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Short Communication

Intrathecal Ziconotide - Time for Revival?

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Chronic pain is a multifaceted condition affecting not only the individuals, but the whole society as well [1]. It has been estimated that 20% of surveyed Europeans suffer from moderate to severe chronic pain which in turn impairs functioning, work and quality of life. Interestingly, direct and indirect health costs for chronic pain exceed those estimated for diabetes, heart disease and cancer.

The intrathecal opioid administration (for example morphine) is one of the options that neuromodulation can offer in patients suffering from cancer-related and noncancer-related pain refractory to other modalities. In the USA, however, only in 2019, over 70% of the 70,630 deaths involved an opioid [2]. In this context, intrathecal analgesia (ITA) with nonopioids may improve the clinical practice. The only nonopioid drug that has been approved by the US Food and Drug Administration (FDA) is ziconotide. Ziconotide is a synthetic snail venom-derived peptide that is rapidly degraded by phase I hydrolytic enzymes but does not interact with cytochrome P450 enzymes [3]. In addition, it does not easily cross the blood-brain barrier [4].

Intrathecal analgesia with ziconotide is under-used in Europe, although it could become a first-line alternative to morphine. In this light, it is of interest to underline the findings of a recent paper on the role of ziconotide in the intrathecal pain management [5]. The article summarizes recommendations proposed by six pain experts tailored to the European settings, since the existing treatment algorithms (Polyanalgesic Consensus Conference, PACC) have been developed for non-European health care systems.

The main points of the paper are summarized below:

- **Patient selection:** Ziconotide is a first-line option in absence of any contraindications (for example psychosis or depression), pain diagnosis should be confirmed, combination of drugs for cancer patients.
- **Trialing:** Necessary for noncancer pain, unnecessary for cancer pain, with the aid of ports (for cancer patients), internal and external pumps.
- **Catheter tip placement:** At the spinal level which corresponds to the dermatomal pain area (usually not higher than T8), the cerebrospinal fluid dynamics should also be taken into account.
- **Dosing:** Start with 0,5μg/day, 1-2 increments/week, maximum dose 19,2 μg (noncancer pain, although the majority of patients have a notable pain relief with a daily dose of less than 10 μg), no maximum dose for cancer pain.
- **Tolerance**: It seems that patients do not develop tolerance to ziconotide and sometimes the dose can even be reduced over time without loss of efficacy.
- **Adverse effects:** Psychosis, hallucinations, suicidal ideation, creatine kinase elevation, ziconotide should not be applied together with baclofen, clonidine, bupivacaine or propofol, careful monitoring with concomitant intrathecal chemotherapy.
- **Outcome assessment:** With a combination of pain scores, disability scales, and quality of life scales.

Of note, the published consensus statement is mainly based on the clinical experiences of the pain experts. In order to prepare to a Pan-European consensus on the ITA with ziconotide, further studies investigating the dosing strategies should be undertaken (titration, switch protocols, internal or external pumps). As a conclusion, the low-and-slow approach practiced in the USA is better tolerated than the fixed high starting dose in Europe. If the trialing is made meticulously, ziconotide can be considered as a first-line effective ITA drug and not as a last resort option. However, a high level of clinical suspicion is necessary to avoid delay in diagnosis of cognitive and neuropsychiatric symptoms.

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