The Art of General Anesthesia

Juggling in a Multidimensional Space

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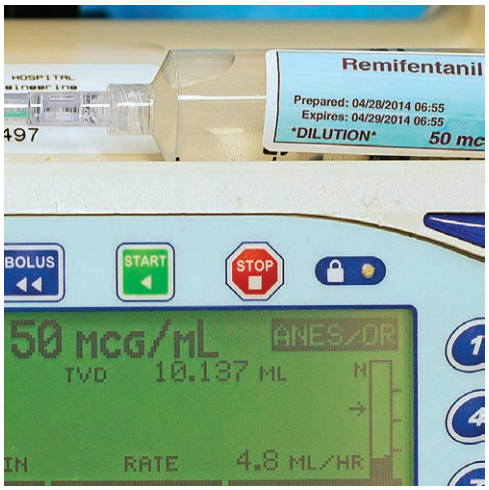
The art of general anesthesia involves making intuitive predictions of how a particular patient will respond to anesthetic drugs and to the noxious stimuli of surgery. Patient responses might consist of somatic movements, various autonomic nervous system effects (including tachycardia, bradycardia, hypertension, sweating, mydriasis), return of consciousness and memory, and endocrine and immune activation. To suppress these responses we use many different classes of anesthetic drugs or adjuncts. Clearly the delivery of anesthesia requires an appreciation of a multiplicity of dimensions. In this issue of Anesthesiology, an article by Kuizenga *et al.*[1] attempts to bring some scientific quantification to the question of hypnotic–opioid interactions. They investigated how the addition of an opioid drug (remifentanil) alters responses to two commonly used hypnotic drugs (propofol and sevoflurane). This sort of study has been done previously,[2–4] but the novelty of the present study was the use of a within-subject design to formally compare the effects of remifentanil on propofol head-to-head with sevoflurane. Thus they studied three input variables (two hypnotic drugs and one analgesic drug) and two output variables (the resting state of the cortical activity as measured by the Patient State Index [a processed electroencephalographic measure], and the probability of behavioral response to graded external stimulation). Because they were looking at perhaps five dimensions, it is hard to represent the totality of their results graphically in a single diagram. Instead we follow the conventional methods of reductive science, and ask separate, tractable (but two-dimensional) questions.



"[How does] the addition of an opioid drug (remifentanil) alter responses to…propofol and sevoflurane?"

1. How does remifentanil affect the relationship between hypnotic drug concentrations and the probability of quantal behavioral response to stimuli? (and ignore the cortical state)
2. Does remifentanil alter the state of cortical activity at each concentration of hypnotic drug? (and ignore the behavioral response)
3. How does remifentanil affect the relationship between the unstimulated resting cortical state and the probability of behavioral response to stimuli? (and ignore the hypnotic drug concentrations)

To answer the first question we find that the addition of even a low concentration of remifentanil dramatically reduces the responses to stimuli for propofol; furthermore, the effects are more marked for the more painful stimulus. This comes as no surprise to any clinician. Because it is one of the standard descriptive parameters estimated in the mathematical model, the remifentanil effect is usually reported as a left shift in the concentration of propofol required to prevent a response in 50% of the population (EC50; shown as a horizontal black arrow in fig. 1A). However the practicing clinician is more interested in the probability that a patient—when given at a particular propofol effect site concentration—will move in response to surgery. With this perspective, the effect of adding some remifentanil is shown by the vertical black arrows in figure 1. We can see that, for low and moderate concentrations of hypnotic (less than 3μg/ml propofol and less than 1.5% sevoflurane), the addition of remifentanil causes dramatic reductions in probability of response. For example, at the

Image: J. P. Rathmell.

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EC50 propofol concentration of 2.8 μg/ml, even 2 ng/ml of remifentanil (equivalent to a steady-state infusion of about 0.1 ng/kg/min) reduces the probability of response from 50% to less than 5%. The lesser leftward shift of the EC50 for sevoflurane suggests a lesser additive remifentanil effect. This conclusion is illusory. Because the slope of the sevoflurane curves are steeper than those for propofol, the clinical beneficial hypnotic-sparing effect of remifentanil for sevoflurane is actually comparable with that of propofol (*i.e.*, both vertical black arrows in fig. 1 are similar in length). With the proviso that the tetanic stimulus is less than that of a surgical incision, these figures would suggest that giving concentrations of remifentanil greater than 2 ng/ml has diminishing benefit for preventing patient movement.

