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REVIEW ARTICLE

The Pharmacology of Spinal Opioids and Ziconotide for the Treatment of Non-Cancer Pain

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Abstract: ***Background*:** Intrathecal drug delivery has undergone a revitalization following a better understanding of this delivery route and its pharmacokinetics. Driven by patient safety and outcomes, clinicians are motivated to rethink the traditional spinal infusion pump patient selection criteria and indications. We review the current understanding of the pharmacology of commonly employed intrathecal agents and the clinical relevance.

***Methods*:** Search strategies for data acquisition included Medline database, PubMed, Google scholar, along with international and national professional meeting content, with key words including pharmacology of opioids, intrathecal therapy, ziconotide, pharmacokinetics, and intrathecal drug delivery. The search results were limited to the English language.

***Results*:** Over 300 papers were identified. The literature was condensed and digested to evaluate the most commonly used medications in practice, sto serve as a foundation for review. We review on-label medications: ziconotide and morphine, and off label medications including fentanyl, sufentail, and hydromorphine.

***Conclusion*:** Intrathecal therapy has level-one evidence for use for malignant pain and nonmalignant pain, with continued cost savings and improved safety. To most effectively serve our patients, a clear appreciation for the pharmacology of these commonly employed medication is paramount..

Keywords: Pharmacokinetics, pharmacodynamics, morphine, dilaudid, hydromorphone, fentanyl, sufentanil, intrathecal therapy, ziconotide, prialt.

INTRODUCTION

Intrathecal therapy has undergone a relative resurgence in pain care. Improved pharmacokinetic and pharmacodynamic understanding of the intrathecal space coupled with expert guidance statements has improved patient safety and outcomes [1, 2]. Interestingly, the positioning of intrathecal therapy as salvage therapy innately reduces the treatment therapies likelihood of success, as parallels can be drawn to research in spinal cord stimulation [3]. Positioning intrathecal therapy as salvage therapy after failure of high dose systemic opioids is no longer the standard of care based on best practices.

Recent data suggests an epidemic of opioid misuse in the United States, with approximately 15,000 deaths annually in a reported by the Center for Disease Control (CDC) [4]. The intrathecal delivery route for opioids has advantages over systemic medication delivery in that reduced systemic exposure is thought to improve the side effect profile, while intrathecal delivery may provide a better analgesic effect because of advantages in potency. Also this route of delivery dramatically impacts the risks of diversion and misuse.

Intrathecal therapy, for both end of life pain care and chronic conditions has leveled evidence to demonstrate efficacy [5]. Historically defined, intrathecal therapy has challenges, including impacts on hormonal balance, space occupying granuloma, opioid dose escalation, platform inefficiencies, and limited agents that are Food and Drug Administration (FDA) labeled for this use [2, 5-8]. Importantly, intrathecal therapy requires a platform to deliver a medicine; it does not define the medicine employed. In the United States, intrathecal agents are delivered by approved devices that are carefully monitored for safety and efficacy. In the past, only one device has been commonly used for this purpose. (Synchromed II, Medtronic Neurological, Minneapolis, Mn). In 2014, the FDA approved a second device that allowed for intrathecal delivery (Prometra I, Flowonix, Jersey City, New Jersey). Common platform choices are now more completely MRI conditional with the introduction of the Prometra 2 by Flowonix [9]. Currently, the Medtronic Synchromed II is the only therapy with the patient therapy manager (PTM), although Flowonix has a patient controlled dosing strategy awaiting FDA approval. These options allow the physician

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and health care team to preprogram an intermittent bolus that can be delivered by the patient.

The purpose of this review is to describe the pharmacokinetic and dynamic differences of opioid therapy and ziconotide therapy currently employed for use as intrathecal agents. This review describes both on label and off-label medications. We will review each medication separately and then provide summative comments.

Table 1. Reported benefits from intrathecal drug delivery.

Improved side effect profile
Increased potency
Reduced Risk of Diversion and Misuse

METHODS

Search strategies for data acquisition included Medline database, PubMed, Google scholar, along with international and national professional meeting content, with key words including pharmacology of opioids, intrathecal therapy, ziconotide, pharmacokinetics, and intrathecal drug delivery. The search results were limited to the English language.

