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SCIENTIFIC LETTERS

Oral methadone for the management of difficult to control pain in Fabry disease☆

Metadona oral para el manejo del dolor neuropático de difícil control en la enfermedad de Fabry

Sr. Editor:

Neuropathic pain (NP) is usually the only manifestation of Fabry disease (FD) during childhood, along with angiokeratoma. It results from the dysfunction of the nervous system due to glycolipid accumulation in the dorsal root ganglia of sensory nerves and loss of nociceptors in peripheral tissues, manifesting with acroparaesthesia (burning sensation, paraesthesia, allodynia, hyperaesthesia, ...) that intensifies with physical exertion and changes in temperature, may be disabling, and impacts the patient's quality of life.

Although the management of NP has improved in recent years with the use of opioids and coadjuvants,[1] it probably is the pain state whose management is most challenging for paediatricians. Difficult pain is defined as pain that persists despite adequate use of opioids (optimal doses, switching opioid agents, adjuvant drugs, ...).

Methadone is the opioid of choice for the treatment of NP that responds poorly to opioid drugs.[2] It is a synthetic opioid that is slightly more potent than morphine, with unique pharmacokinetic and pharmacodynamic properties that may be advantageous in NP, but with a different safety profile that requires a thorough knowledge for its management. Its mechanism of analgesia involves opioid receptor agonism, NMDA antagonism and inhibition of serotonin and noradrenaline reuptake in the CNS. Its usefulness in the management of NP stems mainly from NMDA antagonism. It is highly lipophilic (has a high affinity for fatty tissues), with a large volume distribution that results in its gradual and delayed release to the bloodstream following its administration. It is metabolised by the liver and eliminated through the kidney and in stools.[3,4]

There is considerable variability in methadone plasma concentrations and elimination in children. On account of the former, it is impossible to predict when and how much of the drug will be released from fatty tissues, which can cause delayed toxicity due to the uncontrolled release of methadone to the blood, and even death in case of a massive release. On account of the latter, it is difficult to estimate its half-life. These particularities pose the main challenge to establishing dosages in children and hinder the calculation of an equianalgesic dose in patients that are already undergoing opioid treatment.

Studies in adults have proposed different morphine-methadone dose conversion ratios (based on the previous morphine dose, the reason for switching and the route of administration), as there is evidence that patients receiving higher doses of morphine require a proportionally smaller amount of methadone. The rotation scheme proposed by Ripamonti et al. (summarised in Table 1) continues to be among those used most widely.[5]

Most studies in the paediatric population analyse the use of methadone for nociceptive cancer pain, in end-of-life care or in the context of opioid weaning to prevent withdrawal syndrome after prolonged sedation. Fewer data are available on cancer NP, but to our knowledge, there are no data of its use in patients with refractory non-cancer NP, nor, despite the recent publication of studies focused on the paediatric age group,[6] equianalgesia charts developed exclusively for this population.

We present the case of a boy aged 14 years with a diagnosis of FD (p.W262X mutation in exon 5 of the *GLA* gene in chromosome X) presenting with disabling acroparaesthesias that were difficult to control, who had an excellent response to the switch from transdermal fentanyl to oral methadone.

As early as age 1 year, the patient had desperate crying fits associated with pain in the hands and feet. His baseline psychological status was one of increasing sadness, with refusal to feed, changes in everyday activities and moderate to severe malnutrition (BMI, weight and height percentiles < 1). Once NP was diagnosed, the patient initiated treatment with oral morphine at increasing doses, with was switched to transdermal fentanyl at equianalgesic doses for ease of administration combined with gabapentin (at the maximum dose), transdermal lidocaine and an anxiolytic agent, with no response. The patient experienced increasing pain with multiple hospital admissions during which treatment with IV ketamine was tried, resulting in a partial response that did not persist. This situation led to the switch to oral methadone, following the recommendations of Ripamonti (in this particular case, with a morphine:methadone equianalgesic conversion ratio of 8:1), with the total daily dose distributed in doses given every 8 h. After 9 days, the interval during which the drug was impregnating the fatty tissues, with a sustained intensity of pain and no signs of toxicity, the patient exhibited a response (from a baseline

☆ Please cite this article as: Carmona ML, Bueno SG, Tudela LR, Rodríguez JA, Sanchez F. Metadona oral para el manejo del dolor neuropático de difícil control en la enfermedad de Fabry. An Pediatr (Barc). 2018;88:47–48.

score of 5 in the visual analogue scale [VAS] rising to 10 during exacerbations, to a baseline VAS score of 1 and no exacerbations) accompanied by mild itching. The patient was managed with a multidisciplinary approach (nasogastric tube feeding, social support, normalisation of wake–sleep cycles, behavioural psychotherapy, ...) which he received well. At present, 6 months after the switch, the patient maintains the initial response, has discontinued the use of topical lidocaine and anxiolytic treatment, is pain-free and has a normal lifestyle (goes out with friends, attends school, is recovering his appetite, ...), with no signs of toxicity or side effects (normal ECG).

Despite having observed a single case, we can assert that the switch to oral methadone for the management of difficult-to-control non-cancer NP in children is a therapeutic option that should be contemplated if it can be delivered by experienced professionals and under strict in-hospital supervision.

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2341-2879/

Management and prognosis of intestinal epithelial dysplasia☆

Manejo y pronóstico de la displasia epitelial intestinal

Sr. Editor:

Intestinal epithelial dysplasia (IED) is a rare cause of untreatable diarrhoea.[1] It usually has onset in the neonatal period with severe secretory diarrhoea resulting in irreversible intestinal failure and indefinite dependence on parenteral nutrition (PN). Although cases with a favourable outcome have been described,[2] most of these patients depend on NP, so bowel transplantation is a treatment option that may help achieve enteral autonomy.[3]

We made a retrospective review of 3 patients with an epithelial dysplasia diagnosis. We analysed epidemiologic, clinical, diagnostic, treatment and outcome variables.

Secretory diarrhoea developed in the first month of life in all 3 patients. One patient was female and the other 2 were male. The former patient was of Ecuadorean descent and the other 2 were brothers of Moroccan descent born to consanguineous parents. All had been born to term and had adequate birth weights. The prenatal ultrasound examinations had been normal. None of the patients presented with atresia or punctuated keratitis. The immunological study was unremarkable. Histological examination of the intestinal mucosa revealed villous shortening and focal crowding of enterocytes resembling tufts (Figs. 1 and 2). The presence of a homozygous mutation in the *EpCAM* gene was confirmed in patients 2 and 3, with detection of a 17-base pair intragenic deletion (c.352_368del, NM_002354,2). The first patient did not undergo genetic testing.

All patients required PN to prevent dehydration. In the first patient, bowel transplantation was indicated on account of severe malnutrition and high electrolyte requirements. In the second and third patient, it was indicated following the development of PN complications, sepsis and liver disease.

At present, the 3 patients remain alive. Patient 1 has lived with a multivisceral graft for 8 years, patient 2 has lived with a multivisceral graft for 7 years, and patient 3 is awaiting re-evaluation after losing the graft to exfoliative rejection. The first 2 patients have achieved exclusive oral nutrition, exhibit improvement in weight gain and have a good quality of life.

☆ Please cite this article as: Rodríguez LT, de Lucas CL, García LNM, Nodal EM-O, Boluda ER. Manejo y pronóstico de la displasia epitelial intestinal. An Pediatr. 2018;88:48–49.