Adverse Cutaneous Reactions to Phenobarbital in Epileptic Children

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Abstract

Introduction : Cutaneous adverse reaction to phenobarbital is not uncommon. According to previous studies, around 3 per cent of children taking phenobarbital have reactions. However, there has been no report in Thai children.

Objective : To study adverse cutaneous reactions to phenobarbital in children with epilepsy.

Patients and Method : A retrospective study from medical records of epileptic children aged under 15 years diagnosed at the Department of Pediatrics, Ramathibodi Hospital, Bangkok, Thailand from January 1989 to December 1993 was done. Adverse cutaneous reactions were categorized into 3 groups according to severity. Duration from the initiation of phenobarbital to the onset of reactions and the clinical course were collected for analysis.

Result : There were 18 children from the total of 572-retrievable medical records of children with epilepsy who had adverse cutaneous reactions. The prevalence was 3.2%. There were 5, 10 and 3 patients categorized into mild-form, moderate-form, and severe form respectively. All except one patient had the onset of cuteneous reactions within 3 weeks. No morbidity or mortality was observed in these patients. Recovery of the cutaneous reactions was obtained between 5 and 14 days in those with mild or moderate form.

Conclusion : Adverse cutaneous reactions to phenobarbital observed in Thai epileptic children were similar to those found in previous reports. Physicians who prescribe phenobarbital must be aware of the serious adverse reactions which might occur. Early recognition of the adverse reactions and prompt intervention including discontinuation of the drug must be exercised to prevent any serious complications.

Key word : Phenobarbital, Adverse Cutaneous Reactions, Children

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Phenobarbital has been used as an anticonvulsive drug for the treatment of seizures since 1912 because of its relatively broad-spectrum, low cost and efficacy in administration either orally or parenterally[1]. In recent years, its popularity has declined in Western countries due to the adverse effects on behavior and cognitive function[2]. Because of economical constraints and the effectiveness of treatment on partial and generalized seizures, phenobarbital is still widely used in most developing countries.

The previous reported incidence of adverse cutaneous reactions to Phenobarbital was around 3 per cent[3,4]. The severity of the reactions ranged from fine punctate erythema to large erythematous macules, Steven-Johnsons syndrome, and exfoliative dermatitis[4-8]. The idiosyncratic effects of phenobarbital may manifest only a cutaneous reaction or be associated with systemic manifestations. The latter may be very serious and may result in morbidity or mortality[5,6,9].

Since there has been no report of the prevalence of adverse cutaneous reaction to phenobarbital in Thai children, the authors present experience regarding the prevalence and clinical spectrum of adverse cutaneous reactions to phenobarbital in Ramathibodi Hospital.

PATIENTS AND METHOD

A retrospective study was conducted in the Department of Pediatrics, Ramathibodi Hospital from January 1st, 1989 to December 31st, 1993 by analysis of the medical records of epileptic patients aged under 15 years who received phenobarbital therapy for their seizures. The medical records of all the patients who had adverse cutaneous reaction were reviewed in detail. The possibility of cutaneous reactions to co-commitment medication with other drugs or viral illness was evaluated carefully. The diagnosis of cutaneous reactions to phenobarbital was concluded on the clinical basis of exclusion of any possible causes along with the clinical improvement after discontinuation of phenobarbital.

Adverse reactions to phenobarbital were classified into 3 groups according to the severity as follows.

1. Mild form: characterized as generalized maculopapular rash without significant systemic symptoms.

2. Moderate form: characterized by the presence of cutaneous reactions associated with systemic symptoms.

3. Severe form: Stevens-Johnson syndrome.

The duration from the initiation of phenobarbital treatment to the onset of the adverse reaction as well as the clinical course of each patient was recorded.

RESULTS

There were 616 patients younger than 15 years old who received only phenobarbital treatment for their seizures during the study period. Medical records were retrieved for complete evaluation in 572 patients (92.8%). There were 18 patients (12 boys and 6 girls) who developed adverse cutaneous reactions to phenobarbital. The prevalence was 3.2 per cent. History of allergic reactions to any other drug prior to the initiation of treatment was present in the non-phenobarbital hypersensitivity group and the phenobarbital hypersensitivity group, 6.7 and 5.6 per cent respectively. There were two patients who had a history of adverse cutaneous reactions to phenytoin prior to the initiation of phenobartital.

