The Options for Neuraxial Drug Administration

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Abstract

Neuraxial drug administration, i.e., the injection of drugs into the epidural or intrathecal space to produce anesthesia or analgesia, is a technique developed more than 120 years ago. Today, it still is widely used in daily practice in anesthesiology and in acute and chronic pain therapy. A multitude of different drugs have been introduced for neuraxial injection, only a part of which have obtained official approval for that indication. A broad understanding of the pharmacology of those agents is essential to the clinician to utilize them in a safe and efficient manner. In the present narrative review, we summarize current knowledge on neuraxial anatomy relevant to clinical practice, including pediatric anatomy. Then, we delineate the general pharmacology of neuraxial drug administration, with particular attention to specific aspects of epidural and intrathecal pharmacokinetics and pharmacodynamics. Furthermore, we describe the most common clinical indications for neuraxial drug administration, including the perioperative setting, obstetrics, and chronic pain. Then, we discuss possible neurotoxic effects of neuraxial drugs, and moreover, we detail the specific properties of the most commonly used neuraxial drugs that are relevant to clinicians who employ epidural or intrathecal drug administration, in order to ensure adequate treatment and patient safety in these techniques. Finally, we give a brief overview on new developments in neuraxial drug therapy.

1 Introduction

Administration of drugs via the epidural or intrathecal route, both of which together are referred to as neuraxial anesthesia, is a technique that is predominantly used by anesthesiologists and pain specialists. Today, more than 120 years after the first spinal anesthesia, performed by August Bier using cocaine [1], neuraxial techniques are an integral part of modern anesthesia concepts.

In the vast majority of cases, local anesthetics are administered to achieve anesthesia or analgesia in a wide variety of settings, comprising surgery, labor pain, acute and chronic pain management, or spasticity [2]. In addition to opioids, which are commonly added to neuraxially administered local anesthetics, or more uncommonly used as the sole neuraxial drug, a large number of other pharmacologic agents have been used. Most of these as adjuvants, such as clonidine, dexmedetomidine, ketamine, or dexamethasone [3]; others as the sole drug, such as ziconotide or baclofen. Based on the proximity to the spinal cord, neurotoxicity limits the use of some agents for intrathecal administration (e.g., ketamine) whereas for others, fast epidural resorption does not outweigh the benefits compared to a direct systemic application. Furthermore, it is important to realize that many of...
those drugs have not been approved for neuraxial use, and are hence used off-label, even when clinically established.

The application of medication via the neuraxial route has unique pharmacokinetic and pharmacodynamic characteristics. These are affected by the anatomy of the respective compartments, bypassing the first-pass metabolism and the vicinity of the primary effector sites, next to the general physicochemical properties of the respective drugs.

A profound knowledge on factors that affect the clinical effects of neuraxially injected agents is essential to anesthesiologists or pain specialists to secure efficient and safe use of this technique. In this article, we focus first on the anatomical and pharmacological aspects of neuraxial drug administration, clinical indications, as well as their potential neurotoxicity, and then provide a concise overview on the drugs that are clinically used on a regular basis.

2 Anatomy Relevant to Neuraxial Drug Administration

The epidural space reaches from the skull base to the sacral hiatus and consists predominantly of adipose tissue and abundant vessels, mostly veins. It encircles the spinal canal containing the dural sac and the spinal cord. Each intervertebral foramen connects the epidural with the paravertebral space without any barrier. Even within the intervertebral foramen, the epidural space is perforated by a spinal nerve and its duplicated dura sheath. Furthermore, the epidural space is in connection with the paravertebral space and attached anatomical structures. Thus, the epidural space is neither an anatomical distinct compartment nor a homogenous compartment. The posterior epidural space is traversed by thin fibrous dorsal meningo-vertebral ligaments connecting the dorsal dura to the lamina and ligamenta flava [6]. A dorsal midline structure called plica mediana dorsalis from the dorsal end of the dura to the laminae may compartmentalize the right and left posterior epidural spaces. Although these ligaments should not hinder epidural spread, they can influence catheter advancement and may facilitate catheter migration through the intervertebral foramen [4]. Vice versa, paravertebral catheters can migrate into the epidural space and local anesthetics, if injected with high pressure around the lumbar plexus, can spread into the epidural space [5]. Although this anatomical structure can frequently be seen during epiduroscopy, it rarely completely compartmentalizes the epidural space [6, 7]. To what extent the plica mediana dorsalis is responsible for unilateral and asymmetric epidural spread is unknown. Furthermore, high-definition 7T three-dimensional magnetic resonance imaging reconstruction has recently visualized another hitherto unknown compartmentalization of the epidural space and has been confirmed in cadavers [8]. While the vertebral laminae are closely attached to the dural sac by fibrous tissues, pyramidal-shaped fat pads are found between the laminae under the ligamenta flava. Those fat pads could further explain the inhomogeneous spread of a local anesthetic and the deviation of epidural catheters.

Finally, a significant percentage of patients have ligament flava with a midline gap, as has been demonstrated in three-dimensional magnetic resonance imaging as well as anatomical dissections [9, 10]. These gaps are about 1 mm wide in the midline at the upper border of the lamina and can extend to the lower border of the next lamina. Most frequently, those gaps are seen from C3/4 to T2/3 (60–75%), while between T10/11 and L1/2 they occur in a frequency of 28–35% and are infrequent at lower lumbar levels (0–11%) [9–11]. Thus, these midline gaps connect the epidural space with the retrolaminar compartment and may be responsible for some leakage of local anesthetics. More importantly, these midline gaps may interfere with the “Loss of resistance” that is used by the anesthesiologist to identify the epidural space, facilitating the inadvertent dural tap.

This challenging anatomical composition of the epidural space is properly illustrated by Arendt and Segal “For those who have studied the epidural space, it may seem amazing that epidurals ever work.” [12]. Considering these anatomical features, it is not astonishing that epidural spread and intensity vary considerably. Therefore, the success percentage of epidural anesthesia varies between 53 and 87% [13]. Nevertheless, with catheter retraction or new placement the success percentage can be increased to almost 100% [14]. This contradiction of the primary success rate and success rate after top-ups, partial catheter retraction, and a newly placed epidural may be explained by the great variability of the epidural space. It is difficult to place a catheter at the right place, but with replacement of a catheter, retraction of the catheter tip, or added volume a sufficient spread of local anesthetics can be achieved in a very high percentage of cases.

