



## Overdose with Vitamin D in Newborns (Morocco): 4 Case Reports

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### ABSTRACT

*It is established that children, especially infants, are subject to adverse drug reactions in view of the physiological immaturity of their renal, hepatic and immune functions as well as the lack of marketing authorization for certain pediatric forms, particularly in neonatology, increases this risk. Currently, for some diseases, children are not treated according to age. Doctors are often required to prescribe medicines designed for adults, which can have serious or even dramatic consequences. Pharmacovigilance aims to ensure the safe use of medicines and to monitor adverse drug reactions not only under normal conditions of use but also in case of medication errors. Here we report four cases of overdose by vitamin D in a prospective study in relation with drugs side effects who was conducted for 6 months in 2013 at children's hospital of Rabat in Morocco (HER, Hôpital d'Enfants de Rabat). The description of the clinical and paraclinic effects of the four cases was severe dehydration with hypercalcemia and nephrocalcinosis, vomiting, refusal of breastfeeding, weight loss. The four infants had taken a dose of 600,000 international units (IU) during the first fifteen days of life. They were hospitalized, followed a corrective treatment, the evolution after treatment was favorable with a follow-up of growth.*

**Keywords:** Newborns; Vitamin D; Overdose; Nephrocalcinosis; Pharmacovigilance

### INTRODUCTION

Vitamin D is known to play an important role in bone metabolism through regulation of calcium and phosphate homeostasis and may also play an important role in immune system regulation. Vitamin D is produced by the body during exposure to sunlight, but is also found in oily fish, eggs and fortified food products. Infants are born with low vitamin D stores and are dependent on breast milk, sunlight or supplements as sources of vitamin D in the first few months of life. As the vitamin D content of breast milk is dependent on maternal vitamin D status and is often low, and sun exposure may be restricted for infants living at higher latitudes or for cultural or other reasons, infants are particularly vulnerable to vitamin D deficiency. Vitamin D deficiency in infants can lead to bone malformation (rickets), seizures and difficulty breathing. The incidence of nutritional rickets (NR) is rising globally [1]. Current evidence suggests that vitamin D supplements may be effective in preventing rickets, particularly for infants and children who may be at higher risk due to limited sun exposure or those with darker skin pigmentation, however further research is needed before specific recommendations can be made [2]. However, Infants are particularly vulnerable to toxicity associated with vitamin D overdose. Worldwide; the dosages recommended by the authorities of health differ according to the various existing specialities on the market and the mode of supply (breast-feeding or artificial feeding with or without milk enriched in vitamin D. In Morocco until 2013, the vitamin D was represented on the Moroccan market by a single patent drug in the form of injectable or drinkable bulb of 600.000 IU.

In Morocco the recommendation until 2013 of vitamin D in order to reduce the prevalence of nutritional rickets is one dose of 600.000 IU at birth and the same dose at 6 months of life [3].

Among the objectives is to study the cases of adverse effects of drugs and especially to make health professionals aware of the importance of the notification of adverse drug events to avoid serious consequences on the health of the pediatric population. Doctors are often required to prescribe medicines designed for adults, which can have serious or even dramatic consequences. The objective also was to propose preventive strategies and encourage regulatory authorities to carry out corrective actions.

## EXPERIMENTAL SECTION

A prospective observational study about adverse drug event in children was conducted for 6 months at Children's Hospital of Rabat (HER) between February and June 2013. The population included in this study was hospitalized patients in the various pediatric services of the hospital having an adverse drug event which was the subject of consultation or hospitalization. The study was authorized by the Ministry of Health and presented to the members of the hospital committee with the sensitization of the health professionals concerned with regard to the importance of spontaneous notification of cases of adverse reactions occurring during the duration of the study. So cases of adverse events in newborns that ingested an overdose of vitamin D were notified. These cases transcribed on notices of adverse events were reported to the Poison Control and Pharmacovigilance center Morocco (CAPM). These cases have joined other cases of overdose of vitamin D registered at the CAPM's database. The accountability of the cases was carried out according to the French method for the cause-effect study. A technical committee met and a national alert was triggered to raise the awareness of a greater number of public and health professionals (doctors, pharmacists, nurses) about the recommended dose of vitamin D for newborns and which is 200,000 IU (1/3 of 600,000 IU) unique pharmaceutical form present in 2013 on the Moroccan Market was an ampoule dosed at 600.000 IU. The other recommendations were also to adjust doses if the infant takes milk supplemented with vitamin D to avoid over-dosing and advice parents not to give extra doses of vitamin D without medical advice.

## RESULTS

The four cases admitted in the Children Hospital of Rabat and have been hospitalized presented various effects:

The first case notified by Nephrology Department was (S.A) (2 kg) (female) present Clinical and Para-Clinical Description of Adverse Event with severe dehydration, hypercalcemia and renal ultrasonography showed an image consistent with nephrocalcinosis. The time to onset of the adverse event after taking at fifteen days of life 600.000 UI of vitamin D was 5 days, the differential diagnoses eliminated were hyperparathyroidism and tubulopathy. The evolution of the adverse event was favorable with aftermath and monitoring of growth. The second case (M.R) (male) notified by Neonatology Department present Clinical and Para-Clinical Description of Adverse Event with dehydration, vomiting, refusal of breastfeeding, weight loss and nephrocalcinosis. The dose taken at the public health center of vitamin D was 600.000 UI at seven days of life. The evolution of the adverse event was favorable after the corrective treatment (rehydration hydro-electrolytic correction) and hospitalization with monitoring of growth. The third case (Y.M) (2.40 kg) (male) notified by the Nephrology Department present Clinical and Para-Clinical Description of Adverse Event with weight loss and ultrasonography showed an image consistent with nephrocalcinosis. The time to onset of the adverse event after taking at eight days of life 600.000 UI of vitamin D was 02 days. Subject not restored. The fourth case (A.M) (2.140 kg) (male) notified by Gastroenterology department present Clinical and Para-Clinical Description of Adverse Event with severe dehydration and secondary malnutrition after taking vitamin D, renal ultrasonography showed an image consistent with bilateral nephrocalcinosis. The time to onset of the adverse event after taking at fifteen days of his life 600.000 UI of vitamin D was 10 days, the differential diagnoses eliminated were the intolerance to cow's milk proteins and heart disease. The concentration of (25-OH) was 160 nmol/L. The evolution of the adverse event was favorable after the corrective treatment and hospitalization with monitoring of growth.

