Introduction

Widespread medical use of unprocessed opium was a common practice along the centuries until morphine was first discovered in 1804 by Friedrich Sertürner, a German Pharmacist, who first distributed this drug in 1817 [1]. The Romanian surgeon Racoviceanu-Pitesti, who reported his experience using a mixture of cocaine and morphine in 1901, made the first publication concerning the use of opioids in spinal anesthesia [2]. After the development of new opioid in the 1940s, scientists began to believe that there must exist original binding sites within the brain for these opiate-like drugs. The problems were overcome in 1973 when Pert and Snyder further characterized the properties of this opiate binding from nervous tissue [3]. Not only did these binding sites reside within the brain, but they also lay in the gelatinous substance of the spinal cord. Fields et al., found that primary afferent tissue of the dorsal root and the dorsal horn of the spinal cord contained multiple receptor types [4]. The year 1975 was a crucial one regarding the discovery of endogenous enkephalins by Kosterlitz et al. [5]. Further, it was proven by Yaksh et al., that direct application of morphine into the spine of rats by a chronic intrathecal (IT) catheter produced analgesia [6] and this practice became a reality when Wang et al., successfully used intrathecal morphine bolus dose injection in humans [7]. The publication by Behar et al., in 1979 was the first paper on the use of epidural morphine at 2 mg doses for the treatment of acute and chronic pain [8]. The latter authors suggested that there was a direct spinal opioid effect on the specific receptors of the spinal cord. Therefore, more than a hundred years passed until it became routine to use neuraxial opioids for acute pain analgesia.

The objective of this review was to assess, by the available evidence, which opioids reach high enough concentrations to produce spinally selective analgesia by epidural or intrathecal administration and to make some recommendations regarding their rationale use for postoperative and chronic pain. To this purpose, we conducted a search of Medline to identify all articles published up to May 2017 using the keywords: “spinal”, “analgesia”, “intrathecal” “epidural”, “acute pain”, “chronic pain” and “opioids”.

Mechanisms Governing Spinal Opioid Distribution

All opioids in clinical use produce analgesia by the same molecular mechanism that is 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⁺⁺ channels, all of which decrease neuronal excitability. Given the common mechanism, pain...
In general, all substances diffuse down their concentration away from the epidural space and individually crossing a range the gray matter of the spinal cord posterior horn. Therefore, move from the epidural space to the particular site of action in the epidural fat rather than CSF and so will no longer be available to spinal opioid receptors \[9\].

Recently, scientific effort in this field has been focused on defining which opioids are suitable for spinal use and which not. It had been assumed that any opioid administered epidurally or intrathecally would produce better spinally selective analgesia than any other route of administration and without more severe adverse effects, such as respiratory depression, that may be life threatening. Unfortunately, this tends not to be the case, as many drugs can reach higher brain centers through the cerebrospinal fluid (CSF) or via the blood, and often they produce supraspinal analgesic effects while their spinal bioavailability remains very low \[10\]. It has been demonstrated that the spinal administration of local anesthetics (LA) provides segmental analgesia. An open debate is still open to whether opioids alone or together with LA, administered by the spinal route, have the same analgesic effect in the perioperative period \[11\].

Any opioid administered to any part of the body will produce analgesia on reaching brain receptors through the blood, in proportion to the degree of absorption, and hence the analgesia obtained following spinal administration is not governed by a spine-specific mechanism. Moreover, even if it were to be, for the use of spinal administration to be justified, it should be shown to produce better analgesia with fewer secondary effects than other less invasive options such as the intravenous route \[9\]. Many of the differences observed among opioids can be attributed to their ability to reach their specific spinal receptors. For this review, we define bioavailability of an opioid following spinal administration as an indicator of whether a substance can reach the site of action or biophase. In this case, the biophase is in the dorsal horn of the spinal cord gray matter at Rexed Lamina II: Substantia Gelatinosa of Rolando, surrounded by white matter. Therefore, a drug administered epidurally, as well as spreading through the epidural space itself, needs to diffuse through the meninges, CSF and white matter. Clearly, with intradural administration, the drug has to cross fewer barriers to reach the site of action. In any case, in adults, the distance to be traveled is 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 thin wall of the blood vessels in the blood–brain barrier. These differences in diffusion distances help to explain the relative strengths of effect of different opioids according to their route of administration \[9\–11\].

**Epidural diffusion**

It is assumed that for opioid drugs to take effect they must move from the epidural space to the particular site of action in the gray matter of the spinal cord posterior horn. Therefore, one of the most important factors to consider is the ability of the drugs to redistribute to the neighboring tissues, diffusing away from the epidural space and individually crossing a range of barriers such as the meninges, CSF and spinal white matter. In general, all substances diffuse down their concentration gradient; hence, any opioid placed into the epidural space will tend to spread into the surrounding tissues. The rate and distance a drug moves into a particular tissue, however, depends on the volume of that tissue and its physical and chemical properties about those of the drug. 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 so will no longer be available to spinal opioid receptors \[9\–11\].