2.1 Pediatric Anatomy

Classically, it was hawked that in babies and neonates the conus medullaris ends at the third lumbar vertebra (L3) or lower in contrast to L1/2 in adults. Furthermore, the dural sac was supposed to ascend from S3–4 in infants to L1–2 in toddlers. More recent ultrasound studies, however, illustrated that even in neonates the median termination of the spinal cord is located at L2 and that a spinal cord descending to mid-L3 or lower is suspicious for a tethered cord [15, 16]. Similarly, the dural sac in infants rarely reaches to a level below S2 [17]. These differences are partially explained by
is much higher in neonates. Spinal anesthesia from about 3 hours in adults to approximately 1 hour in neonates, although the dose per kilogram is much faster reducing the duration of action of a single-shot spinal anesthesia from Table 1 [19]. Furthermore, the resorption of local anesthetics from liquor into the systemic circulation in infants is higher than in children or adults. Therefore, the weight-adapted dose is relatively lower for small infants compared with older children or adults. Moreover, small infants have a higher liquor volume compared with older children and adults. Thus, in the same position where the neuraxial blockade is performed. Therefore, the ultrasound investigations are a better representation of the anatomy as it is approached by the anesthesiologist.

Spinal anesthesia is frequently performed in young infants for a variety of reasons: improved hemodynamic stability, less early postoperative apnea, and possibly reduced neurotoxicity of general anesthetics. However, small infants have a relatively higher liquor volume compared with older children or adults. Therefore, the weight-adapted dose is relatively higher in small infants compared with older children (Table 1 [19]). Furthermore, the resorption of local anesthetics from liquor into the systemic circulation in infants is much faster reducing the duration of action of a single-shot spinal anesthesia from about 3 hours in adults to approximately 1 hour in neonates, although the dose per kilogram is much higher in neonates.

### 3 Pharmacology of Neuraxial Drugs

When drugs are administered neuraxially, it is of crucial importance to understand the pharmacokinetics and pharmacodynamics of the agents employed in order to ensure adequate anesthesia/analgesia as well as safety. In general, neuraxially administered drugs need to reach their primary site of action to work. Absorption to the main target site (i.e., the spinal cord and intrathecal dorsal nerve root [20]) as well as local and systemic (re-)distribution determine the onset and duration of action of epidural and intrathecal drugs. First, the general pharmacological properties and mechanisms of action of the respective drugs apply.

| Weight (kg) | Bupivacaine dose (mg/kg) |
|------------|--------------------------|
| < 5\(^a\)  | 1                        |
| 5–15       | 0.4                      |
| > 15       | 0.3                      |

\(^a\)Also for neonates and premature newborns

### 3.1 General Pharmacological Aspects of Neuraxial Drug Administration

For local anesthetics, the most relevant properties are the ionization constant (pKa value), lipophilicity, and the degree of protein binding. While the potency of a local anesthetic is related to its lipid solubility (those with higher lipid solubility more easily permeate neuronal membranes), the speed of onset predominantly depends on the pKa (a lower pKa would effectuate a higher speed of onset), and the duration of action is significantly influenced by the degree of protein binding (increased protein binding is associated with a longer duration of action) [21].

The primary mechanism of action of local anesthetics is the blockade of voltage-gated sodium channels [22]. However, a plethora of different ion channels, receptors, and other molecular targets have been shown to be additional targets of local anesthetics, as shown predominantly from experimental studies on lidocaine [23].

Neuraxial administration of local anesthetics frequently causes hypotension, both with and without adjuvants, and is related to height of the block [24–26]. Lower doses of local anesthetics and the addition of synergistic low doses of opioids significantly reduce the risk of hypotension in both epidural and spinal anesthesia [25, 27].

Systemic absorption of local anesthetics may, in large doses, have deleterious effects [28]. Toxic symptoms, mainly neurological and cardiovascular, following an epidural injection are rare [29], but may occur through rapid systemic absorption or an accidental intravascular injection of a local anesthetic [28, 29]. Important in the management of local anesthetic toxicity are the discontinuation of administration of local anesthetics and supportive care. In cases of severe local anesthetic toxicity, the use of intravenous lipid emulsions is recommended [30].

Concerning opioids, lipid solubility is the essential determining factor for pharmacological effects after neuraxial application. Hydrophilic opioids such as morphine have a slower onset and a longer duration of action, while lipophilic opioids such as fentanyl produce a rapid onset and shorter duration of action. Neuraxial lipophilic opioids have a more rapid distribution and clearance from the spinal cord and epidural space than hydrophilic opioids, resulting in a lower rate of (delayed) respiratory depression and sedation [31, 32].

The mechanism of action of neuraxial opioids, mediated largely by μ-opioid receptors, is an interplay of local effects within the spinal cord, supraspinal effects due to rostral spread especially for hydrophilic opioids, and systemic effects after absorption of the opioid, primarily from the vasculature in epidural fat tissue. The significance of cerebral or systemic effects is variable as is the extent of segmental
or spinal cord action, and hinge particularly on the physicochemical properties of the respective opioid [33, 34]. Neuraxial administration of opioids causes similar side effects as systemic administration, including sedation, nausea, pruritus, and (delayed) respiratory depression [35]. As with systemic administration, administering neuraxial hydrophilic opioids (e.g., morphine) provides long-lasting analgesia, which is enhanced when given together with a local anesthetic [20]. Neuraxial administration of hydrophilic opioids, which have higher bioavailability and spinal cord selectivity [36], can cause delayed respiratory depression up to 24 hours after intrathecal or epidural administration [37]. It is not yet entirely clear whether this is due to active metabolites (e.g., morphine-6-glucuronide, the active metabolite of morphine, has very strong analgesic properties) or to the rostral migration of the hydrophilic opioid via the cerebrospinal fluid to the brainstem [31].

The incidence of delayed respiratory depression caused by neuraxial hydrophilic opioids seems to be similar to systemic administration [37, 38]. However, it is important to consider the heterogeneity in the reporting studies, both in terms of study populations, dosages administered, and definitions used for delayed respiratory depression [37, 38]. Alongside general pharmacological and drug-specific properties, owing to distinct anatomy, pharmacokinetic mechanisms differ between epidural and spinal routes of administration and account for relevant differences in clinical effects between these two techniques.

