

Epidural morphine for chronic pain in a patient with peripheral neuropathy and DRESS syndrome. Case report

Morfina peridural para tratamento de dor crônica em paciente com polineuropatia periférica e síndrome DRESS. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: Peripheral neuropathy is a rare condition with many etiologies. Common symptoms are numbness, paresthesia, weakness and neuropathic pain. Treatment consists in first-line agents such as anticonvulsants and some antidepressants. The aim of this study was to report a case of chronic pain refractory to several therapies in a patient with absolute contraindication to the use of all anticonvulsants and antidepressants drugs.

CASE REPORT: Female patient, a 40-year-old treated for trigeminal neuralgia with decompression that developed chronic occipital pain refractory to radiofrequency and onset of transient and bilateral T4 sensory and motor polyneuropathy after viral meningitis. In addition, she showed a severe pharmacodermis (Drug Rash with Eosinophilia and Systemic Symptoms- DRESS Syndrome) after using carbamazepine and other anticonvulsants, as well as allergy to all analgesics and opioids except morphine. Epidural puncture with insertion of a catheter was performed aiming at a 5-day test through intermittent epidural morphine bolus to assess the possibility of morphine pump implantation.

CONCLUSION: The test was successful and the patient referred to the neurosurgery team. At the 6-month follow-up after the insertion of the morphine intrathecal pump, the strategy has proven to be effective in controlling pain secondary to polyneuropathy.

Keywords: Analgesia, Drug hypersensitivity, Epidural, Morphine. Peripheral nervous system diseases. Syndrome. Trigeminal neuralgia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Neuropatia periférica é uma condição rara, de etiologia multifatorial. Dormência, parestesia, redução de força muscular e dor neuropática são sintomas comuns. O tratamento consiste em uso de anticonvulsivantes e antidepressivos. O objetivo deste estudo foi relatar o caso de dor crônica refratária a diversas terapias de uma paciente com contraindicação absoluta para uso de todos os fármacos anticonvulsivantes e antidepressivos.

RELATO DO CASO: Paciente do sexo feminino, 40 anos, com história de neuralgia do trigêmeo abordada previamente com cirurgia, com cefaleia occipital crônica refratária à radiofrequência e polineuropatia bilateral T4 sensorial e motora após meningite viral. No curso do tratamento, apresentou grave farmacodermia (*Drug Rash with Eosinophilia and Systemic Symptoms - Síndrome DRESS*) após o uso de carbamazepina e outros anticonvulsivantes, além de reação alérgica a todos analgésicos e opioides, exceto morfina. Optou-se por analgesia teste por via peridural, durante 5 dias, com *bolus* intermitentes e diários de morfina para avaliação de possibilidade de implante de bomba de morfina peridural.

CONCLUSÃO: O teste foi considerado bem-sucedido e a paciente encaminhada para neurocirurgia. No seguimento de 6 meses após implante de bomba por via subaracnoidea, esta estratégia se mostrou eficaz no controle da dor secundária à polineuropatia.

Descritores: Analgesia, Hipersensibilidade, Morfina, Neuralgia do trigêmeo, Peridural, Polineuropatias, Trigeminal neuralgia.

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HIGHLIGHTS

- A case report of a patient with a rare and potentially fatal allergic condition, the DRESS Syndrome, and refractory peripheral neuropathy;
- Morphine via epidural and later subarachnoid was used with satisfactory pain control, a treatment that is not considered first-line;
- Discussion of the mechanism of action of epidural and subarachnoid opioids in neuropathies.

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INTRODUCTION

Peripheral neuropathy includes all conditions resulting in injury to the peripheral nervous system and is best categorized by the location of the nerve injury¹. Distal symmetric polyneuropathy, mononeuropathy, and lumbar/cervical radiculopathy are the most common peripheral neuropathies². First-line agents include anticonvulsants that block the presynaptic calcium channel and thereby decrease nociceptive transmission, tricyclic antidepressants or selective serotonin-norepinephrine reuptake inhibitors. Second and third-line agents include opioid analgesics³.

These agents are effective for neuropathic pain but have a higher long-term risk profile and should only be used in carefully selected patients with predefined pain relief and functional goals⁴. When there is contraindication to anticonvulsants and antidepressants, neuropathic pain treatment becomes challenging. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, complex, potentially life-threatening, drug induced hypersensitivity reaction that often includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement. It is a severe cutaneous adverse reaction to drugs whose diagnosis and management require the involvement of various specialists⁵.

Cross-reactivity between aromatic anticonvulsant drugs (phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine) is well documented, varying between 40% and 80%⁵. These agents should be avoided in the future for antiepileptic drug therapy, as should tricyclic antidepressant agents, which cross-react mainly with amitriptyline⁵. Nonaromatic anticonvulsant drugs (gabapentin, topiramate, pregabalin and valproic acid) are, in general, considered safe alternatives⁵.

The present case report describes a scenario of pain refractory to several therapies in a patient with absolute contraindication to the use of all anticonvulsants and antidepressants. The patient was effectively treated with epidural morphine and posterior intrathecal pump.

CASE REPORT

The CARE (Case Report) checklist was used to report information in this manuscript do reduce risk of bias and increase transparency⁶.

This case report was approved by the Ethics and Research Committee (CAAE: 59617522.4.0000.0048). The patient was a 40-year-old woman, with history of trigeminal neuralgia (successfully addressed by trigeminal nerve decompression), who developed chronic occipital pain refractory to radiofrequency and also presented viral meningitis, with the onset of transient and bilateral T4 sensory and motor polyneuropathy (diagnosed as critically ill polyneuropathy). The Free Informed Consent Term (FICT) was obtained from the patient.

