

## CASE REPORT

Iran J Allergy Asthma Immunol

June 2014; 13(3):214-217.

# A Patch Test Confirmed Phenobarbital-Induced Fixed Drug Eruption in a Child

Zohra Chadly<sup>1</sup>, Karim Aouam<sup>1</sup>, Amel Chaabane<sup>1</sup>, Hichem Belhadjali<sup>2</sup>,  
Naceur Abderrazzak Boughattas<sup>1</sup>, and Jamel Eddine Zili<sup>2</sup>

<sup>1</sup> Department of Pharmacology, University Hospital, Monastir, Tunisia

<sup>2</sup> Department of Dermatology, University Hospital, Monastir, Tunisia

Received: 29 May 2013; Received in revised form: 23 July 2013; Accepted: 19 August 2013

## ABSTRACT

A 10-year-old girl was referred to our department for multiple hyperpigmented plaques. One week previously, she had been given one suppository of acetylsalicylic acid – phenobarbital for fever.

Twelve hours after the drug intake the child developed pruritic red plaques on the left thigh. Six weeks after resolution of the acute reaction, patch tests were performed separately, with phenobarbital and acetylsalicylic acid. On 48-hour reading, only the phenobarbital patch test on residual pigmented lesion was positive. Because of possible cross-reactions between aromatic anticonvulsants, subsequent patch tests using carbamazepine and phenytoin on residual pigmented lesions were performed.

They were all negative at 48-hour reading. To our knowledge, only two isolated pediatric cases of Phenobarbital-induced FDE have been reported in the literature.

In this case report, as it was difficult to determine whether phenobarbital or acetylsalicylic acid was responsible for this reaction, subsequent patch tests allowed the identification of the culprit component since it was positive to phenobarbital.

**Keywords:** Child; Cross reaction; Fixed drug eruption; Patch test; Phenobarbital

## INTRODUCTION

Phenobarbital, a barbiturate, is mainly used as an anticonvulsant agent.<sup>1</sup> Its most common side effect is sleepiness or fatigue. Cutaneous side effects including toxic epidermal necrolysis, pemphigus vulgaris,

photosensitivity, acneiform rash, and purpura have been reported.<sup>1,2</sup> Fixed drug eruption (FDE) is commonly reported with phenobarbital in adults,<sup>2</sup> but it is unusual in children.<sup>3,4</sup> We present herein a case of phenobarbital-induced FDE in a 10-year-old child confirmed by a positive patch-test.

## CASE REPORT

A 10-year-old girl, with a history of recurrent urinary tract infections treated with Sulfametoxazole-Trimethoprim (Bactrim<sup>®</sup>, TERIAK, Tunisia) was

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**Corresponding Author:** Karim Aouam, MD;  
Laboratoire de Pharmacologie, Faculté de Médecine de Monastir,  
Rue Avicenne, 5019 Monastir, Tunisia. Tel: (+216 52) 773 359, Fax:  
(+216 73) 460 737, E-mail: aouam\_k@yahoo.fr

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referred to our department for multiple hyperpigmented plaques. One week previously, she had been given one suppository of acetylsalicylic acid (250mg)–Phenobarbital (20 mg) (Phénaspirine®, SIPHAT, Tunisia) for fever. Twelve hours after the drug intake, the child developed pruritic red oedematous plaques on the left thigh. Sulfametoxazole-Trimethoprim was discontinued and the lesions improved within five days. The physical examination revealed four circumscribed oval and round hyperpigmented plaques on the left thigh (Figure 1). Their diameters varied between 10 and 15 cm. No lesion was found on the mucous membranes. Blood cell counts, kidney and liver function tests were all within normal limits. After a detailed questioning, the mother reported three other previous episodes that had occurred on the same sites with the same morphological features of eruption. The lesions disappeared spontaneously in 5 to 10 days leaving residual hyperpigmentation. Just before each episode, the child had received Acetylsalicylic acid-Phenobarbital and Paracetamol (Efferalgan®, BMS-UPSA-TUN-SAID, Tunisia) for fever. The mother reported that a few weeks before the last episode, the child had received Paracetamol for three days, without any recurrence of skin lesions. Six weeks after resolution of the acute reaction, patch tests were applied separately, with Phenobarbital and



**Figure 1.** Oval hyperpigmentation on the left thigh



**Figure 2.** Positive patch test on a residual pigmented lesion to phenobarbital

Acetylsalicylic acid, both prepared at 10% in water and in petrolatum according to the European Network for Drug Allergy (ENDA) recommendations. The patch test was applied on pigmented sequellae and on normal skin of the back. At 48-hour reading, only the Phenobarbital patch test on a residual pigmented lesion was positive (Figure 2).

Due to possible cross-reactions between aromatic anticonvulsants, subsequent patch tests using Carbamazepine and Phenytoin on residual pigmented lesions were performed. They were all negative at 48-hour reading. The child carried on taking Sulfametoxazole-Trimethoprim and Paracetamol. There was no relapse during a six-month follow-up period.

