (amount of drug needed for half-maximum effect), but they are clearly determined in very different ways. Now, back to MAC.

Even before Drs. Saidman and Eger determined the MAC of halothane in patients, Drs. Merkel and Eger first introduced the concept of MAC.[4] They determined the MAC of halothane in dogs. In each of six dogs, they determined

Image: J. P. Rathmell.

This editorial accompanies the article on p. 985.

Accepted for publication March 22, 2022.

Evan D. Kharasch, M.D., Ph.D.: Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina.

 Anesthesiology 2022; 136:885–7. DOI: 10.1097/ALN.0000000000004217

<zdoi;. DOI: 10.1097/ALN.0000000000004217>

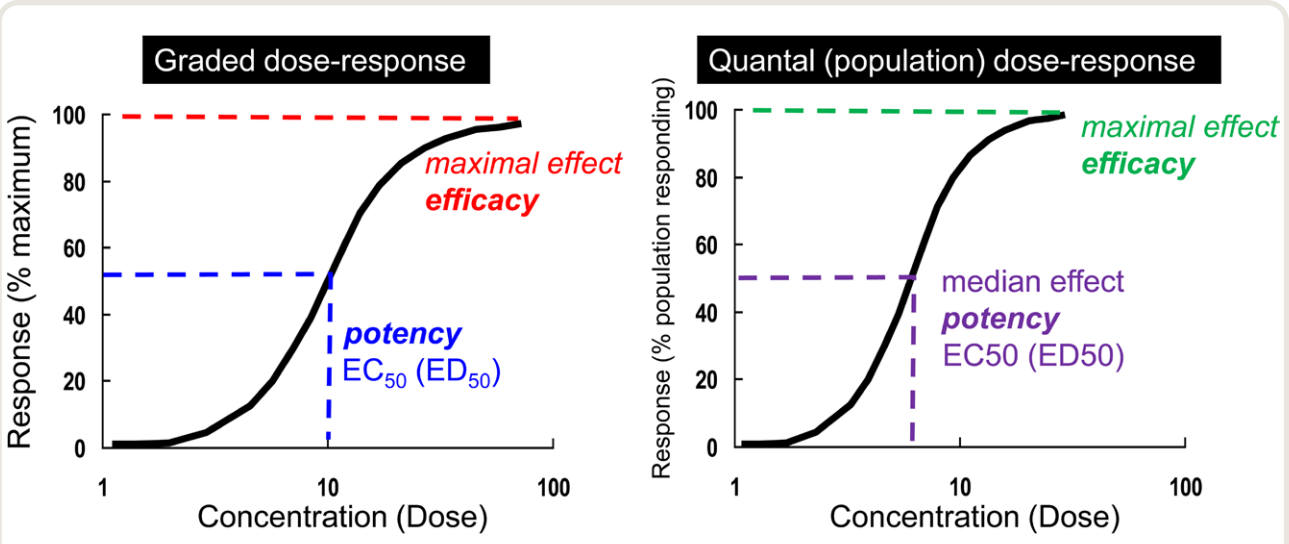


Fig. 1. Types of concentration (or dose)–response curves. (*Left*) Graded curve, showing percentage of maximum response (efficacy) in a single unit (*e.g.*, cell, organ, animal, or human). The dose (or concentration) of drug producing a half-maximum effect is the ED_{50} or EC_{50}. (*Right*) Quantal curve, showing the percentage of a study population showing a response to an all-or-nothing outcome. The dose (or concentration) of drug needed to produce a quantal response in 50% of the population is the ED50 or EC50 (also known as the median dose or concentration).

the *minimum* end-expired halothane concentration required to keep the dog from responding with gross movement to a painful stimulus (tail clamp or electrical stimulus). This was termed the "minimal anesthetic concentration" (1 MAC). Multiple, higher concentrations of halothane were also evaluated. The average MAC was determined from individual experiments in the six dogs. This was a classical, single-unit dose-response experiment, and truly determined the effective *minimum* anesthetic concentration. Later, in an analogous experiment, Drs. Saidman and Eger anesthetized four surgical patients, each one at multiple halothane concentrations, and determined the end-tidal halothane concentration that just eliminated movement to an electrical stimulus.[2] This was termed the "minimum alveolar concentration" (1 MAC). The average MAC was determined from the four patients. This too was a classical, single-unit dose-response experiment and truly determined the *minimum* anesthetic concentration. Drs. Saidman and Eger also did an experiment in which they anesthetized 68 surgical patients with halothane, each at a *single* concentration, and recorded the absence or presence of a muscular response to skin incision. The halothane concentration at which half the patient population moved and half did not was termed the "minimum alveolar concentration" (1 MAC). However, this was a classical population *quantal* dose-response experiment that did not determine the *minimum* effective concentration, but rather the *median* effective concentration. A totally different construct, yet the same term (and abbreviation) were used to refer to both individual (minimum) and population (median) values—only one of which is correct.

Drs. Hendrickx and De Wolf identify that the term "MAC" is thus plagued with semantic issues.[3] Should the "M" in MAC refer to "minimal" or "median"? In addition, while alveolar and end-tidal terms have been used interchangeably, they also point out that alveolar and end-tidal anesthetic concentrations (what we actually measure) may not be the same. They propose that MAC should be redefined ("backronymed") as the "median alveolar concentration." Excellent suggestion. Or even more precisely, perhaps should it be redefined as the "median end-tidal anesthetic concentration": METAC? They also ask whether the acronym "MAC" should be abandoned altogether and replaced with the more universal EC50, because EC50 is conceptually and semantically more correct and aligns volatile anesthetic terminology with that of intravenous anesthetics and all other drugs. They suggest that MAC should not be abandoned, largely for practical reasons. This is because MAC describes anesthetic potency in a unifying manner across different anesthetics, allows the same anesthetic machine alarm limit (fraction of a MAC) to be applied to all volatile anesthetics, and is already hard-wired into anesthesia machine displays. Good point. Moreover, the use of MAC may contribute to patient safety.

MAC has withstood the test of time. It remains conceptually accurate, clinically useful, and helpful to the practicing clinician. And yet, in an era of precision medicine, we should use more precise terminology. It is time to call a MAC (minimum alveolar concentration) a MAC (median alveolar concentration).

Competing Interests

Dr. Kharasch is Editor-in-Chief of Anesthesiology.

Correspondence

Address correspondence to Dr. Kharasch: evan.kharasch@duke.edu

References

1. Saidman LJ: Serendipity: Being in the right place at the right time. Anesthesiology 2022; 136:823–6
2. Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964; 25:302–6
3. Hendrickx JFA, De Wolf AM: End-tidal anesthetic concentration: Monitoring, interpretation, and clinical application. Anesthesiology 2022; 136: 985–94
4. Merkel G, Eger EI II: A comparative study of halothane and halopropane anesthesia including method for determining equipotency. Anesthesiology 1963; 24:346–57