The epidural fat, mostly located in the lateral and posterior parts of the epidural space, cushions the pulsation of the dural sac and facilitates the movement of the periosteum into the spinal canal, during flexion and extension of the spine. Given its lipophilic nature, it behaves as a reservoir of lipid-soluble drugs, resulting in sustained release of the drug and prolonged analgesia \[11\].

In an animal model, Bernards et al. \[12\], explored giving various epidural opioids by bolus (morphine, fentanyl, alfentanil and sufentanil) and also measuring their concentration over the time in the epidural space and fat, intradural space, venous plasma and epidural venous plexus. They demonstrated that the residence time in the epidural space and concentration in the epidural fat were directly correlated to the drug lipidsolubility, both being higher for sufentanil and fentanyl and lower for morphine. Further, as could be expected, the proportion of drug reaching the CSF was higher for morphine than the lipophilic opioids, which were sequestered in the fat, and they found that alfentanil had a higher plasma concentration due to its rapid clearance towards the blood compartment. 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 reach the spinal biophase.

**Meningeal diffusion**

Experimental studies suggest that the primary mechanism by which opioids reach the CSF is simple diffusion through the meninges, aided by kinetic energy from the pulsatile flow of the CSF associated with the movement of the spinal cord. Specifically, it has been observed that diffusion through the arachnoid villi in the roots of the spinal cord \[13\] and the radicular arteries involved in the irrigation of the spinal cord \[14\], 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 to the subarachnoid spaces.

There is a biphasic relationship between drug lipidsolubility and permeability of the arachnoid mater \[15\]. At first, permeability increases with increasing lipid solubility, but only up to moderate values of the octanol/buffer distribution coefficient (about 125). At higher values, permeability significantly decreases with solubility. In line with this, the meningal permeability coefficients of (M) morphine and (S) sufentanil are similar, 0.6 and 0.75 respectively, their octanol/buffer distribution coefficients being very different, (M) 1 and 0.22.
The explanation for this biphasic relationship lies in the fact that the drugs have first to cross the lipid bilayers of the arachnoid mater cells and then, through the fluids of the extra and intracellular spaces. Highly lipophilic drugs complete the first step quickly but the second one with difficulty, while for hydrophilic drugs the opposite is true. Together with the fact that the arachnoid mater is the primary barrier for meningeal permeability (90%), explains why drugs with intermediate values of lipid solubility (lidocaine, alfentanil) achieve better rates of transfer in this type of tissue.

Though the meninges do not play an essential role as a selective physical barrier for the spinal diffusion of opioids, it is nevertheless worth highlighting their important function as a site for the intrathecal clearance of drugs, given the dense network capillaries on the inner surface of the dura mater. This conclusion is based on the results of a couple of experimental studies in animals. Kozody et al. [16], demonstrated that the spinal administration of adrenaline and phenylephrine significantly reduces blood flow to the dura mater without affecting that of the spinal cord. Bernard et al. [17], observed that administering adrenaline together with a hydrophilic epidural morphine reduces plasma clearance of the drug probably due to constriction of blood flow to the dura mater.

**Intradural diffusion**

Without taking into account the baricity and volume of drug given, site of injection or the kinetic energy provided the injection itself, opioids that reach the CSF should behave whether they have been injected directly or moved to the injection itself, opioids that reach the CSF should behave. Drug given, site of injection or the kinetic energy provided

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fentanyl together with the same dose of (M) morphine, in the lowest palpable interspace L5-S1, and samples of CSF, were taken from the highest possible level in the lumbar space L2-L3. Data were analysed up to 120 minutes after injection. It was found that both drugs reached their peak concentration at the cephalic site at similar times (41 ± 13 min for F and 57 ± 12 min for M). Moreover, the concentration ratio of M: F increased from 2.1 after 36 minutes to 4.1 after 103 minutes, and no rate constants correlated with the weight, height or CSF volume. These findings were explained using a simple pharmacokinetic model with relatively high individual variability. The authors concluded [22], that fentanyl is cleared more rapidly than morphine from the CSF, although the distribution in the first hour after administration is similar to the two drugs.

Recently in an experimental study in animals, Bernard et al. [23], found that following continuous infusion of bupivacaine and baclofen, there was poor internal distribution through the CSF, and differences in drug concentrations at posterior and anterior surfaces of the spinal cord, as well as a rostral–caudal gradient. This latter gradient, previously noted for albumin and glucose, is attributable to a small transfer of kinetic energy from systole phase of the cardiac cycle 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 at
the site of injection and higher levels at the posterior than the anterior surface of the spinal cord.

At this point, we could first conclude that main factors that are clinically relevant for analgesia are primary the rate of drug clearance from the CSF and the amount of drug available in the spinal biophase, and secondary the opioid mean elimination half-life. Clearly, drug bioavailability will be higher when it is delivered directly to the posterior horn of the spinal cord intrathecally rather than distributed through blood or the epidural space. We should also ascertain what fraction of the analgesic effect can be attributed to a spinal action and what to a supraspinal action (higher for fentanyl and sufentanil), as well as whether the latter is necessary for the overall effect. It’s has been calculated that less than 5% from epidural morphine, administered as a bolus, can reach medular opioid biophase [9-22].

