REVIEW ARTICLE

Spinal Opioid Bioavailability in Postoperative Pain

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Abstract: Opioids have been used for spinal analgesia for more than a century, and their injection epidurally and intrathecally has a key role in the control of postoperative pain. Since the discovery of the endogenous opioid system, 3 decades ago, their use has become more generalized in obstetric analgesia, the management of chronic pain, and acute postoperative pain. To use opioids effectively for this type of analgesia, it is important to understand the pharmacokinetics and clinical pharmacology of these drugs, specifically those that produce analgesia by an intrinsic spinal mechanism. Evidence from animal and human experiments indicates that hydrophilic opioids (such as hydromorphone and morphine) bind more strongly to specific receptors within the dorsal horn of the spinal cord than lipophilic opioids (such as alfentanil, fentanyl, and sufentanil). This can be understood by considering the spinal cord selectivity and bioavailability of these opioids. This difference is attributable to differences in the pharmacokinetic and pharmacodynamic properties of the 2 groups. It is more difficult for lipophilic opioids to reach and remain at sufficiently high concentrations at the site of action due to their sequestration in epidural fat and rapid plasma clearance from both epidural and intrathecal spaces, resulting in analgesia with a limited spread and duration, as well as the appearance of early supraspinal side effects. In contrast, morphine has very different properties, including greater spinal bioavailability and therefore administered neuraxially, it is suitable choice for the treatment of acute postoperative pain. However, when using morphine, a greater incidence of adverse effects can be expected, and it requires careful patient selection.

Key Words: postoperative pain, neuraxial opioid analgesia, opioid receptors, epidural analgesia, intrathecal analgesia

HISTORICAL NOTE

The natural alkaloids extracted from the opium poppy have been widely used for centuries for both medical and recreational purposes. In 1804, a pharmacist’s apprentice, Friedrich Sertürner, isolated an extract of the plant, calling it morphia, after the Greek god of dreams; this was later renamed morphine and commercialized in 1817. In 1901, the Romanian surgeon Racoviceanu-Pitesti published the first manuscript on the use of spinal opioids, morphine together with cocaine. Through the 1940s, new opioid substances were identified and progress was made in understanding their mechanism of action, and many doubts being resolved in 1973 when Pert and Snyder discovered opioid receptors in nerve tissue. Subsequently, it has been confirmed that this type of receptor is present not only in the brain, but also throughout the substantia gelatinosa in the dorsal horn and dorsal root ganglia of the spinal cord. Another key year was 1975, with the discovery by Kosterlitz et al. of the endogenous opioid system and messengers involved, namely enkephalins. Further advances continued to be made as Yaksh et al. demonstrated that spinal
administration of morphine produced analgesia in rats and, in a study by Wang et al., involving patients with severe cancer-related pain, it was demonstrated that intrathecal injections of 0.5 to 1 mg of morphine could almost completely relieve pain for 12 to 24 hours.

The use of epidural morphine was first mentioned in The Lancet in 1979 by Behar et al.; the study showed that morphine administered by this route relieved pain for 6 to 24 hours in 10 patients with acute or chronic pain, probably by acting directly on the dorsal horn receptors. Overall, it took the scientific community more than a century to adopt the use of neuraxial opioids in routine practice for the management of both acute and chronic pain.

INTRODUCTION

All opioid drugs produce analgesia by the same molecular mechanism, which causes a decrease in the excitability of nerve cells. To achieve this, they need to bind to the G-protein, inhibit the enzyme adenylate cyclase, and stimulate the activation of potassium channels, as well as the inhibition of voltage-dependent calcium channels. Given this common mechanism, it is natural to ask why there is so much difference in pharmacokinetic and pharmacodynamic characteristics among opioids and what these differences mean when selecting the optimal postoperative drug regimen. Over the last 3 decades, scientific effort in this field has focused on conducting controlled clinical trials to ascertain which of the available opioids is most suitable for spinal use.

It has been assumed that the administration of opioids neuraxially would produce better analgesia than the use of parenteral routes. It has also been assumed that fewer adverse effects including respiratory depression would result. Unfortunately, this is not always true, as many opioids can reach higher brain centers through the cerebrospinal fluid (CSF) or the blood, while their spinal bioavailability remains very low. It is well recognized that the neuraxial administration of local anesthetics (LA) produces segmental analgesia by direct spinal action. However, there is an open debate as to whether opioids alone or together with LA, administered by the neuraxial route, have the same analgesic effect in the perioperative period. Experimental and also clinical trials support the theory that bioavailability of opioid at the spinal site of action is inversely proportional to the drug lipid solubility, which is higher for hydrophilic opioids such as morphine than for lipophilic ones such as fentanyl, sufentanil, or alfentanil.

The purpose of this review is to examine which opioids reach high enough concentrations to produce spinal selective analgesia when given by epidural or intrathecal routes and to make some recommendations regarding their rational use for the management of postoperative pain. To this end, a search of Ovid/Medline was conducted to identify all articles published up to December 2012 using the keywords: “spinal analgesia;” “epidural opioids;” “intrathecal opioids;” and “postoperative pain.”

