Epidural and Intrathecal Opiods: Which Drugs Should We Choose and How Should They Be Used?

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All opiates in clinical use produce analgesia via the same molecular mechanism, i.e., binding to G-protein coupled opioid receptors with subsequent inhibition of adenylate cyclase, activation of inwardly rectifying K^+ channels, and inhibition of voltage-gated Ca^{2+} channels, all of which decrease neuronal excitability. Given the commonality of mechanism, one might reasonably ask why there are such clear clinical differences among opioids with respect to pharmacokinetic and pharmacodynamic characteristics.

A large part of the explanation for pharmacologic differences among opioids lies in the fact that opioids differ in their ability to reach opioid receptors. In essence, the net analgesic effect of any opiate is the result of numerous processes that must occur prior to G-protein activation. This is particularly true for spinally administered opioids (epidural and intrathecal). For example, epidurally administered opioids must traverse the dura and arachnoid mater, diffuse through the CSF, traverse the pia mater to reach the surface of the spinal cord, diffuse through the white mater and then the gray mater to reach opioid receptors in the dorsal horn. The rate and extent to which any opioid completes these steps (and importantly avoids competing paths like uptake into epidural fat or systemic circulation) is largely dependent on its physicochemical properties. Thus, it is an opioid's physicochemical properties that largely determine its bioavailability in the spinal cord dorsal horn and thus its suitability for spinal administration.

Unfortunately, following their introduction, the clinical use of spinal opioids proceeded at a more rapid pace than did our understanding of basic mechanisms governing the bioavailability of epidurally and intrathecally administered opioids. Consequently, multiple drugs have been widely promoted for spinal use that do not, in fact, reach the spinal cord in sufficient concentration to produce spinally mediated analgesia. Rather, their analgesic effect is mediated by systemic uptake and redistribution to brain. This fact raises an important point with respect to evaluating the efficacy of the spinal route of administration for any opioid, namely, that all spinally administered opioids will eventually reach the plasma and be redistributed to brain where they can produce analgesia. Consequently, all opioids administered spinally will produce good quality analgesia, but that fact alone does not prove that the drug's site of analgesic action resides in the spinal cord.

With this background in mind, the goals of this lecture are, 1] to describe what is known about the mechanisms by which opioids redistribute from the epidural and intrathecal spaces to the spinal cord, 2] to describe what physical and chemical properties do and do not govern the rate and extent to which opioids redistribute to the dorsal horn, and, 3] to identify which opioids and methods of administration (i.e., bolus vs. infusion) are appropriate for spinal administration. Thus, following this lecture the listener will be able to explain the following case.

Case: A 53 year old woman with metastatic ovarian cancer receives a Med-Tronics pump for epidural delivery of morphine. She obtains good pain relief with a total of 8 mg MS per day, but after approximately three weeks her MS requirements begin to increase. Over the next 2 weeks her MS dose is increased to 32 mg/day still with incomplete relief. She is switched to epidural sufentanil and obtains excellent relief with 400µg/day. After approximately 2 weeks, her sufentanil requirements begin to escalate and when she reaches a daily dose of 1,200 µg/day she is switched back to epidural morphine and obtains excellent analgesia with only 10 mg/day.

Spinal Drug Distribution

All drugs placed in the epidural space are subject to multiple potential fates, most of which decrease the probability that the drug will reach the spinal cord. Specifically, drugs may 1] exit the intervertebral foramina to reach the paraspinous muscle space, 2] drugs may diffuse into epidural fat, 3] drugs may diffuse into ligaments that border the epidural space, and finally, 4] drugs may diffuse across the spinal meninges.

Which of these fates will be met by a particular drug is largely dependant on its physicochemical properties, particularly, lipid solubility. For example, using an in vivo pig model we have recently found that the amount of opioid sequestered in the epidural fat after epidural administration is entirely dependant on the drug's octanol:buffer distribution coefficient (Fig 1).