3.2 Pharmacological Aspects Specific to Epidural Drug Administration

Redistribution from the epidural space through the meninges into the cerebrospinal fluid (CSF) is the major mechanism for epidural drugs to reach the primary target site [39]. Diffusion among the arachnoid mater depends on the concentration gradient, volume (effectuating surface area), lipid solubility, and protein binding of the respective drug. The predominant factor determining CSF bioavailability of epidural drugs is their lipid solubility [40]. Here, hydrophilic drugs such as morphine reach higher spinal bioavailability, while lipophilic drugs such as fentanyl and sufentanil are easily sequestrated to epidural adipose tissue. The overall spinal bioavailability of epidurally administered drugs is low, with a range between approximately 5% and 20% [36, 41–44]. Lipophilic drugs are also readily cleared into the plasma and can hence produce undesired central nervous system side effects. In turn, this clearance rate is dependent on vascularization and local blood flow in the capillary network of the dura mater, which can be lowered by the addition of vasoconstrictors such as epinephrine.

### 3.3 Pharmacological Aspects Specific to Intrathecal Drug Administration

In contrast to epidural drug administration, the rate of diffusion into target tissue after spinal injection is rapid, owing to a high CSF concentration and a short diffusion distance of only a few millimeters [39]. This is reflected by a much smaller dose required to reach similar effects, when compared with an epidural injection. In turn, this accounts for the lower risk of systemic toxicity of the respective drug. Furthermore, the onset of effect is significantly faster than with the epidural route.

In general, and similar to the epidural space, lipophilicity of drugs is the major determinant of intrathecal pharmacokinetics. Further relevant factors affecting CSF distribution are drug volume, baricity, CSF flow rate, and intrathecal residence time [45]. Factors that affect the intrathecal spread of local anesthetics are manifold, as shown in Table 2.

When a drug is injected into the intrathecal space, systemic absorption is considerably slower than after epidural injection, given the latter is significantly more vascularized, permitting rapid uptake. Hence, given there is likewise no relevant local drug metabolism, pharmacological agents that would systemically be rapidly metabolized or distributed, especially hydrophilic drugs can display persisting effects. These factors also explain why, for example, intrathecal morphine can cause delayed respiratory depression due to rostral spread within the subarachnoid space.

### 4 Clinical Use of Neuraxial Drug Administration

#### 4.1 Perioperative

In the perioperative setting, different methods of neuraxial drug administration can be distinguished: intrathecal drugs, i.e., spinal anesthesia, the administration of epidural drugs, and a combination of these two techniques, i.e., combined-spinal epidural (CSE) procedures. Typical indications for spinal anesthesia include surgical procedures involving the lower abdomen (including cesarean section), pelvis, and lower extremities [46]. In addition to these classic indications,
other options for spinal anesthesia are under investigation, for
instance, the use of spinal anesthesia for laparoscopic proce-
dures of the upper abdomen such as laparoscopic cholecys-
tectomy [47] or peritoneal inguinal mesh repairs [48] and for
spinal surgeries such as single-level discectomy [49]. In car-
diact surgery, the use of a high spinal anesthetic technique in
addition to general anesthesia has been reported [50]. Goals
of spinal anesthesia for these ‘newer’ indications comprise
possible lower stress responses with a reduction in inflam-
atory mediators [50], cost effectiveness, less post-operative
nausea and vomiting, better post-operative analgesia, quicker
recovery, and possibly earlier extubation after cardiac sur-
gery compared with general anesthesia only [51]. However,
these advantages are questionable, as negative side effects
and complications are reported such as hypotension, urinary
retention, post-dural puncture headache, shoulder pain during
laparoscopic interventions in awake patients, and the need for
conversion to general anesthesia [52]. In conclusion, spinal
anesthesia is indicated for surgical procedures involving the
lower abdomen, pelvis, and lower extremities and may be an
option for other procedures in selected patients with signifi-
cant risks associated with general anesthesia [52] provided
that the surgical procedure and anticipated duration of the
procedure are appropriate.

Epidural analgesia is regularly used to provide pain relief
for major open abdominal surgeries and thoracotomies [53,
54]. For pain management after major open abdominal sur-
geries, the use of epidural analgesia has been reported to
be superior in terms of decreased pain scores compared with
continuous wound infiltration and patient-controlled
analgesia with intravenous opioids [55, 56]. However, the
historically reported beneficial effects of epidural analgesia
on morbidity, mortality, complication rates, return of bowel
functioning, and reduced length of hospital stay have been
questioned, whereby even higher complication rates (hypo-
tension with consecutive fluid overload, urinary retention)
and an increased length of hospital stay have been reported
[56]. Other factors such as the avoidance of fluid overload,
bowel stimulation, and postoperative rehabilitation programs
have led to reduced complications rates also in patients
treated with alternatives for epidural analgesia. [55]

Furthermore, with the implementation of minimally inva-
sive surgical methods and an increasing awareness for the
more frequently than expected occurring (1:1000-1: 6000
cases) serious complications of epidural analgesia, the over-
all trend seems to move away from neuraxial blocks in favor
of truncal blocks, peripheral nerve blocks, and local anes-
thetic wound infiltration where possible [54]. In addition,
use of epidural anesthesia and peripheral nerve blocks seems
to vary in different hospital types and locations. A study
evaluating the use of neuraxial anesthesia versus peripheral
nerve blocks for total hip and knee arthroplasties from 2006
to 2013 showed a decreasing trend for the use of neuraxial
anesthesia in most hospitals toward the end of the study
period (2012–2013). However, the contrary applied to rural
hospitals, where neuraxial anesthesia was in fact increasing.
For peripheral nerve blocks, an increasing trend was seen,
with a significantly higher use in total knee arthroplasty
compared with total hip arthroplasty, and a strong increase
was observed in large teaching hospitals [57].

In cytoreductive surgery and cancer-related abdominal
debulking procedures, epidural analgesia remains the gold
standard, based on the available literature [54, 58]. However,
the coagulation status and occurrence of thrombocytopenia
can be a limiting factor in widespread use of this modality
in these patients [58].

