Neuromodulation Special Interest Group
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Intrathecal Dosing and Medication Selection

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Background

Selection of initial intrathecal medication and initial dosing depends largely on the results of the trial. However, it is not unusual for intrathecal medication and dosing to evolve with time after implant. The current intrathecal drug delivery systems (IDDS) are approved by the Food and Drug Administration (FDA) for administration of a single agent and there are only 3 FDA approved agents: baclofen for spasticity and morphine and ziconotide for pain. However, in practice there are other agents used that are considered standard of care and include the opioids hydromorphone and fentanyl, the local anesthetic bupivacaine and the alpha-2 agonist clonidine. And in practice, the vast majority of infusions delivered in IDDS are off-label with also more combination therapy used than monotherapy(1).

Best Practice

A number of factors are important in consideration of medication selection. Most importantly, these decisions need to be patient-centric. Factors such as patient's diagnosis (cancer vs. noncancer related pain), localized vs. diffuse pain, patient's age and comorbidities and patient's baseline opioid dosage:

- Patient with cancer or terminal pain may have limited survival(2). Hence, concerns about opioid dose escalation, opioid-induced hyperalgesia and other adverse effects including catheter tip granuloma formation take a secondary seat to pain control
- Patients with localized pain may be candidates for use of the local anesthetic adjuvant bupivacaine which may help also curb opioid dose escalation(3)

- Younger patients tend to escalate their opioid dosages faster than older patients(4). This may be of concern in chronic noncancer pain whereby a normal life span may be expected
- Patients on high baseline opioid dosage tend to escalate their opioids at a much faster rate than patients on little or no opioids prior to pump trialing. A number of practitioners now advocate opioid weaning prior to intrathecal trialing(5, 6)

In addition, guidelines have been published that suggest an algorithmic approach to medication choices. The PolyAnalgesic Consensus Conference (PACC) has made recommendations for different lines of therapy for the various medication—including in neuropathic and nociceptive pain(7). In addition, the PACC has published reference ranges for intrathecal medication maximum doses and concentrations. While these recommendations are based mostly on consensus, they act as general guidelines for care of patients considered for intrathecal drug delivery.

Recommendations for starting doses of IT therapy

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

Recommendations for maximum Concentrations of IT Agents

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

Recommendations for maximum dose per day of IT agents

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

Table 1. 2012 Polyanalgesic Algorithm for Intrathecal (IT) Therapies in Neuropathic Pain.

Line 1	Morphine	Ziconotide		Morphine + bupivacaine
Line 2	Hydromorphone	Hydromorphone + bupivacaine or Hydromorphone + clonidine		Morphine + clonidine
Line 3	Clonidine	Ziconotide + opioid	Fentanyl	Fentanyl + bupivacaine or Fentanyl + clonidine
Line 4	Opioid + clonidine + bupivacaine		Bupivacaine + clonidine	
Line 5	Baclofen			

Line 1: Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for neuropathic pain. The combination of morphine and bupivacaine is recommended for neuropathic pain on the basis of clinical use and apparent safety. **Line 2:** Hydromorphone, alone or in combination with bupivacaine or clonidine, is recommended. Alternatively, the combination of morphine and clonidine may be used. **Line 3:** Third-line recommendations for neuropathic pain include clonidine, ziconotide plus an opioid, and fentanyl alone or in combination with bupivacaine or clonidine. **Line 4:** The combination of bupivacaine and clonidine (with or without an opioid drug) is recommended. **Line 5:** Baclofen is recommended on the basis of safety, although reports of efficacy are limited.

Table 2. 2012 Polyanalgesic Algorithm for Intrathecal (IT) Therapies in Nociceptive Pain.

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + bupivacaine	Ziconotide + opioid	Hydromorphone + bupivacaine	Fentanyl + bupivacaine
Line 3	Opioid (morphine, hydromorphone, or fentanyl) + clonidine			Sufentanil
Line 4	Opioid + clonidine + bupivacaine		Sufentanil + bupivacaine or clonidine	
Line 5	Sufentanil + bupivacaine + clonidine			

Line 1: Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for nociceptive pain. Hydromorphone is recommended on the basis of widespread clinical use and apparent safety. Fentanyl has been upgraded to first-line use by the consensus conference. **Line 2:** Bupivacaine in combination with morphine, hydromorphone, or fentanyl is recommended. Alternatively, the combination of ziconotide and an opioid drug can be employed. **Line 3:** Recommendations include clonidine plus an opioid (i.e., morphine, hydromorphone, or fentanyl) or sufentanil monotherapy. **Line 4:** The triple combination of an opioid, clonidine, and bupivacaine is recommended. An alternate recommendation is sufentanil in combination with either bupivacaine or clonidine. **Line 5:** The triple combination of sufentanil, bupivacaine, and clonidine is suggested.

References

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