MECHANISMS GOVERNING SPINAL DISTRIBUTION OF OPIOIDS

In this section, we will analyze mechanisms that govern the distribution of opioids in or near the desired site of action. Epidural diffusion will be treated first and then diffusion over the meninges. Intrathecal transport involves a complex mixture of mechanical flow, buoyancy, and diffusion that has a large effect on whether the opioids reach the required biophase and diffuse into the spine. Lastly, the actual location and factors affecting the sensitivity of the opioid receptors are treated.

Any opioid, regardless of the route or site of administration, will produce analgesia if it reaches brain receptors through the blood stream. Analgesia will be produced in proportion to the degree of absorption in the CNS, and therefore, the analgesia obtained following spinal administration does not always imply a spine-specific mechanism. Moreover, even if this was the case, for the use of spinal administration to be justified, it should be shown to achieve better analgesia and/or a lower incidence of adverse events than other less invasive options such as the intravenous route (IV).

Many of the clinical differences observed among opioids can be attributed to their ability to reach their specific spinal receptors. In this review, bioavailability of an opioid following perispinal administration is an indicator of whether a substance is able to reach the spinal biophase, located in the spinal cord gray matter dorsal horn (Rexed lamina II: Substantia Gelatinosa of Rolando). A drug administered epidurally, as well as spreading throughout the epidural space itself, needs to move across the meninges, CSF, and white matter. Clearly, with intradural administration, the opioid has to traverse fewer barriers to reach the site of action. In adults, this distance can be as much as tens of millimeters. In contrast, following systemic administration, the blood can carry the opioid much closer, a few microns from the spinal biophase, and it only has to cross the capillary wall.
of the blood vessels in the brain and spine: the blood–brain barrier (BBB). These differences in diffusion distances help to explain the relative potency variability among opioids according their route of administration.9

Drug transport across the BBB depends on various factors such as local blood flow, capillary flow area, and intrinsic drug permeability. The physicochemical characteristics of drugs like hydrophilicity, lipophilicity, and hydrogen bonding potential largely determine their passive transport across the BBB, and through hydrophilic para-cellular and lipophilic transcellular enviroments.11 Indeed, the morphine metabolites Morphine-6-glucuronide (M6G) and Morphine-3-glucuronide are both highly hydrophilic, but they display differing diffusion across the BBB.12 The analgesic activity of M6G is extremely potent following intracerebroventricular administration but markedly lower than morphine following systemic administration, due to poor BBB permeability to M6G. In vivo and in vitro studies have shown that some opioid analogesics given systemically have limited access to the central nervous system due to cationic properties, these drugs exhibit under physiological conditions. The mechanism underlying opioid permeation of the BBB cannot be fully explained by simple diffusion alone. Moreover, various types of transporters that exhibit substrate specificity have been localized on the BBB.11

Some of the ATP-binding cassette (ABC) transporters like P-glycoprotein (P-gp) that are present at the BBB influence the brain pharmacokinetics of their substrates by restricting their uptake or enhancing their clearance from the brain into the blood, which has consequences for their CNS pharmacodynamics. The effects of morphine and methadone on the CNS are modulated by P-gp. Exposure to opioids may also alter the expression of ABC transporters, and P-gp can be overproduced during morphine treatment, suggesting an additional indirect action.12

Epidural Diffusion

For an opioid drug to have analgesic effect, it must necessarily move from the injection site, in this case epidural space, to the specific opioid receptors in the gray matter of the medullar posterior horn. Therefore, the determining factor is the opioid's ability to redistribute to the neighboring tissues, diffusing away from the epidural space and specifically crossing a range of barriers such as the meninges, CSF, and spinal white matter. The distance and rate an opioid can move across a specific tissue, however, depends on the characteristics of the tissue and its chemical and physical properties relative to those of the opioid. In particular, the laws of thermodynamics favor hydrophobic drugs accumulating in tissues with similar properties. Given this, fentanyl and sufentanil can be expected to diffuse preferentially into epidural fat rather than CSF and will therefore be less available to spinal opioid receptors.9

The epidural fat, mostly distributed in the posterior and lateral parts of the epidural space, does not form a uniform sheet and lies in discrete pockets. It cushions the pulsation of the spinal meninges and its main function is to protect the medullar cord from the periosteum during forced extension and flexion of the vertebral column. Given its fatty nature, it behaves as a reservoir of lipid-soluble drugs resulting in sustained release of the drug and prolonged analgesia.13

In an animal model, Bernards et al.14 gave different epidural opioids as a bolus (morphine, fentanyl, alfentanil, and sufentanil) and measured their concentration over time in different compartments as follows: epidural space; epidural fat; epidural venous plexus; intrathecal space; and central venous plasma. They demonstrated that the epidural mean residence time and the epidural terminal elimination halftime were both directly correlated with the drug lipid solubility, which is higher for sufentanil and fentanyl, and lower for morphine (Figure 1). Further, the proportion of drug reaching the CSF (defined as “AUC” and measured as dose-normalized area under the curve by the authors) was higher for the most hydrophobic opioid (morphine) compared with the other more lipophilic opioids tested, which were sequestered in fat (Figure 2). Specifically, the concentration accumulated in the epidural fat was found to be 32 and 20 times higher for fentanyl and alfentanil, respectively, than for morphine, and, accordingly, lower quantities of the former drugs reached the spinal biophase. The authors found that after epidural injection, the plasma concentration of alfentanil was unexpectedly higher at all times, than that of all the other opioids studied (Figure 3). The authors explained this result by the fact that alfentanil presented a greater partition into all studied tissues and also exhibited faster clearance toward the plasma in relation to morphine, and consequently, had lower CSF bioavailability and spinal selectivity.

