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Epidural and intrathecal analgesia for cancer pain

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The three-step analgesic ladder approach developed by the World Health Organization works well in treating the vast majority (70–90%) of patients suffering from pain related to cancer. In those patients who do not get pain relief by this three-step approach, intraspinal agents can be a fourth step in managing pain of malignant origin. Although morphine is the only opioid approved by the US Food and Drug Administration for intraspinal use, many different opioid analgesics are used intraspinally, including hydromorphone, fentanyl, sufentanil, meperidine and methadone in the treatment of cancer pain. Many non-opioid agents have also been used intraspinally either alone or in combination with opioids in the treatment of intractable cancer pain. This chapter summarizes the clinical use of these agents with some practical points.

Key words: cancer pain; intraspinal injections; opioids.

The analgesic effect of intrathecal morphine in experimental animals was first reported in 1976 by Yaksh and Rudy¹. In 1979, two different studies reported that the intrathecal² and epidural³ use of morphine in human beings could effectively control pain. Spinal administration of morphine for pain control in cancer patients was first reported by Wang et al² and it was well documented by Ventafridda et al.⁴ In 1986 the World Health Organization developed a three-step approach to managing cancer-related pain. This works very well in treating the vast majority of patients suffering from pain related to cancer. In those patients who do not get pain relief by the three-step approach, intraspinal opioids can be a fourth step in attacking pain of malignant origin. Selected reported studies on the use of intraspinal morphine for cancer pain are summarized in [Table 1](#).^{4–33} Many other agents have also been used intraspinally

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Table 1. Selected published reports on the use of intraspinal morphine for the treatment of cancer pain.

Investigators, year (ref)	Number of patients/route	Mean follow-up duration	Results	Adverse effects/ complications
Wang et al (1979) ²	8/Intrathecal	Single injection	75% good 25% poor	None reported
Ventafriidda et al (1979) ⁴	38/Intrathecal	Single & multiple injections	78% decrease in VAS	Not reported
Cousins et al (1979) ⁵	5/Intrathecal Morphine or pethidine	Single injections	100% good	None reported
Rico et al (1982) ⁶	10/Intrathecal 18/Epidural	Multiple injections	78% satisfactory 22% failures	Minor transient complications in 55%
Lazorthes et al (1983) ⁷	9/Intrathecal	3.5 months	90% decrease in VAS	Not reported
Coombs et al (1984) ⁸	6/Intrathecal 8/Epidural	7 months	16% good 16% fair 67% poor	CSF hygroma, urinary retention
Penn et al (1984) ⁹	8/Epidural 6/Intrathecal	3.9 months	50% excellent 42% good 8% poor	Not reported
Cobb et al (1984) ¹⁰	10/Intrathecal	3.9 months	30% excellent 30% fair 40% poor	CSF leak
Krames et al (1985) ¹¹	16/Intrathecal	5.5 months	19% excellent 44% good 37% fair	Catheter dislodgement, urinary retention, constipation
Wang (1985) ¹²	46/Intrathecal	Unknown	52% fair 48% poor	Pruritus, sphincter disorder, somnolence
Shetter et al (1986) ¹³	14/Intrathecal-epidural	3 months	50% excellent 29% good 21% fair	Cerebrospinal fluid fistula
Ventafriidda et al (1987) ¹⁴	53/Intrathecal	1.5 months	15% good 19% fair 66% poor	Not reported
Penn and Paice (1987) ¹⁵	35/Intrathecal	5.4 months	49% excellent 31% good 20% poor	Urinary retention
Madrid et al (1987) ¹⁶	35/Intrathecal	Unknown	44% excellent 34% good 11% poor	Three CSF fistula
Brazenor (1987) ¹⁷	26/Intrathecal	5 months	76% excellent 12% good 12% poor	Four catheter blockages
Onofrio and Yaksh (1990) ¹⁸	53/Intrathecal	4 months	64% excellent/ good 36% fair/poor	Not reported

