

Adjuvant Drugs In Central Neuraxial Analgesia- A Review

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Abstract

Central neuraxial adjuvant drugs, alone or in combination, are used intrathecally or epidurally for the treatment of acute and chronic painful conditions. A brief review of the physiology, mechanism of action, usual doses and modes of administration are discussed.

INTRODUCTION

Adjuvant drugs are pharmacological agents possessing little pharmacological effect by themselves, but enhance or potentiate the action of other drugs when given at the same time.

Neuraxial drug administration describes the technique of delivering analgesics and adjuvant drugs in close proximity to the spinal cord i.e. intrathecally into cerebrospinal fluid (CSF) or epidurally into the epidural space.

Drugs deposited into CSF or epidural space traverses different meningeal layers to gain access to receptors located in the spinal cord gray matter. Drugs absorbed by the systemic circulation also reach the central nervous system (CNS) to produce its effects.

Neuraxial analgesia is achieved in the perioperative period with local anesthetic (LA) drugs. Adjuvant drugs modify LA effects and reduce side effects.

1. Perioperatively these drugs affect:
2. Latency i.e. time of onset of LA block
3. Duration of analgesia i.e. duration of sensory and motor block
4. Quality of analgesia i.e. complete, incomplete (partial or patchy analgesia requiring supplemental drugs)

Postoperatively adjuvant drugs affect:

1. Analgesic gap i.e. time interval between subsequent doses administered

2. Quality of analgesia i.e. patient satisfaction, care providers' impression of pain relief
3. Side effects i.e. reduction of untoward effects of LA drugs

Knowledge and use of adjuvant drug therapy has rendered neuraxial analgesia more effective in the management of both acute and chronic pain conditions.

PAIN PHYSIOLOGY

Three neuron pathways transmit painful stimuli from the periphery to the cerebral cortex via the dorsal horn of the spinal cord. The nerve impulse causes release of neurotransmitters at both peripheral and central levels. Neurotransmitters acting on specific receptors can either produce excitation and pain, or inhibition and analgesia. Drugs cause analgesia by antagonizing the effect of excitatory neurotransmitters or by stimulating production and/or preventing breakdown of inhibitory neurotransmitters. Exogenously administered drugs also mimic the effect of inhibitory neurotransmitters.

Pain and analgesia result from the interaction of multiple factors. Pain impulses transduced from peripheral receptors are transmitted through nerve fibers, modulated at the spinal and supraspinal levels, and finally propagated through ascending and descending spinal tracts causing excitation or inhibition.

MAJOR NEUROTRANSMITTERS MEDIATING OR MODULATING PAIN

Figure 1

<u>NEUROTRANSMITTER</u>	<u>RECEPTOR</u>	<u>EFFECT</u>
Substance P	NK 1	Excitatory
CGRP		Excitatory
Glutamate	NMDA	Excitatory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	Mu,kappa,delta	Inhibitory
Endorphins	Mu,kappa,delta	Inhibitory
Norepinephrine	Alpha 2	Inhibitory
Adenosine	A1	Inhibitory
GABA	A, B	Inhibitory
Somatostatin		Inhibitory

DRUGS COMMONLY USED AS NEURAXIAL ANALGESIC ADJUVANTS

1. Opioids: can be hydrophilic or lipophilic
 - Hydrophilic opioids - morphine, diamorphine
 - Lipophilic opioids - fentanyl, alfentanil, sufentanil
2. Adrenergics: Nonspecific alpha stimulation causes alpha1(a1) and alpha2 (a2) stimulation.
 - Nonspecific stimulants: epinephrine, norepinephrine, phenylephrine
 - Alpha2 (a2) stimulants: clonidine, dexmedetomidine
3. GABA receptor agonists: Two receptor subtypes A and B exist. Benzodiazepines such as midazolam acts as a GABA A receptor agonist, whereas baclofen acts through the GABA B receptor.
4. NMDA receptor antagonist: ketamine
5. Calcium (Ca++) channel antagonist: ziconotide
6. Cholinesterase inhibitor (CHEI): neostigmine
7. Calcitonin
8. Adenosine
9. Miscellaneous drugs:
 - Cyclooxygenase Inhibitor-Ketorolac
 - Gabapentin

