Received:
5 January 2015
Accepted:
25 February 2016
Available online
14 April 2016

Neonatal transient hypophosphatemic hypercalciuric rickets in dizygous twins: A role for maternal alendronate therapy before pregnancy or antireflux medications?

Rachitisme néonatal hypophosphatémique hypercalciurique transitoire chez deux jumeaux dizygotes : un rôle de l'alendronate maternel ou des traitements anti-reflux ?

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Summary

Background. Bisphosphonates (BP) are sometimes used in children and young women, but their use requires expertise and caution due to the relative lack of long-term efficacy and safety data.

Clinical cases. We report on two dizygotic male twins with a past of mild prematurity who presented at the age of 2 months with moderate clinical craniotabes, hypophosphatemia, normal circulating calcium, severe hypercalciuria, and low parathyroid hormone levels. Following supplementation with oral phosphorus and native vitamin D, the clinical and biological abnormalities disappeared within 2 months. Since the twins were dizygotic and were identical in terms of clinical presentation and progression, the only likely explanation for these transient mineral abnormalities was prenatal or neonatal exposure to a toxic agent. Taking into account their medical past, two drugs were possibly involved: either oral alendronate that their mother had received before pregnancy for misdiagnosed osteoporosis or antireflux medications, or both.

Discussion. We believe that these two cases could correspond to the first description of a potential mother-to-fetus transmission of alendronate, inducing early and transient hypophosphatemic rickets, the clinical picture being worsened by the antireflux drugs impairing intestinal phosphate absorption. For pediatric rheumatologists, this

Résumé

Introduction. Les biphosphonates (BP) sont parfois utilisés chez l'enfant et les femmes jeunes, mais leur utilisation nécessite expertise et prudence du fait de données limitées sur leur efficacité et leur sécurité à long terme.

Cas clinique. Nous rapportons le cas de deux jumeaux nés avec une prématurité modérée qui ont présenté à l'âge de 2 mois un tableau de craniotabès modéré associé à hypophosphatémie, normocalcémie, hypercalciurie importante et un certain degré d'hypoparathyroïdie. Avec une supplémentation en phosphore et en vitamine D, les anomalies cliniques et biologiques ont disparu complètement en 2 mois. Comme les jumeaux étaient dizygotes, et comme leur présentation et leur évolution clinique avaient été complètement parallèles, l'hypothèse d'une exposition transitoire néonatale ou prénatale à un toxique était la plus probable pour expliquer le tableau. Deux agents ont été identifiés à l'interrogatoire : l'alendronate oral que la mère avait pris avant la grossesse pour une « ostéoporose », et les médicaments à visée anti-reflux (utilisés à doses habituelles), les deux pouvant être en cause séparément ou ensemble.

Discussion. Ces deux cas peuvent correspondre à la première description d'un passage transplacentaire de BP ayant des conséquences cliniques, dans un contexte de traitement anti-reflux pouvant limiter

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http://dx.doi.org/10.1016/j.arcped.2016.03.001 Archives de Pédiatrie 2016;23:957-962
0929-693X/

raises the question of more clearly defining the indications for BP in female children and teenagers; for rheumatologists, this also demonstrates the importance of correctly diagnosing osteoporosis and not using BP off-label, especially in women of child-bearing age.

par ailleurs l'absorption intestinale de phosphore chez des anciens prématurés. Pour les rhumatologues pédiatres, cela pose la question d'une définition plus claire des indications de BP chez les jeunes filles ; pour les rhumatologues, cela pose la question des ostéoporoses mal diagnostiquées et sur-traitées par des BP, surtout chez les femmes jeunes encore en âge de procréer.

