

DILI (drug induced liver injury) in a 9-month-old infant: a rare case of phenobarbital-induced hepatotoxicity

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Abstract

Phenobarbital is one of the most commonly prescribed antiepileptic drugs in childhood, but it can rarely cause serious adverse effects, such as hepatotoxicity that includes a broad clinical spectrum (from isolate hypertransaminasemia to acute liver failure). We describe a case of DILI in a 9-month-old infant caused by chronic therapy with phenobarbital.

Keywords

DILI, infant, phenobarbital, CYP3A4.

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Introduction

Introduced in clinical practice in 1911, phenobarbital represents one of the most commonly prescribed antiepileptic drugs in childhood and it is generally considered to be a fairly safe and effective drug. Phenobarbital has been reported, from the early fifties, to be associated to adverse effects, exfoliative dermatitis, morbilliform or scarlatiniform rash and hepatitis being the most frequently reported reactions to this drug [1].

Tubule-interstitial nephritis due to phenobarbital hypersensitivity has been rarely reported [2]. Phenobarbital-induced hepatotoxicity is an infrequent (8 cases to our knowledge [3-10]), but potentially serious, adverse effect [3]

and can present itself with asymptomatic and clinically insignificant elevation of transaminases or with hepatotoxic, cholestatic or mixed hepatitis (**Tab. 1**). Acute liver failure can be induced by several antiepileptic drugs, including phenobarbital, and may represent a very serious clinical problem, leading to death or acute liver transplantation [11]. Phenobarbital is well known to modify the metabolism of other associated drugs, by stimulating the synthesis of a broad range of hepatic conjugated enzymes, eventually reducing the half-life and action of many drugs [12]. Mechanisms of hepatotoxicity are various and complex [7, 13, 14]. Here we present a case on a child under chronic therapy with phenobarbital causing drug induced liver injury (DILI).

Case report

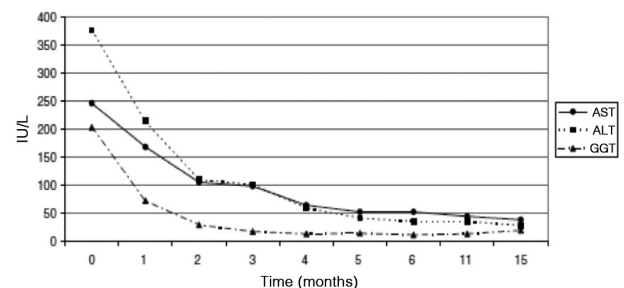
A 40 day-old female presented to our Hospital with *status epilepticus*. She was born at term, after physiological pregnancy and normal delivery. The family anamnesis evidenced a diagnosis of Gilbert syndrome in the mother and grandmother affected by autoimmune hepatitis. The infant was acutely treated with midazolam (0.025 mg/kg/h). Clinical and electroencephalographic features allowed us to diagnose a focal epilepsy and to initiate an oral therapy with phenobarbital (5 mg/kg/day). The patient underwent neurologic follow up. At 9 months of age, chemical-clinical data showed an increase in serum levels of AST (290 IU/L ; normal values < 40), ALT (493 IU/L; normal values < 40), gamma GT (278 IU/L; normal values < 32), without any other clinical manifestation. Viral markers were negative and all markers evidenced increased serum levels of antinuclear antibodies (ANA; 1:180) and of liver-kidney microsomal type 1 antibodies (LKM; 1:640). At abdominal ultrasonography, liver was in the normal range. Withdrawal of phenobarbital treatment, associated with switching to a better tolerated antiepileptic drug (Levetiracetam), was followed by a rapid decrease of serum transaminases and gamma GT levels, that reached normal reference values within one week (**Fig. 1**).

Discussion

The case here reported of phenobarbital-related liver disease shows some considerations. It is one of the few cases of phenobarbital hepatotoxicity reported in the literature under the first year of age. In general, DILI is infrequently reported in children, and represents about 1% of total adverse drug reactions

Table 1. Adult and pediatric cases of phenobarbital-induced hepatotoxicity.

Author and year	Age	Spectrum of DILI
Lane T et al.; 1984 [4]	No data available	Hepatitis
Palomeque A et al.; 1986 [5]	No data available	Cholestatic hepatitis
Mockli G et al.; 1989 [6]	2-year-old	Massive hepatic necrosis
Roberts EA et al.; 1990 [7]	8-month-old	Hepatocellular failure developed 3 weeks after phenobarbital



Transaminase values before treatment and during first months of therapy were normal.

Figure 1. Serum values of transaminases and GGT after phenobarbital withdrawal.

[15], being phenobarbital generally well tolerated in patients with normal liver [16]. The previously reported rare cases of phenobarbital-induced DILI in children under 1 year of age were associated with other severe diseases, including sepsis [7]. In our case we found high serum levels of ANA and LKM in the absence of any other significant clinical or laboratory pathological change. According with these data, we might suggest an autoimmune pathogenesis of phenobarbital-induced liver disease, which could be the basis of this idiosyncratic event. Data on the effects of antiepileptic drugs including phenobarbital on immune system are frequently inconsistent and sometimes conflicting [17]. The underlying mechanisms behind hepatotoxicity induced by phenobarbital may be different: i) a defect in drug detoxification responsible for children susceptibility to phenobarbital [7]; ii) hypersensitivity of the immune system, with activation of drug-specific CD4+ and CD8+ T-lymphocytes, leading to autoimmune hepatitis [13]; iii) mitochondrial oxidative phosphorylation [14]. Idiosyncrasy reaction may be a result of genetic or acquired differences in drug metabolism,

mitochondrial defects, canalicular secretion, or cell death receptor signaling. Anticonvulsant drugs are metabolized by the cytochrome P-450 isoenzymes, with generation of reactive arene oxide intermediates, whose detoxification is performed by epoxide hydrolases. Hepatotoxicity can involve an immune-mediated process, even if direct toxicity is also possible. The autoimmune reaction has been hypothesized to be related to phenobarbital-induced neoantigen formation, inducing immunoallergic mechanisms [11]. The autoantigen more frequently involved in autoimmune hepatitis type 2 is cytochrome P450 2D6 [18], whereas phenobarbital and other anticonvulsants induce hepatitis with anti-CYP3A4, the most abundant of the CYPs and the responsible for half of all drugs metabolism [19]. In conclusion the case here reported underlines the possibility that chronic phenobarbital treatment may cause DILI even in infants, through a possible autoimmune mechanism.

Declaration of interest

The Authors declare that there is no conflict of interest.

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