Nordberg et al.,15 studied plasma (during 6 hours) and CSF (over 24 hours) concentrations in 5 patients after 6 mg epidural morphine injection. Peak plasma morphine levels were measured at 12 ± 3 minutes, and
the estimated terminal elimination half-life was 213 ± 24 minutes. They observed that the pharmacokinetic profile was very similar to that observed after an intramuscular injection. Morphine reached a maximum level in CSF after 135 ± 40 minutes and its terminal elimination half-life was as long as 239 ± 10 minutes. The total amount of the opioid drug that ultimately was in position to reach the specific receptors in the spinal cord after an epidural bolus in man, defined as CSF bioavailability, was calculated for morphine to be approximately 2% (1.9 ± 0.5%).

Meningeal Diffusion

Experimental studies suggest that the main mechanism by which opioids reach the CSF is simple diffusion through the meninges, helped by kinetic energy from the pulsatile CSF flow associated with the spinal cord movement. Specifically, it has been observed that diffusion through the arachnoid villi in the spine and the radicular arteries involved in the vascularization of the spinal cord do not participate in this process. Although there are differences between opioid drugs, these do not seem to be important in the redistribution from the epidural space to the intrathecal sanctuary.

The ability to cross the meningeal barrier has been described as a relationship between the permeability of the arachnoid mater and drug lipid solubility. Permeability increases with increasing lipid solubility, but only up to moderate values of the octanol/buffer distribution coefficient (about 129). However, at higher values, permeability significantly decreases with solubility. Accordingly, the meningeal permeability coefficients of morphine (M) and of sufentanil (S) are similar, 0.6 and 0.75, respectively, but their octanol/buffer distribution coefficients are very different, 1 (M) and 1787 (S).
This biphasic relationship has been explained by the fact that the drugs have to first cross the arachnoid mater cells, mainly composed of lipid bilayers and second, cross through the fluids of the extracellular and intracellular spaces which are more hydrophilic environments. Highly lipophilic drugs complete the first step easily, but the second one with difficulty, while for hydrophilic drugs, the opposite is true. This fact, added to the important fact that the arachnoid mater presents the main barrier for meningeal permeability (90%) (Figure 5), explains why drugs with intermediate values of lipid solubility (lidocaine, alfentanil) have the highest permeability coefficients.18,19

Although the meninges, as a whole, do not represent a selective physical barrier for spinal diffusion of opioids, it is nevertheless worth highlighting their important function as a site for intrathecal clearance of drugs, given the dense network capillaries on the dura mater, specifically lying on its inner surface. This conclusion is based on the results of 2 experimental studies in animals: Kozody et al.20 demonstrated that the spinal administration of adrenaline and phenylephrine significantly reduced dura mater blood flow without affecting the spinal cord blood flow, and Bernards et al.21 discovered that after epidural adrenaline administration together with a hydrophilic opioid, morphine plasma clearance was reduced probably due to local dura mater blood flow constriction.

**Intrathecal Transport**

Apart from the baricity, volume of drug given, level of administration, or the kinetic energy provided by the injection itself, opioids that reach the CSF should behave as they would have if injected directly into CSF. In a preclinical study, Ummenhofer et al.,22 found that the

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**Figure 4.** Relationship between the octanol-buffer (pH = 7.40) distribution coefficient and the experimentally determined meningeal permeability coefficient in monkeys (Data from Bernards and Hill18).

**Figure 5.** Permeability of morphine and alfentanil through the meninges of the monkey: Dura (Dura matter), Pia (Pia matter), Arach (Arachnoids) (Data from Bernards and Hill19).

**Figure 6.** Apparent volumes of distribution (mL) in the spinal cord for different opioids after intrathecal administration of equimolar doses (Data from Ummenhofer et al.22).
apparent volume of distribution of intrathecal opioids was directly related to their lipid solubility, this volume being 40 times larger for sufentanil than morphine (Figure 6). This observation is very important because the opioid concentration in the extracellular fluid space needs to be sufficient to allow binding to specific receptors situated in the gray matter of the spinal cord dorsal horn. Rapid redistribution from the intrathecal compartment toward more lipophilic environments reduces drug availability at the site of action. In that study, the most important clearance route was found to be through the meninges toward the epidural space (Figure 7). Key implications regarding lipophilic opioids are their limited rostral spread through the CSF, and their relatively poor spinal bioavailability compared with hydrophilic agents.

The main manner in which drugs spread through the CSF is by the circulation of the fluid itself. All the associated energy comes from the pulsatile flow inside the central nervous system. The energy-giving wave modifies the volume of the brain, increasing it in a transitory way, and is also transmitted to the spinal cord to a lesser extent, forcing CSF downwards at the dorsal surface and upwards near the ventral surface. The principal observation here is that this transportation mechanism does not cause any clinical difference among opioids as they are all transported equally by this mechanism.