Table 1. *Continued.*

Investigators, year (ref)	Number of patients/route	Mean follow-up duration	Results	Adverse effects/ complications
Hassenbusch et al (1990) ¹⁹	41/Epidural	≤ 27 months	100% excellent	Wound infection, catheter migration, voiding problems
Plummer et al (1991) ²⁰	17/Intrathecal 284/Epidural	3 months	47% excellent 41% fair 12% poor	Pain on injection, occlusion, infection
Anderson et al (1991) ²¹	9/Intrathecal	2 months	89% excellent 11% poor	Catheter kinking
Watermen et al (1991) ²²	33/Epidural	≤ 8 months	55% excellent 15% good 18% fair 12% poor	Respiratory depression, urinary retention, seroma
Follett et al (1992) ²³	35/Intrathecal	8 months	77% good 23% fair	Spinal headache, nausea, lethargy
Schultheiss et al (1992) ²⁴	79/Intrathecal	3 months	48% excellent 48% good 4% poor	Nausea, vomiting, urinary retention, obstipation
Chambers and MacSullivan (1994) ²⁵	12/Intrathecal	6.2 months	83% excellent 17% good	14 mechanical and surgical complications
Devulder et al (1994) ²⁶	33/Intrathecal	2.2 months	76% good 24% poor	three meningitis
Paice et al (1996) ²⁷	133/Intrathecal	≤ 24 months	52% excellent 43% good 5% poor	Delivery system problems, nausea and vomiting, pruritus, oedema
Erdine and Yucel (1996) ²⁸	54/Intrathecal	≤ 24 months	91% good 9% poor	Spinal headache in 17 patients
Ballantyne et al (1996) ²⁹	186/Intrathecal/ epidural/ intraventricular	Unknown	58% excellent 6.3% poor	Persistent nausea, urinary retention, and pruritus
Gestin et al (1997) ³⁰	50/Intrathecal	5 months	50% good 50% fair	CSF leak, headache
Smitt et al (1998) ³¹	91/Epidural	38 days	Adequate pain relief in 73–76%	Technical complication in 43%
Sallerin-Caute et al (1998) ³²	159/Intrathecal	3 months	40% excellent 40% good 17% fair 3% poor	Tolerance
Gilmer et al (1999) ³³	9/Intrathecal	4.5 months	100% good/ excellent	Not reported

VAS, visual analogue scale

Table 2. Non-opioid agents used for intraspinal analgesia.^{34,35}

Drug category	Agents
Sodium channel antagonists (local anaesthetics)	Bupivacaine Ropivacaine Tetracaine
Alpha 2-adrenergic agonists	Clonidine Tizanidine
NMDA antagonists	Ketamine Dextromethorphan
Calcium channel antagonists	Ziconotide Verapamil
Somatostatins	Somatostatin
GABA agonists	Baclofen (GABA _B) Midazolam (GABA _A)
Adenosine agonists	Adenosine
Acetylcholinesterase inhibitors	Neostigmine Physostigmine

either alone or in combination with opioids in the treatment of intractable cancer pain.^{34,35} Table 2 lists different non-opioid agents which have been used intraspinally in pain management; only a few of these, namely clonidine, bupivacaine and ziconotide, are currently used in cancer pain management.

DIFFERENT ANALGESIC AGENTS USED INTRASPINALLY

Opioids

Opioid analgesics reduce pain by binding to opioid receptors in the brain and the spinal cord. When administered orally, rectally or parenterally relatively large amounts may be needed in order to achieve desired analgesia. These approaches, while usually successful in controlling most cancer pain, can lead to side-effects such as constipation, sedation and respiratory depression with uncontrolled pain in some cases. For this reason, intrathecal and epidural administration of opioids has been used to provide quality analgesia and to avoid some of the systemic side-effects of high-dose opioids given by more indirect routes. The most widely accepted indication is for patients treated with systemic opioids with effective pain relief but with unacceptable side-effects or unsuccessful treatment with sequential strong opioid drug trials despite escalating doses.³⁶

Although morphine is the only opioid approved by the US Food and Drug Administration (FDA) for intraspinal use, many different opioid analgesics are used intraspinally – including hydromorphone, fentanyl, sufentanil, meperidine and methadone – in the treatment of cancer pain. The choice of agent is frequently determined by the unique properties of the medication and the goal of each particular situation. The properties of different opioids are given in Table 3.