In conclusion, alternative analgesic techniques, including
(among others) continuous wound infiltration and truncal
and paravertebral blocks, are increasingly used in surgical
procedures with a historical preference for the use of epi-
dural analgesia [56]. Epidural analgesia is no longer a routine
choice in enhanced recovery protocols for open intestinal,
colon, colorectal, or aortic surgery [55]. Alternative analgesic
techniques can be considered; however, some benefits (e.g.,
statistically significant superior pain relief and improved
patient satisfaction) of epidural analgesia provided to patients
undergoing major open surgical procedures have been proven
[53]. We underscore an individualized perioperative analge-
sic approach depending on patient and surgical characteris-
tics, as the severity of postoperative pain varies for minimally
invasive surgery to major open procedures [58].

4.2 Obstetrics

Epidural analgesia is the gold standard for analgesia in the
obstetric setting as efficacy is proven and complications
and permanent neurological damage are rare in young and
healthy women [56]. In addition to epidural analgesia, other
neuraxial techniques can be distinguished, such as single-
shot spinal anesthesia and CSE or a dural puncture epidural
(DPE) technique.

For labor analgesia, CSE has the fastest onset time of
analgesia. Combined-spinal epidural procedures during a
cesarean section may offer the advantage of an intraoperative
addition of epidural drugs in the case of prolonged surgery
or an inadequate surgical block from the intrathecal anesthetic,
next to the possibility of postoperative administration of neu-
raxial opioids and local anesthetics. However, after CSE, a
higher incidence of urinary retention, nausea and vomiting,
pruritus, and maternal hypotension compared with traditional
epidural analgesia was reported [59, 60]. Combined-spinal
epidural procedures might be an option in selected patients
with a higher likelihood of neuraxial block failure [60]. The
DPE technique is a modification of conventional epidural or
CSE techniques that involves the intentional puncture of the
dura with a spinal needle, without the intrathecal injection of
drugs, next to the placement of an epidural catheter into the epidural space. The drugs administered through the epidural catheter in the epidural space may enter the subarachnoid space by the previous punctured dura. With this theory, it is believed that the DPE technique combines the advantages of both CSE and epidural analgesia while mitigating the disadvantages [61]. However, there is a lack of clear evidence on the benefits and risks of the DPE technique, such that a recommendation for or against its routine use is premature [62].

Regarding the dosage of neuraxial drugs during labor, low-concentration local anesthetic solutions (bupivacaine less than 0.1% or equivalent) are preferred for the initiation and maintenance of labor epidural analgesia, as the quality of analgesia does not seem to be compromised, but lower rates of instrumental vaginal delivery and a shorter duration of second-stage labor were reported for women who received epidural analgesia with a low concentration of local anesthetics [63]. Overall, the use of neuraxial anesthesia for obstetric indications is widely implemented and provides excellent analgesia with minimal risks.

### 4.3 Chronic Malignant and Non-malignant Pain

Neuraxial techniques may be suitable for treating chronic pain refractory to standard treatments and include epidural or intrathecal drug-delivery systems [56]. The incidence of cancer-related pain is 39% after curative treatment and 55% during anticancer treatment, such as chemotherapy, radiation therapy, and surgery. The incidence of cancer-related pain in advanced, metastatic, or terminal disease is in the order of 66% [58]. Epidural and intrathecal analgesia is reported to be effective with decreased pain intensity [64]. Regarding neuraxial techniques in patients with cancer, there can be specific anatomical considerations to take into account. Vertebral metastases, spinal stenosis, loss of epidural fat in cachexia, and epidural invasion by tumors may complicate administration of neuraxial applied drugs and drug distribution [65]. Non-malignant pain conditions that may benefit from neuraxial drug-delivery systems comprise (among others) failed back surgery syndrome, lumbar post-laminectomy syndrome, complex regional pain syndrome and causalgia (complex regional pain syndrome type 2), phantom limb pain, and plexopathy [66].

To date, the US Food and Drug Administration and European Medicines Agency approve only ziconotide (a neuronal calcium channel blocker) and morphine for an intrathecal infusion for pain management. However, off-label drugs such as hydromorphone, fentanyl, sufentanil, bupivacaine, and clonidine are used in clinical practice, as monotherapies or combined agents [67]. The use of neuraxial techniques in patients with chronic pain, both patients with malignant and non-malignant pain, is often based on expert opinion. It can be considered for patients refractory to conventional pain treatments. Concerns for the use of neuraxial implantable devices in patients with chronic pain for the long-term administration of neuraxial drugs comprise infectious complications, risks of respiratory depression, withdrawal with drug discontinuation or pump malfunction, and the development of tolerance. Careful patient selection and management is important [68]. In a retrospective study evaluating a total of 1001 reports from a database of patients treated with intrathecal drug delivery systems from 2018 to 2019, the top three reasons for adverse reports are infection/erosion (15.7%, \( n = 157 \)), motor stall (12.4%, \( n = 125 \)), and adverse medication reactions (11.8%, \( n = 119 \)). Five deaths were reported in the study period due to bacterial meningitis, spinal epidural hematoma, sepsis after device implant, and two cases of possible opioid overdose. Epidural hematoma (\( n = 3 \)) after intrathecal drug delivery system surgery resulted in death, cauda equina syndrome 36 hours after intrathecal drug delivery system implantation, lower extremity sensory deficits, and residual neurological deficits after surgical evacuation. Granuloma, an intrathecal inflammatory mass, was reported in 19 (1.9%) cases within this analysis. The presentation ranged from an asymptomatic incidental diagnosis on magnetic resonance imaging to new back pain, lack of efficacy, reservoir volume discrepancy, worsening leg weakness, and paralysis-like symptoms. Patients were treated with a device explant (\( n = 6 \)), catheter repositioning (\( n = 3 \)), catheter replacement (\( n = 2 \)), unclear surgical intervention (\( n = 2 \)), termination of neuraxial applied drug [device filled with saline] (\( n = 1 \)), and conservative treatment comprising follow-up imaging (\( n = 1 \)). Neuraxial drug delivery systems may be considered, but possible complications are not negligible. Alternatives for epidural or intrathecal analgesia are sympathetic neurolysis, spinal neurolysis, nerve blocks, or plexus blocks depending on the location of the disease.

