Vitamin D and its receptor: Reflections on the unusual tendency to create supposed diseases☆

La vitamina D y su receptor. Reflexiones sobre la inusitada tendencia a crear supuestas enfermedades

To the Editor

Since the middle of the last decade, there is consensus that in the adult population, vitamin D deficiency can be defined as levels of calcifediol (25(OH)D) of less than 50 nmol/L (20 ng/mL) and vitamin D insufficiency as levels between 50 and 80 nmol/L (20–32 ng/mL), while values greater than 80 nmol/L are considered sufficient. These thresholds are also taken as valid in everyday paediatric clinical practice.[1]

The consequence of these definitions is that levels of calcifediol of less than 32 ng/mL may be considered pathological and consequently an indication for replacement therapy, with the drawback that healthy children are considered to be in the stage preceding disease.

In 2017, we gathered the calcifediol measurements recorded in our hospital over a period of 18 months ($n = 161$). We found that 41 patients (25.5%) had normal levels, 85 (52.8%) insufficient levels and 35 (21.7%) deficient levels. The levels of intact parathyroid hormone (iPTH) were low (<10 pg/mL) in 12 patients (7.5%) and normal (10–65 pg/mL) in the rest. We did not find statistically significant differences in the levels of iPTH in relation to the 3 groups of calcifediol levels (ANOVA).[2]

Recently, we measured calcifediol levels in 42 obese children. We compared the results with those of a group of 76 healthy children in the same geographical area. The levels of calcifediol in the obese group were lower compared to the other group (24.7 ± 7.9 vs 28.9 ± 7.7 ng/mL, $P = .006$). In the obese group, 24.4% of children had sufficient levels, 42.9% insufficiency and 35.7% deficiency. In the healthy group, 35.5% had sufficient levels, 55.3% insufficiency and 9.2% deficiency. The differences in the proportion of children corresponding to each range of calcifediol levels were statistically significant ($P = .002$). None of the children had manifestations compatible with rickets (subclinical vitamin D deficiency) or elevated levels of iPTH.[3]

How can it be that in 3 different samples of children residing in the island of Tenerife, which receives more than 3000 h a year of sunshine, this many have vitamin D deficiency or insufficiency?

Leaving aside that calcifediol levels do not always accurately reflect the levels of calcitriol, which is the active form of vitamin D, the assessment of vitamin D metabolism should take into account other basic and influential aspects, such as the levels of vitamin D binding protein (DBP), the existence of variants of this transport protein with different affinities for vitamin D metabolites, and the variability in the functionality, density and number of nuclear vitamin D receptors (VDRs). In regard to the latter, a study conducted in 1993 demonstrated that rats with spontaneous hypercalciuria (genetic hypercalciuric stone-forming rats) exhibited increased VDR gene expression in intestinal cells. Yao et al. demonstrated that these animals had hyperresponsiveness of VDR gene expression even at low levels of calcitriol.[4]

Thus, a child or adult with levels of vitamin D considered insufficient or lower that happens to carry a genetic variant promoting the function of DBP or VDR and/or with an adequate density of VDRs is likely to exhibit adequate intestinal absorption of calcium. While all of these factors cannot be assessed in everyday clinical practice, clinicians should be cautious in prescribing vitamin D replacement based solely on calcifediol levels and consider other clinical or biochemical parameters. We also believe that while awaiting further data, it would be advisable that the ''insufficiency'' term that often accompanies values in the normal range in laboratory reports no longer be used.

In our region, vitamin D supplementation is frequently used in children and adults with insufficient levels of calcifediol, and we assume that this practice is also widespread in all of Spain. In this regard, the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices) recently published an *informational note* citing cases of hypercalcaemia in children receiving ''daily doses much higher than recommended for prevention of vitamin D deficiency.'' It is important to consider that this note does not differentiate between overdosing and toxic doses. We must not forget the cases of so-called ''idiopathic hypercalcaemia'' that emerged in the United Kingdom in the 1950s as a result of vitamin D fortification of foods consumed by children, which gave rise to the novel concept of vitamin D hypersensitivity.[5] Let us hope that in upcoming years we will not be reminded of the historic quote that ''those who cannot remember the past are condemned to repeat it.''

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☆ Please cite this article as: García-Nieto V, Cristina Ontoria Betancort M, Martin PC, Pons MR. La vitamina D y su receptor. Reflexiones sobre la inusitada tendencia a crear supuestas enfermedades. An Pediatr (Barc). 2020;92:167–168.

