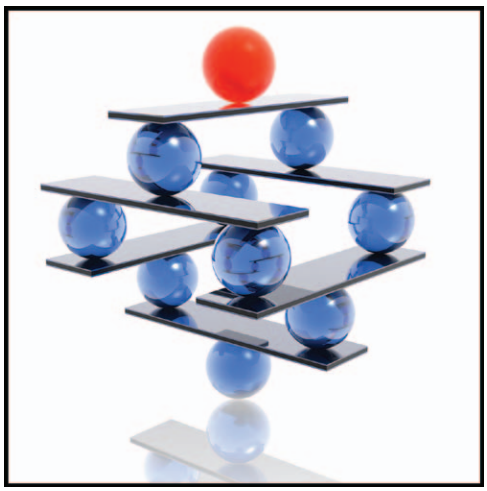
Assessing the Utility of the Utility Function

OVER the last 40 yr, anesthesiologists have incorporated a series of new pharmacologic concepts that give us a better understanding of how drugs behave when administered as intravenous bolus or infusion. Each of these concepts initially seemed arcane and theoretical, but most are now accepted as a fundamental part of anesthesia practice. For example, the rapid administration of neuromuscular-blocking drugs produces effects that are not well-described by their plasma concentrations (after all, they do not work in plasma). This discrepancy lead to the development of "pharmacokinetic–pharmacodynamic modeling" and the concept of a hypothetical "biophase" or "effect compartment."[1,2] More than 50 yr ago, clinicians noted that the recovery from opioid infusions had a poor correlation with the elimination half-life.[3] This eventually lead to the development of the "context-sensitive half-time," which describes the minutes required for a 50% decrement in plasma drug concentration after stopping infusions of varying durations.[4–6] Traditional pharmacokinetics focused predominantly on drug elimination, but an understanding of anesthetic onset required models that described drug disposition from the moment of injection.[7] Thus, the concept of recirculatory pharmacokinetic models, or "front-end kinetics" was introduced to anesthesiology.[8] Subsequent to their introduction, these new concepts were validated through extensive additional investigation.



"Boom et al. *report a mathematical model they developed that characterizes opioid benefit* versus *risk (analgesia* vs. *respiratory depression) using a single number called a utility function."*

In this issue of Anesthesiology, Boom *et al.*[9] report a mathematical model they developed that characterizes opioid benefit *versus* risk (analgesia *vs.* respiratory depression) using a single number called a utility function (UF). The UF was first used in economics and was applied to drug therapy decades ago by the eminent clinical pharmacologists Sheiner and Melmon.[10] UF is a method for converting two continuous dose–response or concentration–response curves (for clinical benefit and toxicity) into a single function. It is most applicable during drug development when a single "optimal" dose is being determined. This might be the case during phase II testing when a single dose is to be recommended for large phase III clinical trials. Other models to relate overall the positive and negative effects of drug(s) in a single number have also been reported.[11] The study by Boom *et al.* introduces the UF concept to anesthesiology, and it shows that UF can be determined even though full dose– response or concentration–response relationships are not assessed. This study also demonstrates a number of important factors that can radically affect the calculation of UF and therefore its predictions about opioid safety.

The safety of medications has classically been expressed as the *therapeutic index* (TI), a single number which represents the ratio of doses (or concentrations) that produce toxic effects (TD50) *versus* therapeutic effects (ED50) in 50% of the population (TI = TD50/ED50). If toxic and therapeutic effects occur by the same mechanism (as is the case for many chemotherapeutic drugs), they are described by dose–response curves which are parallel, so the TI is independent of dose. Most often, therapeutic and toxic effects involve different mechanisms and must be measured differently, so the curves are *not* parallel, and the TI is therefore dose-dependent. For this reason, the TI must be defined by comparing doses at a specific level of response. The dose or concentration producing 50% response is chosen because this is the point of maximal slope and therefore greatest precision.