## DISCUSSION

In this case report, the clinical aspect of the lesions and their reactivation on the same sites were in accordance with FDE diagnosis. A clear temporal relationship was observed between Acetylsalicylic acid-Phenobarbital administration and symptoms onset (12 hours, typically within 24 hours),<sup>5</sup> the remission of skin eruption after drug withdrawal and mainly a positive rechallenge. As it was difficult to determine whether Phenobarbital or Acetylsalicylic acid was responsible for this reaction, subsequent patch tests allowed the identification of the culprit component since it was positive to Phenobarbital. Based on the Naranjo algorithm, it is probable that the skin reaction

was due to Phenobarbital.<sup>6</sup> The role of Paracetamol in inducing fixed cutaneous eruptions was unlikely because the lesions did not recur after rechallenge with this drug. Furthermore, Sulfamethoxazole - Trimethoprim could not be responsible for FDE as the cutaneous lesions resolved although this drug was continued. In the literature, several variants of FDE have been described based on their clinical features and the distribution of the lesions. The common morphological presentation is characterized by well demarcated round or oval erythematous macules that recur on the same cutaneous or mucosal site after every intake of the causative drug,<sup>7,8</sup> as seen in our patient. Variation in morphology, namely bullous, morbiliform, scarlatiniform, multiforme, eczematous, urticarial, and nodular has been described as well.<sup>8</sup> The lesions can appear on different parts of the body.<sup>9</sup> The sites of predilection are the hands, feet, face and peri-anal areas.<sup>7</sup> Subsequent exposures may increase the size and the number of the plaques as well as hyperpigmentation intensity.<sup>7,8</sup> The lesions are rarely pruritic but there is often a burning sensation.<sup>8</sup> Systemic manifestations are infrequent: anorexia and malaise may be present.<sup>8</sup> The initial eruption may be associated with a delay of up to 2 weeks following exposure to the offending drug.<sup>10</sup> With subsequent re-exposure, reactivation of the lesions can occur within 30 minutes to 16 hours,<sup>10</sup> as in our case. All ages are prone to FDE.<sup>8</sup> Most cases, however, are seen in the 20-40 age groups.<sup>8</sup> Interestingly, our patient was in paediatric age group. There are few published studies of FDE in this population.<sup>9</sup> Many pediatricians are unaware of this uncommon side effect and thus, the lesions may be misdiagnosed and mistreated leading to recurrent eruptions when the offending drug is readministered. This case report highlights the possibility of this side effect in pediatric cases. Sharma and Dhar have shown in a study including 50 children and adolescents up to 18 years of age with cutaneous drug reactions that the prevalence of FDE was 22%.<sup>11</sup> The most implicated drugs are Trimethoprim-Sulfamethoxazole, Paracetamol, and Acetylsalicylic acid.<sup>11</sup> To our knowledge, only two isolated pediatric cases of Phenobarbital-induced FDE have been reported in the literature.<sup>7,12</sup> The first child is an 18-month-old boy who presented with FDE plaques on the arms and legs after taking some suppositories (Glycerin, Paracetamol, Aspirin and Phenobarbital).<sup>7</sup> These lesions recurred at the same place during subsequent febrile periods.<sup>7</sup> The

second is an 8-year-old boy who presented with genital FDE 7 days after Phenobarbital administration.<sup>12</sup> The role of Phenobarbital was confirmed by a patch test on a residual pigmented lesion in one case, and by oral rechallenge in the other.<sup>7,12</sup> In the present case, the diagnosis of Phenobarbital-induced FDE was substantiated by a positive patch test on a residual pigmented lesion. Indeed, patch testing has proved a simple and safe method to confirm drug accountability, mainly when multiple drugs are suspected as in our patient.<sup>13</sup> Many studies reported that children and adults react in the same way to patch tests. In most cases, patch tests are sufficient to identify the culprit drug. Andrade et al carried out a retrospective analysis, with 52 patients, to evaluate the diagnostic value of patch testing in establishing an etiological diagnosis in FDE.<sup>13</sup> They found the results that skin patch tests, carried out on residual pigmented lesions, confirmed the clinical suspicion and allowed the identification of the culprit drug in nearly half of the patients (40.4%).<sup>13</sup> But, persistent lack of reactivity to certain drug classes such as sulfonamides and Allopurinol represents an important limitation.<sup>13</sup> As expected, the patch test performed on normal skin produced negative results. Andrade et al, have shown that nearly all patients had a negative patch test.<sup>13</sup> This corroborates the fact that skin-resident memory CD8+ T lymphocytes are mostly located in the epidermis of hyperpigmented patches, which explains the exclusive lesional skin reactivity and the tendency to clinical relapses involving the same areas after oral drug re-exposure.<sup>13</sup> The observed exceptional case of positive reactions in both lesional and non-lesional skin is probably attributable to the application of the tests on a non-perceptible normally pigmented post-inflammatory residual lesion.<sup>13</sup> Apart from the expected localized inflammatory signs and pruritus, patch tests did not induce any extension of the FDE lesions, systemic symptoms, or significant adverse events.<sup>13</sup> Therefore, patch tests constitute a valuable and safe tool in the determination of the accountability of suspected drugs in FDE. Sometimes, oral rechallenge is used to identify the culprit drug.<sup>8</sup> However, there are risks involved in this approach, namely intense lesional reactivation with a significant increase in the number and size of the lesions.<sup>8,13</sup> Finally, it is well known that cross-reactivity between aromatic anticonvulsant agents (Phenobarbital, Phenytoin, Carbamazepine and Oxcarbazepine) is possible mainly in delayed hypersensitivity

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reactions.<sup>1,14</sup> To assess an eventual cross reactivity in our patient, we performed patch tests to Carbamazepine and Phenytoin. These tests were negative denoting a lack of cross reactivity between Phenobarbital and the other aromatic anticonvulsant drugs. To our knowledge, no studies or case reports have assessed cross reactivity between aromatic anticonvulsant agents in FDE.

We report a rare case of Phenobarbital-induced FDE in a child and point out the usefulness and safety of patch tests on residual pigmented lesions in establishing the diagnosis. It seems that, in FDE, there is a lack of cross reactivity among aromatic anticonvulsant agents. This hypothesis needs to be confirmed in vivo and in vitro in large scale studies.

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