### 5 Neurotoxicity

All local anesthetics are locally neurotoxic depending on their concentration and duration of action. Although clinically neurotoxicity very rarely leads to permanent neural damage, such damage can be devastating. In the 1990s, the introduction of intrathecal microcatheters led to a number of cauda equina syndromes. This led to a large number of experimental studies assessing the mechanism of local anesthetic-induced neurotoxicity. The mechanism identified was mainly apoptosis and in higher concentrations necrosis [69, 70]. In most models, the concentrations inducing apoptosis (or necrosis) are frequently an order of magnitude lower than the concentrations clinically applied epidurally or intrathecally. However, while the concentrations in most models are...
kept constant for hours or longer, in the clinical situation, the applied concentration of local anesthetic dilutes within minutes by orders of magnitude. The question of whether one local anesthetic is more or less toxic than another is not answered unequivocally. Most studies find a correlation between potency and neurotoxicity, i.e., equipotent local anesthetic doses induce equitoxic effects [71, 72]. The most prominent apoptotic pathways identified inducing apoptosis are the intrinsic (or mitochondrial) caspase pathway of apoptosis, the PI3K pathway, and the MAPK pathway [69].

Lidocaine (and other local anesthetics) when given intrathecally can lead to transient neurologic symptoms (TNS). The exact mechanism of TNS is hitherto unknown. Nevertheless, there are factors influencing the incidence of TNS. Ropivacaine (levo-) bupivacaine, prilocaine, and procaine have an approximately ten times lower risk than lidocaine of inducing TNS after spinal anesthesia, while mepivacaine and 2-chloroprocaine have similar TNS percentages to lidocaine [73]. Furthermore, the patient position influences the incidence of TNS after spinal anesthesia with lidocaine. While the lithotomy position has an incidence of TNS of about 30–36%, in the position for knee arthroscopy it is about 18–22% and in the supine position only 4–8% [74].

As there are many adjuvants used in clinical practice mixed with local anesthetics to enhance their effect and possibly reduce their dose and concentration, this may be a proper method to further reduce the risk of local anesthetic-induced neurotoxicity. However, a prerequisite would be that those adjuvants are at least not neurotoxic or even neuroprotective. In turn, there is hardly any evidence for clinically relevant neurotoxic effects of neuraxial adjuvants. The frequently used adjuvants have been applied in hundreds or thousands of patients without reports of an increased rate of neurological damage. The only exception is epidural corticosteroids, which led to very infrequent but severe neurological damage that led to a Food and Drug Administration warning in 2014.

Experimentally, opioids have the best record of not being neurotoxic themselves nor enhancing local anesthetic-induced neurotoxicity [75]. In contrast, midazolam, (es) ketamine, corticosteroids epidurally, and recently, dexmedetomidine have been demonstrated to induce neurotoxicity at least in some experimental models [76–86]. As many of the adjuvants described exhibit equally or at least partially analgesia-enhancing and block-enhancing effects when given systemically, the systemic application may be considered instead of the epidural application.

In conclusion, opioids applied epidurally or intrathecally can be considered safe. As neurotoxic effects cannot be excluded for most other adjuvants and the mechanism of action seems to be predominantly due to systemic absorption, we do not believe in the superiority of neuraxial administration.

6 Neuraxial Drugs in Clinical Use

A multitude of drugs have been applied via the epidural or intrathecal route since the introduction of these techniques into the clinic. However, only a few agents have gained approval for this indication (see Table 3). As follows, we detail the most relevant drugs used clinically.

6.1 Local Anesthetics

The use of neuraxial techniques for anesthesia and analgesia typically involves the use of local anesthetics, which may or may not be supplemented by adjuvants. Here, we give a brief overview on the clinically most relevant local anesthetics.

6.1.1 Lidocaine

Lidocaine is a hydrophilic local anesthetic of the amide type and a class Ib anti-arrhythmic agent, with a pKa of 7.8. Because of its anti-arrhythmic properties, lidocaine is also used in the treatment of ventricular arrhythmias [87]. In cardiac muscle fibers, lidocaine inhibits the large transient increase in membrane permeability to sodium during the plateau phase of the action potential. It also increases potassium efflux during the repolarization phase. Excitation conduction in the sinus node and supraventricular areas remains virtually unaffected. Lidocaine slows excitation conduction and produces negative inotropy, negative chronotropy, and hypotension [88].

Lidocaine is mainly used as an intrathecal local anesthetic in ambulatory surgery. The duration of action of lidocaine is relatively short and thus it is not suitable for use in lengthy procedures. It is safe to use as an intravenous analgesic given its favorable properties concerning cardiotoxicity and has the largest therapeutic window among local anesthetics [89–91].

Transient neurologic symptoms in the postoperative period occur more frequently when intrathecal lidocaine is used, compared with bupivacaine, levobupivacaine, or ropivacaine, a notion also confirmed in a recent Cochrane review of 24 trials [73]. Symptoms include non-permanent hypotension, negative inotropy, negative chronotropy, and hypotension [88].

Bupivacaine is a long-acting local anesthetic of the amide type, with a pKa of 8.1. Bupivacaine is completely and biphazically absorbed from the epidural space. Slow absorption is the rate-determining factor in the elimination of bupivacaine. It has a plasma binding of 96%. Clearing of bupivacaine occurs primarily through metabolism in the liver, and it is more sensitive to changes in intrinsic hepatic enzyme function than of blood flow in the liver [92, 93].

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After administration, the effect occurs slowly (after more than 10 minutes) and persists for 3–3.5 hours [93]. In low doses, the sensory blockade is more pronounced than the motor blockade. Intrathecal bupivacaine is also available in a hyperbaric and hypobaric solution, which increases the steerability of nerve blocks. Hyperbaric bupivacaine is produced by the addition of glucose to isobaric (plain) bupivacaine, while dilution with distilled water renders bupivacaine hypobaric. The difference in density affects diffusion patterns and distribution after injection into the intrathecal space.

Bupivacaine has strong cardiotoxic properties (e.g., cardiac arrhythmias, myocardial depression) due to slow dissociation from the sodium ion channel [91]. This makes the drug unsuitable for intravenous analgesia.