**Spinal diffusion**

**Experimental animal studies:** Finally, the last step for opioids reaching the spinal cord is to cross the white matter and bind to the specific receptors in the gray matter. Von Cube et al. [24], injected radioactively labelled morphine, dihydromorphine and fentanyl into the CSF in the lateral ventricles of rabbits, and measured the distance reached in the adjacent tissues of the central nervous system over time. They found that all three drugs penetrated 700 μm within the first 7 minutes, but as time passed, fentanyl advanced no further and was cleared from the brain within 120 minutes. In contrast, the distribution of morphine and hydromorphone continued and by the end of the study, that is, after 5 hours, morphine had reached a tissue depth of around 3000 μm. An even more striking observation was that fentanyl had a greater affinity for white matter, compared to the water-soluble drugs, which had more affinity for the gray matter. Recently, this fact was confirmed in an experimental model in pigs [18], with intrathecal administration of morphine, alfentanil, sufentanil, and fentanyl, at equimolar doses, and subsequent measurements of the concentrations of the drugs in the extracellular space of the spinal cord. The exposure to morphine was higher than that of all the lipophilic drugs, morphine having as much as a 3-fold higher concentration and slower clearance, both in the lumbar spine at the level of the injection L2–3 and the thoracic spine T11. The explanation for these observations could be 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. Since gray matter does not contain myelin, it is relatively hydrophilic and therefore has a higher affinity for morphine [9].

Bernards et al. [25], carried out an elegant review of experimental studies in animals measuring the concentrations of opioids in the epidural and intradural spaces, spinal cord and surrounding tissues following spinal administration. He concluded that 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 towards the opioid receptors of the brain.

**Experimental human studies:** Both, heart rate and CSF stroke volume of the patient strongly influence drug distribution after intrathecal administration. Doubling the heart rate, from 60 to 120 bpm, caused a 26.4% decrease in peak concentration in CSF after injection. Increasing twice the CSF stroke volume diminished the peak level after injection by 38.1%. Computations show that potentially toxic peak drug levels due to injection can be avoided by changing the infusion rate. Using slower infusion rates could avoid high peak concentrations in CSF while maintaining drug levels above the therapeutic threshold [26].

In another recent study, the authors acquired anatomical data from magnetic resonance imaging (MRI) and velocity measurements in the spinal cerebrospinal fluid with CINE MRI for two subjects. A bench-top surrogate of the subject-specific central nervous system was constructed to match measured anatomical dimensions and volumes. They generated a computational mesh for the bench-top model. Idealized simulations of tracer distribution were then compared with bench-top measurements for validation. Using reconstructions from MRI data, they also introduced a subject-specific computer model for predicting drug spread for the human volunteer. Very interesting results were found: MRI velocity measurements at three spinal regions of interest reasonably matched the simulated flow fields in a subject-specific computer mesh. Comparison between the idealized spine computations and bench-top tracer distribution experiments demonstrate agreement of the drug transport predictions to this physical model. Simulated multi-bolus drug infusion theoretically localizes drug to the cervical and thoracic region. Continuous drug pump and single bolus injection were advantageous to target the lumbar spine in the simulations. The parenchyma might be targeted suitably by multiple boluses followed by a flush infusion. The authors present potential guidelines that take into account drug specific kinetics for tissue uptake, which influence the speed of drug dispersion in the model and potentially affect tissue targeting [27]. This study also quantifies how reaction kinetics changes the specific location of drug action. Because of differing tissue uptakes of 3 agents (morphine, sufentanil, alfentanil), a higher fraction of sufentanil and morphine remains in the CSF, thus reaching further along the neuroaxis, thereby inducing stronger action in the upper cervical region. In chronic clinical management of cervical pain, these agents could be utilized with more potency, while the preliminary simulation demonstrates that alfentanil could be better suited for low back pain based on our high rate of tissue uptake assumption. However, for a cancer-associated pain, morphine more readily distributes along the spinal axis [27].

From all the aforementioned experimental studies, we can deduce that the bioavailability of the hydrophilic opioids to the spinal opioid receptors, such as morphine, is higher than that of lipophilic opioids, such as fentanyl or sufentanil (Table 1). In fact, the U.S. Food and Drugs Administration (FDA) has so far only approved hydrophilic opioids (morphine, hydromorphone) as first-line drugs for spinal use. Other
opiates are recommended only if these drugs are not well tolerated or effective, though pain physicians used them on an off-label basis for either postoperative or chronic pain, given the multiple studies indicating that these opioids can be useful [28].

Conclusions

As Professor Bernards CM, used to say: "Every opioid injected into the human body from the right ear to the left foot will induce an analgesic effect due to systemic distribution to brain receptors. Therefore, the spinal administration of an opioid does not always guarantee a selective spinal effect".

References