Drugs can also spread into CSF by diffusion. The simple diffusion rate of any molecule in an ideal fluid is directly proportional to the fluid temperature (in Kelvin) and inversely proportional to the square root of its molecular weight. However, the temperature of the CSF usually remains constant, and any physiological variations in temperature are minor compared with the 310 K body temperature. As there are no great differences among opioids molecular weight (from morphine 285.33 to alfentanil 416.52), the square root does not vary much (only from 17 to 20). Theoretical rates of diffusion are therefore similar for all opioids and cannot explain the differences observed in their spread through the CSF. These differences can be explained by the variations in the clearance rate from the CSF. If a drug is rapidly cleared, by definition, there is little left to produce spinal analgesia. For example, in humans, the clearance rate of sufentanil (27 μg/kg/minutes) is almost 10-fold higher than morphine (2.8 μg/kg/minutes). For this reason, morphine stays longer in the CSF, is more likely to spread toward the brain, and ultimately causes other supraspinal effects such as sedation and respiratory depression.

There is some evidence that respiratory depression, somnolence, and pruritus are associated with the extent of rostral migration of opioids. Different opioids have different times of onset of adverse effects. This is principally due to differences in liposolubility. It has been estimated that morphine administered into the lumbar cistern reaches the cisterna magna in about 1 to 2 hours and in 3 to 6 hours it can be detected in the 4th and lateral ventricles. Lipophilic opioids can also have a central effect, because they are more rapidly redistributed into the blood stream, reaching the central nervous system through that route. To a lesser extent, distribution also occurs via the CSF, and in fact, traces of
opioids, even sufentanil, have been found in the cisterna magna only 30 minutes after the intrathecal injection at the lumbar site. Fentanyl has been found to reach a maximum cervical CSF concentration as early as 10 minutes after lumbar epidural injection. The detected average was about 10% of the maximum concentration measured previously in the CSF at lumbar site, but is associated with large individual variability.

In the same study, fentanyl’s capacity to permeate the CSF after IV or epidural injection given as a bolus was compared at lumbar and cervical sites. Only 4 of the 60 samples studied had detectable CSF concentrations of fentanyl after IV administration. After lumbar epidural administration, fentanyl’s spread across the meninges was rapid and greater than with the IV route.

To investigate cephalic spread of opioids, healthy volunteers were given intrathecal injections of 50 µg of fentanyl (F) together with the same dose of morphine (M) in the lowest palpable interspace (L5 to S1). Samples of CSF taken from the highest possible level in the lumbar space (L2 to L3) were analyzed up to 120 minutes after injection. It was found that both drugs reached their peak concentration at the cephalic site at similar times, fentanyl first after 41 ± 13 minutes followed by morphine after 57 ± 12 minutes. Meanwhile, M: F concentration ratio increased from 2:1 after 36 minutes to 4:1 after 103 minutes, and no rate constants correlated with the patient’s weight, height, or CSF volume. These findings were explained using a simple pharmacokinetic model with relatively high individual variability. The authors concluded that fentanyl is more quickly removed than morphine from the CSF; however, no differences were observed between the spread of the 2 compared opioids during the first hour of the trial.

Gourlay et al., also studied the cephalic morphine diffusion into CSF in oncologic patients, after 10 mg epidural bolus injection at the lumbar level. They found a rapid vascular uptake reaching the maximum blood concentration at 5.1 ± 2.3 minutes, but a 3-hours delay in the CSF peak concentration was noted. Sixty minutes passed until morphine was measured in high enough concentration to produce analgesia (300 ng/mL) in the intrathecal samples at the cervical level.

More recently, in an experimental study in animals, Bernard found that following continuous infusion of bupivacaine and baclofen, there was poor internal distribution through the CSF, and there were differences in drug concentrations at the posterior and anterior surfaces of the spinal cord, as well as a rostral-caudal gradient. This gradient, previously noted for albumin and glucose, is attributable to a relatively slow flow of the CSF and the high degree of internal anatomical compartmentalization. After 8 hours of infusion, the drugs had spread no further than 7 cm and were detected at this distance at much lower concentrations than the level of infusion and also at higher concentrations in the posterior medullar segment than in the anterior medullar segment.

Clinical Implications of the Density of Spinal Anesthetic Opioid Intrathecal Mixtures. The ratio between density of a drug (LA, an opioid, or a mixture of both) and the CSF, known as baricity, is one of the most relevant factors to explain the distribution of a drug in the intrathecal space, together with the injection velocity and patient position. If the density of the injected drug is different from the density of the CSF, the injected drug may either have a tendency to float up or to sink down according to Archimedes principle. The density of a solution is defined as its mass divided by unit volume (g/mL) at a given temperature. CSF density is not constant, being known to vary with age and sex (> in males), as well as under various conditions such as pregnancy, menopause, and certain diseases. However, the temperature of the CSF is fairly constant at core body temperature (37°C). Most spinal drugs are administered at the temperature of the operating theater (perhaps 21°C), and their properties may change as they warm to the temperature of the CSF. To predict the final spread of LA and/or opioids, their baricity should be calculated, alone and in mixtures, at body temperature. By definition, solutions with a baricity approaching 1.0000 are isobaric; above or below this value, they are hyperbaric and hypobaric, respectively. Some authors have suggested that solutions with densities that exceed the confidence interval upper limit of the CSF density (1.00059 ± 0.00040 g/mL) should be considered hyperbaric, while those below the lower limit should be considered hypobaric.

