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The Direct Search Procedure

A New Approach to Evaluating Clinical Regimens

ANESTHETIC practice typically involves administration of many drugs, including anesthetics, muscle relaxants, sedative/hypnotics, local anesthetics, and opioids. These agents may interact in additive, synergistic, or antagonistic ways. The multitude of potential drug combinations prevents researchers from evaluating all possible relevant combinations. This is particularly evident in the drug development process, during which the effects of a new agent are typically evaluated while holding constant

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all other anesthetic drugs. For example, to evaluate the potentiating effects of inhaled anesthetics on rapacuronium, an investigator might give a single 1.5-mg/kg bolus dose during anesthesia with each of isoflurane, desflurane, and sevoflurane anesthesia. Differences in the onset or recovery profile would be considered evidence of potentiation. If the investigator is interested in the interaction of two interventions, a more complex study design might be appropriate. For example, one might create a two-dimensional grid in which one dimension is the different anesthetic agents and the other dimension is the minimum alveolar concentration–multiple of those agents. If all possible combinations of three anesthetics and four minimum alveolar concentration levels were tested, there would be 12 groups. This large number of groups confounds the statistical analysis—there are 66 (12 · 11/2) possible statistical comparisons, so that a Bonferroni correction for multiple comparisons requires a P value < 0.001 (0.05/66) for individual comparisons. In turn, studying a reasonable number of patients in each group requires enrollment of an excessive number of patients. Experience as an editor and reviewer indicates that studies with large numbers of groups rarely succeed in attaining the desired statistical outcomes.

Certain clinical issues involve even a larger number of dimensions. In this issue of ANESTHESIOLOGY, Curatolo

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et al.[1] tackle the interesting clinical question of optimizing postoperative epidural analgesia. They consider the joint administration of three drugs—bupivacaine, fentanyl, and clonidine—and a possible role of the hourly volume in which these drugs are given. The previously proposed grid approach would likely be doomed in seeking the optimal regimen. To avoid this problem, Curatolo *et al.* invoke a technique not previously reported in the medical literature, despite being promulgated by Berenbaum, an investigator well known for his statistical analysis of synergy.[2] The technique is a search procedure in which regimens to be tested are determined iteratively. The investigator initially selects a group of regimens, evaluates these regimens in the usual manner, then ranks them based on some scoring system (*e.g.*, best pain relief, highest incidence of adverse effects). The best regimens are grouped, as are the worst; then, parameters (*e.g.*, doses) from each group are averaged. For example, the best three regimens might use bupivacaine doses of 15, 12, and 18 mg/h (mean, 15 mg/h), and the worst regimens might use 5, 11, and 8 mg/h (mean, 8 mg/h). In this fictitious example, it seems that larger doses of bupivacaine are desirable. These average values are used to select a bupivacaine dose for a new regimen. Interpolation between the mean of the best and worst regimens, a possibly intuitive approach, is flawed because it moves the value toward the worst outcome. Instead, the investigators extrapolate beyond the best regimen, *i.e.*, if 8 mg/h is "bad" and 15 mg/h is "good," then perhaps 24 mg/h is "better." New regimens are added (and unsatisfactory ones deleted) until there is little evidence that changing doses changes outcome (known statistically as "finding a minimum in the parameter space").

Using this approach, Curatolo *et al.* identify three regimens that differ little in both their success and adverse outcomes and recommend that these regimens be tested in large clinical trials. They expect that one of these three regimens is likely to be similar to the optimal one that would have been identified by the grid approach rejected previously.

The approach of Curatolo *et al.* is appealing because it may permit investigators to screen polypharmaceutic regimens more rapidly than can be accomplished with traditional techniques. However, this being the

first application of the direct search method in humans, several technical issues remain to be optimized. For example, the equation used for this extrapolation is:

$$\text{dose}_{\text{new regimen}} = \text{dose}_{\text{best}} \cdot (1 + \alpha) - \text{Dose}_{\text{worst}} \cdot \alpha$$

where α is constrained to be > 0.0. This is equivalent to "start from $\text{Dose}_{\text{best}}$ and move away from $\text{Dose}_{\text{worst}}$ by a factor α." If α is close to 0.0 (*e.g.*, 0.1), incremental changes are small, and the technique converges slowly. In contrast, large values for α might produce large changes in the doses tested, possibly into a toxic range. The value for α selected by Curatolo *et al.*, 1.3, is based on a single publication[3] and has not been evaluated rigorously. Therefore, it remains to be determined if it is the optimal value.