To evaluate the UF, the investigators administered intravenous fentanyl (3.5 μg/kg) to subjects on separate days. On one day, they measured experimental analgesia as an increase

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in the intensity of electrical stimulation (in mA) that the subject could tolerate. On the other day, they measured respiratory depression as the decrease in minute ventilation while breathing a fixed, increased concentration of carbon dioxide. A population pharmacokinetic–pharmacodynamic model was then used to calculate effect-site or steady-state concentrations producing a 25% increase in tolerable pain stimulus intensity (EC_{25} for analgesia) and a 50% decrease in minute ventilation (TC_{50} for respiratory depression). Using the pharmacokinetic–pharmacodynamic parameter estimates and interindividual variabilities, computer simulations were then performed to determine the UF, defined as the probability of 50% analgesia (an increase in tolerated electrical pain current of least 50%) minus the probability of at least 50% respiratory depression. Thus, the UF is a difference of predicted probabilities, whereas the TI is a ratio of actual doses (or concentrations).

The authors found that at low fentanyl concentrations (<0.7 ng/ml), the UF was positive, indicating that the probability of analgesia was greater than that of respiratory depression. At higher concentrations, the UF was negative, indicating that the probability of respiratory depression exceeded that of analgesia. They concluded, appropriately, that further studies are required to assess whether this risk–benefit analysis is clinically applicable and if it can be used for comparing the safety profile among experimental drugs.

One essential feature of the UF is that it involves quantal (or binary) data points for effectiveness and toxicity. A continuous measure (*e.g.*, increase in mA of current) must first be dichotomized (changed to analgesia—yes or no). Boom *et al.* defined the threshold for desired and toxic effects as a 50% increase in current or a 50% decrease in minute ventilation, respectively. The investigators have used these pain and respiratory measures often and expertly in numerous laboratory studies. But it is not clear how the 50% thresholds correspond to a clinically relevant degree of intraoperative or postoperative analgesia, or to clinically important changes in respiratory rate or the partial pressure of carbon dioxide in blood. The practice of changing continuous data to dichotomized responses also has important statistical implications. The loss of information can lead to a decrease in precision of conclusions and power.[12,13] The information lost when dichotomizing a normal distribution at the mean or median is at least 36%, and even more information is lost when other cut points are used.[13] Dichotomization also requires an increase of at least 1.6 times in sample size to maintain statistical power.[12,13]

Another important factor affecting the UF is the relative sensitivity of the two measures. That is, the measures of analgesia and toxicity should be comparably sensitive. If the measure of respiratory depression is much more sensitive than that of analgesia, then the UF will always be negative; if it is much less sensitive, then the UF will always be positive. Boom *et al.* performed a sensitivity analysis (their fig. 7) by systematically varying the threshold definitions for analgesia and respiratory depression. As predicted, they demonstrated a marked effect of the threshold (25, 50, or 75%) for change (dichotomization) in the positivity or negativity, and magnitude, of the UF. As stated by the authors, their UF is very "context sensitive" (to numerical thresholds), and which of the response thresholds is most appropriate will require much further study.

The drug concentration range tested can markedly affect the magnitude and direction (positive or negative) of the UF. Figure 1 shows the relationship of fentanyl effect-site concentration and the change that Boom *et al.* determined for the two continuous variables (expressed as mA and l/min). The graphs were constructed using the authors' model (equations 1 and 2) and the data from table 2. These data show clearly that these are very different concentration–effect curves, and that they are not parallel. Thus, like a TI in this setting, the UF will also be dose (or concentration)-dependent. In addition, respiratory effects increased uniformly with effect-site concentration, whereas analgesia changed dramatically over a small range of concentrations. This means that a large increase in analgesia might be required to make a small increase in the estimated EC_{50} (concentration producing 50% of maximal therapeutic effect) and shift the UF positively. Conversely, a much smaller increase in respiratory depression would be required to make a small increase in the estimated TC_{50} (concentration producing 50% of maximal toxic effect) and shift the UF negatively. Thus, these data seem inherently to favor a negative UF.