In a novel study, the baricity of various different LA was very accurately determined at 5, 20, 30, and 37°C. These authors observed a decrease in the density with increasing temperature and, using a logarithmic curve, determined the ideal injection temperature at which LA would behave as if they were isobaric at body temperature, with the following results: bupivacaine and ropivacaine (both 5 mg/mL), 35.1°C; l-bupivacaine 5 mg/mL, 37°C; and articaine 20 mg/mL, 39°C.

Another study, comparing intrathecal use of medications without glucose, found that the density
of the solutions was negatively correlated with temperature. The density decreased as the temperature rose to that of the body, with increments of + 0.20°C leading to changes in density of −0.00007 g/mL. They also observed that, except for 2% and 1.5% lidocaine with epinephrine, which were both hyperbaric, all the samples were hypobaric, including opioids alone and combined with LA, as were combinations of opioids diluted with saline at usual clinical doses (morphine 250 μg, fentanyl 2.5 to 25 μg and sufentanyl 3.3 to 12.5 μg). Similarly, in a Brazilian study, authors used a latest generation densitometer (DMA 4500), based on harmonic mechanical oscillations with a precision of 0.00001 g/mL, to measure the density of the range of LA and most commonly used coadjuvants in spinal anesthesia. The densities of the LA and their combinations with opioids were measured at 20, 25, and 37°C. Both groups showed a decrease in density with increasing temperature. At 37°C, all the solutions containing glucose were hyperbaric alone and in their respective mixtures, while those without glucose were hypobaric. The opioids (morphine 100 μg, fentanyl 20 μg and sufentanil 5 μg), which are isobaric at room temperature, were hypobaric at 37°C. When combined with LA, the density of the solution fell, making it slightly more hypobaric, although the change was not expected to be clinically significant, consistent with previous reports. Finally, when the hyperbaric LA (8% glucose) was mixed with the same isobaric formula at equal volumes, the mixture remained hyperbaric in the final state (4% glucose).

A recent publication studied the various drug concentrations typically used for intrathecal infusion in chronic pain management, namely bupivacaine (2.5, 5, 10, and 20 mg/mL), morphine (1, 10, 25, and 50 mg/mL), baclofen (1, 1.5, 2, and 4 mg/mL), and clonidine (0.05, 0.5, 1, and 3 mg/mL), all at 37°C ± 0.01. All preparations of baclofen and clonidine were hypobaric. In contrast, morphine (M) and bupivacaine (B) were hyperbaric at high concentrations (B > 12 mg/mL and M > 8 mg/mL) and hypobaric at low concentrations (B < 7 mg/mL and M < 4 mg/mL), the relationship between density and concentration being linear (r² > 0.99). These data confirm that concentration affects baricity and suggest that it may also affect the final spread of the drugs. This is, however, not clinically important in the context of acute postoperative pain because drugs concentrations are lower than those prepared for chronic pain.

Spinal Diffusion

The last step for opioids already present in the spinal cord is to cross the white matter and reach the specific medullar site of action or biophase. In a classic animal trial, von Cube et al. injected radioactively labeled fentanyl, morphine, and dihydromorphine into the lateral ventricles, and measured the distance reached in the neighboring tissues of the central nervous system over time. The results were conclusive and the 3 opioids spread 700 μm across the neural tissue within the first 7 minutes. As time passed, fentanyl advanced no further because it was eliminated from the CNS within 120 minutes. Five hours later, the distribution of hydromorphine and morphine continued, and by the end of the study, only morphine had reached tissue depth of around 3000 μm. An even more striking observation was that fentanyl had a greater affinity for white matter, compared with the water-soluble drugs, which had more affinity for gray matter. Recently, this fact was confirmed in an experimental model (pigs), with intrathecal injection of different opioids at equimolar doses (fentanyl, sufentanil, alfentanil, and morphine), and subsequent measurements of the concentrations of the drugs in the extracellular compartment around the spinal cord. The exposure to morphine was higher than exposure to all of the lipophilic drugs, morphine having as much as a 3-fold higher concentration and slower clearance, both at the lumbar (L2 to L3) and at the thoracic level injection (T11) (Figure 8), whereas the clearance rate for alfentanil was nearly 10 times higher than for any other opioid (Figure 9). The probable explanation for these observations is that the white matter is mainly composed of axonal plasma membranes surrounded by layers of Schwann cells. Accordingly, it has a lipid content of around 80% and therefore greater affinity for lipophilic opioids. As the gray matter does not contain myelin, it is relatively hydrophilic and as a result has a greater affinity for morphine.