For the second question: does the addition of remifentanil have a direct effect on the relationship between the hypnotic drugs and resting state cortical activity? The answer seems to be: "a little effect with propofol at these concentrations of remifentanil" and "no effect on sevoflurane." The propofol–Patient State Index curve is slightly shifted to the left, and the effect on the sevoflurane–Patient State Index relationship is almost nil. Other work[5] suggests that the EC50 of the remifentanil sigmoid dose–electroencephalogram response curve—which is in turn acting to shift the propofol–electroencephalogram sigmoid curve—is higher (5 to 10 ng/ml of remifentanil) than the 4 ng/ml achieved in the present study.

The third question looks at whether the preexisting unstimulated state of cortical activity (the Patient State Index value) has any correlation with the probability of subsequent behavioral response to stimulus. This question lies at the core of the unending misunderstanding about the role of electroencephalographic monitors in clinical anesthesia. As is clearly shown in figure 5 of their article, the curves for response to verbal command are quite steep; for propofol, most patients will respond at a Patient State Index of 60, and most will not respond at 30. The curve is shifted 20 points to the left by using sevoflurane or adding remifentanil. Again, no clinical surprises here. You can easily give a sevoflurane-only anesthetic, but it is hard to give a propofol-only anesthetic for any serious surgery. Sevoflurane is clearly better than propofol at blocking responses to sensory input. The curves of the probability of behavioral response to a painful stimulus are quite different; the flat slopes of these curves indicate that cortical state is a poor predictor of the probability of subsequent movement in response to pain. Any individual patient could move at almost any value of Patient State Index. Interestingly the addition of remifentanil shifts the curves markedly up and to the left but does not make the slopes any steeper in this study. Somatic movement is largely driven by spinal chord responses. You cannot expect to accurately monitor spinal cord function by looking at the signal from electrodes on the forehead.

The article by Kuizenga *et al.*[1] essentially looks piecemeal at bivariate opioid–hypnotic combinations. In clinical practice we commonly—and effectively—use more complex (multidimensional) combinations consisting of volatile agent, opioid, and infusions of propofol, dexmedetomidine, lidocaine, or ketamine. How do we objectively quantify these multiple simultaneous interactions at an individual patient level? The art of anesthesia is progressing rapidly; can the science keep up?

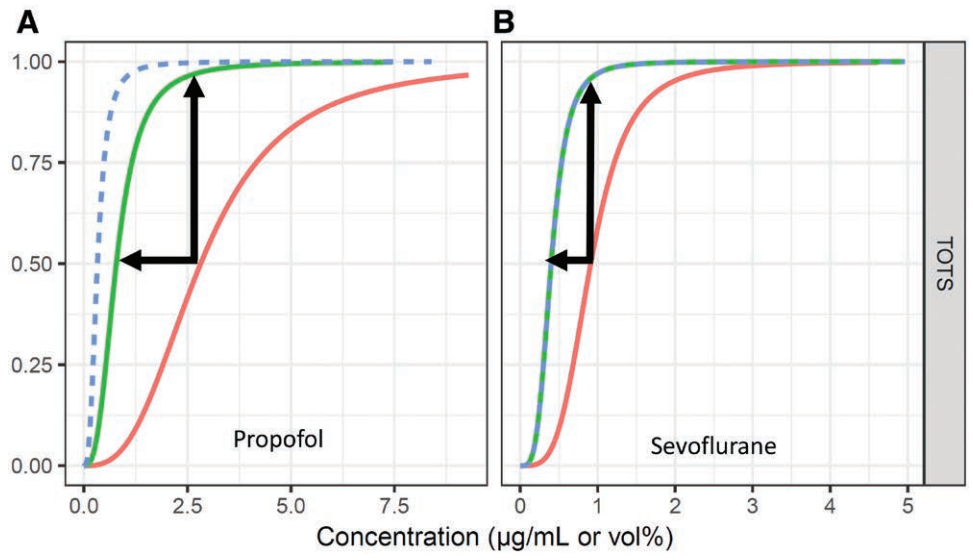

Fig. 1. Effect of addition of remifentanil to probability of response to noxious stimulus, at different concentrations of propofol (*A*) and sevoflurane (*B*). Red lines, remifentanil 0 ng/ml; green, 2 ng/ml, dashed blue, 4 ng/ml. Reproduced with permission from figure 2 of Kuizenga *et al.*[1]

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Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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