A clinician may ask, what is the clinical relevance of the dose and concentration range at which Boom *et al.* defined the fentanyl UF? Plasma fentanyl concentrations of 0.2–20 ng/ml were studied, and effect-site concentrations up to 3 ng/ml were simulated. Boom *et al.* conclude that fentanyl has a predominantly negative UF with a greater probability

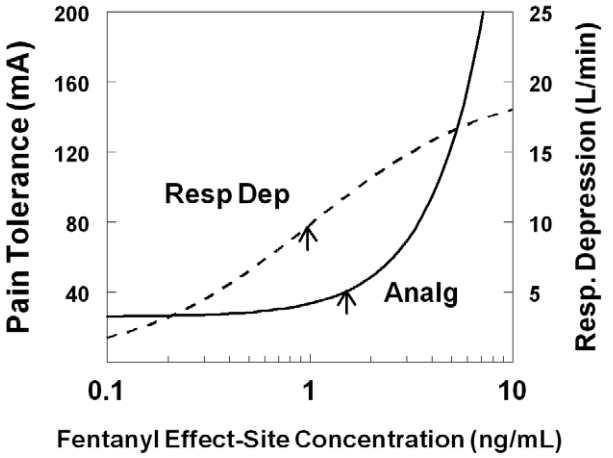

Fig. 1. Effect *versus* effect-site concentration for fentanyl-induced tolerance to electrical stimulus (mA, *solid line*) and depression of ventilation (l/min, *dashed line*) while breathing inspired carbon dioxide. The curves were generated using equations 1 and 2 from the study by Boom *et al*., as well as the values in table 2. Calculated EC_{50} and TC_{50} are indicated by *arrows*.

for respiratory depression than analgesia in "relevant" dose and concentration ranges. Nevertheless, the absolute negative value of the UF was small (only <–0.2 at effect-site concentrations >1 ng/ml), and the UF was negative only at times within 60 min after the bolus (at plasma concentrations approximately >0.8 ng/ml). Clinical data suggest that postoperative pain is effectively treated with plasma fentanyl concentrations averaging 0.6 ng/ml.[14] At these concentrations, the fentanyl UF may not be as negative as suggested. The fentanyl dose tested by Boom *et al.* (3.5 μg/kg) is more likely to be used during anesthetic induction, when the degree of respiratory depression is less relevant because patients are anesthetized. Clearly, additional work is needed to determine the most clinically relevant opioid doses at which to determine a UF.

Thus Boom *et al.* have devised a risk–benefit measure that appears to be precise and reproducible, and also seems to be an excellent method for combining high-quality estimates of population pharmacokinetics and simultaneous pharmacokinetic–pharmacodynamic modeling. However, it requires validation that it predicts relevant clinical endpoints. Anesthesiologists have a good idea of the relationship between the depression of response to carbon dioxide in volunteers and clinical ventilatory depression. We do not have a reliable assay for opioid analgesia in volunteers that accurately predicts clinical analgesia in patients. Boom *et al.* conclude that the UF is most negative at a fentanyl effect-site concentration of 1.7 ng/ml, with a 60% probability of analgesia and an 83% probability of respiratory depression. The 3.5 μg/kg dose of fentanyl resulted in an effect-site concentration of 1 ng/ml, so approximately 6 μg/kg would be needed to reach 1.7 ng/ml. This would be a dose of almost 500 μg in an 80 kg patient, and many clinicians would question whether such a large dose produces only "a 60% probability of analgesia." A lack of sensitivity to electrically induced pain may account for the conclusion that fentanyl has such a low analgesic "benefit." The experiments will need to be repeated using other experimental pain models (*e.g.*, heat-induced pain, depression of minimum alveolar concentration for volatile anesthetics) and then validated against clinical pain.

Sheiner and Melmon identified the difficulty in determining a UF by noting that it involves both factual data and value judgments. We can objectively measure analgesia and respiratory depression. But how much analgesia is enough and how much respiratory depression is too much? As they articulated so eloquently: "*Some may argue that the utility function creates unnecessary complications, and diffuses our efforts. We argue that the concept rather is capable of intensifying the vigor of research and narrowing the focus of its objectives by not allowing over-interpretation of limited results. Keeping the concept of a utility function in mind will encourage critically important investigation.*"[10] We look forward to additional investigations that will refine, validate, and ultimately determine the utility of the UF and its applicability in anesthesia.

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