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Allergic Rash Due to Antiepileptic Drugs: Clinical Features and Management

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Summary: Optimal management of allergic rash from antiepileptic drugs (AEDs) is unclear. We identified 50 patients with 68 reactions (36 to one AED, 10 to two AEDs, and four to three AEDs). The AEDs implicated were carbamazepine, 30; phenobarbital (PB), 20; phenytoin, 16; ethosuximide, one; and AED combination, one. Sixty-three reactions were cutaneous eruptions, three exfoliative dermatitis, and two Stevens–Johnson syndrome. Forty-six reactions were mild (rash only), 18 moderate (systemic symptoms or other organ system involvement), and four life-threatening (all with PB). In most patients with >1 reaction, the second and third reactions were not more severe than the first. Prior antibiotic allergies or nonmedication allergies were no more common than in a control group without reactions. The AED was ceased abruptly in 59 patients (22 of whom did not receive a new AED), tapered in five, and continued unchanged in four. Despite this, there was no status epilepticus (SE) during the reaction or its treatment, and no patient's seizure control deteriorated. In 40 cases, a new AED was added—16 after the reaction had resolved and 24 before total resolution. Rash recurred with the new AED in 50 and 42% respectively (NS). We conclude that, though allergic rashes to AEDs are usually mild, the rare occurrence of severe reactions indicates that the AED should be ceased. This can be done abruptly with minimal risk of SE. A new AED can be added, if necessary, prior to the resolution of the rash without increasing the risk of further reactions. **Key Words:** Allergic—Rash—Anticonvulsant.

Idiosyncratic side effects to antiepileptic drugs (AEDs) warrant stopping medication in 15–20% of patients with epilepsy (Cowan et al., 1989; Camfield et al., 1985; Wolf and Forsyth, 1978). Several recent reviews have addressed the problem of reactions to AEDs (Booker, 1975; Plaa, 1975; Reynolds, 1975), mainly in adults. In childhood, the incidence of side effects to phenobarbital (PB) (Wolf and Forsyth, 1978; Camfield et al., 1979) and valproate (VPA) (Egger and Brett, 1981; Dreifuss et al., 1987) are well-documented, but reactions to other AEDs have not been studied as thoroughly.

Skin reactions occur in 2–3% of patients receiving carbamazepine (CBZ) (Sillanpaa, 1981), and probably a similar percentage for PB and phenytoin (PHT). Most of these skin reactions are mild, but optimal management is uncertain, with most authors recommending that the AED be stopped immediately (Schmidt, 1985; Rall and Schleifer, 1985; Abu-Arafeh and Wallace, 1988). Of special concern are patients who have suffered life-threatening reactions or those who have had reactions to several AEDs, since the choice of further medications may be limited.

Practical management questions about the child with epilepsy who develops a skin reaction include the following: If the AED needs to be ceased, can this be done abruptly, or should it be tapered to decrease the chance of status epilepticus (SE)? If the AED is stopped, should another AED be added? If so, should it be added immediately, or should the reaction resolve prior to adding the next drug? Will seizure control change during the reaction and its management? Will the epilepsy be more difficult to control because certain AEDs can no longer be used?

In this study we surveyed the precursors, accompaniments, management, and outcome of 50 children from a pediatric epilepsy clinic with idiosyncratic skin reactions associated with AEDs.

METHODS

Patients who had experienced an idiosyncratic skin rash from an AED within the past 10 years were identified by review of our epilepsy clinic

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records and inpatient hospital charts coded as having adverse reactions to AEDs. We also sent a brief questionnaire to 824 clinic patients with epilepsy who had been seen over the past 3 years. A single mailing had a 44% response rate.

When a patient was identified as having had an allergic rash, the records were reviewed, and if sufficient data could not be abstracted from the chart, the family was contacted directly. This telephone contact was used only to verify information in the medical record and to assess the rate of other allergies. Issues such as concomitant medications or viral illness were not established from the telephone contact. If the child was receiving more than one AED at the time of the reaction, the reaction was ascribed to the most recently added drug. The study was approved by our hospital ethics committee.