A comparison of intrathecal and epidural opioids for pain control is given in Table 4.³⁷ Both epidural and intrathecal routes of administration can be equally effective in managing intractable cancer pain; however, inappropriate use of intraspinal routes should be avoided. Less invasive routes, such as oral, rectal, transdermal, subcutaneous and intravenous should be tried before resorting to complicated

Table 3. Comparison of different opioids for epidural use.

	Morphine	Hydromorphone	Fentanyl/sufentanyl	Meperidine	Metadone
	Lipophilic, lipid solubility 1	Lipid solubility 1.4	Lipophilic, lipid solubility F = 580, S = 1270	Lipid solubility 28	Lipid solubility 82
	Long duration (12–24 hours)	Intermediate duration (6–12 hours)	Short duration (2–4 hours)	Short duration (4–8 hours)	Short duration (4–8 hours)
	Slow onset (30–60 minutes)	Intermediate onset (20–30 minutes)	Rapid onset (5–15 minutes)	Fast onset (10–20 minutes)	Fast onset (10–20 minutes)
	High CSF solubility and spread	Intermediate CSF solubility and spread	Low CSF solubility and spread	Low CSF solubility and spread	Low CSF solubility and spread
	5–10 times more potent than intravenous	5 times more potent than intravenous	Equipotent to intravenous	1–2 times more potent than intravenous	Less potent than intravenous

Table 4. Comparison of intrathecal and epidural opioids.³⁷

Factors	Intrathecal	Epidural
Infection Rate	Same as epidural	Same as intrathecal
Pain relief	Better for long term	Good only for short term
Dose	Lower, 1 : 10	Higher, 10 : 1
Pump refills	Less frequent	More frequent
Side effects	Fewer	More
Technical complication		
First 20 days	25%	8%
Long term	5%	55%
Catheter occlusion and fibrosis	Minimal	High
Epidural metastasis	Less affected	More affected

techniques such as epidural and intrathecal routes.³⁸ Catheter obstruction and epidural fibrosis are more common with the epidural route.³⁹ Hence, intrathecal administration is more appropriate for prolonged duration of therapy. The intrathecal route of drug delivery may also be used effectively in the presence of extensive epidural metastasis.⁴⁰ Subarachnoid catheter tip granulomas can occur with chronic intrathecal catheterization, and if patients with these systems develop new neurological findings it should be thoroughly investigated.⁴¹

Whether given intrathecally or epidurally, the opioid must eventually bind to the mu receptor in the substantia gelatinosa. This means that an opioid given epidurally must pass through the dura in order to work. A lipophilic agent can cross this barrier much more easily than a hydrophilic one. However, this lipophilic medication may be significantly absorbed by the fat and other tissues located within the epidural space and other surrounding structures, resulting in reduced action.⁴²

Techniques of spinally administered opioids

Single-shot epidural and intrathecal opioids can be helpful in providing short-term relief of pain. This may also serve as an indicator to the future success of continuous infusions or patient-controlled analgesia using opioids. Continuous and intermittent bolus treatment are compared in Table 5.⁴³ Adequate relief of pain with trial spinal opioids is mandatory before proceeding to more permanent procedures for long-term treatment. Options for providing this form of pain relief include percutaneous catheters, tunnelled catheters and implantable programmable pumps. If the patient has only a few days to live, placement of a simple percutaneous catheter may be the easiest and most cost-effective option. Unfortunately, the risk of infection and high failure rate limit their use. A tunnelled catheter can be very helpful, providing months of effective

Table 5. Comparison of continuous and intermittent bolus intraspinal opioids.⁴³

Factor	Continuous infusion	Intermittent bolus
Dose escalation	Higher	Lower
Analgesic quality	Better	Fair
Bupivacaine combination	Less motor or haemodynamic complication	Higher motor or haemodynamic complication

analgesia. If spinally administered opioids are to be given for 3 months or more, then an implantable programmable infusion pump is the most cost-effective approach.⁴⁴ It may also provide a better quality of life, improving the patient's function and allowing them to participate in more recreational activities.