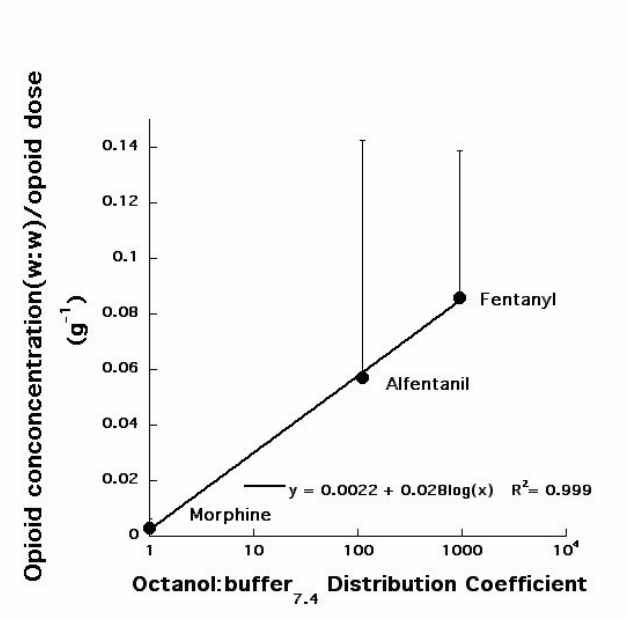

Figure 1: Relationship between lipid solubility and opioid concentration in epidural fat following epidural injection. From Bernards et al., Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids I: Differences Among Opioids, Anesthesiology (in Press) 2003.

Lipid solubility also played an important role in the epidural pharmacokinetics of epidurally administered opioids in this model. For example, both mean residence time (MRT) and terminal elimination half-life were closely related to lipid solubility (Figs 2 and 3).

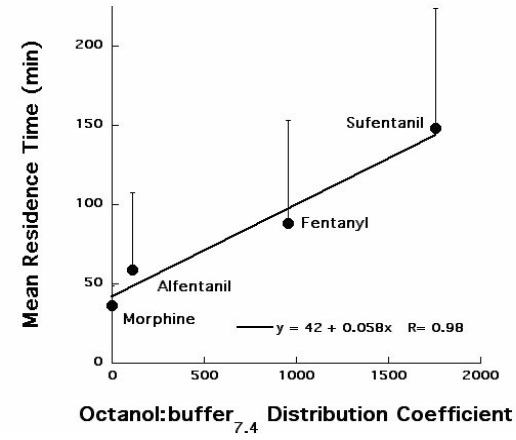

Figure 2: Relationship between lipid solubility and opioid mean residence time in the epidural space. From Bernards et al., Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids I: Differences Among Opioids, Anesthesiology (in Press) 2003.

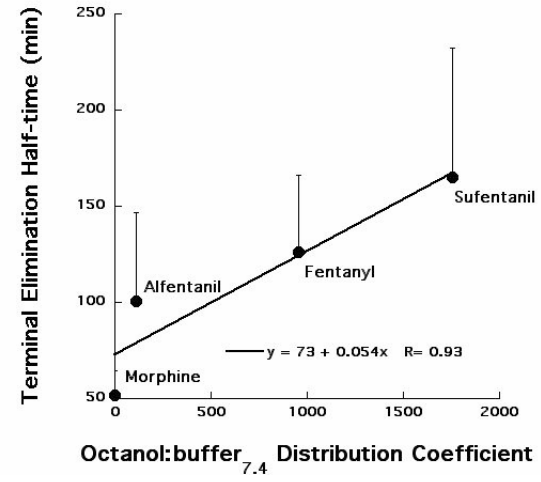

Figure 3: Relationship between lipid solubility and terminal elimination half-life of opioids in the epidural space. From Bernards et al., Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids I: Differences Among Opioids, Anesthesiology

In short, the above data indicate that lipid soluble opioids spend a relatively large amount of time in the epidural space. The important clinical implication of this observation is that an opioid in the epidural space cannot readily reach the spinal cord, which is the ultimate target site for epidurally administered opioids.

If an opioid is to produce spinally mediated analgesia following epidural administration, it must move from the epidural space to the spinal cord. Several mechanisms have been proposed to explain movement of opioids between the epidural space and spinal cord including 1] diffusion through the spinal meninges, 2] preferential diffusion through the spinal nerve root cuff and, 3] uptake by radicular arteries traversing the epidural space with subsequent distribution to the spinal cord. Experimental studies demonstrate that the only mechanism by which drugs redistribute from the epidural space to the spinal cord is diffusion through the spinal meninges (1-4). And importantly, the cellular arachnoid mater is the principal meningeal barrier to diffusion accounting for 95% of the resistance to meningeal permeability(1). This finding is important because, as will be discussed, it explains why drugs of intermediate lipid solubility are more permeable than are drugs which are either very hydrophobic or very hydrophilic(4).

This is not to suggest that the dura mater does not play a role in determining the spinal bioavailability of epidurally administered drugs. In fact, the dura mater is an important site of drug clearance. The human dura mater is a highly vascular structure with a rich network of arterioles/capillaries running along its border with the arachnoid mater. IN effect, drugs diffusing through the dura mater must traverse this "vascular barrier" without being cleared via the capillary network if they are to reach the underlying arachnoid mater. Because lipid soluble molecules traverse capillaries more readily than do more hydrophilic molecules, one can assume that lipid soluble opioids may be cleared by this mechanism more readily than less lipid soluble opioids.