PHARMACOLOGY REVIEW

To facilitate the presentation of the most commonly employed opioid intrathecal agents and ziconotide for pain treatment, both on-label and off-label medications will be reviewed separately. Each medication will have a dedicated description of a historical perspective, discussion of the pharmacokinetics and dynamics within the intrathecal space, a review of the safety and efficacy, and finally summarizing statements. Combination therapy (an opioid or ziconotide with local anesthetics or clonidine) will not be reviewed.

ON LABEL MEDICATIONS

Morphine

Historical Perspective

Opium is the oldest, and best-known opiate analgesic in the world. There is available historical evidence suggesting its utilization to alleviate pain, dating back to 2100 BC. The Sumerians are thought to have been the first to use poppy extracts to treat pain in suffering patients. Arabic physicians utilized opium extensively for pain relief during the second and third centuries. The Persian physician, Avicenna, utilized opium substances for the treatment of diarrhea and various eye ailments, in addition to pain, around the 10^{th} century.

In the 19^{th} century, Friedrich Wilhelm Serturner was the first to isolate purified crystals from crude opium. He was able to demonstrate that the crystals could relief pain far better than opium alone. Sertuner called this extracted substance "morphine", after the Greek God of dreams, Morpheus [10].

Merck began to commercially market morphine in 1827. However, morphine was not widely used until the advent of the hypodermic syringe in 1857. The first published report of intrathecal utilization of morphine was by a Romanian physician, Racoviceanu-Pitesti, in 1901 [11]. Behar and his colleagues published the first report of epidural morphine analgesia in The Lancet in 1979 [12]. The utilization of neuraxial opioids has since become the standard of care in anesthesiology and pain management. Despite significant advances in pharmacology and delivery technology, morphine continues to be the gold standard in intrathecal and epidural pain management due to its established safety and efficacy profiles throughout ancient, as well as recent medical history.

Pharmacodynamics

Morphine's predominant drug effect is through agonism of G-protein mu- opioid receptors. Subtypes of the mu receptor include mu1 and mu2. Opioid receptors inclusively include mu, kappa, and delta [13]. Mu receptors are present in various organ systems throughout the body, including the gastrointestinal tract. These binding sites are especially abundant within the central nervous system (CNS); with higher densities in the thalamus, hypothalamus, amygdala, nucleus caudatus, putamen and some cortical areas. They are also found in the terminal axons of the primary afferent neurons in the substantia gelatinosa, laminae I and II [14].

Morphine and other opiate analgesics reduce the discomfort from the pain, despite the fact that the existence of pain may still be recognized which may be valuable when evaluating pain as a warning sign verses a chronic and undesirable condition.

Side effects of morphine are similar for the opioid class and may include altered mood, drowsiness, dysphoria, euphoria, constipation and respiratory depression. These side effects occur in a route independent fashion, although the severity may vary. Tolerance to the side effects tend to occur with exposure to the molecule.

Morphine is extensively metabolized through the first pass metabolism in the liver and the metabolites are largely excreted through the kidney. If taken orally, only 40-50% of the dosage will reach the CNS environment [13].

Morphine is primarily metabolized to Morphine-3-Glucuronide (M3G, about 60%) and to Morphine-6-Glucuronide (M6G, about 8-10%) [15]. There is also evidence for this type of metabolic activity in the brain and kidneys, to a lesser degree. Although M3G is an inactive metabolite, M6G does have some continued affinity for the mu-receptors. The strength of its affinity is reported to be about 50% of the original molecule [15]. Therefore, M6G is thought to maintain some analgesic properties. The elimination half-life of morphine is about 120 minutes and may vary based on the individual's sex, weight and water distribution. Although morphine can cross the blood-brain barrier, its poor lipid solubility and protein binding capacity render this crossing very difficult [16].

Pharmacokinetics

Despite its hydrophilic nature, animal models demonstrate the limitation in morphine's distribution in the CSF. For example, intrathecal morphine concentrations at 5 cm above

or below the infusion site have been shown to be about 20% of the concentration at the infusion point, itself. The concentration drops to about 5% of the infusion point's concentration within 10 cm above or below the origin of infusion [17]. There is also consistent evidence that changes in the infusion rate, only allow for modest changes in CSF drug distribution [1]. Moreover, CSF flow studies have demonstrated lack of efficacy in drug distribution around the spinal cord, particularly from the ventral to the dorsal aspect [1]. Therefore the dorsal placement of the catheter will allow for a more efficacious distribution of morphine to the anti-nociceptive target sites in the dorsal columns.

