Q&A

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Based off of a live symposium at a national pain meeting held on March 7, 2014

Faculty Responses to Questions from the Live Symposium

Strategies for Success in Intrathecal Pain Management

Q: What's the Medicare reimbursement for trial and implantation?
Is there a concern that intrathecal therapy will not be covered by the US Affordable Care Act?
Medicare pts have to have a catheter trial?
Are you reimbursed for implanting device and also subsequent visits during trialing?

A: *All aspects of intrathecal drug delivery are covered under CMS national coverage determinations. This includes trialing (both "single shot" and continuous catheter trials) implantation and management including evaluations and management in the office, refilling, medications, and programming. The actual amounts and specific guidelines for coverage will vary by carrier. It is important to understand the specific criteria such as allowable ICD diagnoses appropriate CPT codes. Manufacturers of the devices and medications (such as Medtronic and Jazz) have reimbursement specialists that can be very helpful.*

Q: How do you manage a patient with existing ITO therapy and want to switch to ziconotide?
How about transitioning from intrathecal opioids to ziconotide? Washout?

A: *For patients currently failing intrathecal opioid therapy two choices are often considered. One is to transition to oral opioids prior to implementing intrathecal ziconotide. This is the approach used in the pivotal study of ziconotide1 with a success rate of 93% weaning entirely off of IT opioids in 1 to 3 weeks. Ziconotide can then be initiated after achieving a stable oral dose using a slow titration approach as discussed in the same reference.*

Another approach is to add ziconotide to the existing IT opioid. This is an "off-label" but common clinical practice.2 . This would imply that the patient is receiving benefit from IT opioid but it is not adequate or that side effects are limiting upward dose titration. In this situation one would reformulate the medication in the pump holding th opioid dose the same while periodically increasing the ziconotide. Considerations include stability of the drug admixtures and rate of titration of ziconotide. I often start at about 1 mcg per day of ziconotide increasing every 30 days by 1 microgram per day until benefit is appreciated or side effects occur.*

**This is not and FDA approved use of this agent*

Q: Are there exercise limitations with implanted pumps? Can they swim?

A: *There are no specific exercise limitations with intrathecal drug delivery devices. There are minimal risks of slight dosage changes with prolonged hot tube exposure or pressurized environments such as diving. Each manufacturer publishes some warnings in this regard. As is the case with any route of delivery of opioid it is important especially when initiating a drug or changing a dose that operating dangerous equipment, driving or engaging in dangerous activities be avoided until the effect of the drug is stable and that no impairment is assured. Such decisions should be made with consultation of the treating physician.*

Q: Do they have an oral form of this drug? Why not?

A: *No the drug is active and safe only when delivered intrathecally.*

Q: If patient needs breakthrough oral pain medication, do you go to a different one, or similar to what they receive intrathecally?
Do you ever use an oral cover with TDD?

A: *It is important to understand the goals of any "breakthrough" drug requirement. It is possible to give self-administered boluses for rescue pain or activity related pain using a held device as prescribed by the treating physician. If significant doses of oral agents are given many of the advantages of IT drug delivery are diminished. For example, one of the main advantages of targeted drug delivery (TDD) is reduction of the side effects caused by systemic delivery such as constipation, fatigue, somnolence etc. With TDD the physician remains in control of the dosing which minimizes risk of overdosing, diversion and side effects. This in my view there is little advantage and much to lose when adding oral opioids. If the decision is made to do so, the same rationale applies as when prescribing a long acting opioid and "breakthrough" medications. An appropriate and safe dose of a well-tolerated opioid should be used on an as needed basis for specific effect and the patient should be monitored for benefit as well as any side effects that might occur from co-administration.*

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Q: How does ziconotide work? What is the mechanism that allows it to block pain?

A: *Although the mechanism of action of ziconotide has not been established in humans, results in animal models suggest it:*

- *Is a N-type calcium channel blocker (NCCB) that directly and specifically blocks N-type calcium channels at the dorsal horn of the spinal cord to inhibit pain transmission*
- *Does not bind to opioid receptors, and its pharmacologic effects are not blocked by opioid antagonists*
- *Does not potentiate morphine-induced respiratory depression*

The analgesic efficacy of ziconotide likely results from its ability to interrupt pain signaling at the level of the spinal cord. Ziconotide is a peptidic drug and has been approved for the treatment of severe chronic pain in patients only when administered by the intrathecal route. Importantly, prolonged administration of ziconotide does not lead to the development of addiction or tolerance.

