Effectiveness *versus* Efficacy of Calabadion and Sugammadex for Nondepolarizing Neuromuscular Blocking Agent Reversal

To the Editor:

Haerter *et al.*[1] recently published a study on the comparison of calabadion 2 to reverse nondepolarizing neuromuscular blocking agents by binding and inactivation, which they described as comparative effectiveness. The study included *in vitro*, *ex vivo*, and *in vivo* experiments, including assessments of dose–response relationships. Although the article makes some important contributions, our concern focuses on the use of the term and the associated title that includes "comparative effectiveness." Instead, these studies should be described as efficacy research, not effectiveness research. Although this distinction may seem to represent a minor issue, we feel that incorrectly defining the phase of research can lead to misconceptions about the study's goals and objectives, and subsequent interpretation, and lead to misreporting on the current state of research (*e.g.*, in a systematic review with searches based on titles and key terms).

Although Haerter *et al*. do not use the full term of "comparative effectiveness research" (CER), the idea of effectiveness, rather than efficacy, is well described by extensive literature on CER. The Institute of Medicine[2] and Federal Coordinating Council for Comparative Effectiveness Research[3] describe CER as "…the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care." The Institute of Medicine report goes on to state that "The key elements of this definition are … the study of patients in typical day-to-day clinical care." In contrast, efficacy studies evaluate treatments under ideal conditions, with an emphasis on assessing the potential of the intervention to work under ideal or very specific conditions. The study by Haerter *et al*. demonstrates which drugs work best in a laboratory setting and in controlled circumstances. While these findings are absolutely informative and significant, they do not demonstrate *effectiveness* in that they do not reveal which drugs work well in a less controlled, "real-world" clinical setting.

The distinction between efficacy and effectiveness is also emphasized by the phases of translational research,[4] where efficacy studies qualify as T1 or T2 research, but effectiveness studies fall under T3 research. Although the study by Haerter *et al*. compares treatments, the *in vitro*, *ex vivo*, and *in vivo* nature of experiments would still lead to its categorization as T1 research.

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Competing Interests

The authors declare no competing interests.

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In Reply:

We recently reported that speed of reversal of rocuronium- and vecuronium-induced neuromuscular block is faster with calabadion compared with Bridion (sugammadex; Merck & Co., Inc., USA) given at an equimolar concentration.[1]

The question was raised by Drs. Lim and Landsittel as to whether our study should be better characterized as an efficacy study rather than an effectiveness study. There seems to be a general confusion about the proper use of "efficacy and effectiveness" in the literature. We found 6,195 manuscripts listed in PubMed under "comparative effectiveness" and 2,724 manuscripts listed under "comparative efficacy"—it is hard to find in the examples we checked a clear pattern that distinguishes how researchers use these terms. It is also obvious that some researchers use these terms interchangeably, while others use them very specifically.

Our laboratory conducts *preclinical effectiveness* studies to develop new drugs.[2,3] We also conduct formal "*quantitative effectiveness research*" in order to evaluate perioperative treatments in a real-world scenario based on existing perioperative databases.[4,5] Our team uses the terms *efficacy*, *effectiveness*, and *quantitative effectiveness research* intentionally, as described below.

In pharmacology, efficacy (E_{max}) is defined as the maximum response (traditionally at a well-defined receptor) achievable from an agonist given at maximum tolerated doses.[6,7] In our paper under consideration here, we did not test efficacy. Bridion and calabadion are encapsulating agents that do not interact with a receptor, do not leave the blood

vessels to act at the neuromuscular junction, and did not demonstrate so far biologic effects when given in the absence of a neuromuscular blocking agent. We did not administer maximum tolerated doses. Of note, we did not conduct pharmacokinetic/pharmacodynamic analyses required to determine E_{max}, as we did not intend to study if a further increase in blood concentration would have further increased speed of reversal.

In our study, we rather assessed "effectiveness," the power to produce a desired effect[8] between two reversal drugs (sugammadex and calabadion) given at the same molar concentrations in three models, *in vitro*, *ex vivo*, and *in vivo*. We found that calabadion 2 reversed rocuronium- and vecuronium-induced neuromuscular blockade with a 1:1 binding ratio, like sugammadex, but it had a higher *in vitro* binding affinity and a higher molar potency *in vivo*. Therefore, we argue that the *effectiveness* to reverse rocuronium- and vecuronium-induced neuromuscular blockade of calabadion is higher compared with Bridion. To our knowledge, the *efficacy* of these compounds has not been tested by us or by others in any previously published study , probably because E_{max} of encapsulating agents cannot be studied rigorously. In addition, knowledge on maximum speed of reversal of neuromuscular blockade by maximum tolerated doses of calabadion and sugammadex adds marginal value to the available literature on preclinical effectiveness of these encapsulating agents.

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Competing Interests

Dr. Eikermann holds equity shares of Calabash Bioscience, Inc. (College Park, Maryland), which is developing calabadion 2 for biomedical applications. The other author declares no competing interests.

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Should Deidentified Case Data Be Treated as Independent Data Points?

To the Editor:

We read with interest Whitlock *et al.*'s[1] review of perioperative mortality derived from the National Anesthesia Clinical Outcomes Registry database. One shortcoming of the National Anesthesia Clinical Outcomes Registry database they briefly allude to is "the inability to eliminate patients who had multiple anesthetics" from the analysis. We suggest that this can be a major confounder in the retrospective analysis of such databases. For example, analysis of case data for the past 3 yr from our tertiary pediatric center showed a 48-h mortality of 85 per 70,194 cases (0.12%) or 64 per 42,808 patients (0.15%). Fifty patients had one procedure during this 48-h period, nine patients had two procedures, four patients had three procedures, and one patient underwent five procedures. The share of patients who had multiple procedures was even higher for 30-day mortality. This is not unexpected , as the sickest, most-likely-to-die patients are likely to have multiple procedures before their death.

Large databases allow collection of a sufficient number of relatively rare events (*e.g.*, perioperative death) to identify statistically meaningful associations between outcomes of interest (*e.g.*, perioperative mortality) and risk factors. Despite the large numbers of cases included in such analyses, *e.g.*, nearly 3,000,000 in the study by Whitlock *et al.*,[1] or approximately 244,400 in the study by Mathis *et al.*,[2] the actual numbers of index cases are still rather small, *e.g.*, 944 and 232, respectively. Therefore, counting multiple procedures in the same patient as independent data points may introduce significant bias toward attributes found in those patients. This problem is not limited to mortality alone, but may apply to any infrequent serious outcome.