COMPLEX SIDE-EFFECTS OF CLASSIC ANTICONVULSANTS: THE FETAL HYDANTOIN SYNDROME

Gliția Mădălina¹, Matusz Anca Alexandra², Dumitrașcu Victor³

¹No 1 Emergency County Hospital, Timișoara, ²EGPRN Romanian National Representative, ³Victor Babes University of Medicine and Pharmacy Timișoara

Address for correspondence:
Dr. Mădălina Gliția,
Ale. Zorilor Bl. 13, Ap. 10, Tășnad, Satu Mare, PO 445300
Phone: 040075590796
E-mail: lescau.madalina@yahoo.com

Received: 11.03.2012
Accepted: 10.05.2012
Med Con June 2012, Vol 7, No 2, 47-50

Abstract

Classic generation anticonvulsant drugs have shortcomings such as suboptimal response rates, significant adverse effects, several drug interactions, and a narrow therapeutic index.

The authors present a clinical case report of a 12 years old male patient with a complex dysmorphic syndrome induced by chronic maternal exposure to high doses of phenytoin. The patient demonstrated microcephaly with trigonocephaly, hipoplasia of the nails and distal phalanges, multiple skeletal deformities and mental deficit; these anomalies are specific for the “fetal hydantoin syndrome”.

The shown images are suggestive for the phenytoin's teratogenic action.

The discussions allow an evaluation of the pertinent literature data concerning the pharmacology of phenytoin, its anticonvulsant properties and especially the consequences of its chronic exposure in utero.

In correlation with several important side-effects, this case report highlights the particular pharmacokinetics of phenytoin.

The paper reveals the importance of correct survey of pregnant women who take anticonvulsant drugs in order to avoid teratogen-induced malformations.

Keywords: fetal-hydantoin syndrome, chronic maternal exposure, classic anticonvulsants

Introduction

For the health care providers, there is a particular moral dilemma of treating pregnant and nursing women whose medical conditions require drug therapy. In this regard, there are drugs whose widespread and teratogenic potential make them likely candidates for long-term birth defect studies. Approximately 1 of every 200 women is epileptic and 95.7% of them are on anticonvulsant therapy, which is invariably continued throughout pregnancy and lactation [1,2,3]. The evidence indicates that anticonvulsant drugs are responsible for producing a two to three times greater incidence of malformations in the children of epileptic mothers [4,5].

Anticonvulsant-induced malformations, specifically “the hydantoin syndrome”, represent the most
commonly recognized teratogen-induced malformations [6].

Numerous studies suggest that in utero exposure to phenytoin can produce complex congenital malformations; therefore it is very important to study and to recognize its teratogenic actions on the developing human organism [7,8].

**Case report**

We report about a 12 years old male patient, with a particular complex of malformations, known as the "fetal hydantoin syndrome".

From the family history we note that the patient is the single child of a healthy father and an epileptic mother. The course of his mother’s pregnancy was uneventful in the first four months, but later, numerous prolonged jacksonian grand mal seizures occurred. The prevention of prolonged convulsions represented a vital important matter and required high doses of phenytoin (500mg/day) for an extended time period.

From the personal pathological antecedents it results that the child was delivered at term with normal birth weight and length and developed normally during the neonatal period. The plurimalformative syndrome became evident at the age of 4 months, when multiple fractures occurred due to excessive bone fragility. The boy was breast-fed, but his mother required and continued the anticonvulsant therapy with phenytoin with the same high doses.

The objective clinical examination made at the age of 12 years, revealed: Very short stature with infantile body proportions and postural problems; hypoplasias of the nails and distal phalanges (Fig. 1,2).

At the face level: marked disturbance of craniofacial growth with trigonocephaly and microcephaly (anatomic malformations that are specific for the "fetal hydantoin syndrome") (Fig. 3).

At the eyes level: the right eye was completely affected by microphthalmos, chronic blepharitis, loss of lashes and ectropion; the left eye presented with corneal dystrophy without vision impairment (Fig. 4).

