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Short Review

The Effect of Oxcarbazepine on Epilepsy, Neuropathic pain, Inflammatory Pain and Morphine Tolerance

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ABSTRACT

Oxcarbazepine has various actions. It can be used for treatment of epilepsy, trigeminal neuralgia, and diabetic neuropathy. In the animal study, oxcarbazepine has some evidence that it could be used for treatment of inflammatory pain and morphine tolerance.

INTRODUCTION

The Effect of Oxcarbazepine to Epilepsy

Epilepsy is a chronic non-communicable disease of the brain and it affects people of all ages. According to guidelines by the American Academy of Neurology and American Epilepsy Society [1], for the treatment of patients with newly diagnosed epilepsy, standard anticonvulsants such as carbamazepine, phenytoin, valproic acid, valproate semisodium, phenobarbital, or newer anticonvulsants including gabapentin, lamotrigine, oxcarbazepine or topiramate can be prescribed. Carbamazepine is used primarily in the treatment of epilepsy and neuropathic pain [2]. It is also used in schizophrenia, generalized seizures and as a second-line agent in bipolar disorder [2]. Common side effects of carbamazepine are nausea and drowsiness [2]. Serious side effects of carbamazepine may include skin rashes, decreased bone marrow function, suicidal thoughts, or confusion [2].

Oxcarbazepine is a structural analogue of carbamazepine, and it was developed in an effort to avoid side effects of carbamazepine and its active metabolites, and to improve the tolerability and pharmacokinetic profile of the carbamazepine [3]. Oxcarbazepine and carbamazepine appear to be similarly effective and well tolerated, however, oxcarbazepinemay have fewer side effects, except for more risk of hyponatremia compared to carbamazepine [4].

The Effect of Oxcarbamazepine for the Treatment of Neuropathic Pain

In 1994, the definition of neuropathic pain has been published by the International Association for the Study of Pain (IASP) as “pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system” [5]. However, in 2011, the definition of neuropathic pain was changed as 'pain caused by a lesion or disease of the somatosensory nervous system' by IASP [6]. Comparing the old and new definitions of neuropathic pain, tere are two important changes in the new version: (1) the word “dysfunction” has been removed and (2) a lesion or disease affecting the nervous system has been specified to be a lesion or disease of the somatosensory system.

Neuropathic pain manifests primarily as allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (an increased response to a stimulus that is normally painful). The mechanisms responsible for the induction of nerve injury-induced neuropathic pain, however, are not entirely clear [7].

Treatment options for neuropathic pain can be divided into pharmacological and nonpharmacological (e.g., interventional, physical, and psychological therapies) approaches.

(1) First-line pharmacological treatments for neuropathic pain

Amitriptyline (10-150 mg/day) is recommended as a first-line drug and its major side effects are dry mouth, constipation, urinary retention, and orthostatic hypotension [8]. gabapentin/gabapentin ER/enacarbil (1200-3600 mg/day tid) and pregabalin (300-600 mg/day bid), are the first-choice drugs [9]. The major side effects are dizziness, sedation, and peripheral swelling. Carbamazepine (200-400 mg/day) and oxcarbazepine (300-600 mg/day) are recommended for trigeminal neuralgia [10].

(2) Second-line pharmacological treatments for neuropathic pain

The opioid analgesics tramadol/tramadol ER (200-400 mg/day bid) and tapentadol (50-600 mg/day) are second-choice drugs [9]. The most common side effects are nausea, vomiting, and constipation [11]. Lidocaine (5%) plaster and capsaicin (8%) patch are recommended as second-choice drugs [9].

(3) Third-Line Drug Treatments for neuropathic pain

The strongopioids, morphine (10-120 mg/day) and oxycodone (10-120 mg/day), are recommended as third-line pharmacotherapeutic options. The neurotoxin, Botulinum Toxin subcutaneously (50-200 IU: every three months), is a third-choice treatment option.

Oxcarbazepine is a kind of the sodium channel blocker, and it's efficacious in peripheral neuropathic pain patients with the irritable nociceptor phenotype. The irritable nociceptor phenotype was defined as having L0G1, L0G2, L0G3, L2G1, L2G2, and L2G3. Thus, in the patients with the irritable nociceptor phenotype, upregulation of sodium channels on nociceptors is proposed to be an important pain-generating mechanism, and they are characterised by having cold and warmth detection thresholds within the normal [12].

Trigeminal neuralgia is a long-term pain disorder that affects the trigeminal nerve. The trigeminal nerve responsible for sensation in the face and motor functions such as biting and chewing. The typical form results in episodes of severe, sudden, shock-like pain in one side of the face that lasts for seconds to a few minutes and these episodes can occur over a few hours. The atypical form results in a constant burning pain that is less severe. Episodes may be triggered by any touch to the face [13].The treatment of trigeminal neuralgia should begin either with carbamazepine or with oxcarbazepine [14].

Diabetic neuropathy is very broad and heterogeneous term which encompasses a number of mono and polyneuropathies as well as plexopathies and radiculopathies. There is limited data regarding the efficacy of carbamazepine, oxcarbazepine and topiramate. Oxcarbazepine may have some effect, but we cannot be confident that the results [15].

The Effect of Oxcarbamazepinefor the Inflammatory Pain

In the animal study [16], male Wistar rats (180-220g) were included. Predrug hyperalgesia was obtained before intraperitoneal drug administration. Inflammatory hyperalgesia was induced 30min after intraperitoneal drug injection by intraplantar concanavalinA (0.8mg/paw) administration into the right hind paw. Postdrughyperalgesia was measured at 90, 150, 210, 270, and 330min after drug administration. Control animals received the same volume of intraperitoneal vehicle instead of test compound. The antihyperalgesic activity of carbamazepine (10–40 mg/kg; intraperitoneal) and oxcarbazepine (40–160 mg/kg; intraperitoneal) was determined by modified 'paw-pressure' test, using the apparatus for evaluating the force exerted by rat hind paws in order to determine right/left differences. A comparable pattern of antihyperalgesic effect of carbamazepine and oxcarbazepine was observed, and carbamazepine was about three times more potent than oxcarbazepine.

The Effect of Oxcarbamazepine for the Morphine Tolerance

Morphine is one of the most effective drugs currently used for pain management. However, its prolonged administration for chronic pain produces tolerance to the analgesic effects, and thus limiting their therapeutic potential. In the animal study [17], male Sprague-Dawley rats (200−250 g) were included. Tail-flick assay was performed for the measurement of acute nociceptive sensitivity. To induce the morphine tolerance, the

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dose of morphine 15μg was administered to intrathecal space through a polyethylene (PE-10) catheter implanted to the lumbar enlargement for 7 days. Oxcarbazepine (100 μg) was intrathecally co-administered with morphine for 7 days to evaluate the antitolerance effect of Oxcarbazepine. The decrease in morphine effect was completely blocked throughout the entire 7-day period.

CONCLUSION

Oxcarbazepine is a structural analogue of carbamazepine. In addition, oxcarbazepine and carbamazepine appear to be similarly effective and well tolerated, however, oxcarbazepine may have fewer side effects. Oxcarbazepine is a kind of the sodium channel blocker, and it's efficacious in peripheral neuropathic pain patients with the irritable nociceptor phenotype. Carbamazepine and oxcarbazepine are recommended for trigeminal neuralgia. Oxcarbazepine may have some effect for the treatment of diabetic neuropathy. In the animal study, Oxcarbazepine presented anti-inflammatory effect and attenuating effect against morphine tolerance.

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