There is published literature suggesting that the CSF distribution of any given medication, including morphine, depends on several key factors [1]. The five main factors are: lipid solubility, baricity, regional cerebral spinal fluid (CSF) mixing,, flow rate, and residence time within the intrathecal space. Investigations into intrathecal flow dynamics reveal that bulk flow has little impact on dispersion of the medication from the catheter [18, 19].

Wallace and colleagues were able to demonstrate a significant relationship between the daily dose of IT morphine and CSF concentration of that medication. They were also able to show a dwindling concentration of morphine in the CSF as the sampling site was distanced from the infusion site, validating the findings in CSF distribution of intrathecal medications originally described in animal models [20].

Safety and Efficacy

Due to the blood-brain barrier, the systemic concentration of morphine sulfate is much higher than its intrathecal concentration after any type of systemic administration. Expectantly, the CSF concentration of morphine is higher than its systemic concentration after its epidural administration [21]. It is important to note, however, that intrathecal and epidural administration, in terms of pharmacokinetics, dramatically differs.

Table 2. Side-effects from opioid receptor agonism [13].

Mu	respiratory depression
	sedation
	dependence
	anorexia
	pruritis
	urinary retention
	nausea/vomiting
	constipation
Kappa	sedation
	dyspenia
	dysphoria
	dependence
	miosis

Intrathecal morphine has been established as an effective and powerful analgesic. The efficacy and safety of IT morphine has been demonstrated in various research projects and publications [5, 22-25]. Kumar and colleagues published efficacy results of continuous IT morphine infusion in chronic pain patients with moderate to severe pain. The data revealed very good outcomes in deafferentation and mixed type pain and good results in nociceptive type pain [22]. Krames reported the positive efficacy of intrathecal morphine in the treatment of non-malignant chronic pain alone, or with combination with bupivacaine [23].

Evidence further suggests that the flow rate of intrathecal morphine may not contribute to the efficacy of pain control; however, the quality of life may decrease with an increased flow rate due to potential side effects [24]. Veizi *et al.* demonstrated that doses of monotherapy opioids may increase on the order of 535 ± 180% within 12 months of initiation [7]. With dose escalation comes increased intrathecal concentrations, creating concern for granulomas, non-infectious collections of cells around the catheter site [8]. To improve patient outcomes and safety, a group of expert physicians was convened to standardize approached to intrathecal therapy. In its latest iteration, the 2012 Polyanalgesic Consensus Conference., led by Dr. Deer, reiterated morphine to be a first line agent, weighing the available evidence, factoring in safety and efficacy, and expert opinion [26].

The side effect profile for morphine is a consequence of agonism upon the opioid receptors and their subtypes. It has been associated with histamine release, causing hypotension and bradycardia, which can be fatal at high doses intrathecally despite appropriate resuscitative measures. Vasodilitation can also be witnessed in dependent and lower extremity peripheral edema in patients on intrathecal opioid therapy [13, 27].

Challenges with the intrathecal delivery of morphine are largely similar to the systemically administered molecule, although adverse event rates are reportedly less. This is based on several factors including targeted drug delivery, as well as the concentration of the medication within the CNS. This allows for prevention of exposure to various organ systems, such as the gastrointestinal tract, potentially leading to improved tolerability. Other specific side effects related to IT infusion of morphine however, will need to be taken into consideration with IT therapy. This reported side effect profile includes, but it is not limited to, sexual dysfunction, urinary retention, and rarely catheter tip granulomas [28].

Summary

An analgesic of antiquity, morphine has been studied and used in countless studies and therapeutic projects. Morphine continues to be the gold standard in the systemic treatment of both acute and chronic pain. It is no surprise that this medication was also one of the first to be utilized in the intrathecal delivery of opiate analgesics. There is ample evidence in the literature validating the use of this medication in the intrathecal space as a stand alone, or combination therapy. The utilization of intrathecal morphine has not only provided an excellent analgesic alternative for countless

patients, but it has also provided modern neuraxial pain management with a platform to study the pharmacokinetics of this novel delivery method in hopes for future improvements in pain therapeutics and targeted drug delivery.

