

Epidural and CSF pharmacokinetics of drugs

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Neuraxial drug administration was initially developed in the form of spinal anaesthesia 100 years ago. Since then, neuraxial drug administration has evolved and now includes a wide range of techniques to administer a large number of different drugs (local anesthetics, opioids, α_2 -agonists, baclofen, ketamine, midazolam, neostigmine, adenosine, steroids, ziconotide) to provide anesthesia, but also analgesia and treatment of spasticity in a variety of acute and chronic settings.

However, the human literature on epidural and CSF pharmacokinetics of drugs is sparse when compared with that available for animal models.

Pharmacokinetics determines the relationship between drug dose and its concentration of the effector sites. Changes in drug concentration over time in the various compartments such as blood, epidural space, CSF and at the effector site within the spinal cord are determined by physicochemical properties of the drug and by a multitude of biologic functions involved in the processes of absorption, redistribution, biotransformation and elimination.

Epidural Pharmacokinetics

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 a) exit the intervertebral foramina to reach the paraspinal muscle space, b) drugs may diffuse into epidural fat, c) drugs may diffuse into ligaments and finally, d) drugs may diffuse across the spinal meninges.

The only mechanism by which drugs redistribute from the epidural space to the spinal cord is diffusion through the spinal meninges (1) and the cellular arachnoid mater is the principal meningeal barrier to diffusion accounting for 95% of the resistance to meningeal permeability.

Epidurally administered drugs that reach the CSF, also can diffuse back across the meninges into the epidural space, but unless and until the drug concentration in the epidural space falls below that in the CSF, net drug transfer will be directed from the epidural space into the CSF. Diffusion depends mainly of the drug's physicochemical properties, particularly, lipid solubility.

Bernards C M et al (2), using an in vivo pig model has 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. Lipid solubility played an important role in the epidural pharmacokinetics of epidurally administered opioids in this model. Both, Mean Residence Time (MRT) and terminal elimination half-life were closely related to lipid solubility (2).

The amount of epidurally administered morphine that reached the intrathecal space was far greater than for it was for more lipid soluble opioids (2).

In addition, Bernards et al (3) studied the effects of epinephrine on the spinal pharmacokinetics of opioids and found that these effects varied by opioid and sampling site.

Meningeal permeability is not the only determinant of a drug spinal cord bioavailability after epidural administration. Drugs can partition into various environments in the epidural space and be unavailable for transfer across the spinal meninges.

Epidural fat may serve as a sequestration site for lipid soluble drugs (4).

The dura mater is an important site of drug clearance. The human dura mater is a highly vascular structure. Because lipid soluble molecules traverse capillaries more readily than do more hydrophilic molecules, one can assume that lipid soluble drugs may be cleared by this mechanism more readily than less lipid soluble drugs.

Meninges contain multiple enzyme systems, which are potentially capable of drug metabolism. In addition, the meninges express enzymes capable of metabolizing neurotransmitters, including epinephrine, norepinephrine, acetylcholine and neuropeptides among others (5).

After epidural administration, local anesthetics need to cross the spinal meninges to reach their site of action.

However, if the spinal disposition of opioids and clonidine has been studied extensively, the spinal disposition of local anesthetics has been investigated poorly. Studies demonstrated a rather low CSF bioavailability, lower than 4% for pethidine, morphine and sufentanil (6) and 14% for clonidine (7).

Clement R et al (8), determined the intrathecal bioavailability of lidocaine, bupivacaine and a mixture of two drugs (9), in a rabbit model of spinal anesthesia, by using the microdialysis technique. The intrathecal bioavailability of bupivacaine and lidocaine after simultaneous administration was 12,3% and 17,9% respectively, while it was 5,5% and 17,7% following the separate administration of each agent. After epidural administration, the systemic resorption was slower and lower, especially for bupivacaine. Such a reduction in the systemic absorption of bupivacaine, might increase its intrathecal bioavailability, resulting from a vasoconstrictor effect of lidocaine, reducing the systemic absorption of bupivacaine from the epidural space.