Peripheral Opioids Receptors

Opioid receptors are synthesized in neuronal cell bodies in the dorsal root ganglion (DRG) and intra-axonally transported centrally and peripherally to the nerve terminals. They belong to the family of G-protein-coupled receptors with 7 transmembrane domains and may be involved in multiple regulatory processes. Endorphins and locally administered opioids bind and
activate the opioid receptors in the periphery. On
activation, the receptors couple to inhibitory G-proteins
(Gi/Go) and inhibit cyclic AMP production and/or
directly interact with K⁺, Ca²⁺, and other ion channels
in the membrane. Analgesia results from decreased
nociceptor excitability, reduced action potential
propagation, and decreased release of excitatory pro-
inflammatory neuropeptides (substance P and calcitonin
gene-related peptide) at central and peripheral nerve
terminals.⁴⁰

The antinociceptive effects of opioids are markedly
enhanced in the presence of inflammation and are
mediated by peripheral opioid receptor-specific mecha-
nisms. This inflammation gives rise to increased synthe-
sis and axonal transport of opioid receptors in DRG
neurons with resultant μ-opioid receptors (MOR) up-regulation and enhanced MOR G-protein coupling
with a subsequent increased MOR agonist efficacy,
specifically at peripheral nerve terminals. Although
opioid receptor-mediated analgesia is enhanced, opioid
receptor transcription in DRG is not improved in the
early stages of inflammation. However, at later stages,
the number of peripheral opioid receptors appears to
increase and the perineural barrier is disrupted, facili-
tating access of opioid agonists to their receptors,
resulting in enhanced peripheral analgesic efficacy in
inflammation states after opioid administration.⁴¹

SYNTHESIS OF EXPERIMENTAL DATA

In this section, we try to summarize and synthesize the
meaning of the body of experimental data presented in
the previous section as a bridge to clinical utilization of
the different opioids available. Bernards⁴² carried out a
review of experimental studies in animals measuring the
concentrations of opioids from multiple compartments
such as the intrathecal and epidural spaces and also
spinal cord and surrounding tissues, following neuraxial
administration. The conclusions from these animal data
help us to understand the findings of multiple clinical
trials concerning the analgesic effect of lipophilic
opioids, namely that the effect is due in part, or even
exclusively in some cases, to the uptake into plasma and
redistribution toward brain opioid receptors.

Lipophilic opioids, such as sufentanil, fentanyl, and
alfentanil, quickly cross the BBB, have a high seques-
tration degree in the epidural fat, good vascular uptake,
and finally bind similarly in the spinal white and gray
matter. Clinically, this would result in short latency,
limited rostral diffusion, spinal analgesia at the level of
the injection site, and short time of action, but also
with a risk of early respiratory apnea. In contrast,
morphine, due to its hydrophilicity, goes through this
barrier at a slow pace, sticking to the epidural fat to a
lower degree, but directly reaching the specific gray
matter opioid receptors, with slow plasma reuptake.
This results in higher drug concentrations in the CSF.
for longer time than lipophilic opioids. This also leads to a later onset of action, a greater area of effect in the spine due to cephalic diffusion, and a longer clinical effect together with potential delayed respiratory depression.10

The pharmacokinetic factors that are clinically relevant for analgesia are the rate of drug clearance from the CSF, the amount of drug available in the spinal biophase, as well as the mean elimination half-life. Clearly, drug bioavailability will be higher when it is delivered directly to the posterior horn of the spinal cord rather than distributed through blood or the epidural space. Bernardes9,42 emphasized the importance of determining which fraction of the analgesic effect might be attributed to a supraspinal or spinal action and which to systemic action, as well as establishing which effect individually or in combination is necessary to achieve the overall analgesic effect.

On the basis of the all the aforementioned experimental studies,13–22,24–28,39,42 we can deduce that the bioavailability of hydrophilic opioids to the spinal opioid receptors, such as morphine, is higher than that for lipophilic opioids, (alfentanil, sufentanil, or fentanyl). In fact, U.S. Food and Drugs Administration (FDA) have so far only approved hydrophilic opioids (morphine and hydromorphone) as first-line drugs for spinal use in the context of chronic pain.1 Other opioids are recommended only if these drugs are not indicated, effective or well tolerated, although they are also used on an off-label basis for acute postoperative pain, given the multiple studies indicating that they are an effective choice.10

**Clinical Recommendations for Postoperative Pain**

After spinal administration, opioids distribute in a complex way, which can be described by multicompartamental models. A drug deposited directly into or which otherwise reaches the intrathecal space simultaneously undergoes movement in a caudal direction on the dorsal side of the spinal cord and then up the ventral side toward the head. Diffusion into the spinal cord results in binding to specific receptors in the gray matter and also to nonspecific receptors in the white matter, as well as egress in the opposite direction into the epidural space, becoming sequestered in the epidural fat. Finally, there is clearance from each of these compartments into the blood. The balance between all of these processes, described in terms of the spinal bioavailability of the drug, determines its clinical characteristics and relates to the overall effectiveness14,23 (Table 1).