Ziconotide

Historical Perspective

A large number of patients continue to suffer from severe chronic pain even after treatment with opioids following the 3-step analgesic ladder developed by the World Health Organization in 1996 for cancer pain. Intraspinal agents, including morphine, have been tried as a fourth step. However, approximately 20% of cases remain refractory [29]. Over the past 30 years, peptide toxins have been recognized as potential therapeutic candidates due to their exquisite selectivity and high potency at a range of different ion channels and receptors [30]. Michael McIntosh, a research scientist at the University of Utah while working with Baldomero Olivera, discovered ziconotide in the early 1980s. Ziconotide (Prialt, formerly SNX-1111, Jazz Pharmaceuticals, Philadelphia, PA) is an intrathecally infused synthetic conopeptide that inhibits N-type presynaptic calcium channels [31]. Importantly, its mechanism of action is not opioid receptor related. Ziconotide was granted final FDA approval and intrathecal labeling on December 28, 2004 [31].

Pharmacodynamics

Ziconotide is a selective, potent, and reversible blocker of N-type voltage-sensitive calcium channels (VSCCs). N-type VSCCs are found at presynaptic nerve terminals in the dorsal horn of the spinal cord, receiving input from small myelinated and unmyelinated nociceptive afferents from the dorsal roots [31]. N-type calcium channels are present in highest density in the superficial layers (Rexed laminae I and II) of the dorsal horn, which is the site of primary afferent nociceptive synapses. Although the mechanism of action has not been established in humans, ziconotide appears to produce analgesia by binding to VSCCs and thus, blocking pro-nociceptive neurotransmitter release terminal including glutamate, calcitonin gene-related peptide (CGRP), and substance P from primary nociceptive afferents terminating in the superficial layers of the spinal cord dorsal horn [32]. Ziconotide may also influence neuronal excitability modulation, as calcium channels may be involved with maintenance of spontaneous ectopic discharges in injured primary afferent nociceptors and with mediation of persistent tactile allodynia after nerve injury. Importantly, it does not bind to mu-opioid receptors, thus opiate antagonists such as nalaxone do not block its pharmacological effects. Long-term administration of intrathecal ziconotide does not appear to lead to tolerance and abrupt cessation does not induce a withdrawal syndrome, as its mechanism of action is not G-protein mediated [31].

Pharmacokinetics

Unlike the other medications in this review, ziconotide is only administered therapeutically *via* the intrathecal route. Ziconotide follows linear kinetics, whether given as a single bolus or continuous infusion [31, 35, 37, 38]. The mean volume of distribution within the CSF nears the estimated total CSF volume of 140 ml [34], with a clearance from the CSF approximates the adult CSF turnover rate of 0.3-0.4 ml/minute. The terminal half-life of ziconotide from CSF is 4.6 +/- 0.9 hours [35-37] and is cleaved by endopeptidases and exopeptidases at multiple sites on the peptide [33, 37].

Noted by pharmacokinetic study, diffusion to the site of action requires a time interval that needs to be accommodated when titration of the drug is performed. This may lesson the incidence of side effects [31, 38]. The slow diffusion of ziconotide in neural tissue may also explain the slower-than-expected time course of resolution of adverse side effects with discontinuation of ziconotide therapy [39]. As appreciated from the side effect profile of the fast titration studies as compared to the slow titration studies, initial doses should therefore be initiated low and titrated slowly [31].

Intrathecal Safety and Efficacy

Ziconotide has been studied very robustly, as it has undergone three randomized controlled trials [40-42]. In a very difficult patient group, positioned a salvage therapy, 16% of those patients exposed to the ziconotide treatment arm had a reduction in pain scores of at least 30 percent [42]. This is quite remarkable, and important to put into context, as the majority of the patients had failed surgery, spinal cord stimulation, systemic opioids, and failing intrathecal opioid therapy, with mean duration of pain near 15 years and visual analog scale pain index (VASPI) of 80.7mm on average.

Efficacy has been demonstrated by multiple studies [40, 43-50], for both non-malignant and malignant pain. Further, in an upcoming published manuscript by some of the authors of this manuscript, it appears ziconotide can be safely administered in a variety indwelling pumps, although currently ziconotide is only used on-label in the CADD microambulatory infusion pump and the Medtronic Synchromed II system [31].