Finally**,** in addition to being a physical barrier to drug movement, the arachnoid mater is also a metabolic barrier. For example, the meninges contain multiple enzyme systems that are potentially capable of drug metabolism (e.g., cytochrome P450, glucuronysl transferase). In addition, the meninges express enzymes capable of metabolizing neurotransmitters including epinephrine, norepinephrine, acetylcholine, and neuropeptides among others. In fact, acetylcholinesterase activity in the spinal meninges is equal to that in the spinal cord(5). This raises the possibility that the analgesic effect of neostigmine is, at least in part, mediated by actions in the arachnoid mater.

Once drugs traverse the arachnoid mater to reach the CSF, their residence time in CSF is dependant on their relative aqueous solubility, which explains the clinical observation that morphine undergoes greater rostral spread than do more hydrophobic drugs. Obviously baricity of the injectate has no effect of CSF distribution of epidurally administered drugs but can affect the initial distribution of intrathecally administered drugs. Another important difference between epidurally and intrathecally administered opioids is that a significant amount of an intrathecally administered drugs is "lost" by diffusion into the epidural space. In fact, diffusion into the epidural space is a major route of elimination for many drugs administered intrathecally(6).

After drugs diffuse through the CSF they must penetrate the spinal cord to reach their site of action in the dorsal horn. As has been shown for opioid diffusion through brain tissue(7), increasing lipid solubility actually decreases the ability of an opioid to diffuse into the spinal cord and increases the likelihood that the drug will preferentially end up in the white mater instead of the gray matter. Similarly, animal studies demonstrate that following intrathecal injection opioid bioavailability in the extracellular fluid space of the spinal cord is more than an order of magnitude less for the hydrophobic opioids fentanyl and sufentanil than for the hydrophilic drug morphine(6). Bioavailability in the extracellular fluid space is critical because it is the drug in this environment that is able to reach opioid receptors.

In short, *in vivo* and *in vitro* animal studies to date demonstrate that increasing lipid solubility decreases the spinal cord bioavailability of spinally administered drugs. As is discussed below, these findings are consistent with what is now known about the clinical use of epidural and intrathecal opioids.

Clinical Use of Spinal Opioids: Which Drugs Make Sense

As noted above, any opioid administered anywhere in the body will produce analgesia, if for no other reason than because the drug reaches the plasma and is redistributed to brain opioid receptors. Thus, the fact that epidurally and intrathecally administered opioids produce analgesia does not in itself justify this route of administration. Rather, spinal administration can only be rationalized if it can be shown that the quality of analgesia is superior and/or the magnitude of side effects are less than that which results when the drug is administered by less invasive, less expensive routes of administration (e.g. PCA). What follows is a brief review of clinical studies which point to the suitability (or non-suitability) of several opioids commonly used for spinal administration.

Morphine: Morphine clearly produces analgesia by a spinal mechanism whether administered epidurally or intrathecally and it should probably be considered the "Gold-Standard" for spinally administered opioids.

Fentanyl: Based solely on "conventional wisdom" fentanyl was widely touted as an ideal drug for spinal administration in the mid-eighties. In fact, continuous fentanyl infusion (± local anesthetic) was arguably the most common spinal analgesic at one time. However, several investigators questioned the conventional wisdom and demonstrated that continuous fentanyl infusion produced the same quality analgesia, the same side-effects, required the same fentanyl dose, and (not surprisingly) produced the same fentanyl plasma concentrations whether the drug was infused intravenously or epidurally(8-10). In short, continuous fentanyl infusion as the sole agent for epidural analgesia appears to produce analgesia by systemic uptake and redistribution to brain.

One caveat to be aware of is that there appears to be a "time component" in these studies. Specifically, plasma concentrations following initiation of epidural fentanyl infusion did not equal the plasma concentrations that resulted from intravenous administration immediately; rather it took several hours for plasma concentrations to equalize. This suggests that fentanyl boluses or "short term" administration may result in a more spinally mediated analgesic effect than that which occurs with longer-term continuous administration. This may help to explain the fact that addition of fentanyl to local anesthetic infusions for labor analgesia does appear to improve analgesia by a spinal mechanism(16,17). Other reasons that epidural fentanyl may be spinally active in labor analgesia but not in post-operative analgesia include the fact that labor pain is different (qualitatively, mechanistically) than post-operative pain, maternal endogenous analgesic physiology may be fundamentally different than endogenous analgesic mechanisms activated by post-operative pain (e.g., pregnant women have been shown to be more sensitive to local anesthetics, to have a lower MAC for volatile anesthetic agents, etc.). Thus, multiple factors may cause fentanyl to be active in the spinal cord at much lower concentrations in labor than it is in post-operative pain.

