

◆ EDITORIAL VIEWS

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Rostral Spread of Epidural Morphine

The Expected and the Unexpected

ARGUABLY, most clinicians who use opioids spinally believe that these drugs can spread rostrally in cerebrospinal fluid (CSF) to reach supraspinal sites. Therefore, many may be tempted to dismiss the work by Angst *et al.*¹ in this month's ANESTHESIOLOGY as an unnecessary study with a predictable result. However, to do so would be inappropriate. The history of clinical medicine is embarrassingly full of "obvious truths" that were subsequently shown to be false when appropriately examined.

Angst *et al.*¹ use a double-blind, randomized, crossover study design, coupled with segmental analgesia measurements for 24 h to investigate rostral spread of epidurally administered morphine. This powerful study design is a significant improvement over previous studies that sought to investigate rostral spread of spinally administered morphine.^{2,3} As such, this study provides the strongest evidence to date that epidurally administered morphine does spread rostrally in CSF to reach brain stem levels.

A further improvement over previous studies is the measurement of morphine plasma concentrations throughout the study period. The demonstration that morphine plasma concentrations bear no relation to the segmental analgesia produced by epidurally administered morphine is a clear indication of morphine's spinal site of action. Demonstration of a spinal site of action is an underappreciated but essential component of any study investigating epidurally administered opioids. Demonstrating a spinal site of action is critical because any opioid placed in the epidural space in sufficient quantity will produce analgesia, if for no other reason than that the drug will eventually reach the plasma and

be redistributed to brain stem opioid receptors. Consequently, the demonstration of analgesia alone is not evidence of a selective spinal site of action. Failure to recognize this fact has led to the widespread use of alfentanil and sufentanil (and to some extent fentanyl) in the epidural space, despite mounting evidence that these opioids do not produce analgesia by a selective spinal mechanism.^{4–8} Therefore, the authors' study design serves as a useful example of the appropriate method to investigate the analgesia produced by any epidurally administered drug that can act at sites other than the spinal cord.

The study is, however, disappointing in some respects. In particular, the authors settled for a purely observational study when they could have used this model to address some important mechanistic issues. For example, comparison of morphine with other opioids would have permitted the authors to determine whether there really are differences in the rate or extent of rostral spread between so-called "lipid soluble" and "water-soluble" opioids. It has been assumed that hydrophobic opioids undergo slower and more limited rostral spread than hydrophilic drugs because of the lower incidence of delayed respiratory depression associated with their use. Angst *et al.*¹ report here that epidural morphine required between 5 and 10 h to reach sufficient concentration in the brain stem to produce measurable trigeminal analgesia. This time course is consistent with the timing of delayed respiratory depression after epidural morphine.^{9,10} In contrast, Gourlay *et al.*¹¹ sampled cervical CSF (C7–T1 interspace) in volunteers after lumbar epidural fentanyl administration (1 µg/kg) and reported that peak fentanyl concentrations were reached in only 10–30 min. This is a remarkable disparity in the rate at which morphine and fentanyl have been reported to move rostrally.

This disparity is all the more perplexing when one considers that drug movement in CSF after epidural administration must be the result of bulk CSF movement because diffusion is too slow to explain observed rates of rostral movement (of note, intrathecal drug administration has the added feature of baricity effects on drug movement, which are, of course, absent with epidural drug administration). The energy for movement of CSF

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derives from the movement of the brain and spinal cord as they expand and contract during cardiac systole and diastole.¹² The resulting motion of CSF is quite heterogeneous, both in terms of direction (caudad *vs.* craniad) and velocity,¹³ but all comparably sized drug molecules would be expected to move nearly identically as the CSF in which they are suspended moves. Consequently, the rate of rostral spread should be essentially the same for all opioids, although the quantity of drug moving rostrally will vary among different drugs and will depend on how rapidly they are cleared from the CSF. Unfortunately, Angst *et al.*¹ missed their opportunity to shed some light on differences in rates of rostral spread by limiting their investigation to a single opioid.

An additional missed opportunity was the authors' failure to more rigidly characterize the time course of morphine's rostral spread by testing analgesia at more sites and at more frequent time intervals. To have done so would have added useful information with little additional effort required.

Interestingly, this study may provide some unintended insight into the related question of whether there is a synergistic analgesic effect when opioids are present at both spinal and supraspinal sites in humans. Multiple animal studies clearly show a multiplicative analgesic effect when opioid receptor agonists are concurrently administered spinally and supraspinally.¹⁴⁻¹⁷ Animal studies provide such clear evidence of spinal-supraspinal synergy because animals can be instrumented in such a way as to permit localized administration of opioids at both spinal and brain stem sites. The obvious difficulty with instrumenting people similarly precludes comparable human studies.

However, the documentation of Angst *et al.*¹ of morphine's rostral spread provides a unique opportunity to examine morphine's analgesic effect when simultaneously present at both spinal and supraspinal sites in humans. The significant increase in heat pain tolerance in the trigeminal dermatome at 10 h indicates that morphine was present at brain stem levels by that time. If the simultaneous presence of morphine at brain stem and spinal sites resulted in analgesic synergy, it would be manifest as a leftward shift in the morphine concentration-*versus*-analgesia relation at lumbar and thoracic levels. The fact that the magnitude of thermal analgesia is relatively constant at spinal levels for 24 h, despite the inevitable decrease in morphine concentration at these sites, is consistent with a leftward shift in morphine's concentration-response relation. Although this observation by no means proves spinal-supraspinal synergy for

opioids in humans, it is consistent with that possibility. In fact, perhaps the relatively long duration of potent analgesia produced by spinally administered morphine is the result of the drug's propensity for rostral spread and the consequent analgesic synergy compensating for the steady decrease in morphine concentration within the spinal cord.

There is value in performing studies that some may view as unnecessary and likely to produce predictable results. Not uncommonly, the results obtained are something other than what was expected and our understanding is thereby advanced. Often, as is the case here, the predicted result is obtained, in which case our clinical understanding is placed on a more solid, scientifically based footing. And sometimes well-performed studies that yield predictable results can provide unintended insights into questions they had not sought to address; and that also is the case here.

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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

all other anesthetic drugs. For example, to evaluate the potentiating effects of inhaled anesthetics on rapacurium, 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 ($12 \cdot 11/2$) 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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