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Oral formulation of pyridoxine for the treatment of pyridoxine-dependent epilepsy in a paediatric patient

Elaboración de una fórmula magistral de Piridoxina para el tratamiento de la epilepsia dependiente de piridoxina en un paciente pediátrico

Introduction

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive condition. The main cause of PDE is a deficiency of the alpha-aminoacidic semialdehyde (α -AASA) dehydrogenase or antiquitin involved in lysine breakdown, and which causes a build-up of α -AASA and pipercolic acid (PA) in urine and plasma. Classic PDE seizures appear during the first month of life. They are typically refractory to traditional antiepileptic drugs, such as valproic acid (VA), phenytoin, phenobarbital and levetiracetam, and show response to exogenous administration of pyridoxine^{1,2}.

The purpose of this letter is to describe the preparation of a formulation of pyridoxine in oral solution, for the treatment of a paediatric patient with PDE diagnosis.

Description of the Case

Female infant, born at term, was brought to the Emergency Department when she was 16 days old, due to hyperexcitability with myoclonic seizures. Treatment with phenobarbital and phenytoin was initiated, the first dose was an intravenous bolus, and then continued orally. After that, seizures ceased and phenytoin was withdrawn, and VA was initiated.

In order to conduct a neurometabolic study, samples of blood, urine, and spinal fluid (SF) were taken because the patient was refractory to conventional treatment and paediatrics suspected a potential vitamin deficiency. The patient was administered treatment with intravenous pyridoxine, intramuscular biotin, and oral folic

acid (FA), which was subsequently replaced by oral pyridoxal phosphate during 4 days.

After two days without seizures, new tests were conducted, and hyperammonemia (ammonium = 248 μ g/L, normal value (NV): 18.0-72.0 mol/l) secondary to VA was observed. The patient did not present severe symptomatology or hepatic or brain involvement. However, VA was replaced by levetiracetam. Carnitine and arginine were also administered, and treatment with carglumic acid was initiated. Regardless of these measures, ammonium levels were not sufficiently reduced, and doctors decided to move the patient to the ICU. After several days, ammonium levels became normal, and she was transferred to the ward.

The neurometabolic study showed normal levels of aminoacids, organic acids, lactate, neurotransmitters and biotinidase; therefore, treatment was reduced to antiepileptics only, and the patient was discharged.

However, high levels of PA in plasma: 4.04 μ mol/L and 0.91 μ mol/L in SF, as well as α -AASA in urine 13.53 (NV 0.27-2.85) were also observed, and undetectable levels of biotin in SF and very reduced in blood: 6 mmol/L (NV: 24-123).

At the same time, a genetic study was conducted on the patient's parents, which showed various mutations in the AASA dehydrogenase (ALDH7A1) in both of them, inherited by the patient. Consequently, PDE was diagnosed, and oral pyridoxine was administered, and the levetiracetam dose was reduced until its withdrawal.

In order to adjust the dose to the patient's weight (10 mg/kg/day), the Paediatrics Department requested pyridoxine in oral solution. Even though there is a commercial formulation (Conductasa[®]) with 153.3 mg/5 ml of pyridoxine alphacetogluturate, this formulation, is not suitable for the volume required. Furthermore, in order to respond immediately to the needs of the patient we were not able to use pyridoxine as raw material. Following the recent Guidelines for Good Practice in Preparation of Medications in Hospital Pharmacy Departments (GBPP)³, which allows the elaboration of compounded formulas from marketed drugs, we decided to prepara-



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re a compounded formula at 25 mg/ml, based on formulations described in bibliography at 1 mg/ml⁴. To this aim, we used Benadon® in vial, simple syrup and drops of strawberry flavour, following the recommendations published by the WHO for paediatric formulations⁵. Benadon® contains 150 mg/ml of pyridoxine hydrochloride equivalent to 123.36 of vitamin B6, the rest of their components are: disodium edetate, sodium metabisulfite, phenol, sodium hydroxide and water for injection. Although commercial vials of Benadon® contain phenol, its dose is very low and it is unlikely to be toxic for oral administration⁶. The syrup contains saccharose 64%, water 36% and methyl parahydroxybenzoate 0.1%, with pH 6.4 marketed by Fagron Ibérica as provider.

As the concentration was different to the one described in bibliography, an initial beyond use date (BUD) of 14 days was assigned following recommendations from non-sterile preparations risk matrix included in GBPP³. Pyridoxine is water-soluble and photosensitive. A weekly galenic study of stability was conducted during two months, according to Pharmacopoeia for aqueous solutions with oral administration, assessing: colour, smell, taste, homogeneity, lack of crystallization, transparency, and pH; stored refrigerated and protected from light. The particle control was done visually with a black and white background, and pH measure with an universal indicator paper pH. The following results were obtained: solution with a transparent and homogeneous colour, intense smell, sweet taste, without any particles present, and pH 5. All parameters stayed unaltered during the period of the study. However, we still assigned a BUD of 14 days stored refrigerated and protected from light

until further physicochemical data would be investigated³. As limitation of the study, we do not have available a high performance liquid chromatography (HPLC) technique.

The patient is currently on treatment with pyridoxine at 15 mg/kg, she is stable and without seizures. The good tolerability to the formula and the lack of adverse effects should be highlighted.