1. Introduction

Bisphosphonates (BPs) are pharmacological agents inhibiting bone resorption by osteoclasts. They are sometimes used in children and young women of child-bearing age but their use requires expertise and caution due to inadequate long-term efficacy and safety data [1]. In this setting of limited evidence on the use of BPs during childhood and young adulthood, some reports have highlighted a potential risk for young girls and women receiving BPs before pregnancy, since the total elimination of BP from the body is a multiphasic and long-term procedure, due to the prolonged binding of BP to bone and progressive release [2]. In this report, we describe two dizygotic male twins presenting at 2 months of age with a phenotype of mild clinical rickets and biological abnormalities of calcium and phosphate metabolism, two toxic agents possibly being involved: either oral alendronate that their mother had received before pregnancy for misdiagnosed osteoporosis or antireflux medications, or both.

2. Clinical cases

These two dizygotic male twins were born at 34 weeks of gestation. They had a family history of vitamin D deficiency and maternal fractures. There was no history of specific genetic diseases or consanguinity. Fetal growth was normal, birth body weight was at the 50th percentile for gestational age. The progression of their prematurity was normal for respiratory comorbidities and growth (discharge at the age of 10 days). However, they presented with gastrointestinal complications, leading to a diagnosis of cow's milk protein allergy in the first twin associated with reflux, while the second twin only suffered from reflux: they both received sodium alginate and esomeprazole at usual doses. Indeed, the two twins received a formula for premature neonates (Premodilac®) from birth to day 10; they were then switched to Peptijunior® from day 10 to day 29, and then to Neocate® from day 29, and their mother fed them properly. Esomeprazole (1 mg/kg per day) and the combination of sodium alginate/sodium bicarbonate/calcium carbonate (Gaviscon®) was added at day 49; in the first twin esomeprazole was increased up to 2 mg/kg per day from day 64.

The two twins presented at 68 days of age with similar abnormalities appearing at the same time, namely a clinical phenotype of moderate craniotabes and biochemical mineral abnormalities including hypophosphatemia, normal circulating calcium, severe hypercalciuria, low parathormone (PTH) levels, and increased total (and bone) alkaline phosphatase levels (the latter biomarkers reflect the severity of rickets), as summarized in *table I* for one of the twins. Skeletal radiographs of the hand, legs, and skull revealed very moderate rickets (if present as illustrated in *fig. 1A–C*). The twins initially received calcium (100 mg/kg per day), ergocalciferol (300 IU/kg per day), and oral phosphorus supplementation (25 mg/kg per day). No active vitamin D was required to correct serum phosphorus.

They were referred to our unit 1 month after initiating these therapies. Calcium supplementation was withdrawn and the dose of vitamin D was decreased because of the presence of severe hypercalciuria. Following supplementation with oral phosphorus and native vitamin D, all clinical and biological abnormalities disappeared within 2 months: phosphorus supplementation was withdrawn at the age of 5 months for the first twin and 6 months for the other one. All the biological values and therapies are reported in *table I*. *Fig. 1*B illustrates the hand X-rays 7 months after the onset of clinical symptoms (and 2 months after phosphorus withdrawal). Total alkaline phosphatases rapidly normalized. At the last follow-up (at 19 months of age), both twins had normal growth, and mineral biochemicals were completely normal without any supplementation (except oral vitamin D as recommended by French pediatric guidelines).

We found no obvious explanation for this unusual phenotype. Since the twins were dizygotic and were identical in terms of clinical presentation and progression, the only likely explanation was exposure to the same exogenous agent. We first discussed the role of gastrointestinal antacids since they are known to decrease intestinal phosphate absorption; however, since esomeprazole had been used at usual doses only for 2.5 weeks at the onset of symptoms, we ruled out that this could explain the complete clinical phenotype. However, we knew that there was a family history of vitamin D deficiency: the mother had been diagnosed with osteoporosis by her general practitioner at the age of 23 years: she complained of muscular pain, asthenia, weight loss, and anorexia. Biological investigations revealed severe vitamin D deficiency. She had already presented two traumatic fractures (wrist and collar bone 5 and 10 years earlier, respectively). A dual energy X-ray absorptiometry (DXA) was performed at that time,