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9 February 2019 26 April 2019

https://doi.org/10.1016/j.anpede.2019.04.016
2341-2879/

Levamisole in the treatment of nephrotic syndrome☆

Experiencia con levamisole en el tratamiento del síndrome nefrótico primario corticodependiente

To the Editor:

The use of levamisole in the management of nephrotic syndrome started soon after the authorisation of steroid therapy.[1] It is an antihelminthic agent with immunomodulatory properties that are not well understood, and without immunosuppressive effects, unlike the rest of the drugs used in these patients.[2] On the other hand, it is the least toxic and least expensive drug.[3] In 2004, it was withdrawn from commercial markets due to the lack of clear indications and its infrequent use in humans.[4] It has proven effective in some patients with steroid-dependent primary nephrotic syndrome as a steroid-sparing agent.[4]

We conducted a retrospective descriptive study on the population of patients with nephrotic syndrome and high-dose steroid dependency given levamisole at the paediatric nephrology unit of our hospital between January 1, 2000 and December 31, 2017. Of the 104 cases of nephrotic syndrome we reviewed, we excluded 38% due to missing data. Levamisole was given to patients with steroid-dependent nephrotic syndrome treated with high-dose prednisone (> 0.5 mg/kg/48 h). In some cases, this followed treatment with oral cyclophosphamide and in others it preceded administration of cyclophosphamide (second step treatment). A histopathological examination was not performed, as this diagnostic test is performed prior to initiation of the third step of treatment. We classified patient response to levamisole into 2 categories: ''complete'' when patients experienced no recurrences over at least 2 years of treatment, and ''partial'' when patients experienced 2 or fewer recurrences in 1 year, allowing discontinuation of steroid therapy. The drug was compounded in the prescribed dose in gel cap form at the hospital's pharmacy. All patients received the standard dose of 2.5 mg/kg of body weight every 48 h, administered orally.

A total of 18 patients received levamisole, 10 girls and 8 boys, aged 2–6 years. Of these 18 patients, 12 (66.6%) responded to the treatment: 5 exhibited complete remission (27.7%) and 7 (38.8%) partial remission (Fig. 1). Treatment was discontinued after 2 years in patients that responded, but it had to be reintroduced in 7 out of the 12 due to recurrence. The mean duration of treatment was 4.3 years. One patient with levamisole dependence continued treatment through his transition to adult care. As for adverse reactions, only 2 patients developed transient urticaria attributable to levamisole that did not require discontinuation of the drug.

In recent years, few studies have assessed the efficacy of levamisole. Furthermore, it is inexplicably absent from most guidelines and clinical management protocols, except in France, and thus not assigned a specific timing in the stepwise management of nephrotic syndrome, unlike the rest of the treatment options.[5] The few studies that have been published had study periods of at most 1 year, and usually did not have a prospective design, except for an interesting multicentre clinical trial published in 2018 with a 1-year follow-up.[3] In this trial, 26% of patients treated with levamisole had not experience recurrences at 1 year, a percentage similar to the one found in our sample at 2 years (27.7%). Another study involved administration of higher doses (double) when patients did not respond to the standard dose, which had positive results.[6]

When it comes to adverse reactions, in addition to urticaria, there have been reports of mild to moderate neutropenia, which did not occur in any of the patients in our sample.[3]

In Spain, levamisole is available under the regulation applied to foreign drugs. At present, authorised drugs that are used off-label are requested according to this protocol

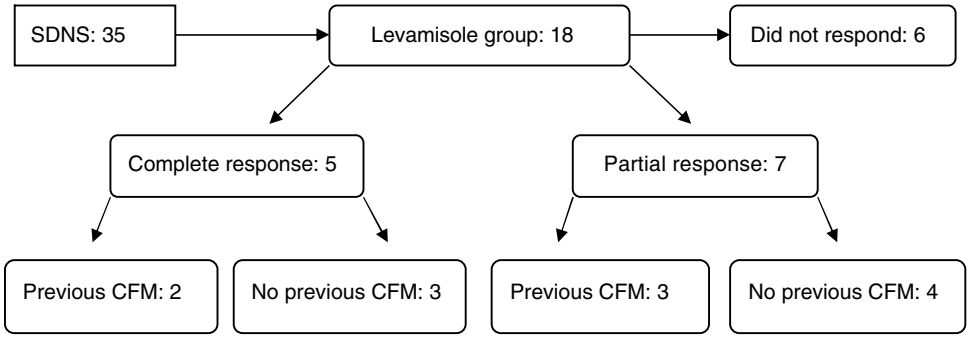

Fig. 1 Flowchart representing the response to levamisole and its association with the previous use of cyclophosphamide. CFM, cyclophosphamide; SDNS, steroid-dependent nephrotic syndrome.

☆ Please cite this article as: Soto LG, Romera PM, Andrade JEV, Llorente MAG, Fernández PdD. Experiencia con levamisole en el tratamiento del síndrome nefrótico primario corticodependiente. An Pediatr (Barc). 2020;92:168–169.