Dose of opioids for intraspinal use

The exact dosage comparison of different opioid analgesic agents for intraspinal use is difficult. As a general rule, the higher the lipid solubility the lesser the analgesic potency when the drug is administered intraspinally.⁴⁵ It is generally accepted that the dose of *morphine sulphate* for intrathecal route is one-tenth the dose for the epidural route, which, in turn, is one-tenth the intravenous dose. For example, if a cancer patient requires 100 mg of intravenous morphine per day, he or she would most likely need 10 mg epidural or 1 mg of intrathecal morphine per day. However, there is wide variation among patients in many aspects, including the degree of opioid tolerance which affects dose determination.

Adverse effects and complications

The adverse effects of spinally administered opioids are similar to those experienced with other routes of administration such as sedation, nausea, itching, urinary retention, constipation and respiratory depression; adverse effects of chronic intraspinal infusion of opioids are listed below:

- Constipation
- Urinary retention
- Nausea
- Vomiting
- Impotence
- Pruritus
- Minor sedation
- Nightmares
- Hyperalgesia (higher doses)
- Myoclonus (higher doses)
- Sweating
- Oedema
- Impaired libido
- Fatigue
- Dry mouth
- Tolerance
- Withdrawal syndrome

However, the degree of these problems may be significantly less severe compared to systemic use. Other complications unique to these invasive techniques with continuous infusion catheters are listed in [Table 6.46](#)

Table 6. Complications associated with chronic intraspinal therapy.

Surgery-related	Skin breakdown at surgical site Wound infection Bleeding, haematoma Catheter infection Epidural abscess Meningitis
Catheter-related	Withdrawal/dislodgement Occlusion Breakage/leakage Kinking/disconnections Scarring/pocketing Catheter tip granuloma
Pump-related	Pump failures Irregular flow rate Battery failures Pump torsion Filling errors Programming errors

Sodium channel antagonists (local anaesthetics)

Bupivacaine

Bupivacaine is an amide class local anaesthetic agent which acts by blocking the sodium channel. It has been used both epidurally and intrathecally to manage acute post-operative and labour pain and chronic intrathecal infusion either alone or in combination with opiates for cancer pain. It has been shown to be more effective in relieving the neuropathic component of pain. Studies, primarily in cancer patients with chronic infusion of bupivacaine and morphine combination, show no significant neurotoxicity.^{47,48} There appears to be an additive effect of bupivacaine in combination with opioids for chronic pain management in some studies.^{49,50} The reported daily dose of preservative-free bupivacaine 4% (40 mg/ml) for intrathecal use starts from 3 mg up to 11 mg, and clinically significant side-effects are not usually observed with doses < 15 mg/day. Liposomal encapsulation of bupivacaine has been shown to decrease central nervous system and cardiovascular toxicity and also to increase the duration of analgesia twofold when used epidurally.⁵¹

Ropivacaine

Another amide class local anaesthetic agent used intraspinally is ropivacaine. There has been no study on the efficacy and safety of this agent with chronic intrathecal administration. Studies show that it is slightly less lipid-soluble and causes less motor blockade with more selective sensory blockade after epidural administration compared to bupivacaine. Toxicity data suggest that ropivacaine is about 25% less toxic compared to bupivacaine on the cardiovascular system.^{52,53}