The role of the administered dose was evoked; in fact, the dose of vitamin D administered for these new-borns in the public health centers was 600.000 IU. The accountability of the case carried out in to the Poison Control and Pharmacovigilance center of Rabat (CAPM) using the French method revealed a causal relationship with a "plausible" convincing effect. On the chronological level: the time of appearance of the adverse reactions is compatible. On the semiological level: Semiology is plausible because it is suggestive of the role of the drug. Indeed, the undesirable effects occurred are the symptoms of the overdose in Vitamin D (Table 1).

**Table 1: Representation of the 4 cases with overdose of vitamin D**

Hospital service notifier and date of notification (Children's Hospital of Rabat)	Patient	Description of the clinical and paraclinic effect	Dose and route of administration	Dose start date and	Conduct adopted	Evolution of the patient after corrective treatment
Nephrology Department 25-02-2013	S.A	severe dehydration, hypercalcemia and nephrocalcinose	600.000 UI Oral dose of vitamin D	15 days of life	hospitalization, corrective treatment and patient follow-up	Favorable
Neonatology Department 24-04-2013	M.R	dehydration vomiting, refusal of breastfeeding weight loss nephrocalcinosis	600.000 UI Oral dose of vitamin D	7 days of life	hospitalization, corrective treatment and patient follow-up	favorable
Nephrology Department 17-05-2013	Y.M	weight loss and nephrocalcinosis	600.000 UI Oral dose of vitamin D	8 days of life	hospitalization, corrective treatment and patient follow-up	Subject not restored
Gastroenterology Department 13-06-2013	A.M	severe dehydration and secondary malnutrition after taking vitamin D	600.000 UI Oral dose of vitamin D	15 days of life	hospitalization, corrective treatment and patient follow-up	favorable

## DISCUSSION

Vitamin D intoxication occurs secondarily from excessive uptake of vitamin D. In many reported cases, intoxication is associated with accidental excessive uptake of prescribed vitamin D or consumption of OTC supplements containing vitamin D in high doses [4].

Worldwide, the daily intake recommended by the health authorities (the Institute of Medicine of the USA, the EU Scientific Committee on Food, WHO) for the pediatric population differ depending on the power mode (infants under breastfeeding or formula feeding with or without milk fortified with vitamin D or children fed with milk or other fortified foods or not vitamin D), sun exposure and other factors. Recommended intakes should reflect the real estimation of needs according to age, the existence of diseases and other factors that may interfere, all to avoid an overdose of Vitamin D. The recommended daily dose for the age of 0 to 1 year is 400 IU/day for bone health and 1000 IU/day to maintain a blood level of 25 (OH) D greater than 30 ng/ml [5]. In Turkey, since 2005, according to the recommendations of the Turkish Ministry of Health, vitamin D supplements (400 IU/day) are regularly prescribed to infants, free of charge in order to reduce the prevalence of nutritional rickets [6]. To prevent rickets and osteopenia in pre-term neonates, international guidelines vary between 800 and 1000 IU per day of vitamin D in Europe and recommend 400 IU per day in the USA, the diagnosis of vitamin D overdose in preterm infants should be considered in the presence of nephrocalcinosis or hypercalcemia or hypercalciuria in the neonatal period [7]. Preterm newborns of low birth weight are particularly at risk for envitamin D and rickets. Grant et al. showed that there was a direct relationship between the 25 (OH) D concentrations at the cord and maternal vitamin status [8]. Imputable mechanisms include low weight, changes in distribution volumes (low fat and muscle mass) and hepatic and renal immaturity leading to immaturity of vitamin D metabolism [9].

In Morocco, some improvements have been made in the area of nutrition. Indeed, the Ministry of Health has established a set of specific interventions to improve the nutritional status of vulnerable populations such as growth monitoring, promotion of the practice of breastfeeding, supplementation with vitamins and minerals for children and women during pregnancy and post-partum and the promotion of the consumption of foods fortified with micronutrients that have been set up on CIN (intersectoral Committee on Nutrition and CNN (Committee national Nutrition) to monitor the national Nutrition Strategy of 2011-2019 [10]. Nevertheless, there must be a consensus in Morocco on the real estimation of intake recommended for any age group and especially the pediatric population. In addition, health professionals should be alert continuously on the need to respect the terms of administration of pharmaceutical forms of vitamin D in newborns and infants as well as risks related to errors and overdoses.

## CONCLUSION

In our case, the notification of those four cases of intoxication with vitamin D added to the other cases collected at the pharmacovigilance center (CAPM) database triggered a technical committee and the national alert that followed which raised even more awareness about vitamin D intoxication with this excessive intake of 600,000 UI which has led to efforts being made by all professionals in the health sector to bring pediatric dosages to market. Currently, the

Moroccan Market contains several proprietary medicines based on vitamin D at dosages of 25,000 IU and 200,000 IU.

#### ACKNOWLEDGEMENTS

We thank the Colleagues in the Anti- Poison and Pharmacovigilance Centre in Rabat, all the Doctors in the Children's Hospital Committee and the Pharmacy Department of the Hospital for his support on the project

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