During clinical study protocols an overdose occurred that led to a dose of 45 times the FDA approved maximum dose given in a clinical trial. Despite this overwhelming overdose no cardiopulmonary depression resulted and no withdrawal symptoms are noted [41]. There are no reported cases in the literature of death from ziconotide overdose. This is in stark contrast to opioid overdose.

Side effects range from nausea, vomiting, urinary retention, ataxia, somulence, auditory and visual hallucinations, and speech disorders [32, 40-42]. Creatine Kinase levels have been reported to be elevated. The drug labeling also carries a Black Box Warning regarding the potential serious adverse side effects in patients with a history of psychosis, and this a contraindication in its use [37]. Recent reports suggest that side effects from ziconotide may be further mitigated by reduction in contaminate exposure to antidepressants or anticonvulsants [51].

Summary

Although a relatively new intrathecal analgesic as compared to its opioid counterparts, ziconotide is the only effective non-opioid, FDA-approved option for the management of severe chronic pain. It has been placed as first tier treatment for both neuropathic and nociceptive pain in the latest

iteration of the PACC in 2012 [26]. New dosing strategies to improve the longevity of monotherapy ziconotide, and a proposed trialing strategy, are currently underway [38].

COMMONLY USED AGENTS NOT CURRENTLY LABELED FOR INTRATHECAL USE

Hydromorphone

Historical Perspective

Hydromorphone is a highly potent, semi-synthetic opioid analgesic, which was first synthesized by pharmaceutical scientists in Germany in 1924. Knoll Pharmaceuticals was the first to market this new opioid under the brand name of Dilaudid in 1926.

Regarded as a more potent mu-receptor agonist than morphine by approximately 5-10 times, hydromorphone has been widely used in the treatment of acute and chronic pain in a wide variety of systemic methods since its initial presentation to the market. Most recently oral, long acting versions of the medication have come to the market for the treatment of moderate to severe chronic intractable pain. Systemic utilization of hydromorphone has gained increasing popularity based on its superior potency and its more tolerable side effect profile. Intrathecally, it may have less side effect profile as compared to morphine. Currently, it is off-label when used intrathecally, efforts to have an FDA approved indication is underway.

Pharmacodynamics

Hydromorphone is a hydrogenated ketone of morphine, rendering it a semi-synthetic, more potent mu-receptor agonist than its ingredient [13]. Due to its high affinity for the mu-receptor, it is generally thought to be approximately 5-10 times more potent than morphine. The ketone hydrogenation renders the molecule to have slightly higher lipid solubility, allowing for facilitated mobility across the blood-brain barrier [13].

Hydromorphone is metabolized by glucuronidation, similar to morphine, to hydromorphone-3-glucuronide. This inactive metabolite is then excreted through the renal system. A build up of the residual metabolites in the system due to renal dysfunction [52] can lead to a neuro-excitatory state causing restlessness or myoclonus. The elimination half-life of hydromorphone is approximately 2.3 hours and slightly variable based on the individual's age, sex and percent body fat.

It is notable that in the metabolic process of morphine, a small portion has been shown to convert to hydromorphone [53].

Pharmacokinetics

Intrathecal pharmacokinetics of hydromorphone, studied in the animal model, suggest CSF distribution behavior more similar to the hydrophilic opioids. Payne and colleagues demonstrated the slow distribution of hydromorphone in the CSF in the sheep model [54].

Although, the chemical structure of the hydromorphone allows more lipid solubility, as evidenced with the facilitated crossing of the blood-brain barrier, the molecule is still considered more hydrophilic than lipophilic, especially in the intrathecal environment [55]. Therefore hydromorphone is regarded to have intermediate lipid solubility properties [56]. The flow kinetic properties of hydromorphone, within the CSF have not been well studied in human subjects. However, due to its increased lipid solubility causing increased absorption, and based on the animal studies by Payne and associates, the distribution is thought to be slower and more targeted around the infusion site.

Safety and Efficacy

In the United States, no manufacturer has petitioned the FDA for labeling of intrathecal hydromorphone in clinical practice. In clinical practice, hydromorphone has gained increasing popularity as an opioid alternative to morphine for intrathecal analgesic therapy of moderate to severe, chronic non-malignant pain. There is also ample published literature regarding its superior efficacy and tolerability for spinal post-operative pain control.