- Octreotide
- Xen 2174
- CGX 1160
- Resiniferatoxin
- P-saporin I

OPIOIDS

Opioids cause analgesia by acting on opioid receptors which are abundant throughout the CNS including lamina II or substantia gelatinosa of the dorsal horn. These receptors belong to a subfamily of G protein coupled receptors. Four types of opioid receptors mu (M), kappa (K), sigma (S), and delta (D) have been described. Receptors M,K, S have been cloned. The M receptor is further subdivided into M1 and M2 receptors. The endogenous opioid system acts via enkephalins, endorphins and dynorphin. Neuraxial opioids produce analgesia by directly acting on the opioid receptors of the CNS. They may also inhibit release of other excitatory neurotransmitters. Spinal opioids along with LA drugs are the mainstay of postoperative acute pain treatment (1). They are also helpful in painful conditions alone or in combination with other drugs (2,3,13). Analgesia is not associated with autonomic denervation, is dose- related, and is specific for visceral pain, not somatic pain.

Not all opioids administered neuraxially acts at the level of the spinal cord. Opioids administered intrathecally eventually reach the plasma by absorption and thereby reach different areas of the cerebral cortex. Consequently, their effects are produced at the postcentral gyrus, nucleus raphe magna, reticular activating system, and medulla. This is more true for lipophilic opioids such that following epidural administration systemic blood levels are nearly equal to those observed after systemic administration. Despite minimal CSF concentrations, spinal effects cannot be ruled out (4,5). Hydrophilic opioids such as morphine produce analgesia at much lower blood levels and at much lower doses after spinal administration compared to their lipophilic counterparts. They have been shown to have spinally mediated analgesic effects(6).

Side effects include respiratory depression, nausea and pruritus (7).

1. Respiratory depression: Early respiratory depression may be seen with lipophilic opioids. Delayed respiratory depression due to rostral spread in CSF

is typically seen after 12 hours of administration of hydrophilic agents.

The incidence of respiratory depression associated with neuraxial opioids is dose dependent and typically ranges from 0.1% to 0.9%. Risk factors for respiratory depression include increasing doses, advanced age, concomitant use of systemic sedative and analgesic drugs, and the presence of comorbid factors. The American Society of Anesthesiologists (ASA) task force has recommended measures for the prevention and treatment of opioid-induced respiratory depression (8).

2. Nausea and vomiting: This dose-related side effect occurs in 20%-50% of patients. Nausea and vomiting is postulated to be due to spread of opioids to the area postrema of the CNS.

3. Pruritus: Approximately 60% patients complain of itching. This side effect is believed to be caused by activation of the itch centre in the medulla and by opioid receptor activation in the trigeminal nucleus (9).

Antidotes for these described side effects include opioid antagonists such as naloxone and naltrexone. Nausea and vomiting can also be treated with droperidol, dexamethasone, or propofol.

Usual Doses:

Figure 2

Intrathecal:

Morphine	0.4-1mg
Fentanyl	15-25 mcg
Sufentanil	10 mcg

Epidural:

	<u>Bolus Dose</u>	<u>Infusion Rate</u>
Morphine	2-5 mg bolus	0.3-0.9 mg/hour
Fentanyl	50-100 mcg bolus	10-50 mcg/hour
Sufentanil	20-50 mcg bolus	10-25 mcg/hour

ADRENERGICS

a) Nonspecific alpha agonists:

Nonspecific alpha agonists are vasoconstrictor drugs like epinephrine, norepinephrine and phenylephrine. LA duration of action is directly proportional to the amount of time the LA drug is exposed to the nerve. The addition of vasoconstrictors limits LA absorption, increases neuronal exposure, enhances duration of action, enhances the quality

of block, and limits toxicity of LA drugs. Leicht and Carlson in a double blinded study involving twenty- eight subjects showed that epinephrine and phenylephrine significantly prolonged the duration of spinal lidocaine(10). Conception et al compared the effects of two doses of epinephrine and phenylephrine added to tetracaine and found that both prolonged the duration of sensory and motor analgesia (11). Vaida et al worked with two doses of spinal phenylephrine (2mg and 5mg) added to lidocaine and found significantly longer duration of spinal analgesia with both doses compared to plain lidocaine. There was no difference found in height of block. Patients who received 5 mg of intrathecal phenylephrine with lidocaine demonstrated the longest regression time of blockade in comparison to patients who had received the 2 mg dose of phenylephrine (12).

Epinephrine is commonly used in clinical practice as a 1:200 000 solution i.e. 5 mcg/ml, although a concentration of 1: 400 000 or 1:600 000 may also be equally effective.

Phenylephrine is typically used in doses of 1- 5 mg for intrathecal anesthesia.

b) Alpha2 (a2) agonists:

Clonidine and dexmedetomidine are a2 agonists. Clonidine acts as a selective partial agonist of the a2 receptor with a ratio of 200:1 (a2 to a1) whereas dexmedetomidine is highly selective with a ratio of 1600:1. Other selective a2a, a2b, and a2c agonist drugs include uk14304 and moxonidine. These drugs are currently undergoing many clinical trials and experimentation due to their immense popularity for use in pain medicine.

The mechanism of action of these drugs involve activation of a2 adrenoreceptors which reduce peripheral norepinephrine (NE) release by a negative feedback mechanism. Stimulation of central a2 receptors activate noradrenergic imidazoline receptors and also act on descending inhibitory tracts. The overall effect is sympatholysis resulting in analgesia, hypotension, bradycardia, and sedation.

A strong correlation exists between CSF clonidine concentration and duration of analgesia. This shows that neuraxial clonidine acts at the spinal cord, supporting spinal administration of this drug.

Spinal clonidine causes a 30% prolongation of sensory and motor block of LA. A dose response study using intrathecal clonidine doses of 37.5 mcg to 150 mcg administered with

bupivacaine found a dose- dependent increase in sensory blockade and more pain-free intervals in the postoperative period. An intrathecal dose of 150 mcg was noted to be associated with more motor blockade (13). Dobrydnjov et al in a double blind study of patients undergoing hip arthroplasty with combined spinal epidural anesthesia found that intrathecal clonidine doses as low as 15 mcg resulted in an increased duration of anesthesia, analgesia and motor blockade. Epidural clonidine in the postoperative period reduced VAS score and also decreased morphine consumption. Addition of clonidine intrathecally or epidurally was associated with significant reduction of heart rate and blood pressure (14). Epidural clonidine 1 mcg/ml when added to morphine 0.1mg/ml in 0.2% ropivacaine significantly reduced postoperative pain scores of total knee arthroplasty patients. Increasing the dose of epidural clonidine to 4mcg/ml did not result in a statistical difference in analgesic consumption but caused severe sedation and prolonged sensory motor blockade (15). Neuraxially administered opioids and α_2 agonists exhibit synergism. Differential localization of α_2 adrenergics (α_2A , α_2B , α_2C) and opioids (M,K,S,D) suggests differential involvement of opioids-adrenergics analgesic synergy. The addition of clonidine to opioids for postoperative analgesia as a continuous epidural infusion reduces opioid requirements by 20-60% (16).

Neuraxial clonidine is indicated for the treatment of intractable pain in cancer patients unresponsive to maximum doses of opioids. This formed the basis for the approval of epidural clonidine by the FDA (17).

