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What if Half of Your Patients Moved (or Remembered or Did Something Else Bad) at Incision?

NUMBERS are part of medical education—everyone learns normal values for blood pressure, laboratory values, and so on; then, during training, one acquires numbers specific for one's specialty. One category of numbers—minimum alveolar concentration (MAC)—permeates the anesthesia community. For each inhaled anesthetic, that number is branded onto one's brain as a guide to dosing. However, there is a problem with MAC: If patients were dosed with 1 MAC, by definition, 50% of patients would move on incision. Surgeons would be unhappy, patients might be harmed, and anesthesiologists' professional standing would be compromised. Realistically, one of two things happens when inhaled anesthetics are given: Either larger doses are given routinely or movement is prevented by administration of other drugs.

One could argue that MAC, an ED_{50}, is not an inherently useful number; instead, it makes more sense to report ED_{95} (*i.e.*, a dose preventing movement in 95% of subjects). Yet, studies of every inhaled anesthetic in the modern era have focused on ED_{50} rather than any other measure of potency. This oddity can be explained through some history. The earliest studies of MAC, performed by Eger and associates, estimated MAC semiquantitatively and did not apply rigorous statistical evaluation (personal communication, Edmond I. Eger II, M.D., Professor, Department of Anesthesia, University of California, San Francisco, January 30, 2007). After the first several studies were reported, Eger learned of the "up–down" method in which the dose for a particular subject in a clinical trial is selected as a function of the response of the previous subject. This method was coupled with a variety of statistical techniques to estimate ED_{50}. One advantage of these approaches was that studies could be quite small—MAC was estimated in as few as 10–20 subjects; in turn, MAC studies proliferated.

These MAC studies proved to be clinically useful, guiding numerous generations of anesthesiologists. Why would that be the case if the number that they provided could result in a high incidence of patient movement? The answer is simple. In Eger's early studies, it became apparent that doses minimally larger than ED_{50} typically prevented movement. For example, with halothane, in which ED_{50} was estimated to be 0.75%, none of the subjects with end-tidal concentrations larger than 0.78% moved.[1] This observation suggested that the concentration–response relation for inhaled anesthetics was steep, *i.e.*, ED_{95} differed minimally from ED_{50}. In turn, knowledge of ED_{50} would have been sufficient to guide clinical dosing (and trials that formally estimated ED_{95} for inhaled anesthetics would not be needed).

Subsequently, de Jong and Eger[2] formally evaluated the premise that, for inhaled anesthetics, the ratio of ED_{95} to ED_{50} is not markedly larger than 1. A study of nine inhaled anesthetics showed that ED_{95} was typically less than 20% larger than ED_{50}; the ratio of ED_{95} to ED_{50} exceeded 25% only for ethylene and xenon (neither of which is used clinically). In that the safety margin of inhaled anesthetics is reasonably large, clinicians could dose inhaled anesthetics with concentrations sufficiently above ED_{50} to ensure lack of movement without compromising safety; in turn, knowledge of ED_{50} was sufficient to guide dosing (*i.e.*, "give a little more than 1 MAC and things will be OK").

Over ensuing decades, statistical techniques for the conduct/evaluation of MAC studies evolved minimally. Meanwhile, researchers in anesthesia extended traditional up–down methodologies to drugs other than inhaled anesthetics, *e.g.*, local anesthetics. Unfortunately, published studies of these other drug classes have not formally evaluated steepness of the dose–response curve; in turn, relevance of ED_{50} to clinical dosing of anesthetic drugs other than inhaled anesthetics is understood less well. Perhaps the only evolution in statistical methods for estimation of potency of anesthetic drugs was the introduction of logistic regression to estimate ED_{50}. Although I used logistic regression in one study,[3] I understand now that it can yield flawed and biased estimates[4] (logistic regression assumes that the independent variable, concentration, is selected randomly, whereas successive values are assigned systematically).

In contrast, statistical methods for estimation of dose–response have evolved significantly in other fields, driven by needs in therapeutic areas such as oncology (for which therapeutic margins are typically small and there is a need to minimize trial size). In the current issue of ANESTHESIOLOGY, Pace and Stylianou[4] review historic and new statistical methods for the determination of potency. Their important contribution to the anesthe-

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sia community is the description of methods to estimate ED_g, potency at the *g*th percentile. The review is of particular importance to investigators who perform potency studies in which the outcome is quantal (*e.g.*, movement *vs.* no movement). In addition, others interested in clinical research can learn much from the article.

During the review process for this article, two things became evident. First, as Paul and I[5] reported several years ago in this journal, regardless of the methodology used for dose selection and analysis, studies with small numbers of subjects may yield biased and imprecise estimates (*i.e.*, broad confidence limits), even for ED_{50}. Second, as the potency estimate deviates further from 50% (*e.g.*, ED_{95}), problems of bias and imprecision become worse.

The anesthesia research community has benefited from studies that had relatively small sample sizes and reported ED_{50}. If ED_{50} is useful, this practice can probably continue without harm: The long history with inhaled anesthetics suggests that this is the case. However, for other anesthetic drugs, *e.g.*, local anesthetics, clinical utility of ED_{50} remains to be seen. Pace and Stylianou offer guidance on how to obtain other, possibly more useful, potency estimates.

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Anesthetic Neurotoxicity in Newborns

Should We Change Clinical Practice?

PUBLICATION of findings that ketamine or other *N*-methyl-D-aspartate receptor antagonists accentuate apoptosis in the newborn brain,[1] and that commonly used anesthetic agents (isoflurane, midazolam, and nitrous oxide) not only enhance neuroapoptosis but also promote long-term learning deficits,[2] sparked controversy in the pages of ANESTHESIOLOGY.[3] This editorial aims to update anesthesiologists on further investigations on the neurotoxic effects of anesthetic agents and methods for extrapolating neurodevelopmental data from animal models to humans, in order to reexamine the clinical applicability of these findings.

Anesthetic-induced Neurotoxicity: A Brief Update

Neurodegenerative changes after anesthesia occur at both ends of the life span. Epidemiologic observations suggested that onset of Alzheimer disease was related to cumulative anesthetic exposure before the age of 50 yr.[4]

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Animal studies confirmed that inhaled anesthetics enhance the production, aggregation, and neurotoxicity of amyloid-β peptides,[5] appearance of brain plaques and learning/memory deficits characterizing Alzheimer disease,[6] and increased apoptosis,[6] probably in hippocampal areas.[7] This report, however, focuses on the anesthetic neurotoxicity after fetal–neonatal exposure, coincident with developmentally occurring apoptosis, which affects 0.5–1% of rodent neurons and more than 50% of human neurons.[8]

The original finding that *N*-methyl-D-aspartate receptor antagonists such as ketamine enhance apoptosis in immature neurons has been confirmed in different animal models and by multiple authors (reviewed recently by Mellon *et al.*[9]). Anesthetic neurotoxicity peaks at postnatal day 7 (P7) in rats[2,10–12] and requires prolonged exposures in rats and monkeys.[2,10,12–16] Single large doses of ketamine (50 mg/kg) or benzodiazepines activate apoptosis in mice,[17,18] signifying developmental differences across species.[19] Further, anesthetic neurotoxicity primarily results from apoptosis in rodents,[2,10–12,17,18] whereas infant monkeys at P5 (but not at P35) exhibit both excitotoxicity and apoptosis.[10,13,15,16]

Despite the accumulating data, practicing anesthesiologists must consider important limitations in applying such experimental results to clinical practice. These include developmental differences across mammalian species, the huge doses and prolonged exposures required to produce