At the thorax level: shortening of the trunk with severe kyphoscoliosis; respiratory insufficiency due to a defective thoracic cage (Fig. 5).
At the legs level: inequality of leg length; bilateral chondromalacia of the patella with deformities of the knee joint; left tibia vara (Fig. 6).

Roentgenograms reveal severe bone fragility which lead to progressive skeletal deformities (Fig. 7, 8).

Marked abdominal distension and hepatosplenomegaly with elevation of the diaphragm and compression of both lungs with reduced ventilation; no ascites were present (Fig. 9).

The neurological examination revealed several behavioral and neurologic deficits resulting in delayed motor development, persistent locomotor dysfunction and maze learning.

The laboratory data revealed low serum levels of calcium and phosphorus, but elevated levels of serum alkaline phosphatase, despite adequate vitamin D intake.

Therapeutic regimens including supplements of calcium, fluoride, vitamin C and of magnesium oxide have shown no clear benefit. Even calcitonin therapy is investigative at present.

The mainstay of management is an aggressive orthopedic regimen aimed at prompt splinting of fractures and correction of deformities, which have adverse psychological effects on the child. Surgical improvement may be attempted, especially when deformities are severe or if compression causes pulmonary difficulties.

**Discussions**

Phenytoin (diphenylhydantoin) is one of the most efficacious and widely used anticonvulsants, with the following chemical structure:

![Phenytoin Chemical Structure](image)

Phenytoin’s primary anticonvulsant effect at therapeutic concentrations is related to use-dependent blockade of voltage-sensitive sodium channels, thus inhibiting repetitive neuronal firing [9].

It has been suggested that patients with “fetal hydantoine syndrome” have low serum levels of 25-OH-D₃. Phenytoin can induce liver enzymes of the cytochrome 450 system of mixed oxidases, producing accelerated degradation of vitamin D and its excretion into bile as inactive glucuronides [10]. These data can explain the bone fragility and multiple fractures that occurred in our case.

Due to the nonlinear kinetics, it is prudent to initiate phenytoin therapy with the lower end of the dosing range and increase incrementally until clinical response, assessing for toxicity. The initial maintenance dosages are based on age and weight (for adults, including pregnant women, 4 to 7 mg per kg per day) [11]. Experimental studies on rabbits and mice revealed that the malformation rate was dose dependent [12].

Unrelated to its anticonvulsant properties, phenytoin is also an inducer of hepatic CYP-dependent monooxygenase enzymes that normally metabolize fatty acids, prostaglandins, steroids and xenobiotics; therefore, the long-term early exposure to phenytoin induces the so-called silent defect in the hepatic monooxygenase system [13]. In our studied case, the clinical expression of these biochemical changes was revealed by the presence of hepatosplenomegaly.

Chronic exposure to diphenylhydantoin has been suggested to present a maximum of 10 per cent risk for the full syndrome and a maximum of 30 per cent risk for some anomalies [14,15]. The hydantoin syndrome has been reviewed by Hanson and colleagues [16]. In accordance with this review, we revealed that trigonocephaly, microcephaly, hipoplasia of the nails and distal phalanges and mental deficit are specific anomalies for the “fetal hydantoin syndrome”.

Although rarely reported in the literature, the phenytoin’s teratogenic action represents a serious problem of medical practice. Several new anticonvulsants have been discovered and approved in response to the need for more effective and less toxic agents [17].

**Conclusions**

The “fetal hydantoin syndrome” represents an important aspect of perinatal pharmacology. Very few patients with “fetal hydantoin syndrome” reach adulthood; a considerable proportion of patients succumb to cardiorespiratory complications in infancy and childhood.
Phenytoin dosage in pregnant women must be slowly adjusted according to the individual patient’s requirements and response. Therapeutic drug monitoring is recommended for phenytoin to optimize therapeutic effect and minimize the chances of toxicity.

References