Alpha-2-adrenergic agonist

Clonidine

Epidural clonidine was approved by the FDA in October 1996 for the treatment of intractable cancer pain. It is commercially available in the USA in 100 µg/ml

concentration as Duraclon, and in Europe and Australia in 150 µg/ml concentration as Catapresan. Clonidine produces analgesia by the action on alpha-2-adrenergic receptors in superficial dorsal horn regions of the spinal cord.⁵⁴ Alpha-2 receptor binding is pre-synaptic on primary afferents and post-synaptic on dorsal horn neurons.⁵⁵ This causes a decrease in C fibre transmitters such as substance P and suppresses pre-ganglionic sympathetic flow.^{56,57} Other data suggest that stimulation of spinal alpha 2-adrenergic receptors results in activation of cholinergic interneurons in the spinal cord to produce analgesia. Epidural clonidine injection in humans has been shown to increase acetylcholine concentrations in cerebrospinal fluid (CSF).⁵⁸ Analgesia from epidural clonidine is enhanced by intrathecal injection of the cholinesterase inhibitor, neostigmine, in animals⁵⁹ and in humans.^{60,61}

Published studies on the use and efficacy of intraspinal clonidine for cancer pain are summarized in Table 7.^{62–66} Clinically, intraspinal clonidine is usually used in combination with morphine or other opioid and is more effective than opioids in treating neuropathic pain. Epidural infusion of clonidine at a rate of 30 µg/hour produces analgesia in patients with cancer and neuropathic pain⁶⁴, and infusion rates of 10–40 µg/hour are typically used in this patient population. In the placebo-controlled study of 85 cancer patients by Eisenach et al⁶⁴, clonidine produced lower pain scores than placebo in patients receiving epidural morphine rescue. The average range of clonidine dose in this study was 720 µg/day. Coombs et al reported the intrathecal infusion of clonidine and hydromorphone for chronic intractable cancer pain.⁶² The most common side-effects are hypotension, bradycardia and sedation.⁶⁴ The hypotension and bradycardia are due to the effects of the drug on the pre-ganglionic fibres in the thoracic spinal cord so that there is a larger drop in blood pressure with injections in the mid-thoracic region.⁶⁷ The sedative effect is most probably due to the actions on the locus ceruleus in the brainstem.⁶⁸

N-methyl-D-aspartate (NMDA) receptor antagonist

Ketamine

The NMDA receptors are activated by excitatory amino acid glutamate, which causes influx of calcium into the neuron and activates numerous second-messenger systems. These receptors are concentrated in the substantia gelatinosa of the dorsal horn and in dorsal root ganglia.^{69,70} Ketamine is a non-competitive NMDA antagonist which, when administered intraspinally, blocks central facilitation.⁷¹ There are no good studies on the chronic intrathecal use of ketamine for chronic pain. There are reports of the use of morphine and ketamine combination with good results in cancer pain.⁷² The long-term safety of intrathecal ketamine is questionable. A subpial vacuolar myelopathy was reported after a 3-week infusion of intrathecal ketamine in a cancer patient.⁷³ Dose-dependent incidence of motor dysfunction characterized by weakness and hypotension is also reported.

N-type voltage-gated calcium-channel antagonist

Ziconotide (SNX111)

Ziconotide is a synthetic form of ω-conotoxin with three disulphide bridges. A ω-conotoxin is a neurotoxic peptide produced by carnivorous snails of the genus *Conus*. Ziconotide selectively and reversibly binds to N-type voltage-sensitive calcium channels and blocks the calcium influx.⁷⁴ Daily doses range from 2.5 to 25 µg. It has an

Table 7. Published reports on the use of intraspinal clonidine (as single agent or combination) for the treatment of cancer pain.

Investigators, year (ref)	Drugs	Number of patients/route	Follow-up duration	Results	Adverse effects/ complications
Coombs et al (1986) ⁶²	Clonidine + hydromorphone	1-Intrathecal	Unknown	Good analgesia	Not reported
Eisenach et al (1989) ⁶³	Clonidine + morphine	7-Epidural	5 months	Good analgesia	Hypotension
Eisenach et al (1995) ⁶⁴	Clonidine	85-Epidural	8 weeks	Better pain relief than placebo	Hypotension
Tumber et al (1998) ⁶⁵	Clonidine + bupivacaine + morphine	1-Intrathecal	Unknown	Good analgesia	None reported
Portas et al (1998) ⁶⁶	Clonidine + sufentanil + bupivacaine	7-Epidural	Unknown	Five patients had good analgesia	Catheter displacement, bacterial contamination

