
Location, Location, Location

THE three most important things in real estate are location, location, and location. In this issue of ANESTHESIOLOGY, Ummenhofer et al. show that the same is true for intrathecal drug delivery. The spinal space is not pharmacokinetically homogenous in the way that the arterial blood is homogenous. Because of the homogeneity of arterial blood, the pharmacokinetics observed in samples from the radial artery will be the same as those observed using samples from the dorsalis pedis artery. As a result, the physiologic complexity of the body almost magically resolves into the simple mammillary compartment model. The “simple” intrathecal space does not easily resolve into mammillary models. The slow flow of drug in the spinal space, combined with the rapid uptake by intrathecal tissues, produces large drug gradients within the intrathecal space. These gradients affect both the therapeutic dose and the intrinsic safety of intrathecally administered drugs. In 1977, Partain et al. represented spinal pharmacokinetics using eight sequential compartments. Recently, we turned to diffusion equations, with distributional components, to represent the spread of drug through the cerebrospinal fluid (CSF). The model of Ummenhofer et al. pushes the envelop further, using 20 compartments to describe the intrathecal pharmacokinetics of morphine, fentanyl, alfentanil, and sufentanil. Because their model incorporates nonhomogenous drug distribution within the CSF, we can use it to explore doses and relative safety.

We used NONMEM (University of California, San Francisco, CA) to find the infusion profile of morphine, fentanyl, alfentanil, and sufentanil, administered at L2–L3 that would produce a steady concentration of 1 μmol/l in CSF at L2–L3 and T7. The results for morphine and sufentanil are shown in figure 1. Not surprisingly, the infusion rate initially starts off high and decreases steadily over the first hour. Figure 1 demonstrates the expected effects of lipophilicity and how distance from injection site magnifies the lipophilic effect. The sufentanil infusion rate is approximately 10-fold higher than the morphine infusion rate when drug is being given at L2–L3, and L2–L3 is the target spinal level. Changing the target spinal level to T7 increases the morphine and sufentanil infusion rates by 200- and 3,000-fold, respectively. One can similarly calculate that changing the target from L2–L3 to T7 increases the infusion rates for alfentanil and fentanyl 300- and 2,400-fold, respectively. This simulation shows that it is theoretically possible to infuse opioids to obtain a steady drug concentration in the CSF at any level. It also shows that location matters: far more opioid is required to reach the same concentration of drug when the site of infusion is distant from the target tissue.

Similarly, the models permit us to analyze safety during continuous drug administration. Figure 2 shows the con-
centrations of fentanyl, alfentanil, and sufentanil at T3, relative to the concentration of morphine, during an infusion of drug into the L2–L3 space that targets a concentration of 1 at the L2–L3 space. Interestingly, alfentanil is initially higher than 1, showing more cephalic spread relative to morphine during the infusion, possibly increasing risk. As expected, fentanyl and sufentanil are far lower than 1, showing relative safety compared with morphine with regard to cephalic spread. There are no data about the distribution of drug during continuous infusions, but we can use these models to draw inferences about dosing and toxicity.

These simulations examine opioid concentrations in the CSF. We did not extend them to examine opioid concentrations in the spinal cord because the experimental design only collected cord samples at 240 min. If future studies collect cord samples at multiple intervals, it may be possible to predict with confidence the relationship between dose, time, spinal level, and opioid concentrations in the spinal cord. This may change the interpretation of the CSF predictions. For example, if the CSF ratio of alfentanil to morphine at T3 is greater than 1, but alfentanil has a much steeper gradient into tissue than morphine, then alfentanil might be “safer” than morphine.

These simulations show how pharmacokinetic models can be used to design innovative dosing regimens, even for the spinal space. However, our knowledge of spinal pharmacokinetics is still very rudimentary. First, these models assume linearity, as do virtually all other published models of spinal pharmacokinetics. In other words, the model assumes that if you double the dose, you will double the concentrations. To date, nobody has studied the linearity of intrathecal pharmacokinetics sufficiently to be sure that there are not saturable (and hence nonlinear) processes. The infusion profiles shown in figure 1 could be used to test for linearity. If the profiles really do provide concentrations of 1 μmol/ml at the target site, this constitutes strong evidence for the linearity of intrathecal opioid pharmacokinetics.

Second, these are results in pigs, not humans. Not only are pigs better to eat, but there are intriguing paradoxes between clinical observations with intrathecal opioids for analgesia and these closely controlled studies in pigs. For example, Ummenhofer et al. suggest that morphine has a greater intrathecal to systemic potency ratio for analgesia than sufentanil because of its distribution in spinal cord. However, the relative potencies of intrathecally administered morphine and sufentanil depend on the clinical pain syndrome. For example, morphine is extremely potent for post–cesarean section analgesia (effective dose approximately 100–200 μg) but much less so for labor analgesia (effective dose probably > 1–2 mg). In contrast, the potency of sufentanil in these two patient populations is approximately equal. An even greater paradox relates to rostral distribution of lipophilic opioids. These data in pigs suggest that sufentanil does not move in CSF more cephalad than the lower thoracic area after lumbar intrathecal injection, whereas clinical studies have observed rostral spread to upper thoracic or low cervical dermatomes within 15–20 min of lumbar intrathecal sufentanil injection, accompanied in some cases by significant respiratory depression. This agrees with preliminary experiments in...
How Do We Measure (the Cost of) Pain Relief?

HOW do we measure the cost of pain relief? In this issue of Anesthesiology, Macario et al. estimate that the expected cost to society of epidural analgesia for pain relief during labor ranges from $259 to $338 greater than the expected cost of intravenous analgesia. The manuscript is instructive, and my initial reaction is that epidural analgesia is a bargain! However, it seems appropriate to ask two questions: (1) Is the authors’ question a valid one? and (2) Is the analysis valid?

The Question

Most studies of healthcare cost include an analysis of the benefit of the intervention. For example, many studies report quality-adjusted life years as an outcome measure. Macario et al. chose not to do a cost-effectiveness analysis, suggesting that this approach may not apply to the management of labor pain. The authors state that “valid techniques to value quality of life from better analgesia do not exist.” (Indeed, how does one assign a dollar value to the provision of a service that is deemed essential during performance of surgery?) Thus, Macario et al. did not ascribe a monetary value to the benefit of pain relief obtained from epidural analgesia. Rather, the authors cited a meta-analysis that quantified and summa-