### 6.1.3 Levobupivacaine

Levobupivacaine is a long-acting amide-type local anesthetic used in both intrathecal and epidural anesthesia and analgesia with a pKa of 8.1 and is the left-handed enantiomer of bupivacaine with a plasma binding of > 97%. Similar to bupivacaine, it blocks nerve conduction in sensory and motor nerves largely by interacting with voltage-gated sodium channels on the cell membrane, but potassium and calcium channels are also blocked [94, 95]. In addition, levobupivacaine affects stimulus transmission.
and conduction in other tissues, with its effects on the cardiovascular system and central nervous system being of great importance to the occurrence of clinical adverse events [94, 95]. Levobupivacaine has similar anesthetic and analgesic effects to bupivacaine [96]. Additionally, the metabolism of levobupivacaine and bupivacaine is similar, with levobupivacaine being extensively metabolized and no unchanged levobupivacaine being found in the urine or feces [94, 95].

After neuraxial administration, there are some studies that showed that plasma concentrations of levobupivacaine were higher than those of bupivacaine [97, 98], although this was not found in other studies [99]. There may be a smaller risk of central nervous system toxicity in levobupivacaine compared with bupivacaine [100, 101]. Furthermore, levobupivacaine may provide a longer motor block than bupivacaine, but the block is not as pronounced [97]. Levobupivacaine has less cardiotoxic properties than bupivacaine, possibly owing to a lower affinity for cardiac sodium channels, although other cardiotoxic pathophysiology also seems to be involved [100–102]. The doses at which clinically relevant differences in cardiotoxicity occurred between bupivacaine and levobupivacaine were high enough for central nervous system symptoms to occur [100, 101].

6.1.4 Ropivacaine

Ropivacaine is a long-acting local anesthetic of the amide type that has a pKa of 8.1. It has a chiral center and is available as a pure S-enantiomer. It is less lipid soluble (94%) than (levo-)bupivacaine. All metabolites have a local anesthetic effect, but significantly lower efficacy and a shorter duration of action than ropivacaine [103, 104]. As with bupivacaine, slow absorption is the rate-determining factor for the elimination of ropivacaine. Because ropivacaine has a low-to-moderate intermediate hepatic extraction rate, the elimination rate depends on the free unbound plasma concentration [103, 104].

When ropivacaine was initially marketed it was reported to have better differentiation in terms of sensory/motor blockade than the other local anesthetics; however, several conflicting results have since been reported [105]. Ropivacaine is thought to be safer in regard to toxicity than racemic bupivacaine. When ropivacaine was administered systemically to healthy volunteers, the tolerated maximum dose before cardiovascular or neurological effects occurred was about twice as high as when racemic bupivacaine was used [106, 107]. However, ropivacaine is about 30–50% less potent than racemic bupivacaine and levobupivacaine [108, 109] and it is also approximately two and a half times less lipophilic [110]. Moreover, taking into account some cases of serious complications that have occurred with an accidental intrathecal or intravenous injection of ropivacaine [111, 112], it remains uncertain whether ropivacaine actually has an increased safety profile at equipotent doses and an associated clinically relevant lower cardiotoxicity compared to other local anesthetics.

6.2 Opioids

In most cases, neuraxial opiates are given as adjuvants to long-acting local anesthetics [32, 113]. This provides, among other things, a longer analgesic effect and a reduction in the required local anesthetic dose, therefore reducing the risk of adverse effects. Usually, a lipophilic (e.g., fentanyl, sufentanil) opioid is chosen to prevent any late respiratory depression, although intrathecal morphine is frequently added for post-cesarean section pain relief, owing to its prolonged postoperative analgesic effects [114].

Opioids are, at times, used as the primary neuraxial drug, mainly in cases of severe chronic (palliative) pain where patients have received a spinal catheter for this specific indication [115–117]. We summarize next the clinically most used opioids for neuraxial administration.

6.2.1 Morphine

Neuraxial morphine has a long duration of action with good analgesia because of its hydrophilicity, making it a suitable opioid for single-bolus epidural but mainly spinal administration. However, the duration of action is directly dependent on the dosage chosen, with higher doses dramatically increasing the risk of adverse events [118]. Furthermore, morphine is also administered by continuous infusion through a spinal catheter in patients with severe chronic pain and palliative patients [115, 116].

To ensure adequate long-term analgesia (up to 48 hours), an extended-release epidural morphine containing multivesicular liposomes, giving it a depot function, was marketed to be administered without a local anesthetic. However, a large number of adverse events were observed with the initial dosing recommendations [119–124], which led to the dosing recommendation being adjusted downwards (i.e., ≤ 15 mg). This reduced the side effects but also shortened the duration of analgesia [125].

6.2.2 Hydromorphone

The potent hydrophilic opioid hydromorphone is used both epidurally [126] and intrathecally [117]. The analgesic effect of hydromorphone appears similar to that of other opioids when administered neuraxially [127–129], but its onset is
relatively slow. Less delayed respiratory depression than with morphine is reported for hydromorphone, although respiratory depression has been reported up to 4.5 hours after epidural administration [130]. These characteristics made hydromorphone a less favorable opioid for epidural administration compared with for example, fentanyl and sufentanil [36, 131]. Like morphine, intrathecal hydromorphone is used in severe chronic and cancer-related pain [117, 132].

6.2.3 Diamorphine

Diamorphine is a highly lipophilic prodrug with a rapid onset of action. Diamorphine is used both intrathecally [133] and epidurally [134] and appears to have a better risk profile than morphine with less risk of (late) respiratory depression [135]. Although some have suggested that this may be more related to the more variable doses of diamorphine and the fact that there are significantly more studies of neuraxial morphine compared with diamorphine, which could give a biased picture [118]. Additionally, diamorphine is characterized by a longer duration of action than the most commonly used other lipophilic opioids [136]. This is possibly related to diamorphine being metabolized in the spinal cord tissue to active metabolites, which are less lipid soluble than diamorphine and thus less likely to diffuse back into the CSF [137]. Neuraxial diamorphine is only available in the UK.

6.2.4 Fentanyl

Fentanyl is a lipophilic opioid with a rapid onset of action. As with most other lipophilic opioids, it is rapidly distributed to the spinal cord and epidural space and cleared quickly. Therefore, compared with hydrophilic opioids such as morphine, the risk of delayed respiratory depression with neuraxial administration is reduced [31]. The same applies to other side effects such as the risk of sedation [32]. Like most epidural adjuvants, fentanyl has a supra-additive local anesthetic-sparing effect [138]. However, epidurally administered fentanyl is supposed to have a primarily systemic, rather than neuraxial, effect [139].

