SCIENTIFIC LETTER

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

Dear 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, 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. 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.

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.

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, 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

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Please cite this article as: Carmona ML, Bueno SG, Tudela LR, Rodriguez JA, Sanchez F. Metadona oral para el manejo del dolor neuropático de difícil control en la enfermedad de Fabry. An Pediatr (Barc). 2017. https://doi.org/10.1016/j.anpedi.2016.11.010

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response that did not persist. This situation led to the switch
to oral methadone, following the recommendations of Ripa-
monti (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
score of 5 in the visual analogue scale [VAS] rising to 10
during exacerbations, to a baseline VAS score of 1 and no exacer-
bations) 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 therapeu-
tic option that should be contemplated if it can be delivered
by experienced professionals and under strict in-hospital
supervision.

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