The study was not designed to assess the overall risk of rash with the prescription of each AED, and therefore this information was not gathered.

RESULTS

The overall results are summarized in Table 1.

TABLE 1. *Summary of clinical features of patients with antiepileptic drug (AED) reaction*

Number of patients	50 (68 reactions)
Reaction to 1 AED	36
Reaction to 2 AEDs	10
Reaction to 3 AEDs	4
Severity of reactions	
Mild	44
Moderate	20
Severe	4
Average time of treatment before rash	14.9 ± 18.7 days
Prior antibiotic reaction	8%
Controls	11.5%
Nonmedication allergies	32%
Controls	27.5%
Abrupt cessation of AED with reaction	59
Taper of AED with reaction	5
AED continued through reaction	4
New AED added	40
After resolution of reaction	16
Recurrent rash	8
Before resolution of reaction	24
Recurrent rash	10
Status epilepticus with reaction	0
Rechallenge with the AED	7
Recurrence	6

Clinical details

We identified 50 children (22 girls, 28 boys) who had experienced a total of 68 rashes. Thirty-six patients had a reaction to one AED, 10 to two AEDs, and four to three AEDs. The mean age at onset of the initial reaction for all patients was 90.1 months (range 16–197 months, ±43.7 SD). The AEDs implicated were CBZ, 30; PB, 20; PHT, 16; ethosuximide (ESM), one; and AED combination, one (concurrent PB, PHT, and CBZ).

Indications for AED treatment were complex or simple partial seizures in 18, generalized tonic–clonic or secondarily generalized seizures in 19, generalized absence in two, Lennox–Gastaut syndrome in two, benign sylvian seizures in two, myoclonus in one, febrile seizures in one, acute head trauma in four, and prophylaxis after neurosurgery in one.

Type and severity of reaction

Of the 68 reactions, 63 were cutaneous eruptions (maculopapular, erythematous, morbilliform, urticarial, or vesicular eruptions, or erythroderma), three were exfoliative dermatitis, and two were Stevens–Johnson syndrome.

Forty-four reactions were mild (rash only), 20 moderate (systemic symptoms or other organ involvement), and four life-threatening. Of the 20 moderate cases, the clinical features in addition to rash were as follows: fever only, 11; fever and joint symptoms, three; fever and petechiae, one; fever, petechiae, and elevated serum glutamic-oxaloacetic transaminase, one; fever and clinical hepatitis, one; fever, hepatitis, and neutropenia and thrombocytopenia, one; fever and anemia, one; and fever, anemia, and thrombocytopenia, one.

The clinical features of the four cases who suffered life-threatening reactions are outlined in Table 2.

Duration of treatment prior to onset of the reaction

The mean duration of treatment prior to the onset of the rash in all 68 reactions was 14.9 days (range 1–140 days, SD ± 18.7). It appeared that those with multiple reactions tended to have subsequent reactions after similar intervals.

Time to the onset of reaction varied with the drug: PB, median 9 days (range 1–19 days); PHT, median 12 days (range 1–47), and CBZ, median 10 days (range 1–140) (Fig. 1). Only one CBZ reaction occurred after 28 days. This 13-year-old boy developed exfoliative dermatitis, fever, lethargy, mucous membrane lesions, and mild arthralgia 140 days after start of CBZ. After 6 days of worsening symptoms CBZ was stopped, the fever resolved within 24 h, and he recovered. No alternative explanation for this reaction was identified.