6.2.5 Sufentanil

Sufentanil, like fentanyl, is a lipophilic opioid with a rapid onset of action. Distribution to, and clearance from, the spinal cord and epidural space is similar to fentanyl, resulting in fewer side effects than hydrophilic opioids [140]. Sufentanil has a local anesthetic-sparing effect, lacking an additional effect when administered epidurally compared with systemically [141, 142]. Sufentanil is highly potent, with respiratory depression occurring even at relatively low intrathecal doses [143].

6.3 Alpha-Adrenergic Receptor Agonists

Alpha-adrenergic receptor agonists are added to neuraxial drugs for several reasons: reducing local anesthetic clearance and distribution from the epidural and spinal space, an intrinsic analgesic effect, and a local anesthetic-sparing property [144, 145]. Through the local anesthetic-sparing effect, complications and side effects associated with the use of epidural local anesthetics and/or opioids can potentially be reduced.

Concerning the side effects of those agents, dexmedetomidine and clonidine can cause sedation, hypotension, and bradycardia, among other things, with the extent of the side effects being dose dependent [146]. When clonidine is administered at the thoracic level (compared with the lumbar level), as with morphine, the systemic side effects increase, possibly reflecting rostral spread [42]. Dexmedetomidine has a high incidence of sedation [147] and bradycardia [148]. It is therefore important to make a clear risk-benefit assessment before administering any of these drugs neuraxially.

6.3.1 Clonidine

Clonidine has supposedly a predominantly spinal site of action, suggesting that clonidine may be better administered neuraxially than systemically for its analgesic effect [144, 149]. It exerts its direct analgesic effect by binding to α2-adrenoceptors in the spinal cord, leading to a presynaptic inhibition of Aδ and C-fiber transmitter release. Clinically, however, it is still a matter of discussion whether systemic clonidine is analgesic [150]. Because it is a highly lipophilic substance, there is also systemic absorption, with redistribution to more peripheral sites of action [151]. Neuraxial administration of clonidine has a dose-sparing effect on local anesthetics and local anesthetics combined with an opioid [152–154], which could reduce the incidence of adverse events. Interestingly, orally and intravenously administered clonidine also prolongs the anesthetic effect of intrathecal local anesthetics [155–158]. Intrathecal clonidine prolongs a sensory block by approximately 130 minutes and a motor block by about 45 minutes [159]. To date, it is not entirely understood what causes the local anesthetic-sparing effect. In vitro, clonidine blocks Aδ and C-fiber conduction and increases potassium conductance in isolated neurons and enhances the local anesthetic nerve conduction blockade, suggesting a direct effect of clonidine on neural transmission. Additionally, clonidine can produce local vasoconstriction, decreasing the vascular clearance of the local anesthetic around neural structures. Finally, clonidine may enhance the peripheral or spinal blockade by synergism, even when given systemically [42]. Low epidural doses of clonidine may cause significant hypotension [42, 153, 160]; therefore, adequate hemodynamic monitoring is necessary when administering clonidine to patients.
6.3.2 Dexmedetomidine

Dexmedetomidine is a selective central α₂-adrenergic agonist with sedative properties and works in a similar manner to clonidine. Like clonidine, when administered as a neuraxial adjuvant it reduces the required local anesthetic dose and prolongs and potentiates post-operative analgesia [161]. The sensory and motor block doubles when intrathecal dexmedetomidine is used [162]. Intravenously administered dexmedetomidine also prolongs the anesthetic effect of intrathecal local anesthetics [155, 156, 163]. Similarly, the most common side effects of dexmedetomidine are hypertension and bradycardia [161]. To date, there is no solid evidence to exclude a neurotoxic effect of neuraxial dexmedetomidine, thus neuraxial administration should be used with caution [164].

6.3.3 Epinephrine

Epinephrine is used both epidurally and intrathecally to enhance the duration and intensity of neuraxial drugs. It causes vasoconstriction of blood vessels, which reduces neurovascular clearance [145, 165]. Intrathecal administration was thought to have also a direct analgesic effect through binding to α₂-adrenoceptors in the spinal cord; however, this has not been confirmed [166]. The fear of serious side effects due to the strong vasoconstrictive effects of epinephrine that could lead to spinal cord ischemia appears unfounded at clinically relevant doses (0–200 µg) [167]. Neuraxial epinephrine can potentially exacerbate local anesthetic-induced neurotoxic damage in patients whose spinal cord circulation is compromised (such as can occur with diabetes mellitus or arteriosclerosis) [167, 168]. Based on a systematic review, the beneficial effects of adding epidural epinephrine to a local anesthetic remain uncertain [169].

7 Miscellaneous Adjuvants Commonly Used

7.1 Dexamethasone

Dexamethasone is a water-soluble steroid with analgesic, anti-inflammatory, and anti-emetic properties and has been studied as an intrathecal and epidural adjuvant to local anesthetics [170–172]. Dexamethasone is believed to have a combined analgesic and local anesthetic-sparing effect, with minimal side effects [173]. To date, however, there have been no well-conducted comparative studies of neuraxial dexamethasone as a neuraxial adjuvant compared to other, more common, neuraxial adjuvants. Likewise, epidurally administered dexamethasone has most likely no added value compared to its intravenous administration [174]. Epidural dexamethasone at a high dose (≥15 mg) is associated with transient adrenal suppression [175], neurotoxicity has not been adequately ruled out [176, 177], and neuraxial pharmacokinetic properties have not been adequately studied [178]. Dexamethasone is included in the Food and Drug Administration warning about deleterious effects of epidural steroids.

7.2 Ketamine

Ketamine is a selective, non-competitive N-methyl-D-aspartate receptor antagonist, with analgesic and anti-hyperalgesic effects. The side effects of ketamine include psychological and mild sympathomimetic effects [179]. To date, there is no conclusive evidence that epidural ketamine is superior to intravenous administration [180, 181], although a systematic review showed a statistically significant, but probably clinically irrelevant minimal reduction in pain scores when epidural ketamine was used in conjunction with opioids [182]. Ketamine is also administered intrathecally, with a minimal improvement in outcomes (i.e., time to first analgesia request, onset time of the sensory and motor block, duration of the sensory and motor block) as shown in a recent systematic review, thus its clinical value seems limited [183]. Furthermore, evidence supports the neurotoxic effects of neuraxial ketamine, particularly when preservatives are used [80, 183–185].