There were 5 patients categorized into the group with mild form. Among 10 patients with moderate form of reaction, eight had generalized maculopapular rash, one had urticarial rash, and the other had erythema multiforme. All of these patients had fever and enlarged lymph glands. Mild enlargement of the liver was also observed in 3 patients. Those with severe form had high fever, lymphadenopathy, enlarged liver and conjunctivitis. They also had abnormal elevation of SGOT and SGPT levels.

The duration of phenobarbital treatment prior to the onset of adverse reactions ranged from 2 to 28 days. Seventeen patients developed reactions within 3 weeks. Only one patient developed a reaction on the 28th day after phenobarbital was initiated. Five developed cutaneous reactions within the first week after initiation of treatment, seven had a reaction between the first week and second week, and five had a reaction between the second and third week (Table 1).

Phenobarbital was discontinued one day after the onset of cutaneous reactions in 12 patients, on the second day in 3 patients, and on the third day in 3 patients. Of three patients who developed Stevens-Johnson syndrome, phenobarbital was dis-

Table 1. Duration to onset of cutaneous adverse reactions.

Week	Number of patients	Percentage
1st	5	27.8
2nd	7	38.9
3rd	5	27.8
after 3rd	1	5.5

continued in one patient on the 2nd day, whereas, in the other two the drug was discontinued on the 3rd day (Table 2).

In five children who had only a cutaneous adverse reaction without systemic involvement (mild form), the cutaneous manifestations disappeared within 5 days. In those who had both skin lesions and systemic involvement, recovery of the cutaneous manifestations ranged from 5 to 14 days. Only oral antihistamine therapy was given to these patients. In 3 patients, who developed Stevens-Johnson syndrome, the cutaneous manifestations resolved on the 10th, 15th and 27th days of the clinical course respectively. Systemic corticosteroids and antihistamine along with symptomatic and supportive treatment were deployed in these patients.

There was no permanent morbidity or mortality observed in these 18 children. There was neither status epilepticus nor serious deterioration of seizures during the clinical presentation of cutaneous reactions despite abrupt discontinuation of phenobarbital. A new antiepileptic drug was prescribed to 16 patients after the cutaneous reactions totally resolved, and no adverse reactions occurred thereafter. The other two patients were not given any new antiepileptic drug after the adverse reaction, and were seizure free until their last follow-up visit which was one year after the onset of the cutaneous reactions.

DISCUSSION

Adverse cutaneous reactions to drugs are frequent. Fortunately, most adverse cutaneous reactions are not severe. Aromatic antiepileptic drugs (AEDs) such as phenytoin, phenobarbital, and carbamazepine have also been frequently associated with cutaneous reactions especially during the first few weeks of treatment[2,5,6,10,11]. Adverse cutaneous reactions occurred in 3 - 11 per cent of patients receiving carbamazepine which was similar to the percentage observed in phenobarbital[12-14]. Our findings of adverse cutaneous reactions to phenobarbital in children were similar to previous reports [3,4]. Most of the patients in the present study developed adverse cutaneous reactions to phenobarbital within three weeks after initiation of treatment except for one patient whose reaction was observed on the 28th day of treatment. The majority of patients who had adverse cutaneous reactions had mild to moderate reactions (15 of 18 patients or 79%). Stevens-Johnson syndrome was observed in three patients which was 0.5 per cent of all patients receiving phenobarbital which was similar to a previous report[4].

The first sign of cutaneous reaction to phenobarbital was reported to be a rash that was characterized by generalized exantematous eruptions. These cutaneous manifestations were often preceded by a history of febrile illness[6,10,13,15,16]. The triad of fever, rash and lymphadenopathy was observed in 80 per cent of affected individuals. Evidence of secondary organ involvement including hepatic and hematologic abnormalities such as eosinophilia may also be present[4,6,8,17].

Although most of these adverse cutaneous reactions were mild, immediate discontinuation of the antiepileptic drug was generally recommended to prevent further development of serious reactions [6,18]. Special concern was in patients who had life-threatening reactions. Although these symptoms

Table 2. Distribution of number of patients with severe reaction according to the day after the onset when phenobarbital was discontinued.

Day after the onset	Number of patients	Patients with severe form
1st day	12	0
2nd day	3	1
3rd day	3	2

usually abated in most patients after early discontinuation of phenobarbital[3,4], some developed serious reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)[13,17]. Though the percentage of patients having these reactions was not that high, these reactions might increase the morbidity and mortality rates[5,17]. Therefore, discontinuation of phenobarbital as soon as possible is still the mainstay of management[18]. Supportive and symptomatic treatment is the adjunctive treatment that would help to improve the patient's condition. In severe cases, administration of systemic corticosteroids as recommended in previous reports would help in prevention of further reactions[18,19]. However, there is no randomized, controlled trial demonstrating that systemic administration of the drug would shorten the clinical course or have any effect on either mortality or morbidity[18]. Recently, dramatic response to intravenous immune globulin in combination with methyl prednisolone was demonstrated in a 17-year-old patient with Stevens-Johnson syndrome induced by carbamazepine[20]. However, it was an anecdotal report and more case reports and studies are needed to confirm its efficacy.