Patients who reacted to multiple AEDs

When children reacted to more than one medication, the medications were always PB, CBZ, or PHT, with no consistent pattern in the sequence of treatment with these three AEDs. Children who re-

TABLE 2. *Clinical features of the life-threatening reactions*

	Patient			
	1	2	3	4
Age at time of reaction (mo)	50	109	96	86
Sex	M	F	M	F
AED	CBZ + PB + PHT	PB	PB	PB
Indication for AED	Lennox–Gastaut	1 Seizure, abnormal EEG	Prophylactic after neurosurgery	Complex partial seizures
Reaction type	Toxic erythroderma, lymphadenopathy, splenomegaly, D.I.C.	Stevens–Johnson syndrome, pulmonary, cardiac, renal, arrest	Hematologic, lymphadenopathy, mucosal lesions	Bullae, hematologic, hepatic, coma, renal
Duration of AED prior to onset of rash (days)	<40	19	16	10
Duration of AED after onset of rash (days)	9	2	2	10
Previous exposure to offending AED	No	No	No	No
Other medications at time of rash	Adrenocorticotropic hormone, ethosuximide	None	Dexamethasone	Penicillin
Intercurrent infection	No	Possible mycoplasma	No	Unknown
Recovery (days)	14	90	120	25
Sequelae	None	None	Blindness	None
Treatment of reaction	Steroids	Steroids, ventilation dialysis	Steroids, antihistamine	Steroids

AED, antiepileptic drug; CBZ, carbamazipine; PB, phenobarbital; PHT, phenytoin; D.I.C., disseminated intravascular coagulation.

acted to multiple AEDs appeared to be slightly older than those with one reaction. The mean age at the time of reaction was 84.4 months (range 16–172 months, SD ± 39.6) for single reactors. For patients with two reactions, the mean age for the first reaction was 93.4 months (range 18–167 months, SD ± 47.5). For those with three reactions, mean age at the first reaction was 133.3 months (range 60–197 months, SD ± 55.3).

Of the 14 patients with >1 reaction, the subsequent reactions were of the same severity in nine cases, more severe in two cases, and less severe in three cases.

Possible risk factors for severe or multiple reactions

In only four of 68 reactions had the patient been previously exposed to that AED, and in two of these, the rash occurred within 24 h of reintroducing the AED.

A history of previous medication or nonmedication allergic reactions did not appear to predict an AED skin reaction. For example, prior antibiotic allergies occurred in 8% of patients with reactions compared with 11.5% of questionnaire respondents without reactions. Nonmedication allergies (skin, respiratory, or gastrointestinal) had occurred in 32% of patients with reactions and 27.5% of questionnaire respondents without AED reactions.

Only six of 68 reactions were suspected of being associated with an intercurrent infection, although a total of eight patients were receiving antibiotics at the time of the reaction (three of six with intercurrent infection). Four of these eight had moderate or severe reactions.

For the eight patients receiving concomitant antibiotics, a clinical decision was made that the AED was the most likely causative agent based on the duration of treatment and previous exposure to the antibiotic. For 8 of 68 reactions, the child was receiving two AEDs at the time of reaction, although the reaction was thought to be due to the most recently added drug.

Outcome of reactions

There were no fatalities. Severe permanent morbidity occurred in one child with a Stevens–Johnson syndrome, who developed blindness from corneal scarring (Table 2). With the exception of this child, the median time to complete recovery was 7 days (range 1–90).

