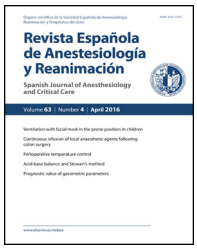
Rev Esp Anestesiol Reanim. 2018;65(5):275–283

Revista Española de Anestesiología y Reanimación

www.elsevier.es/redar



REVIEW

Role of voltage-gated sodium channel blockers in the treatment of chronic pain: Potential uses in clinical practice based on available evidence☆,☆☆

A. Alcántara Montero[a,*], C.I. Sánchez Carnerero[b]

[a] *Unidad del Dolor, Hospital Don Benito-Villanueva de la Serena, Don Benito, Badajoz, Spain*
[b] *Complejo Hospitalario Universitario de Cáceres, Hospital San Pedro de Alcántara, Cáceres, Spain*

Received 16 September 2017; accepted 22 January 2018

KEYWORDS
Eslicarbazepine acetate;
Sodium channel blockers;
Carbamazepine;
Chronic pain management;
Oxcarbazepine;
Adjunct therapy

Abstract Once patients have failed first line therapy, there is an apparent lack of knowledge on how to proceed with choosing subsequent therapy. To choose amongst alternative agents, an understanding of pharmacology, pharmacokinetics, and available evidence in targeting various pain conditions is necessary. This article focuses on the use of the carboxamide class of voltage-gated sodium channel blockers (carbamazepine, oxcarbazepine, eslicarbazepine acetate) for adjunct pain medication management; including research updates in pharmacology, pharmacokinetics, and evidence for pain along on this therapeutic group with promising future areas of research.

Although evidence for voltage-gated sodium channel blockers in chronic pain management is limited, emerging research has identified this area as promising for additional clinical trials to better guide clinical practice.

PALABRAS CLAVE
Acetato de eslicarbazepina;
Bloqueadores de los canales de sodio;

Papel de los bloqueadores de los canales de sodio dependientes de voltaje en el tratamiento del dolor crónico: usos potenciales en la práctica clínica según la evidencia disponible

Resumen Una vez que ha fracasado el tratamiento de primera línea en los pacientes con dolor crónico, parece haber una laguna de conocimiento sobre cómo proceder en la elección de un tratamiento posterior. Este artículo se centra en el uso de los bloqueadores de los canales de sodio dependientes de voltaje que pertenecen a la clase de las carboxamidas

☆ Please cite this article as: Alcántara Montero A, Sánchez Carnerero CI. Papel de los bloqueadores de los canales de sodio dependientes de voltaje en el tratamiento del dolor crónico: usos potenciales en la práctica clínica según la evidencia disponible. Rev Esp Anestesiol Reanim. 2018;65:275–283.

☆☆ This article is part of the Anaesthesiology and Resuscitation Continuing Medical Education Program. An evaluation of the questions on this article can be made through the Internet by accessing the Education Section of the following web page: www.elsevier.es/redar

* Corresponding author.
E-mail address: a.alcantara.montero@hotmail.com (A. Alcántara Montero).

Carbamazepina;
Manejo del dolor crónico;
Oxcarbazepina;
Tratamiento adyuvante

(carbamazepina, oxcarbazepina, acetato de eslicarbazepina) como tratamiento analgésico adyuvante; e incluye actualizaciones sobre farmacología, farmacocinética y evidencias en dolor de este grupo terapéutico, así como prometedoras futuras líneas de investigación.

Aunque la evidencia de los bloqueadores de los canales de sodio dependientes de voltaje en el manejo del dolor crónico es limitada, la investigación emergente ha identificado esta área como esperanzadora para que ensayos clínicos adicionales guíen mejor nuestra práctica clínica.