Estebe JP et al (10) evaluated the effect of epinephrine, on the spinal pharmacokinetic and the CSF bioavailability of ropivacaine using microdialysis sampling after epidural administration in sheep model.

Epidural and intrathecal AUC (0-2hrs) of ropivacaine with epinephrine was increased to 28% and 27% respectively, without differences in Cmax and Tmax, confirming the increased CSF bioavailability of ropivacaine.

Intrathecal Pharmacokinetics

Drugs injected directly into the CSF are cleared by two competing mechanisms: diffusion into the spinal cord and diffusion into the epidural space.

Intrathecal drug pharmacokinetics are poorly understood, because of the difficulty in repeatedly sampling drug concentration in all the relevant compartments (e.g CSF, spinal cord, plasma, epidural space, epidural fat). Ummenhofer et al (4) developed a pig model in which microdialysis techniques were used to continuously sample the freely diffusible opioid concentration in the extracellular fluid space of the CSF and the epidural space after intrathecal administration of morphine, alfentanil sufentanil and fentanyl. They found that the integral exposure of the spinal cord to the opioids was highest for morphine, because of its low spinal cord distribution

volume and slow clearance into plasma. The integral exposure of the spinal cord to the other opioids was relatively low, but for different reasons: alfentanil had a high clearance from spinal cord into plasma, fentanyl distributed rapidly into the epidural space, followed by sequestration in epidural fat and sufentanil has a high spinal cord volume of distribution.

Animal models of pain have demonstrated that intrathecal COX₂ inhibitors reduce hypersensitivity (11) Buvanendran A et al (12) found that CSF rofecoxib levels were approximately 15% of plasma levels, after 50mg oral rofecoxib administration and that repeated daily dosing more than doubles the AUC in CSF.

Pharmacokinetics during continuous spinal delivery

Increasing numbers of patients are receiving chronic intrathecal infusions of local anesthetics, baclofen, opioids and other analgesics via implanted pumps. What makes this mode of drug delivery different from that of a single bolus is the fact, that the delivery rates are so slow, that little if any kinetic energy is imparted to the injectate to facilitate its distribution. Rather, drugs delivered by very slow intrathecal infusion, must be distributed by CSF motion.

Recently Bernards CM (13) performed a study to quantify the distribution of morphine and baclofen during slow (21 and 1000 microliters/hour) continuous infusion into the intrathecal space of pigs. The principal finding was that drug concentration in CSF and spinal cord decreased rapidly as a function of distance from the site of administration, with most drug found within a few centimeters. In addition, there were significant anterior-posterior differences in both CSF and spinal cord drug concentrations.

Ziconotide is a new spinal drug that produces analgesia, by interruption of Ca-dependent primary afferent transmission of pain signals in the spinal cord. Following intrathecal infusion, ziconotide is distributed within the cerebral spinal fluid, where its clearance (0,38 ml/min) corresponds to the rate of turnover of the CSF (14). Negligible amounts of ziconotide are present in the systemic circulation, where it is rapidly degraded by proteolysis.

Several reports have used liposomes either intrathecally or epidurally to deliver opioids, local anesthetics baclofen and chemotherapeutic agents

(15). The premise is that this encapsulation creates a depot, that provides a controlled release of agent into the biophase, which is available for redistribution. "Such diffusion modifier" formulations allow single injection, with high doses being released slowly to provide an extended exposure. Because the sequestered material is not available for immediate redistribution, the peak concentrations of free drug are minimized and side effects relative to the dose delivered are reduced.

Extended-release epidural morphine (EREM, DepoDur) is indicated as a single dose for the management of postoperative pain. EREM is composed of aqueous morphine entrapped in multi vesicular liposomes (DepoFoam) and is designed to slowly release morphine into the epidural space. Gould E.M. et al (16) found that administration of EREM perioperatively reduces C_{max} and maintains AUC dose proportionality, thereby providing prolonged analgesia to patients undergoing major surgery.

The spinal space is not pharmacokinetically homogenous in the way, that the arterial blood is homogenous.

Our knowledge of spinal pharmacokinetics is still very rudimentary and the extrapolation from animals to humans and from models of CSF and tissue kinetics to clinical effects is far from certain.

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