Clinical trials have demonstrated that hydrophilic opioids like morphine,9,10 especially when given as a continuous infusion plus LA,23,43 or by extended-release epidural injections,44–46 provide good postoperative analgesia but are associated with a relatively high rate of adverse effects.47 Most of the analgesic effect of epidural lipophilic opioids such as fentanyl,48–52 sufentanil,53–56 and alfentanil57–59 is due to systemic uptake. When given alone, the epidural route does not seem to offer advantages over parenteral administration. Specifically, current evidence suggests that the benefits of giving lipophilic opioids epidurally alone are unproven or marginal in upper abdominal and thoracic surgery. and in most situations, do not outweigh the risks associated with this route.49,52,54,55,60 Nevertheless, combining them with LA does enhance the analgesic effect, while reducing both the side effects and the doses required, compared with administering the drugs separately.9,10,23 Fentanyl only seems to reach high enough concentrations at the biophase to produce segmental spinal analgesia when given as an epidural bolus.61 However, methadone62,63 seems to be a good option for epidural use, as is hydromorphone,64,65 using epidural patient-controlled analgesia (PCEA). However, more studies are required to define the best regimens.

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<th>Neuraxial Opioid Bioavailability</th>
<th>Epidural</th>
<th>Intradural</th>
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<td>(Grade of Binding to Specific Receptors of the Posterior Medullar Horn to Produce Spinal-Mediated Analgesia)</td>
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<tr>
<td>Opioid</td>
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<tr>
<td>Morphine*(1)23,43,47,67,68</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Hydromorphone (525)64,65</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Methadone (116)52,63</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fentanyl (955)52,66,68</td>
<td>Low as continuous infusion</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sufentanil (1737)53–56,66</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Alfentanil (129)57,59</td>
<td>Very low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

*Into brackets opioid liposolubility in relation to morphine, expressed as octanol/buffer distribution coefficient.9

**Table 1. Level of Spinal Cord Selectivity of Most Common Spinal Opioids Used in the Treatment of Postoperative Pain**9,10,42

The pharmacokinetic factors that are clinically relevant for analgesia are the rate of drug clearance from the CSF, the amount of drug available in the spinal biophase, as well as the mean elimination half-life. Clearly, drug bioavailability will be higher when it is delivered directly to the posterior horn of the spinal cord rather than distributed through blood or the epidural space. Bernardes9,42 emphasized the importance of determining which fraction of the analgesic effect might be attributed to a supraspinal or spinal action and which to systemic action, as well as establishing which effect individually or in combination is necessary to achieve the overall analgesic effect.

On the basis of the all the aforementioned experimental studies,13–22,24–28,39,42 we can deduce that the bioavailability of hydrophilic opioids to the spinal opioid receptors, such as morphine, is higher than that for lipophilic opioids, (alfentanil, sufentanil, or fentanyl). In fact, U.S. Food and Drugs Administration (FDA) have so far only approved hydrophilic opioids (morphine and hydromorphone) as first-line drugs for spinal use in the context of chronic pain.1 Other opioids are recommended only if these drugs are not indicated, effective or well tolerated, although they are also used on an off-label basis for acute postoperative pain, given the multiple studies indicating that they are an effective choice.10
difference is only 10-fold (10 μg vs. 100 μg), which leads one to suspect a low bioavailability at the spinal cord. Nevertheless, fentanyl and sufentanil administered intrathecally have been shown to be effective for the management of postoperative pain, with a rapid onset of action (15 minutes) and short duration (2 to 4 hours). Several studies have shown these opioids are very useful for ambulatory setting, especially in gynecological surgery patients and during labor. The combination of bupivacaine or lidocaine with fentanyl (10 to 20 μg) or sufentanil (5 to 7.5 μg) reduces the time to onset of action, achieves better intraoperative analgesia, and increases the time to the first postoperative dose of rescue analgesia, without extending recovery time of motor function or length of stay in the recovery room. 

Giving intrathecal morphine in the lumbar region, in combination with general anesthesia (without local anesthetics), strengthens the analgesia, decreasing the consumption of rescue opioids. The effect is more significant after abdominal than cardiothoracic surgery. The intrathecal administration of morphine with LA for regional anesthesia in orthopedic and lower abdominal surgery produces excellent quality intraoperative analgesia and reduces pain intensity at rest and on movement in the first 24 hours after the intervention. Despite 3 decades of experience using intrathecal morphine, the ideal dosage has yet to be established, although it is known that the minimum effective dose is 50 to 100 μg, and there seems to be a tacit consensus not to exceed 300 μg to avoid phenomena of delayed respiratory depression, most often occurring 6 to 12 hours after neuraxial administration. For spinal anesthesia with LA, 50 μg has been determined as the optimal dose of intrathecal morphine that produces satisfactory analgesia with minimum side effects in elderly patients undergoing transurethral resection of the prostate. Also, 100 μg has been previously reported to be the optimal dose in a qualitative and quantitative systematic review of randomized controlled trials for Cesarean section. Other clinical trials have demonstrated that the dose of 100 μg of intrathecal morphine with LA provides the best balance between efficacy and side effects, compared with doses of 50 and 200 μg, in older patients undergoing hip arthroplasty. The dose of 200 μg morphine with LA demonstrated the best choice for knee replacement. In a recent meta-analysis, 300 μg was the most common dose used in clinical practice for abdominal surgery. The optimal neuraxial opioid dose is difficult to calculate and should be a balance between the conflicting demands of providing optimal analgesia while minimizing dose-related adverse effects. Based on a recent review on neuraxial morphine, the safe “single shot” intrathecal dose appears to be 75 to 150 μg and the ideal “single shot” epidural morphine dose could be 2.5 to 3.75 mg for the first 24 hours after surgery. 