Drakeford and colleagues demonstrated improved postoperative pain control with intrathecal hydromorphone vs. saline in a randomized trial of patients undergoing joint arthroplasty [56]. Furthermore, neuraxial utilization of hydromorphone has been shown to produce fewer side effects, such as respiratory depression, than morphine [57].

Moreover, intrathecal hydromorphone has been proven to be an effective opioid in the treatment of chronic, non-malignant pain. An expert consensus, the first version of the Polyanalgesic Consensus Conference, led by Hassenbusch and published by Bennett and colleagues established hydromorphone as an effective, second line therapy to morphine in intrathecal analgesic therapy in 2000 [58]. The efficacy of IT hydromorphone was further demonstrated in malignant pain. Anderson *et al.* reported 25% improvement in pain control in a group of cancer patients who had inadequate analgesia from morphine. They also reported a significant reduction in side effects such as nausea, vomiting, pruritus and sedation with hydromorphone vs. morphine [59]. Peripheral edema has been reported, similar to morpine [61]. Opioid systemic effects, similar to morphine, were previously described.

Retrospective studies have suggested a potential superiority of hydromorphone to morphine in terms of pain relief as well as side effect profile [60]. Based on an evaluation of the available evidence and expert opinion, hydromorphone is listed as tier one for nocicpetive pain and tier two for neuropathic pain [26].

Summary

Hydromorphone, although off-label, is very popular in inthrathecal therapy. In a recent study, the majority of pumps managed were hydromorphone, as compared to other opioids [7]. It may serve patients who have failed other opioids, and as demonstrated, can also be sued as first line therapy. Hydromorphone, like morphine, is granulomagenic, and faces similar challenges to other intrathecal opioids.

Fentanyl and Sufentanil

Historical Perspective

Fentanyl was initially synthesized by Paul Jannsen in 1959 as a mu-agonist compound in response to the side effects with morphine-based opioids. Such problems included incomplete amnesia, histamine-related reaction, hyper- or hypotension, and marked intra- and postoperative anesthesia secondary to prolonged respiratory depression [62-65]. Additionally, chemists aimed for an alternative to natural opioids, which could be administered in the perioperative setting intramuscularly or intravenously. The lipophilic agonist, fentanyl, demonstrating approximately 80-100 times the potency of morphine, was particularly able to penetrate the central nervous system (CNS), as demonstrated by the Meyer-Overton correlation [66, 67]. Sufentanil later synthesized in 1974, also by Jannsen, is roughly 5-12 times more potent than fentanyl [68].

Pharmacodynamics

Like morphine, fentanyl and sufentanil act principally on the mu receptor being distributed throughout the CNS: the brain, spinal cord, and other tissues. Fentanyl's lipophilicity yields CNS penetrability 100 times greater than that of morphine [69]. Fentanyl also possesses less emetogenic potential and weaker histamine activity compared with that of either morphine or meperidine. First administered *via* a single intravenous route, fentanyl was initially thought to have a rapid duration of action as a function of rapid metabolization or excretion. As experience mounted, it was determined that either multiple doses or large doses led to delayed recovery and prolonged respiratory depression, suggesting that the duration of action was primarily a function of redistribution within the fatty anatomy rather than elimination [70]. As such, a 3-compartment model best describes the parenteral pharmacokinetics of fentanyl [71, 72]. A distribution time of six minutes, redistribution time of an hour and elimination half-life of 16 hours is usual [73]. Ultimately, fentanyl and sufentanil have similar pharmacodynamic profiles, the latter being 12 times more potent than the former [74]. Both drugs undergo extensive metabolism in humans. Full understanding of metabolism does not exist but systemic elimination occurs primarily by hepatic metabolism followed by renal excretion. Of the six human P450 enzymes, it appears only P450 3A4 exhibits significant fentanyl dealkylation to norfentanyl [75]. All derivatives of 4-anilidopiperidine series, sufentanil, alfentanil and remifentanil, represent modifications of fentanyl itself [76]. All intrathecal opioids selectively modulate C and A-fibers with minimal impact on dorsal root axons [77].