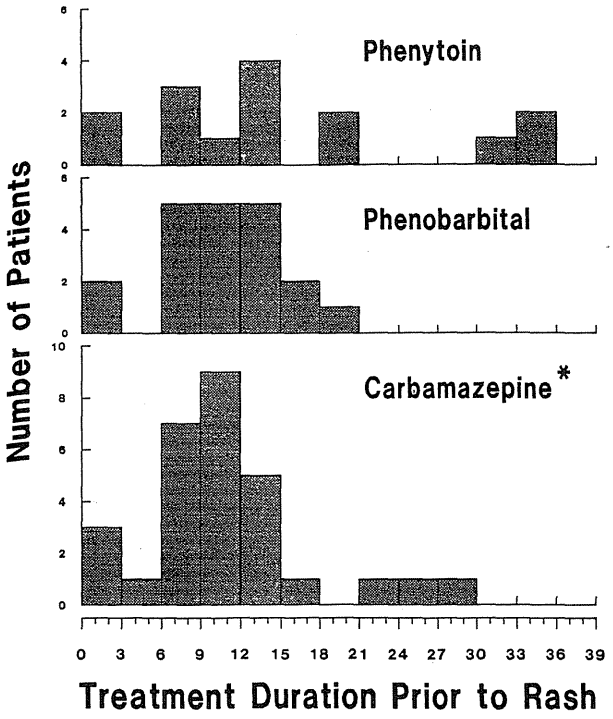

FIG. 1. Duration of treatment (in days) prior to onset of reaction. *A single patient receiving carbamazepine had the reaction at 140 days.

Seven patients were rechallenged with the AED and six of seven recurred. Five of six rechallenged within 12 days of resolution of the initial reaction had a recurrent reaction. One other patient was rechallenged shortly after an initial moderately severe reaction to CBZ and recurred. Five years later he was rechallenged with CBZ using the "desensitization" protocol of Purvis and did not react again (Purvis et al., 1988).

Seizure control during and after reaction

The AED was ceased abruptly in 59 patients (22 of whom did not receive a new AED), tapered in five, and continued unchanged in four. There were no episodes of SE during the reaction or its treatment. The seizure frequency remained unchanged in 28 cases, decreased by 50% in one case, and in 39 there were no seizures during the reaction. No patients had deterioration in seizure control during the reaction.

In 40 cases, a new AED was added, 16 after the reaction had totally resolved and 24 before resolution. Rash recurred with the new AED in 50 and 42% respectively (p = NS). For 29 of 40, the AED was added prophylactically and in 11 because of seizures. The mean interval between ceasing the first AED and adding the second AED was 3.8 days. Although it is difficult to ascertain, the future management of seizures may have been rendered more problematic by a lack of a suitable alternative AED following 17 of 68 reactions.

DISCUSSION

The most important finding of this study is that no patient's seizure control deteriorated, and there were no episodes of SE, despite the fact that the majority of cases had the AED ceased abruptly when a skin reaction was detected. It has long been held that the sudden cessation of AEDs can precipitate seizures, in particular SE. Two recent papers have reviewed SE in childhood (Dunn, 1988; Yager et al., 1988). In one study, inadequate blood levels of AEDs were thought to play a role in precipitating SE in 32 of 60 episodes in children with prior seizures (Dunn, 1988). Another study, however, failed to mention previous AEDs as playing a role in SE in 52 children (Yager et al., 1988). Theodore et al. (1987) found no relationship between the rate of PB discontinuation and seizure frequency. In these studies it should be noted that the patients had been receiving AEDs for prolonged periods of time prior to drug discontinuation, while our patients had received AEDs for an average of only 15 days before abruptly stopping. While four of our patients continued receiving the AED and the reaction resolved, two of four patients with severe reactions appeared to continue their AEDs for relatively long times after the onset of their reaction (7 and 9 days, Table 2).

Our case finding method likely tended to overemphasize severe reactions; however, 65% of the reactions were mild, which is comparable to previous reports (Sillanpaa, 1981). The time from starting AED to the onset of the reactions for CBZ and PB were almost identical. All except one CBZ reaction occurred within 3 weeks of starting the AED. One reaction linked to CBZ after 140 days of treatment draws attention to the fact that late reactions are rare but possible. The time to onset of reaction for PHT was slightly different than that for PB and CBZ, with a fairly even distribution of occurrence up to about 6 weeks after start of AED (Fig. 1). We are unable to explain this difference.

Delattre et al. (1988) recently introduced the concept that several factors could act in synergy to precipitate the development of severe skin reactions. They reported eight cases of severe cutaneous reactions following the combination of PHT therapy with radiotherapy. None of our patients was receiving radiotherapy at the time of reaction.

We were not able to identify predictive factors for patients with single, multiple, or very severe reac-

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