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Intrathecal Ziconotide for Cancer Pain Relief: When, How and Why

Pasquale De Negri*, Tiziana Tirri, Sergio Mameli and Alfonso Papa

IRCCS, Centro di Riferimento, Oncologico della, Basilicata Rionero in Vulture, Italy

The Polyanalgesic Consensus Conference called the intrathecal administration of opioids and ziconotide as first-line therapy for chronic cancer pain.

Morphine acts on the μ-opioid receptor, linking to calcium channels via a G protein–coupled mechanism. Ziconotide, an N-type calcium channel antagonist, effective in the treatment of neuropathic, nociceptive, and mixed neuropathic/nociceptive pain [1,2] blocks calcium influx into the presynaptic nerve terminal, preventing the release of neurotransmitters into the synapse. Unlike morphine, which acts indirectly and only partially (because some of the μ-opioid receptors are not linked to N-type calcium channels), ziconotide directly inhibits the N-type calcium channel. The phenomenon of tolerance observed with opioids, given the lack of coupling of μ-opioid receptors with calcium channels, has not been observed with ziconotide because it acts directly on calcium channels.

An algorithm allowing identification of the "*ideal*" patient for intrathecal analgesic therapy and clear information on the use of ziconotide in cancer pain are not still available.

In a conference with Italian experts on intrathecal treatment of chronic cancer pain was asked them to indicate which features would make a patient eligible to receive intrathecal treatment and predict response to intrathecal analgesia. The first aspect highlighted during the conference has been the lack of guidelines on when to discontinue systemic analgesic therapy (oral or parenteral), and when to use intrathecal therapy. Based on the clinical experience of the participants, the features of cancer patients which could be of particular importance in the decision to start intrathecal analgesic therapy include:

- Lack of adequate analgesic response to opioids or the need for tightly spaced increments of systemic opioid (according to some > 25% per week)
- Presence of adverse events with an unacceptable impact on the quality of life of patients
- Mixed neuropathic/nociceptive pain

Life expectancy has not been considered a limiting factor when considering the intrathecal route because, as shown by available data in the literature [3,4]: lifespan could be significantly prolonged by appropriate pain treatment. The consensus expert panel agrees that the amount of pain relief is more important than survival itself. In conclusion, based on the expert opinion of the panel and clinical practice, intrathecal therapy seems to be indicated in the following cases:

- Patients with mixed nociceptive/neuropathic pain inadequately controlled with systemic opioids (NRS> 6-7) or with intense localized pain.
- Patients with adequate pain control but with adverse effects not responding to common symptomatic treatments, reducing the quality of life.

Experts agree that all candidates for intrathecal analgesia should undergo a psychological/psychiatric evaluation, regardless of the drug to be used.

Although not supported by the international literature, the experts recommend that the desired site for the tip of the implanted subarachnoid catheter should vary according to the site of pain and should preferably be placed at the site of pain within the spinal cord [5].

Once the intrathecal route has been decided upon, the question that arises is which drug should be administered. Ziconotide has been used intrathecally for treatment of mixed neuropathic/nociceptive pain, in cancer and non cancer patients [6]. Unfortunately ziconotide-related adverse events (AE) reported from the FDA for the five years following ziconotide approval, include those of a psychiatric nature (confusion, dissociation and hallucinatory phenomena, dizziness, gait abnormalities), nausea, elevation in creatine kinase levels and rhabdomyolysis, Ziconotide has been suggested to be associated with an increased risk of suicidality, even in patients without symptoms of depression. A previous study of ziconotide use in malignant pain, using a fast titration protocol with rapid increases in ziconotide dose over 5–10 days, reported a significant improvement in pain correlated with a high discontinuation rate in the ziconotide group [6]. Another study reporting slow ziconotide titration over 3 weeks showed a significant change in pain in the ziconotide group with a lower discontinuation rate and better tolerability [7]. In these studies, the effective analgesic dose of ziconotide varied, the duration of the titration was not specified and the analgesic efficacy could not be fully achieved for several days after ziconotide dose adjustment. On the other hand patients suffering from cancer pain require quick and adequate pain relief, which precludes the use of ziconotide as monotherapy due to time-consuming titration periods. The experts do not recommend the use of ziconotide bolus during the trialing period, due to a lack of sufficient clinical experience, and express concerns about the increased incidence of adverse events.

The addition of ziconotide and other IT agents for chronic non cancer pain has been described in various paper [8-11]. The experts unanimously agree on the need to use, in patients with cancer pain, an opioid in combination with ziconotide as recommended by the 2012 Consensus Conference [2]. Experts believe, basing on actual literature, that the concomitant administration of drugs with a different mechanism of action, like opioids and ziconotide at low doses, represents a therapeutic advantage particularly in cancer pain refractory to high doses of systemic opioids, due to possible synergistic interactions, allowing a reduction in the dosage of individual drugs, a lower incidence of adverse effect and a rapid pain control. In their daily experience, the experts report the absence of breakthrough pain when using ziconotide in combination with opioids. They suggest,

***Corresponding author:** Pasquale De Negri, IRCCS Centro di Riferimento Oncologico della Basilicata Rionero in Vulture, Italy, E-mail: PASQUALE.DENEGRI@CROB.IT

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based on their clinical experience, the use of a starting dose of ≤ 0.05 mcg/h or ≤ 1.2 mcg/day and to carry out ziconotide titration according to the following schedule: weekly increments of ≤ 0.05 mcg/h, always maintaining a stable dose of intrathecal opioid. In the intervals between dose adjustments, patients should have free access to the use of systemic opioids or NSAIDs/acetaminophen. In the case of failure to achieve adequate pain relief with ziconotide or in the case of side effects related to the use of ziconotide, the experts recommend increasing the dose of intrathecal opioid. However with the use of an intrathecal combination therapy, is mandatory to consider drug stability as mixing drug with low stabilities requires a more frequent pump refill: morphine apparently can interfere with ziconotide stability [12,13].

Experts point out that during continuous intrathecal administration of morphine/ziconotide at low doses and with incremental increases of low magnitude, the incidence of AE is low and the decrease in pain intensity is significant. They advise that ziconotide, anyway, should never be used in psychiatric patients (major depression, bipolar disorder, etc.) as it is not possible to exclude a possible interaction between ziconotide and psychiatric drugs, which may be used to treat major depression in cancer patients. Serious cognitive adverse events related to ziconotide have been shown to be reversible with drug withdrawal, while minor adverse events required a reduction in drug dosage [14,15]. However, the experts observe that resolution of serious adverse events related to ziconotide is not immediate, can be time-varying and sometimes prolonged [16]. The panel suggests that the appearance of ziconotide-induced adverse effects does not necessarily preclude the possibility of re-using the drug, but this must be determined on an individual basis, and the panel underlines that under these circumstances ziconotide must be re-titrated [17].

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