Dexmedetomidine is the next generation α_2 agonist with a high sensitivity for α_2 receptors. This agent is associated with fewer hemodynamic and systemic side effects. A dose of 3 mcg of intrathecal dexmedetomidine was found to be equipotent with 30 mcg of clonidine (18). Intrathecal dexmedetomidine 5 mcg and fentanyl 25 mcg were compared for vaginal surgeries with bupivacaine anesthesia. Dexmedetomidine caused significantly longer sensory and motor blockade whereas peak effect and onset time were not different (19). Caudal dexmedetomidine in a dose of 1mcg/kg with bupivacaine was used in pediatric patients undergoing hernia repair or orchiopexy. Dexmedetomidine was found to cause more sedation, more analgesia, less anesthetic consumption, and less irritability. There were no hemodynamic differences when compared to patients who had received only bupivacaine (20).

Side effects of these drugs are limited to hemodynamic

effects i.e. bradycardia and hypotension.

Figure 3

Doses

Clonidine

Intrathecal 30-225 mcg

Epidural 6-8 mcg/kg bolus 1-2 mcg/kg/hour infusion

Dexmedetomidine

Intrathecal 3-5 mcg

Epidural 1 mcg/kg

GABA RECEPTOR AGONIST

BACLOFEN

GABA is an amino acid which acts as an inhibitory neurotransmitter in the CNS. Baclofen is an agonist of the GABA- B receptor.

Intrathecal baclofen is specifically used for spasticity and dystonia due to various conditions such as cerebral palsy and spastic post traumatic spinal cord injury (21,22).

A typical intrathecal dose of baclofen is 25mcg-200mcg/day and is administered with the help of a programmable intrathecal pump.

Common side effects include sedation, drowsiness, headache, nausea, and weakness. More serious side effects such as rhabdomyolysis and multiple organ failure have also been reported.

BENZODIAZEPINES

Benzodiazepines are GABA-A receptor agonists. A high density of benzodiazepine receptors (GABA-A) have been found in lamina II of the dorsal horn of the spinal cord, suggesting a possible role in pain modulation.

Benzodiazepines have also been shown to act at opioid receptors. While chlordiazepoxide, diazepam, and midazolam have been shown to act at kappa receptors, midazolam has also demonstrated a weak agonist effect at delta receptors (23).

Intrathecal midazolam in a dose of 2 mg has been shown to prolong spinal analgesia.

It is effective more for somatic pain than visceral pain (24,25). It also decreases postoperative analgesic requirements. The incidence of postoperative nausea and vomiting is much less with midazolam than fentanyl (26).

Midazolam can be successfully combined with other drugs like opioids and clonidine for additive effects (27). It has been used as a continuous infusion (12mg/day) in patients with refractory pain (28).

The most serious side effect of intrathecal midazolam is neurotoxicity, shown in animal studies. However, a dose of 2 mg has not been shown to cause any neurodeficits in humans and can be used safely. (29,30,31).

NMDA RECEPTOR ANTAGONIST: KETAMINE

Neuraxial ketamine can produce surgical anesthesia alone without producing hypotension or respiratory depression. This effect was successfully utilized for providing surgical anesthesia in mass war casualties and was first used by Bion in 1984 (32). More commonly it is combined with LA drugs for surgical anesthesia.

Ketamine is a noncompetitive antagonist of NMDA receptors. With prolonged, repetitive nociceptive stimulation NMDA receptors are activated, releasing excitatory neurotransmitters glutamate, aspartate and neurokinin 1. These neurotransmitters are associated with many activities including central sensitization, wind-up and the generation of plasticity of various systems such as memory, vision, motor function, and spinal sensory transmission. Ketamine acts synergistically with opioids, dopaminergic receptors, serotonin receptors, and AMPA receptors to produce dissociation between the thalamocortical and limbic systems. Intrathecal ketamine has been shown to decrease morphine requirements in patients with terminal cancer and is useful in opioid tolerant patients (38).

Ketamine's spectrum of actions has made it a valuable drug for neuraxial administration in a wide variety of clinical situations. Indications for its use include producing surgical anesthesia, treating acute postoperative pain (33,34) and as an agent for chronic pain syndromes either alone or in combination with other drugs. The WHO has recognized ketamine as an important drug for the treatment of refractory cancer pain.