Initiation of any other antiepileptic drug to those who have had a cutaneous adverse reaction to phenobarbital must be done with caution to avoid new reactions. Risk of cross-reactions particularly with carbamazepine or phenytoin must be considered according to their similar chemical structure [5,7,11]. Valproate, which does not share the common metabolic pathway, has been suggested as a possible alternative agent[7,15,16]. However, in patients with systemic involvement, hepatotoxic effects of valproate must be considered. Definite diagnosis of cutaneous reaction to certain drugs can be done by performing a skin patch test[21,22]. This will be an alternative approach to avoid further cutaneous adverse reactions to a new antiepileptic drug in those who have had a cutaneous reaction to phenobarbital.

Phenobarbital is a useful antiepileptic drug for the treatment of partial and generalized tonic-clonic epilepsy especially in developing countries. Physicians who prescribe the drug to any patient must be familiar with every form of adverse reaction. The parents must be educated regarding the adverse reactions of the drug including the early manifestation of cutaneous adverse reactions. If there is any suspicion of an adverse reaction, appropriate medical advice must be sought. In case of doubt, immediate discontinuation of the drug should be advised to prevent progressive serious adverse reactions that might result in severe morbidity.

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ปฏิกิริยาไม่พึงประสงค์ทางผิวหนังจากยากันชัก ฟีโนบาร์บิตัล ในผู้ป่วยเด็กโรคลมชัก

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ปฏิกิริยาไม่พึงประสงค์ที่แสดงออกทางผิวหนัง เกิดกับการใช้ยากันชักได้หลายชนิด คณะผู้รายงานได้ทำการศึกษาแบบย้อนหลังถึงปฏิกิริยาไม่พึงประสงค์ที่แสดงออกทางผิวหนังในผู้ป่วยเด็กโรคลมชักอายุต่ำกว่า 15 ปี ที่ได้รับยากันชักชนิด phenobarbital ที่ได้รับการรักษาที่ภาควิชากุมารเวชศาสตร์ โรงพยาบาลรามาธิบดี ในระหว่างเดือนมกราคม 2532 ถึงเดือนธันวาคม 2536 พบว่าในจำนวนผู้ป่วยทั้งสิ้น 572 คน ที่เป็นโรคลมชักและได้รับยาชนิดนี้ มีปฏิกิริยาไม่พึงประสงค์ที่แสดงออกทางผิวหนังจำนวน 18 คน คิดเป็นอุบัติการณ์ 3.2% โดยจำแนกความรุนแรงออกเป็น 3 กลุ่มอาการ คือ กลุ่มที่มีอาการน้อยโดยที่ไม่มีความผิดปกติของระบบอื่น จำนวน 5 คน กลุ่มที่มีอาการปานกลางคือมีอาการผิดปกติของระบบอื่นร่วม 10 คน และกลุ่มที่มีความรุนแรงมากที่สุดซึ่งเข้าได้กับกลุ่มอาการ Stevens-Johnson จำนวน 3 คน ผู้ป่วยส่วนใหญ่ (17 ใน 18 คน) จะแสดงอาการไม่พึงประสงค์นี้ภายใน 3 สัปดาห์แรกหลังจากที่ได้รับยาแล้ว ในการศึกษานี้ไม่พบความผิดปกติหลงเหลืออยู่หรือผลแทรกซ้อนใด ๆ คณะผู้รายงานได้เน้นถึงความจำเป็นที่แพทย์จะต้องมีความรู้ความสามารถในการวินิจฉัยปฏิกิริยาไม่พึงประสงค์ที่แสดงออกทางผิวหนังจากการใช้ยากันชัก ทั้งนี้การหยุดยาที่ใช้ร่วมกับการรักษาแบบประคับประคองที่เหมาะสมจะสามารถช่วยป้องกันโรคแทรกซ้อนที่อาจจะเกิดขึ้นได้

คำสำคัญ : ฟีโนบาร์บิตัล, ปฏิกิริยาไม่พึงประสงค์ที่ผิวหนัง, โรคลมชักในเด็ก

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