What about adding fentanyl to local anesthetic infusions for post-operative pain? Recently Berti et al. used a double-blind randomized, patient controlled epidural analgesia study design to compare analgesia and side-effects for plain ropivacaine (0.2%) with ropivacaine (0.2%) plus fentanyl (2μg/ml)(18). All patients had "major abdominal surgery" with the epidural catheter placed at $T_{8\text{-}10}$. These authors found that addition of fentanyl did decrease the amount of local anesthetic necessary for adequate analgesia, although the decrease was not very dramatic (230 ml/48 hrs for plain ropivacaine versus 204 ml/48 hours for ropivacaine plus fentanyl). However, there were no differences in pain control at rest or with coughing, no differences in motor block, no differences in episodes of hypotension or bradycardia, no difference in time to bowel recovery. However, the fentanyl group demonstrated significantly lower hemoglobin oxygen saturation between 12 and 48 hours. Thus, addition of fentanyl did not provide better analgesia nor did it reduce side-effects. In fact, as one would suspect, addition of fentanyl increased respiratory depression.

Thus, current evidence would suggest that there is little reason to infuse fentanyl into the epidural space as the sole agent for post-operative analgesia. Nor, as the work of Berti et al suggests, is there much reason to add fentanyl to local anesthetic infusions for post-operative analgesia. However, as will be discussed, there are situations in which occasional epidural fentanyl boluses or intrathecal fentanyl administration makes some sense.

Sufentanil: Even more dramatically than with fentanyl, epidural sufentanil, has been shown to produce analgesia solely by systemic uptake and redistribution to brain following epidural administration(11). Thus, there is no reason to administer sufentanil into the epidural space. Intrathecal sufentanil has gained some popularity for labor analgesia, but human studies suggest that the analgesia that results is at least in part the result of systemic uptake and redistribution to brain. Specifically, Liu et al showed that the plasma concentrations produced by intrathecal administration of 12.5μg sufentanil exceeds the threshold required for postoperative analgesia(12). However, the significant plasma concentrations of sufentanil following intrathecal administration may in fact be important in its analgesic effect in labor because of the potential for spinal/supraspinal synergy. This potential synergy is not possible with morphine because its systemic plasma concentration is negligible.

Further evidence that the spinal bioavailability of intrathecal sufentanil is poor derives from the observation that there is a marked decrease in the drug's relative potency when administered intrathecally instead of intravenously. For example, the typical intrathecal dose of 10 μg sufentanil is equivalent to 10 mg of morphine when the drugs are administered intravenously. However, 10 mg is nearly 100 times the dose of morphine required to produce very long lasting analgesia in the intrathecal space. This marked decrease in the relative potency of sufentanil compared to morphine likely results from sufentanil's poor bioavailability in the spinal cord.

An additional interesting aspect of intrathecal sufentanil use is the fact that there is a "ceiling effect" on analgesia. Doses greater than 5 or 10 μg do not produce greater analgesia but do produce greater systemic side-effects (e.g., respiratory depression, sedation) because of increased plasma concentrations. The reason for this is as yet unexplained.

Alfentanil: The available evidence clearly indicates that epidural alfentanil produces analgesia largely by systemic uptake and redistribution to brain (13-15). Thus, there appears to be little reason to administer alfentanil epidurally. Intrathecal alfentanil has not been well studied in humans, but based upon animal studies one would expect rapid onset of a very short duration analgesia.

In summary, spinal opioid delivery offers an important option for treating acute, chronic and malignant pain. However, to use this technique to best advantage it is essential that we choose the most appropriate opioids, routes of administration (e.g., epidural vs. intrathecal) and methods of administration (continuous infusion vs. intermittent bolus). Unfortunately, because we did not lay the proper scientific foundations to understand spinal opioid administration before the technique entered widespread clinical practice, we have not always employed these drugs as wisely as we might have. This probably occurred because our long experience with epidural and spinal local anesthetics led us to naively believe that spinal opioid administration was simply "more of the same."

Importantly, the work of multiple investigators makes clear that diverse classes of spinally active analgesic drugs (e.g., cholinesterase inhibitors, neuronal calcium channel blockers, antisense oligonucleotides) are likely to play an ever increasing role in pain management. However, it is imperative that we lay the proper foundations for the use of these drugs before they enter widespread clinical use lest we repeat the errors encountered in use of spinal opioids.

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