Pharmacokinetics

Well over 100 years ago, August Bier performed the first successful spinal anesthesia on a surgical patient [78]. In 1976, Yaksh and Rudy were first to conclusively demonstrate direct opioid analgesia at the spinal cord level, studying subarachnoid fentanyl and morphine in rats [79]. The exact site of action for local anesthetic action remains inconclusive, but the work of Jaffe and Rowe surmised that both fentanyl and sufentanil exhibited activity on the dorsal root entry zone [80]. While intrathecal hydrophilic opioids are some hundred times more potent when administered intraspinally than intravenously, lipophilic opioids demonstrate less relative difference in potency, likely due to the reduction in CNS barrier effect seen in fatty substrates. Thus, fentanyl and sufentanil are only 10-20 times more relatively potent with intrathecal administration [80].

In contrast to the rostral ascension rate proposed by Bromage of approximately six hours for morphine, it was believed the lipophilic opioids tended to be absorbed more rapidly from the cerebral spinal fluid (CSF) at the segment of instillation [81]. Since this early work, much has been invested into understanding CSF flow dynamics as well as the chemical properties of clearance. In particular, with increased drug lipid solubility, cord bioavailability diminished as ease of trans-barrier migration increased. This resulted in a relatively fast clearance from CSF to epidural fat and then quickly to the epidural venous supply and plasma [82-84]. It is also hypothesized that with increased CNS permeability, inflammatory granuloma formation risk diminishes as concentration at the catheter tip drops rapidly with clearance.

Rostral spread of intrathecal drug is generally slow, but is slowest with lipophilic opioids, both fentanyl and sufentanil distribute quickly into epidural fat and spinal cord with a high volume of distribution [84]. It has been suggested that in addition to the local effect of the drug at the site of delivery on the segmental dorsal horn, enough drug may be secondarily redistributed to the epidural vascularity and subsequently to brainstem opioid receptors to generate significant clinical effect [82].

Safety and Efficacy

Both fentanyl and sufentanil are recommended for intrathecal administration. Fentanyl is recommended as a line 1 drug for the treatment of nociceptive pain and line 3 for neuropathic pain [26]. Sufentanil is line 3 for nociceptive pain and is not overtly recommended for neuropathic pain, although it could be placed in line 3 in combination with ziconotide [26]. While the authors were able to find an article describing a granuloma in a patient that received fentanyl, it was not clear what other agents had been employed intrathecally [85], we were unable to find any report of intrathecal granuloma associated with fentanyl specifically. One report was found in association with continuous sufentanil [86]. It has been suggested that intrathecal granulomas arising from opiates result from the degranulation of meningeal mast cells. Therefore, opioids with lower degranulation association, such as the phenylpiperadine

Table 3. Recommendations for starting doses of IT therapy [26].

Morphine	0.1-0.5mg/day
Hydromorphone	0.02-0.5mg/day
Fentanyl	25-75mcg/day
Sufentanil	2.5-7.5 mcg/day
Ziconotide	0.5-2.4mcg/day

Table 4. Recommendations for maximum concentrations of IT agents [26].

Morphine	20mg/mL
Hydromorphine	15mg/mL
Fentanyl	10mg/mL
Sufentanil	10mcg/mL
Ziconotide	100mcg/mL

Table 5. Recommendations for maximum dose per day of IT agents [26].

Morphine	15mg/day
Hydromorphine	10mg/day
Fentanyl	None
Sufentanil	None
Ziconotide	19.2mcg/day

Table 6. Opioid related effects generically [27, 89, 90].

Immunologic Effects	Immunosuppression results from inhibition of antibody mediated immunity, cellular immune responses, reduction in cytokine expression, phagocytic activity, and natural killer cell activity
Hormonal Effects	Decreases testosterone, estrogen, cortisol, luteinizing hormone, gonadotropic releasing hormone, low bone mineral density
Hyperalgesia	Mechanism under investigation, sensitization and increasing pain despite increased opioid doses
Sleep Disturbance	Decreases total sleep time, increased number of sleep-wake states, decreases sleep efficiency, delta sleep, and rapid –eye-movement (REM) sleep

Table 7. Pros and cons of available intrathecal agents.

