

FLUCTUATING PHENYTOIN LEVELS IN A PATIENT WITH EPIDERMOLYSIS BULLOSA DYSTROPHICA

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ABSTRACT:

Epidermolysis bullosa dystrophica being a genetically determined disorder, and when other factors that could cause fluctuations in the serum phenytoin levels are being eliminated, it is likely that the wide fluctuations of phenytoin in the blood could be a pharmacogenetic variation. The only course of action left in such patients could be to monitor the drug frequently and ensure that the levels are within the therapeutic margin.

Keywords : Epidermolysis, Pharmacogenetics, Phenytoin

CASE REPORT :

A 12-year old boy, born to consanguinous parents, presented with a history of blistering lesions on the skin, since birth. He had a strong family history of similar lesions. Clinical findings were typical of a mechanobullous disorder. On the basis of the history and clinical findings, a diagnosis of Epidermolysis bullosa dystrophica, of the recessive variety (EDBR) was made.

The patient was treated with Phenytoin 100 mg twice daily, vitamin E 200 mg once daily, Ferrous sulfate 100 mg once daily, protein rich diet and supportive therapy.

The serum phenytoin levels which were monitored at monthly intervals showed wide fluctuation. (Table - 1). New lesions appeared even 14 months after starting phenytoin therapy, which the parents felt occurred less frequently than before the initiation of phenytoin. They observed that the lesions were more severe when the serum phenytoin levels were low.

This patient showed good compliance to treatment. The formulations of the phenytoin that he had been taking were

standard. The bioequivalence reports of the two batches he had been using were satisfactory. Of the drugs that he was taking, the only ones that could have had any interaction with the phenytoin were Folic acid and Vit. B6 in the B-complex preparations. It was not sure whether the tablets were being kept in air-tight containers.

He was admitted to monitor the therapy and determine the cause for the fluctuations in phenytoin levels. He did not have any manifestations of adverse reactions of phenytoin except for gingival hyperplasia.

Genetic mapping of the siblings and relatives was suggested for genetic counselling.

DISCUSSION :

Recessive dystrophic epidermolysis bullosa (EDBR), which has a poor prognosis, was first described in 1879⁽¹⁾. It is usually carried by a single gene and accounts for 20% of all cases of EB⁽²⁾. The onset is usually at birth or early infancy. Repeated infections in an already nutritionally compromised and anaemic patient is the frequent cause of mortality⁽³⁾.

Many relatively rare disorders are the result of a single mutant gene. Consanguinity increases the risk of siblings being affected^(4,5). Rare, autosomal recessive disorders occur in siblings whose parents are unaffected. Provided that the affected individuals do not marry a relative, their children are unlikely to manifest the disorder.

Following the demonstration that collagenase production is elevated in EDBR, Eisenberg et al⁽⁶⁾ found that collagenase activity was inhibited in vitro by phenytoin, and obtained a clinical response with decreased blistering upon administration of the drug. The clinical response was confirmed by Bauer⁽⁷⁾, Bauer and Cooper⁽⁸⁾, Kero and Abahusseini et al⁽¹⁰⁾. Bauer and Cooper also showed that inhibition of collagenase production but not of collagenase activity⁽⁸⁾. Bauer suggested that the altered collagenase present in patients with EBD may be the result of a structural gene mutation, a defect in post-translocational modification of the enzyme or mutation in a gene that regulates the normal degradation of collagenase⁽¹¹⁾. Studies on the altered collagenase present in patients with EDBR suggest overproduction of collagenase in the role of blister formation⁽¹²⁾.

Some patients with EDBR may demonstrate a reduced number of erosions in response to the use

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of phenytoin. Although the studies of Caldwell-Browne et al do not exclude the possibility that some patients with EDBR may respond to Phenytoin therapy, they do indicate that phenytoin offers no overall benefit when compared with placebo for the treatment of this disorder⁽¹³⁾.

Genetic factors are the major determinants of the normal variability of drug effects and are responsible for a number of striking quantitative and qualitative differences in pharmacological activity. Similar doses of a drug given to different individuals can result in different plasma concentrations and effects. Besides intraindividual differences inter-individual and inter-ethnic variations of drug response are also related to genetic polymorphism involved in drug metabolism, kinetics and side effect⁽¹⁴⁾.

Inherited factors causing different responses to drugs are commonly biochemical, because single genes govern the production of enzymes. Inherited abnormal responses to drugs mediated by single genes can cause increased, decreased or bizarre responses to drugs⁽¹⁵⁾.

It was first reported by Kutt et al in 1964⁽¹⁶⁾ that the same dose of phenytoin could produce toxic effects in persons who have inherited deficiency in

the enzyme that is required for its metabolism. A genetically determined limitation in the ability to metabolise phenytoin has been described^(17,18). The mode of inheritance of this pharmacogenetic variation to phenytoin metabolism is usually found to be autosomal dominant⁽¹³⁾.

TABLE - 1: SERUM PHENYTOIN LEVELS OF THE PATIENT

10.5.1994	10.6 microgm/ml
08.7.1994	10.6 “
28.9.1994	7.63 “
28.11.1994	9.02 “
27.2.1995	not detectable
08.3.1995	5.0 “
08.4.1995	7.3 “
08.5.1995	12.62 “
12.7.1995	6.53 “
28.8.1995	1.77 “
25.9.1995	11.9 “
25.9.1995	9.51 “
26.9.1995	12.57 “
27.9.1995	11.66 “

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