Discussion

The molecular basis for PDEs are the mutations in the ALDH7A1¹ gene which are involved in lysine breakdown. This aminoacid is metabolized in mammals by two convergent pathways (Figure 1). Through the saccharopine pathway, there is α -AASA production by the action of the α -AASA synthase, while through the PA pathway, there is a production of piperidine 6-carboxylic-acid (P6C) which is in balance with α -AASA. P6C is combined with pyridoxine through a Knoevenagel condensation in order to be eliminated. The α -AASA transforms into alpha-aminoapipic acid (α -AA) through antiquitin⁷. The mutation of the gene of this enzyme causes an accumulation of α -AASA and of P6C⁸, and the depletion of pyridoxine. At the same time, an excess of P6C transforms into PA due to P5C reductase. The pathognomonic signs of PDE are that PA and α -AASA levels are elevated in SF, plasma and urine (though these can also be increased in hepatic conditions and diseases of peroxisomes, such as Zellweger's Syndrome).

Pyridoxine is a water-soluble vitamin involved in a great number of metabolic pathways, primarily of aminoacids and neurotransmitters. Its deficiency can trigger

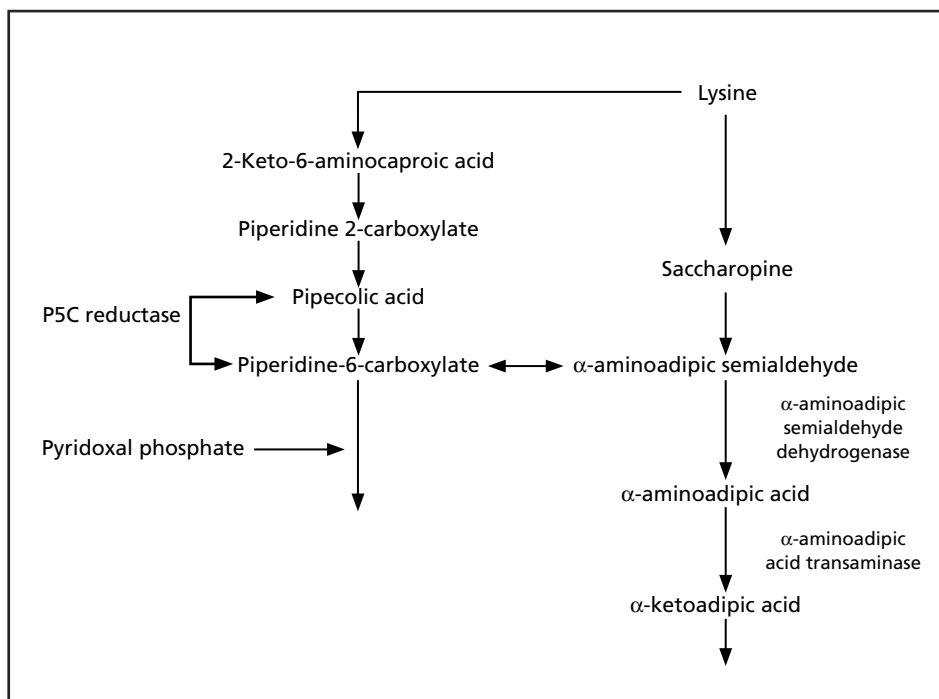


Figure 1. Lysine catabolism.

epileptic seizures due to an alteration in neurotransmitter metabolism, and also through direct toxicity due to the accumulation of PA and α -AASA. An exogenous administration of pyridoxine will normalized serum levels, thus improving the epileptic symptoms.

The preparation of a pyridoxine formula as oral solution has represented an effective alternative for PDE treatment, and has also allowed dose adjustment by weight in a paediatric patient. The patient has not presented any side effects, and has good tolerability to the formula; currently she keeps asymptomatic.

Bibliography

1. Mills PB, Footitt EJ, Mills KA, Tuschl K, Aylett S, Varadkar S, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). *Brain*. 2010 Jul; 133(Pt 7):2148-59.
2. Van Rooij LG, Hellstrom-Westas L, de Vries LS. Treatment of neonatal seizures. *Semin Fetal Neonatal Med* 2013 Aug; 18(4):209-215.
3. Casaus Lara ME, Tarno Fernández ML, Martín de Rosales Cabrera AM, García Salom P. Guía de Buenas Prácticas de Preparación de Medicamentos en Servicios de Farmacia Hospitalaria. Ministerio de Sanidad, Servicios Sociales e Igualdad, Agencia Española de Medicamentos y Productos Sanitarios, Sociedad Española de Farmacia Hospitalaria. Dirección General de Cartera Básica de Servicios del SNS y Farmacia. Subdirección General de Calidad de Medicamentos y Productos Sanitarios. Junio 2014.
4. Takemoto CK, Hodding JH and Kraus DM. *Pediatric & Neonatal dosage handbook*. 18th Edition. 2011.
5. WHO Development of paediatric medicines: points to consider in formulation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth Report. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970).
6. Souza A, Jr, Santos D, Fonseca S, Medeiros M, Batista L, Turner M, et al. Toxic excipients in medications for neonates in Brazil. *Eur J Pediatr* 2014 Jul;173(7):935-945
7. Eduard A. Struys, Cornelis Jakobs. Metabolism of lysine in α -aminoadipic semialdehyde dehydrogenase-deficient fibroblasts: Evidence for an alternative pathway of pipercolic acid formation. *FEBS Letters* 584 (2010) 181-186.
8. Struys EA, Bok LA, Emal D, Houterman S, Willemsen MA, Jakobs C. The measurement of urinary Δ^1 -piperideine-6-carboxylate, the alter ego of α -aminoadipic semialdehyde, in Antiquitin deficiency. *J Inherit Metab Dis*. 2012. Sep; 35(5):909-16.

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