Doses

An intrathecal dose of 50 mg of ketamine was used by Bion for surgical anesthesia (32).

Epidural doses of 10 mg and 30 mg were used by Naguib et al and these authors found that 30 mg produced excellent postoperative pain relief for a longer duration (35).

A low dose of ketamine at 4,6, and 8 mg epidurally was found to be ineffective for postoperative analgesia by KawanaY et al (36).

Caudally administered ketamine 0.5 mg/kg along with 0.175% levobupivacaine 1ml/kg has been used successfully without adverse effects in children for lower abdominal and urological surgeries (37).

CALCIUM CHANNEL BLOCKER: ZICONOTIDE

Ziconotide is a non opioid analgesic approved by the FDA in 2004 for intrathecal delivery. Ziconotide is a highly selective reversible blocker of N type voltage dependent calcium channels which are active in the dorsal horn of the spinal cord, cerebral cortex, and neurohyphysis (39).

Ziconotide is effective for the treatment of both nociceptive and neuropathic pain. Recent clinical experience shows that ziconotide can be combined with a variety of drugs. Its use with morphine in particular allows synergistic action with a reduction in pain and analgesic consumption (40,41).

Doses

Intrathecal doses start at 2.4 mcg/day (0.1 mcg/hr) and are titrated to patient response. The dose may be increased up to 2.4 mcg/day at intervals no more than two to three times per week until a recommended maximum of 19.2 mcg/day (0.8 mcg/hr) is reached. The full analgesic effect of ziconotide may not be apparent for several days after a dosage adjustment. It has been suggested to titrate the change in dose and monitor response once a week and to use an overall titration period of longer than 3 weeks.

Adverse effects of ziconotide include memory loss, dizziness, nystagmus, impaired speech, ataxia, and confusion. Some of these adverse effects are related to the rate of infusion but are not dose dependent (42). Several cases of accidental overdose have not shown any respiratory or cardiovascular complications.

CHOLINESTERASE INHIBITOR DRUG :NEOSTIGMINE

Neostigmine administered spinally inhibits nociception in a dose dependent manner by increasing endogenous acetylcholine. The addition of neostigmine 6.25 - 50 mcg prolonged duration of sensory and motor block but produced a high incidence of side effects, especially nausea and vomiting. This has limited its use in clinical settings (43,44). Intrathecal neostigmine at a dose of 1mcg/kg has been used in pediatric lower abdominal and urological surgeries where

it was found to increase analgesia without any other beneficial effects (45). Adverse gastrointestinal effects have made neostigmine an unpopular choice for neuraxial adjuvant therapy.

CALCITONIN

Calcitonin a naturally occurring hormone which has been recently demonstrated to reduce pain, independent of its peripheral action at bony sites. The analgesic action of calcitonin was found to be comparable to that of fentanyl when given epidurally (46). Side effects of nausea and vomiting have been reported to be as high as 10-58% and can be controlled with granisetron (47).

Epidural and intrathecal dose: 100 IU

ADENOSINE

In the spinal cord adenosine receptors are located in the superficial layers of the dorsal horn. The antinociceptive effect is mediated through the adenosine A1 receptor subtype. Intrathecal adenosine does not inhibit acute pain (48) but rather is more effective in treating allodynia and hyperalgesia. Increasing evidence suggests that adenosine can be effective in the treatment of neuropathic pain (49,50). Intrathecal adenosine has been shown to reduce pain of 6 hours to 12 days duration and is not associated with hypotension, motor blockade or sedation. Following many clinical trials involving animal subjects, intrathecal adenosine 500-2000mcg in human volunteers was shown to decrease allodynia in phase I clinical trials. Few side effects were reported. The only side effect observed was transient lumbar pain after a dose of 2000 mcg (51,52).

Lacking significant side effects and useful for the treatment of hypersensitive states, adenosine is a promising analgesic drug for future research.