7.3 Magnesium

Magnesium is an N-methyl-D-aspartate receptor antagonist and regulates the influx of calcium into cells, both resulting in an analgesic effect. Magnesium is frequently used intravenously. Because magnesium does not cross the blood–brain barrier easily, it is also used neuraxially [186]. Systematic reviews have shown that epidural administration of magnesium prolongs the time to the first analgesic rescue medication, provides minimal difference in early pain scores at rest after intrathecal use, and provides a 30% reduction in cumulative morphine use in the first 24 h after surgery (i.e., average 6 mg less morphine use in 24 h) [186, 187]. Other acute pain-related outcomes showed no differences [186]. Side effects associated with magnesium, such as hypotension, bradycardia, or sedation, were not observed [186, 187]. However, the minimally observed analgesic effect of neuraxial magnesium as an adjuvant must be contrasted with a safety profile that has not been adequately studied. Neuraxial magnesium has a neurotoxic potential based on animal studies and some case reports where supra-therapeutic doses of neuraxial magnesium were administered [82–85]. To date, no optimal intrathecal or epidural magnesium doses are known, which should lead to even more caution [186].
7.4 Midazolam

Midazolam is a benzodiazepine and is an indirect agonist of gamma-aminobutyric acid A receptors in the spinal cord. It causes neural inhibition by facilitating the influx of chloride into cells. Neuraxial administration of midazolam as an adjuvant to local anesthetics appears to have some analgesic effect and might also lead to reduced nausea and vomiting [188–190]. The most commonly described side effects of neuraxial midazolam are sedation and hypotension, although those are rare when the lowest clinically effective dose is chosen [190]. In animal studies, neuraxial midazolam has been associated with neurotoxicity [76–78], although more recent studies have failed to show neurotoxic properties [191, 192] and the quality of animal studies associating neuraxial midazolam with neurotoxicity is currently questioned [193]. Midazolam appears to exacerbate the neurotoxic properties of lidocaine [79] and because all local anesthetics are neurotoxic [72], it is debatable whether midazolam should be given in combination with local anesthetics via the neuraxial route. These features should lead to vigilance among clinicians.

7.5 Neostigmine

Neostigmine, a quaternary ammonium salt, is an indirectly acting parasympathomimetic. Inhibition of cholinesterase prolongs and enhances the effect of acetylcholine on muscarinic and nicotinic receptors. Intrathecal administration of neostigmine appears to prolong the duration of postoperative analgesia and sensory and motor blocks [194, 195]. The significant increase in the motor block (from approximately 160 minutes to roughly 220 minutes) combined with common side effects such as nausea and vomiting has resulted in the use of intrathecal neostigmine not being recommended [196]. Adding neostigmine to epidural morphine increases the time to administration of the first analgesic rescue medication, but total opioid consumption does not change [195, 197]. Neuraxial neostigmine has multiple side effects, including hypotension, sedation, and especially nausea and vomiting [195, 196, 198]. Neuraxial neostigmine does not appear to cause neurotoxicity [79, 199–201].

7.6 Ziconotide

Ziconotide is a synthetic analog of a peptide from the venom of the sea snail Conus magus. It blocks selectively the N-type voltage-gated calcium channel. Ziconotide inhibits calcium influx into the primary nociceptive afferent pathways that terminate in the superficial layers of the dorsal horn of the spinal cord. This inhibits the release of neurotransmitters, including substance P, and thus spinal pain signals [202–204]. Ziconotide is solely used intrathecally in the treatment of severe chronic pain when pain control with spinally administered morphine and potentially other agents is insufficiently effective or is no longer possible because of side effects [205, 206]. It has dose-dependent psychiatric and central nervous system side effects [204, 206, 207] and a narrow therapeutic window [206].

8 New Developments in Neuraxial Drug Administration

In addition to the currently approved drugs for neuraxial administration, a plethora of agents have been approved for other indications/routes of administration but are used off-label for spinal or epidural injections. With respect to local anesthetics, possible future innovations may comprise the use of agents that have hitherto not been used neuraxially on a large scale, such as liposomal bupivacaine, butamben,
or mepivacaine [3, 214, 215]. Furthermore, novel sodium channel blockers such as neosaxitoxin [216] or modality-selective blocking agents could possibly gain interest for neuraxial administration in the future [217].

Concerning opioids, numerous agents that are not approved for neuraxial administration have been used off-label in daily clinical practice, amongst others buprenorphine (which exerts also a local anesthetic-like effect [218]), tramadol, pethidine, methadone, or diamorphine [65]. Their effectiveness has incidentally been described, the safety profiles of those drugs have, however, never been investigated in larger clinical trials.

Beyond local anesthetics, opioids, and drugs that have been initially introduced for other indications or routes of application, there is ongoing research on the development of new neuraxial agents, especially for spinal application in the management of pain (see Table 4). Those efforts also comprise new methods of action such as gene-based approaches using viral vectors, plasmids, or interfering RNAs [20, 219]. Given the large need for new agents with favorable effectiveness and a good safety profile, especially in chronic pain, the development of targeted non-neurotoxic medications that can be administered via the spinal and/or epidural route is highly desirable, and ongoing research should be encouraged.

9 Conclusions

The use of neuraxial drugs to produce anesthesia and/or analgesia is invariably of great interest and clinical relevance. Compared to systemic application, the neuraxial route is characterized by unique pharmacokinetic and pharmacodynamic properties. However, a solid comprehension of the pharmacology of neuraxially administered drugs is indispensable for anesthesiologists and pain practitioners using these techniques in order to safely and efficiently accomplish anesthesia and analgesia.

However, despite extensive use, the amount of approved medications for intrathecal and epidural use remains limited, especially for adjuvants. Hence, there is ongoing off-label use in clinical practice on a regular base. To ensure both patient safety but also legal safety for healthcare givers, a joint effort by practitioners, researchers, pharmaceutical industry, and authorities should be advocated in order to aid the risk-benefit analysis.

In addition to the already approved and/or clinically established drugs, new compounds are under investigation that could potentially increase the armamentarium of neuraxial drug therapy with a favorable risk/benefit relationship. Hence, further experimental and clinical research for neuraxial therapy should be strongly encouraged.

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