advantage over intrathecal morphine in that there is no development of tolerance after prolonged use. Intrathecal ziconotide has been recommended for approval by the FDA for the management of chronic pain.⁷⁵ It has shown efficacy when administered intrathecally to patients with acute post-operative pain.⁷⁶ Multicentre, randomized, double-blind, placebo-controlled studies have evaluated the safety and efficacy of intrathecal ziconotide in intractable chronic pain associated with cancer or AIDS ($n = 111$); the results are reported in Table 8.⁷⁷ Common adverse effects with intrathecal ziconotide are confusion, dizziness, constipation, urinary retention, nystagmus, ataxia and convulsion.⁷⁸ These are more common with prolonged use (see Table 9).

Somatostatin

Intrathecal somatostatin works by binding to one or more of the five somatostatin receptors in the spinal grey matter. Somatostatin was reported to have an analgesic effect in post-operative and cancer pain states. Intraspinal Somatostatin was able to produce analgesia in six of eight patients suffering from terminal cancer pain. However, all patients showed very rapid escalation of the drug dose.⁷⁹

GABA agonists, adenosine agonists, cholinesterase inhibitors

There are no good studies on the clinical use of these agents in treating chronic cancer pain. Baclofen (GABA-B agonist) is effectively used intrathecally and is FDA-approved for the treatment of spasticity. Although it has analgesic properties, its use for pain management is limited by the motor weakness it produces at the analgesic dose. Intrathecal midazolam (GABA-A agonist) has shown some analgesic efficacy.⁸⁰

Table 8. Results of intrathecal ziconotide trial for cancer pain.⁷⁷

Degree of pain relief	Placebo (%)	Ziconotide (%)
Complete relief	0	9
A lot of improvement	19	44
Moderate improvement	3	13
Slight improvement	29	9
No change	26	17
Worse	23	7

Table 9. Adverse effects with intrathecal ziconotide.⁷⁸

Adverse event	Short-term use, ($n = 242$) (%)	Long-term use ($n = 463$)(%)
Confusion	2.9	3.9
Dizziness	2.9	1.7
Urinary retention	2.5	1.5
Convulsion	1.2	0.4
Somnolence	1.2	1.7
Dyspnoea	1.2	1.3
Amblyopia	1.2	0

However, there are some concerns of neurotoxicity with intrathecal midazolam use.⁸¹ Pre-clinical studies have shown analgesic properties of intrathecal adenosine. However, there are no reports of long-term clinical use of intrathecal adenosine – a recent study on the use of intrathecal adenosine for post-operative pain failed to show an analgesic effect.⁸² Intrathecal neostigmine, a cholinesterase inhibitor, has been shown to produce analgesia in a post-operative setting.⁸³ Prolonged motor blockade, nausea and vomiting are the main adverse effects. There have been no studies on the effectiveness of this agent in chronic pain.

SUMMARY AND CONCLUSION

Intraspinally administered opioids, particularly morphine sulphate, have been shown to improve pain management in cancer patients who do not get adequate pain relief with the WHO three-step approach. Better pain management should improve the quality of life for these patients with cancer. Currently there are several other agents that are being used clinically in some patients with cancer pain. Future studies on different new agents individually, and in combinations with opioids, may optimize the use of this advanced mode of pain control in cancer patients.

Practice points

- the exact dose comparison for different opioids for intraspinal use is not available
- the higher the lipid solubility the lesser the analgesic potency when the drug is administered intraspinally
- morphine sulphate dose = 100 mg intravenous = 10 mg epidural = 1 mg intrathecal

Research agenda

- the use of intraspinal opiates other than morphine for cancer pain needs to be studied in a systematic way, and efficacy should be compared with that of morphine sulphate
- many non-opioid agents mentioned in this chapter need to be studied in cancer pain management
- the efficacy of intraspinally administered agents needs to be studied in different types of cancer pain syndromes, for example neuropathic, osteogenic, somatic, and visceral pain due to cancer

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