Guidelines based on a survey conducted by the American Society of Anesthesiology recommend that anesthesiologists managing postoperative pain on a daily basis should employ a broad range of modalities, among them systemic analgesia with opioids administered by PCA, epidural and intrathecal opioids, and regional techniques, assessing the risk/benefit ratio on a case-by-case basis. It is underlined that particular care needs to be taken when giving analgesia by continuous infusion, to avoid side effects caused by overdosing. The choice of treatment should be guided by the experience of the acute pain management expert, as well as the need for a protocol with a suitable level of monitoring given the technique and drug as well as the medical setting.

These are the overall recommendations for the right drug choice between hydrophilic and lipophilic opioids for postoperative pain from an updated report by the American Society of Anesthesiologists Task Force on neuraxial opioids:

1. Single-injection neuraxial opioids may be safely used in place of parenteral opioids without altering the risk of respiratory depression or hypoxemia. 
2. Single-injection neuraxial fentanyl or sufentanil may be safe alternatives to a single-injection of neuraxial morphine. 
3. When clinically suitable, extended-release epidural morphine may be used in place of intravenous or conventional (ie, immediate release) epidural morphine, although extended monitoring may be required. 
4. Continuous epidural opioids are preferred to parenteral opioids for anesthesia and analgesia for reducing the risk of respiratory depression. 
5. When clinically suitable, appropriate doses of continuous epidural infusion of fentanyl or sufentanil may be used in place of continuous infusion of morphine or hydromorphone without increasing the risk of respiratory depression. 
6. Neuraxial morphine or hydromorphone should not be given to surgical outpatients.
In the future, most surgical procedures should be added to the PROSPECT GROUP (evidence-based, procedure-specific postoperative pain management): Nine are currently available online. Dose-ranging studies will need to be designed for various surgical procedures to determine the ideal concentration of the analgesic mixture of LA and opioids, as well as the ratios of the 2 drugs to obtain optimal analgesia with minimal incidence of side effects. 10

CONCLUSIONS

There is a clear consensus in the scientific community that opioids are the most potent centrally acting drugs available in the arsenal for treating postoperative pain. However, the debate continues as to whether the neuraxial route is reliable for obtaining selective opioid spinal analgesia in the perioperative setting. Experiments in both animals and humans support the theory that bioavailability at the spinal site of action is inversely proportional to the drug lipid solubility, which is higher for hydrophilic opioids (eg, hydromorphone and morphine) than for lipophilic ones (eg, alfentanil, fentanyl, and sufentanil). 9,10,14,23,42 Morphine given epidurally is considered very effective in patients with postoperative pain, but its short duration of action (< 24 hours) limits the usefulness of bolus injections, and there are adverse effects associated with increasing the dose. 10,47 For these reasons, it has been recommended to give morphine by continuous epidural infusion in combination with LAs. 10,23,43 Recently, evidence has emerged that single doses prior to surgery in the form of extended-release liposomal injections in the lumbar region, with no need to place an epidural catheter, reliably provide good, long-lasting (up to 48 hours) analgesia, with reasonable levels of tolerance for side effects. 44–46,67 Clinical trials have also shown that the administration of lipophilic opioids by continuous epidural infusion does not cause analgesia by direct spinal action 48–60 (in contrast to epidural bolus injections of fentanyl, where sufficient concentrations of the drug can reach the spinal site of action 61). On the other hand, the addition of opioids, including lipophilic opioids, may enable a reduction in the dose of LA and a commensurate reduction in LA-related side effects. 10,23 All intrathecal opioids produce some of their analgesic effect selectively at the spinal level and some of their effect supraspinally. It should also be noted that lipophilic drugs can also reach higher brain centers by absorption into the blood and, therefore, cause both early excessive sedation and respiratory depression, within less than half an hour of administration. 9,10,24,25,42

Morphine has often been considered to be the opioid with the best overall characteristics for spinal administration due to its bioavailability, but this does not mean that it is the ideal drug in all situations. In particular, it should not be used in ambulatory surgery or in patients with high cardio-respiratory risk. It also causes dose-dependent delayed supraspinal side effects such as respiratory depression, meaning that it requires careful patient selection and monitoring. 57–69 Lipophilic opioids are often considered a better option for obstetrics and ambulatory surgery; 10,66 however, more clinical trials are needed to define the best regimens after major surgery. 77

Lastly, we should remember that all patients given neuraxial opioids must receive suitable surveillance and monitoring focused on insuring sufficient ventilation such as respiratory rate and depth oxygen levels, use of a pulse oximeter when necessary, and an appropriate level of consciousness for a period equivalent to the opioid clinical duration. This duration is around 4 to 6 hours for lipophilic opioids, 12 to 48 hours for morphine in the case of bolus injections, and the full time of the treatment when continuous infusion is necessary to achieve safety analgesic control in patients with postoperative pain. 74–76

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