Introduction

It is estimated that 1 in 5 Europeans (19%) suffer from chronic pain.[1] Although few epidemiological studies have been performed at the national level, recent data suggest that prevalence in Spain is slightly lower than the European average (17%).[2] Chronic pain not only has a major impact on work, and social and family life, but also places a considerable financial burden on the health system.[2]

The lack of good therapeutic and management strategies for chronic pain is part of the problem; however, a limited knowledge of adequate treatments, specifically non-opioid analgesic drugs, is an important factor. Long-term opioid treatment for chronic pain has increased dramatically in recent years, particularly in the United States, despite insufficient evidence of long-term benefits and increasing evidence of harmful effects.[3] There are no studies comparing long term (over 1 year) opioid therapy versus placebo, treatment without opioids, or other therapies.[3] Tapering opioids can be a challenge for both patients and doctors. In clinical practice, long-term opioid treatment is only discontinued in 8–35% of patients, according to cohort studies.[4] However, there is little evidence to guide clinicians through the process of tapering opioid therapy.[5] In addition, the number of alternative therapeutic options is limited, and many clinicians have difficulty distinguishing between non-opioid analgesics.

It is imperative to approach and treat chronic pain with specific therapies for each pain syndrome. Although opioids may be indicated in some patients, it is difficult to control pain and reduce dependence on opioids without fully understanding which non-opioid drug therapies to choose. Therefore, it is essential to understand the risks and benefits of each therapeutic alternative and each adjuvant drug, in order to combat the current opioid epidemic and offer adequate treatment for chronic pain.

Nowadays, clinicians tend to base chronic pain management on the pathogenesis of pain. Therefore, in addition to, clinicians are urged not only to evaluate the pathology that triggers the pain, but also to characterise the type of pain based on the neurophysiological mechanisms involved, differentiating between nociceptive and neuropathic pain.[6] Once this has been determined, the next key step is to choose the right drug for each type of pain. Many clinicians are generally familiar with first-line treatments for inflammatory pain and neuropathic pain. However, once first-line treatment has failed, many doctors admit that they lack the knowledge necessary to differentiate between or effectively administer second-line treatment options.

Voltage-gated sodium channel blockers, specifically, carboxamides, which include carbamazepine (CBZ), oxcarbazepine (OXC) and, more recently, eslicarbazepine acetate (ESL), could be one of the most under-prescribed pain management alternatives. This could be due to the limited amount of experience and data available on these drugs compared to first line treatments. However, good pain management depends on familiarity with second- and third-line treatment, and understanding the role of each therapeutic class in the treatment regimen. In order to choose between alternative therapies, clinicians must understand the pharmacology and pharmacokinetics of each drug, and be aware of the available evidence supporting specific treatments for various chronic pain conditions. The aim of this article is to update evidence for the clinical use of voltage-gated sodium channel blockers, clarify misconceptions surrounding their use, and highlight emerging research on better pain targets that warrant further analysis.

For this purpose, we searched PubMed and Google Scholar for the most significant studies on this topic, using the following search criteria: ''*carbamazepine*'', ''*oxcarbazepine*'' and ''*eslicarbazepine acetate*'' in combination with ''*neuropathic pain*'', ''*inflammatory pain*'', and ''*chronic pain management*''. We also consulted the summary of product characteristics of CBZ, OXC and ESL to ascertain the adverse reactions, bioavailability, pharmacological and pharmacokinetic data of each drug.

Voltage-gated sodium channels as therapeutic targets in pain management

Voltage-gated sodium channels (Nav) contribute to pain syndromes by facilitating electric transmission and increasing the density of sodium channels around the lesion; both these mechanisms cause hyperexcitability and enhanced sensory transmission.[7,8] Nine voltage-gated sodium channels subtypes have been identified (Nav1.1-1.9), and several Navs have been linked to the transmission of inflammatory, nociceptive and neuropathic pain[7–11] (Fig. 1). Researchers have recently identified specific Navs that correlate with specific types of pain. This shows that targeting hyperactive channels may oversimplify the complex biological processes involved in pain signalling.[9,11]

Nav1.9 mainly occurs in the peripheral nervous system, whereas Nav1.8 is mostly found in the C fibres of