Q: For how long can the pump be implanted?

A: *Indefinitely. TDD systems are manufactured by several different companies. The Medtronic SynchroMed® pump is the only one approved for use with ziconotide. The life time of the current pump is rated at 7 years and then will require replacement.*

Q: Is there data to show that if you treat with TDD early it may impact pain level or have preventative effect?

A: *Not specifically that I am aware. There are many general pain studies that demonstrate early rather than late intervention of chronic pain is associated with better outcomes.*

Q: What side effects are most common?

A: *Mild dizziness is the most common side effect but tends to diminish or go way altogether after initial exposure and dose modification. While various side effects can occur as listed below it is important to note that discontinuation rates in carefully conducted RCTs are the same for ziconotide as for placebo at about 5%.*

Common Side Effects[1]	Ziconotide (n = 112)	Placebo (n = 108)
Dizziness	46%	13%
Nausea	40%	29%
Asthenia	18%	6%
Diarrhea	18%	15%
Somnolence	17%	10%
Vomiting	16%	14%
Confusional State	15%	5%
Abnormal Gait	14%	2%
Ataxia	14%	1%
Headache	13%	11%
Blurred Vision	12%	3%
Urinary Retention	9%	0%
Amnesia	8%	0%
Anxiety	8%	3%
Nystagmus	8%	0%
Dysarthria	7%	0%
Memory Impairment	7%	1%
Rigors	7%	5%
Tremor	7%	3%
Vertigo	7%	0%
Anorexia	6%	2%
Muscle Spasms	6%	4%
Pain in Limb	5%	2%
Pyrexia	5%	3%
Sinusitis	5%	2%

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Q: Does ziconotide work in other patients than neuropathic patients?

A: *Yes. In fact the indications for ziconotide and the multiple RCTs demonstrating its efficacy are not limited to neuropathic pain syndromes. In fact, mixed type chronic pain (neuropathic and nociceptive) as well as those often considered mostly nociceptive (such as back pain) are included in these studies with demonstrated efficacy.*

Q: What is the dose you most often see patients on?

A: *The package insert for ziconotide list a dosage range from 1.2 to 19.2 mcg per day in monotherapeutic intrathecal delivery. The pivotal RCT slow titration study resulted in a mean effective dose of 6.9 mcg per day. In my experience the 5 to 8 mcg per day range is common for many patients.*

If used as an adjuvant mediation with IT opioid ("off label") the doses are usually lower. We see patients respond often in the 2 to 5 mcg per day range and this is consistent with other published reports as well2

Q: What is the data that failure to respond to a variety of oral opiates at advanced doses makes one a good candidate for consideration of intrathecal opioids?

A: *Really there are no good data to demonstrate that if a patient simply "fails" to perceive benefit from significant doses of oral opioids that changing the route of delivery to intrathecal is likely to be effective. In fact, this is a good reason to consider a non-opioid analgesic such as IT ziconotide which has a completely different mechanism of action. On the other hand, if a patient is limited by side effects then TDD of opioid may result in significant improvement in these effects and thus allow titration to an analgesic dose of opioid.*

Q: I have a patient with severe COPD, that is on higher dose oral narcotics. Would a ziconotide trial be appropriate?

A: *Yes. Ziconotide does not effect respiratory effort or drive which can be a serious limitation for opioids regardless of the route of delivery when patients have respiratory impairment such as COPD or sleep apnea.*

Q: What is the washout period for oral narcotics prior to a trial technique?

A: *For patients to become opioid naïve with the intent of then starting a trial of low dose IT opioid, many experts feel that 6 to 8 weeks of abstinence is required.3 However, there is not uniform agreement with this approach.*

References

1. Rauck RL, Wallace MS, Leong MS, et al; Ziconotide 301 Study Group. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage*. 2006;31(5):393-406. PMID: 16716870.
2. Deer TR, Kim C, Bowman R, Tolentino D, Stewart C, Tolentino W. Intrathecal ziconotide and opioid combination therapy for noncancer pain: an observational study. *Pain Physician*. 2009;12(4):E291-E296. PMID: 19668287.
3. Grider JS, Harned ME, Etscheidt MA. Patient selection and outcomes using a low-dose intrathecal opioid trialing method for chronic nonmalignant pain. *Pain Physician*. 2011;14(4):343-351. PMID: 21785477.

This comprehensive Q&A list as well as the full archived version of the live symposium can be found at

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