INTRODUCTION

Ziconotide is a non-opioid analgesic drug (1); it is a peptide of 25 amino acids, previously named SNX-111, and synthetic equivalent of \( \omega \)-MVIIA, a venom originated by Conus Magus (a marine snail). It is the first specific neuronal blocker that acts on N-type voltage-dependent calcium channels (present in the presynaptic cleft of the neuron), where the calcium input determines the release of neurotransmitters. These channels are expressed in the afferent primary neurons that terminate in the dorsal horn of the spinal cord. Their inhibition prevents the transmission of pain. Since its inception, ziconotide has emerged as a very promising drug as we reflected in 2007 in an article published by Rev. Neurologí-a (2). However, the reality we face is quite different, since in daily practice, this drug is used much less than expected.

The Multidisciplinary Pain Management Service of the General University Hospital of Valencia is a Level IV Unit in the Spanish Pain Society with multiple interdisciplinary interactions. At our Center, according to technical specifications, the use of ziconotide for continuous intrathecal infusion was proposed to six selected cases; three patients did not achieve adequate result during trial phase (they did not obtain analgesic coverage higher than 50% in previous spinal tests). In the final phase, one patient asked to be withdrawn from the study. Because of this, it has only been possible to establish this therapy in two patients. Why is this so even though the most up-to-date guides refer to it as a first-line treatment?

CASE DESCRIPTIONS

REVIEW OF CLINICAL CASES

CASE REPORT 1

A 50-year-old woman with neuropathic pain irradiated from the lower lumbar spine to the right foot, with fasciculations on the sole of her right foot associated with severe sleep disorders. She was submitted to surgical interventions, interventional pain techniques, spinal cord stimulation, and later intrathecal infusion pump, all with lacking effectiveness. In August 2004, intrathecal administration of ziconotide was initiated.

During these years there have been significant adverse effects that have been controllable: serious psychiatric side effects (auditory and visual hallucinations, major depressive symptomatology and suicidal ideation), together with alteration of the memory and concentration capacity. Also, menin-
gitis by Pseudomonas aeruginosa, that forced to explant the system; it was re-implanted one year later. Adverse effects also included muscle spasms (adding intrathecal baclofen). There was also a mobile tumor in the lumbar catheter insertion area, that required ruling out the existence of a fistulous pathway by magnetic resonance imaging. And finally, there was cicatricial allodynia over the pump area.

**CASE REPORT 2**

A 51-year-old woman with continuous neuropathic cervical pain radiates to the left upper limb with predominance in the fourth and fifth fingers, resulting in severe decreased quality of life. After surgical intervention was rejected, she received infiltrations and cervical radiofrequency, spinal cord stimulation, all with a poor analgesic response. Finally, in 2004 she was included as a candidate for intrathecal infusion of ziconotide.

She has also had multiple adverse effects, and all of them have been handled. In December 2004 she reported abdominal discomfort and oliguria. In September 2005 she presented acute lumbar pain, selective L4-L5, with sciatic irradiation. And on the other hand, in March 2011 after a pump replacement, a large abdominal hematoma occurred.

**DISCUSSION**

This drug emerged as a treatment with high expectations of success in the area of chronic pain (3), approved in 2005 by the European Medicines Agency (EMEA). The Food and Drug Administration (FDA) indicated it to patients with severe chronic pain, intolerant or refractory to other treatments.

Initial good results concluded in 2012 when the PACC (Polyanalgesic Consensus Conference) considered intrathecal infusion of ziconotide as first-line therapy for neuropathic pain associated with nociceptive pain. In 2016 the PACC made new recommendations; now the intrathecal infusion of ziconotide and morphine is the first-line therapy for chronic neuropathic pain associated with nociceptive pain, oncological or non-oncological patients.

However, despite strong clinical evidence of the efficacy of ziconotide, this therapy is restricted to very difficult and selected cases. According to our experience, this reality would be justified by two key points:

1. It is not possible intrathecal infusion at the low doses that ziconotide requires, due to the commercial withdrawal from usual implantable systems (4), such as Medtronic SynchroMed®®, or the external infusion pump CADD-Micro®.

2. High frequency of serious adverse events (5): 71.3-89% of patients experience secondary pharmacokinetic reactions that can be controlled by dose reduction or concomitant treatment. Furthermore, ziconotide does not have a pharmacological antagonist, so an overdose would require the hospitalization of the patient. In any case, death has not been documented due to ziconotide.

**CONCLUSIONS**

- The intrathecal infusion of ziconotide and morphine is presented as first-line treatment of the association of neuropathic pain and nociceptive pain, since 2012. However, in the usual practice it is reserved for exceptionally complex cases.
- This fact happens, according to our experience, for two reasons: firstly, the absence of a system that allows adequate intrathecal infusion at doses required by ziconotide, and secondly, the severity and high frequency of its side effects.

REFERENCES