	Ziconotide	Opioid
Death from Overdose	no	yes
Withdrawal Symptoms if abrupt cessation	no	yes
Need for planned 23 hour observation following trial and implant	no (if no neurologic signs or symptoms post 8 hours from dosing)	yes
Need for accurate dosing	yes	yes
Granulomagenic	no	yes*

*fentanyl may not be granulomagenic.

class (fentanyl and sufentanil), may result in diminished granuloma risk [87]. Lastly, while morphine yields peak respiratory depression in 8-10 hours, both fentanyl and sufentanil yield a peak effect in 5-20 minutes [88].

Summary

Fentanyl and sufentanil have demonstrated reliable safety profiles in terms of drug-CSF pharmacokinetics, rapid onset of action, and diminished risk of granuloma formation, when compared with more hydrophilic opioids. Thus, fentanyl and sufentanil represent excellent options for neuraxial infusion.

DISCUSSION

As can be clearly demonstrated by this review, vigilance with delivery of medications within the intrathecal space is essential. The starting doses, recommended maximum concentrations and daily doses are outlined in the following tables.

Intrathecal opioids, as we have discovered, innately have a dramatic risk:benefit ratio. Iatrogenic error may account for many of the reported challenges [6]. Notwithstanding, innate to delivery of opioids into the intrathecal space, predictable consequences occur, and are outlined in the following table.

Further, benefits of opioids versus non-opioids was reviewed at the 2014 North American Neuromodulation Society Meeting, clearly demonstrating the qualities of the ideal intrathecal agent [91, 92].

Accuracy is dosing and the volume delivered is crucial for patient safety and efficacy. The Prometra I system by Flowonix was demonstrating an accuracy of 97.1%, with a 90% confidence interval of 96.2-98.0%, with follow-up of 6 and 12 months [93, 94]. The Medtronic Synchromed II pump has had issues with accuracy, including challenges with off-label medicines and combination therapy regarding motor stall and gear corrosion with the peristaltic mechanism of delivery [95]. Recently, the accuracy of the pump was evaluated over 6 and 12 months, with over-infusion occurring 1% more than the programmed delivery volume and 2.5% on a per refill basis. These statistics represent a mean ratio, and does not account for large swings in the differences of predicted and actual residual volumes [96]. Further pump advances in accuracy, delivery mechanisms, safety warnings for pocket fill, and advanced programming designs are needed, as is new safer, more concentrated drug solutions.

Local anesthetics and other adjuvants are oftentimes employed concurrently in the intrathecal space, as the majority of the pumps implanted in the United States are not monotherapy. As Veixi *et al.* pointed out, mitigating predictable dose escalations with slow, continuous chronic infusion with local anesthetics may be accomplished by the addition of local anesthetics. Combination therapy is off-label, and discouraged secondary to an increased rate of device failure with the Medtronic Synchromed II system.

New dosing paradigms have been reported, to mitigate the challenges with monotherapy opioid and ziconotide [97, 98]. More prospective, randomized, multicenter studies are necessary to determine their placement in the intrathecal algorithm.

CONCLUSION

Intrathecal therapy has undergone a renaissance since its introduction. Gone are the days of positioning the therapy as a salvage therapy for chronic high systemic opioid doses [91]. Understanding the recent breakthroughs in our pharmacokinetic modeling of the intrathecal space, the aforementioned review provides a stepping-stone for medication selection, considering the unique physiochemical properties of the commonly employed intrathecal agents. Further research is needed in standardizing the selection of the platform, the catheter location, the trialing strategy, the medicine, the dose, and the titration schedule.

CONFLICT OF INTEREST

Dr Pope: Consultant for Medtronic, Flowonix, St Jude, Jazz Pharmaceuticals, Spinal Modulation, Mallinckrodt Pharmaceuticals. **Dr. Deer:** Consultant for Axonics, Bioness, Globus, Flowonix, Jazz, Nevro, Spinal Modulation, St. Jude, Medtronic, Mallinckrodt, Vertos. **Dr. McRoberts:** Consultant for Medtronic, Sanofi-aventis, St Jude, Vertiflex, Gore Industrie, SPR Therapeutics, and Flowonix. **Dr. Amirdelfan:** Consultant for St. Jude, Medtronic, Nevro, Mesoblast. **Dr. Azeem:** No Disclosures.

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