A second potential problem is the influence of a regimen that, by extreme chance, tests markedly better than it should (*e.g.*, if each of the individuals tested is by extreme chance an outlier).* In that the direct search regimen "learns" from its previous results (*i.e.*, results from each set of regimens are used to formulate the next regimen), will an unusual event be carried forth with inappropriate statistical weight? Finally, by not examining the "full parameter space" (*i.e.*, all possible combinations of parameters), it is possible that Curatolo *et al.* may select what is known in statistics as a "local minimum," *i.e.*, a particular set of parameters that produces good results but not the optimal set.

Statistical and research methodology evolves constantly. In two decades of performing pharmacokinetic analyses, I have witnessed tremendous changes in research design. Previously, we obtained large numbers of blood samples from small numbers of individuals, recognizing that these small sample sizes might not describe variability in the population well. Now we often obtain small numbers of samples from a larger number of individuals and apply mixed-effects modeling techniques. Such techniques were met with skepticism when first introduced but are now well accepted. I hope that the direct search method undergoes further evaluation, both in clinical trials as well as simulation at the (computer) "bench." The latter approach may provide additional insight into the aforementioned unresolved issues.

* Note that the regimen "O" of Curatolo *et al.*, evaluated only in step 3, performs best through step 8, despite never being tested in additional subjects.

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Dopamine

One Size Does Not Fit All

THE use of positive inotropic agents to improve organ perfusion varies widely from institution to institution. However, the practice of infusing dopamine at doses at 1-3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ("renal" dose) to improve renal function is fairly ubiquitous. The report by MacGregor et al.[1] in this months's ANESTHESIOLOGY addresses the pharmacokinetic issues underlying this practice. Their results, in conjunction with review of the pharmacodynamic properties of dopamine, provide insight into the ambiguous, and often disappointing, results of attempts to provide "protection" for patients at risk for renal injury.

The use of dopamine to modulate renal function dates from studies in the 1960s that show increased renal plasma flow, glomerular filtration rate (GFR), and diuresis and natriuresis in volunteers and in patients in congestive heart failure.[2,3] In most studies in which cardiac index was measured, the improvement in renal function was associated with increased cardiac index, and it has been difficult to distinguish effects on the renal vasculature from global hemodynamic effects. Selective dopamine-induced renal vasodilation has been observed in studies of animals and healthy human volunteers. In a rat model, administration of dopamine caused dilation of

> This Editorial View accompanies the following article: MacGregor DA, Smith TE, Prielipp RC, Butterworth JF, James RL, Scuderi PE: Pharmacokinetics of dopamine in healthy male subjects. ANESTHESIOLOGY 2000; 92:338-46

renal efferent and afferent arterioles in low concentrations and vasoconstriction at higher concentrations, and α-adrenergic blockade reversed the latter effect. Studies of healthy dogs and humans indicate that renal vasodilation in excess of systemic vasodilation occurs at some doses, although this was not observed in studies of septic animals. There has been no study to confirm selective renal vasodilation in patients at risk for renal injury. Also, dopamine-induced increases in GFR, independent of global hemodynamic effects, have not been shown consistently. Renal vasodilation could actually decrease GFR, depending on the balance of efferent and afferent dilation. The diuresis and natriuresis usually observed after dopamine administration cannot be attributed to increased GFR because increased urine volume and sodium excretion is seen when GFR does not change. Rather, diuresis and natriuresis is caused by inhibition of tubular sodium-potassium adenosine triphosphate (ATPase), an effect independent of either renal or global hemodynamic effects.

Although dopamine is widely used for renal protection, well-controlled trials of dopamine in patients at risk for renal dysfunction or after acute renal injury have not, in general, supported this practice. The tubular effects of dopamine or increased cardiac output may account for reports that show increased urine output and creatinine clearance with dopamine in surgical patients (cardiac surgery and liver transplantation). Certainly, numerous other studies of surgical patients have failed to showed any beneficial renal effect of dopamine. Consideration of the basic pharmacology of dopamine may explain the conflicting results.[4] Dopamine is a relatively nonspecific agonist, with activity at both the dopamine-1 (DA-1) and dopamine-2 (DA-2) receptors and the α- and β-adrener-