The neurologic exam found tetraparesis with muscle strength grade IV, hypoesthesia in stocking-glove pattern, occipital allodynia, distal hypopallesthesia and negative Romberg test. A cranial magnetic resonance image (MRI) showed a vascular loop in close relation to the trigeminal nerve and no parenchymal lesions. The only important findings at the spine magnetic resonance (MR) were small hemangiomas at C6, T1, T8 and L4. Hyperproteinorrachia was found at the liquor exam.

The patient exhibited severe pharmacodermis and DRESS syndrome with carbamazepine and other anticonvulsants, in addition to allergy to all analgesics and opioids except morphine. She was using timed-release morphine every 12 hours, 30 mg, orally, with no improvement in the painful symptoms.

The patient was hospitalized for test analgesia through intermittent epidural morphine bolus for 5 days to assess the pos-

sibility of morphine pump implantation. Venous puncture was performed and monitoring consisted of continuous ECG, pulse oximetry and non-invasive mean blood pressure. Epidural puncture was performed with the patient in the left lateral position at L2-L3 interspace using a 18G Tuohy needle and the loss of resistance to air technique. As a test dose, 6 mL of saline solution associated to 2 mg morphine were used.

Next, the catheter was introduced approximately 3 cm in the cephalad direction. A morphine *bolus* was performed daily, at a dose of 2 mg, and on the third day of administration, the choice was to increase the dose to 2.4 mg. By the fifth day, the patient had reported complete improvement of symptoms in the lower limbs and 70% improvement in the occipital headache, and the catheter was removed. The epidural morphine test was satisfactory, and the patient was referred to the neurosurgery team for scheduling a morphine intrathecal pump.

DISCUSSION

Morphine epidural analgesics has been used for the treatment of pain related to various etiologies and there are several reports on its results and complications⁷. There are few studies, however, that advocate the use of epidural morphine in the treatment of neuropathic pain secondary to polyneuropathies. Animal models of neuropathic pain show a relative decrease in opioid receptor numbers within the dorsal horn of the spinal cord ipsilateral to the site of nerve injury⁸. This probably reflects the loss of function of unmyelinated primary afferent fibers terminating in laminae 1-2, where their presynaptic terminals normally express a high density of mu and delta opioid receptors⁸. This change in receptor numbers is associated with a significant reduction in the anti-nociceptive actions of spinally administered morphine⁸. Studies in rats have shown that morphine reduced allodynia in a neuropathic pain model when administered via systemic and intracerebroventricular, but not by intrathecal route⁸. Morphine acting at a supraspinal level exerts its effects by activating descending inhibitory pathways and also by influencing nociceptive processing at a supraspinal level such as thalamic and cortical sites⁸. Interpreting the results of epidurally administered opioids is difficult because of the uncertainty over the extent to which the resulting analgesia is a consequence of supraspinal or spinal action. A case-control study with healthy volunteers evaluated the analgesic effect of epidural morphine in the trigeminal territory and concluded that some types of pain may be attenuated up to the supraspinal level after lumbar epidural administration of morphine⁹.

Peripheral neuropathy is among the most common neurologic problems encountered by primary care clinicians, but it can be challenging to recognize and evaluate because of its many diverse forms and presentations¹⁰. In this case, the patient had trigeminal neuralgia, which had already been surgically approached with decompression, but developed with radiofrequency refractory chronic occipital headache. In association, she presented bilateral symmetrical polyneuropathy in the lower limbs, with a transient episode of myelitis on T4 and transient sensory and motor impairment after an episode of viral meningitis¹⁰.

Regarding pharmacological therapies in neuropathic pain, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors and gabapentinoids are recommended as first-line treatments, and carbamazepine and oxcarbazepine are the first-choice drugs in trigeminal neuropathy¹¹. However, this patient had a contraindication for the use of anticonvulsants after exhibiting a severe and potentially fatal allergic reaction in one of her hospitalizations. Drug reaction with eosinophilia and systemic symptoms distinguishes it from other drug reactions because viral reactivation characteristically follows the onset of the disease. The disease usually starts abruptly with maculopapular exanthema with fever of $>38^{\circ}\text{C}$, 2-3 weeks after the introduction of the culprit drug^{7,8}. These symptoms usually occur 3 weeks-3 months after starting with a limited number of drugs, mainly anticonvulsants. These signs and symptoms seem to depend more on the individual characteristics of the patient than on the causative drug^{8,9}.

After joint assessment with the pain and neurosurgery team, the choice was to assess analgesia through intermittent morphine bolus for 5 days. After adjusting the daily dose of morphine from 2 mg to 2.4 mg on the third day, the patient reported 100% improvement in symptoms in the lower limbs and 70% improvement in headache, therefore, analgesia was considered satisfactory. The patient had no side effects related to systemic opioid absorption, such as nausea, vomiting, constipation or drowsiness. After removal of the catheter on the fifth day, she was referred to the neurosurgery team for scheduling a morphine pump implant. In a 6-month follow-up, analgesia through intrathecal morphine had satisfactorily relieved pain in this patient.

CONCLUSION

Although the use of opioids is not a first-line treatment for neuropathic pain, the use of epidural morphine was considered satisfactory for the control of pain symptoms related to peripheral neuropathy in the lower limbs and chronic occipital headache

refractory to radiofrequency. Nevertheless, its recommendation requires further studies.

AUTHOR'S CONTRIBUTIONS

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Data Collection, Validation

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Data Collection

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