MISCELLANEOUS DRUGS

KETOROLAC

Ketorolac is a cyclooxygenase (COX) inhibitor drug. COX is released at the spinal level in response to acute pain and inflammation, contributing to central sensitization. Thus the intrathecal delivery of COX inhibitor drugs theoretically would reduce pain and central sensitization. Animal data so far appear promising. Healthy volunteers studies have not identified any adverse neurological or pain regulatory effects (53,54).

GABAPENTIN

Gabapentin acts on voltage dependent calcium channels and

inhibits glutamate release at the dorsal horn of the spinal cord. Given the fact that gabapentin is not well absorbed from the gastrointestinal system and penetrates the blood brain barrier poorly, intrathecal administration is an attractive choice. Though it is not yet FDA approved, a human phase II clinical trial is in progress.

OCTREOTIDE

Octreotide is a synthetic octapeptide of somatostatin. Octreotide given spinally causes analgesia (55,56). Intrathecal octreotide administered to cancer patients for five years reduced pain without any adverse effects (57). One prospective double blinded study involving twenty human subjects showed intrathecal octreotide at a dose of 20 mcg/hour to be as safe as normal saline (58) .

CONOPEPTIDE

Xen 2174 is a conopeptide derived from a marine snail. The drug is found to inhibit norepinephrine transport and activate noradrenergic inhibitory pathways causing antihyperalgesic, antiallodynic and antinociceptive effects (59).

CGX -1160 is a conopeptide that produces analgesia by activation of neurotensin receptor type I (NTR1). Further mechanism of action is unknown. The drug has been found to be safe in a small number of patients with neuropathic pain related to spinal cord injury. A phase 1b clinical trial is currently in progress.

RESINIFERATOXIN

Resiniferatoxin is an investigational drug that desensitizes dorsal root ganglion neurons (60).

P-SAPORIN

P-Saporin is a neurotoxin which destroys cells of NK1 receptors and inhibit pain signal transmission (61).

CONCLUSION

Since the 1980s, neuraxial use of drugs for the treatment of acute and chronic painful conditions has been widely accepted. Lowered dosage requirements, fewer side effects and less toxicity coupled with high efficacy make this alternative route of therapy a practical choice. There are several reasons to believe that the co-delivery of agents with different mechanisms of action will be therapeutically advantageous. It can be assumed that an agent which may modulate one component may not be able to act on a different state. There are several agents which do not display cross tolerance and can help in minimizing concurrent development of tolerance. These agents often act on

different elements of the pain pathway and result in a nonlinear therapeutic result i.e. potentiation or positive synergism. Resultant effects are more than would be expected when used in combination. A group of panelists convened a “Polyanalgesic Consensus Conference “in 2000 for the purpose of formulating an algorithm for drug selection in intrathecal polyanalgesia. These guidelines were published in 2000, 2003 and 2007 and were based on best evidence and expert opinion. Guidelines included the intrathecal drug selection algorithm (62).

2007 Polyanalgesic algorithm for intrathecal therapies:

Figure 4

Treatment category	Intrathecal drugs
First line drugs	Morphine Hydromorphone Ziconotide
Second line drugs	Fentanyl Morphine/hydromorphone + ziconotide Morphine/hydromorphone + bupivacaine/clonidine
Third line drugs	Clonidine Morphine/hydromorphone/fentanyl/bupivacaine + clonidine + ziconotide
Fourth line drugs	Sufentanil Sufentanil + bupivacaine + clonidine + ziconotide
Fifth line drugs	Ropivacaine Buprenorphine Midazolam Meperidine Ketorolac
Sixth line drugs	Experimental agents Gabapentin Octreotide Neostigmine Adenosine Xen 2174 ZGK 160

The knowledge and application of central neuraxial adjuvant drugs is essential for the successful treatment of acute and chronic pain syndromes and is also invaluable for future research. The complex pharmacology and physiology involved in this area warrants further investigation.

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