REVIEW ARTICLE

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The Tolerability of Lamotrigine in Children

John A. Messenheimer,[1] *Luigi Giorgi*[2] and *Marcus E. Risner*[1]

1 GlaxoWellcome Research Institute, Research Triangle Park, North Carolina, USA
2 GlaxoWellcome Research and Development, Greenford, Middlesex, UK

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Abstract

Lamotrigine is a novel anticonvulsant, which has proven to be effective both as add-on and monotherapy. 13 studies have demonstrated efficacy in 1096 children with a variety of seizure types. Tolerability information in these studies was collected in a standard fashion, where investigators reported all adverse events regardless of the perceived relationship to the test therapies. Generally, lamotrigine treatment in these clinical trials was generally given at higher initial doses and faster dose escalations than are currently recommended.

Most adverse events associated with lamotrigine were mild to moderate in severity and did not result in discontinuation of treatment. Results from placebo-controlled, add-on trials showed that 85% of lamotrigine recipients experienced an adverse event compared with 83% of placebo recipients. Lamotrigine was associated with an increased risk of adverse events in the nervous system (dizziness, tremor, ataxia, and diplopia), gastrointestinal tract (nausea), and urinary tract (infection). The incidence of most adverse events was lower among lamotrigine recipients in monotherapy trials than in add-on trials, suggesting that concurrent anticonvulsant treatment or drug interactions can be confounding risk factors above that of lamotrigine treatment alone. Skin rash associated with

hospitalisation and the discontinuation of study drug was reported more frequently by lamotrigine recipients than by placebo recipients and more frequently by children than by adults. The simultaneous use of valproic acid (sodium valproate) was associated with an increased incidence of rash.

Lamotrigine, an effective broad spectrum anticonvulsant, is well tolerated in children. The qualitative features of adverse events that occur with lamotrigine treatment are similar for children and adults. The incidence of rash may be reduced with proper initial dosing and dose escalation.

Lamotrigine is chemically unlike other currently approved anticonvulsants. It acts, in part, by blocking voltage- and use-dependent sodium channels, thus stabilising the neuronal membrane.[1-3] Lamotrigine inhibits the excessive release of excitatory amino acids (e.g. glutamate) that is associated with seizure activity. However, this inhibition is not a generalised effect; neurons with sustained, repetitive firing are most sensitive to the drug (the definition of use-dependency).[4] Because lamotrigine has shown clinical and preclinical evidence of efficacy in typical absence seizures,[5,6] one or more other mechanisms of action are also assumed to be involved in its anticonvulsant effects.

Lamotrigine has found wide clinical usage since its first approval in the Republic of Ireland in 1990. As of November 1998, lamotrigine was approved in 84 countries worldwide as add-on therapy for refractory and partial seizures in patients over 12 years of age. Lamotrigine is also approved in 31 countries as monotherapy for partial and/or generalised seizures. In addition, lamotrigine is available in 49 countries as add-on treatment for partial seizures in children and 15 countries for Lennox-Gastaut syndrome. By May 1999, it was estimated that 2.7 million patients (>1.1 million patient-years of exposure) had received lamotrigine treatment.

The highest annual incidence of epilepsy is during childhood (50 to 100/100 000); the incidence decreases with age and increases again in the elderly.[7] In the first 5 years of life most of the newly diagnosed cases have generalised seizures; after that age, partial seizures predominate. Therefore, clinicians are interested in treatments for children that possess a broad spectrum of efficacy together with an acceptable safety profile. Lamotrigine has not only been demonstrated to be effective for adults with epilepsy,[8-13] but published reports of controlled trials demonstrate broad efficacy in paediatric patients,[14] including adjunctive therapy for partial seizures,[15] adjunctive therapy for the generalised seizures of the Lennox-Gastaut syndrome,[16] and initial monotherapy for typical absence seizures.[5]

This review was conducted to assess the tolerability of lamotrigine in children who took part in clinical trials. These findings will be compared with those previously reported for adults.[17-19]

1. Clinical Trials

This review summarises safety data for paediatric and adolescent patients (aged <16 years except for study US-40 with patients ≤16 years) enrolled in a total of 13 clinical studies of lamotrigine prior to 1 March 1998. This clinical trial database consists of all studies conducted by GlaxoWellcome UK and US to assess the safety and efficacy of lamotrigine in paediatric patients. The database includes 8 studies of lamotrigine added to existing anticonvulsant medications, 3 monotherapy studies, and 2 continuation studies for patients who participated in one of the shorter term primary studies (table I). Three of the studies were ongoing at the time of database closure. Two add-on studies (US-40 and UK-123) were placebo-controlled with 171 placebo recipients and 168 lamotrigine recipients. A third trial involved the use of placebo subsequent to open-label treatment with lamotrigine (US-44). Clinical pharmacology studies are not included in this review, as the duration of drug exposure was insufficient to reasonably assess safety.

Good Clinical Practice guidelines, the Declaration of Helsinki, and the relevant local regulatory requirements (e.g. Investigational New Drugs reg-

Table I. Clinical trials of lamotrigine in children and adolescents with epilepsy

Study no.	Design	Dose (mg/d)	Seizure type(s)	Duration (wks)	Status
Add on studies					
UK-61(1)	OL	12.5-600	All	120	Complete
UK-73	OL	12.5-600	All	48	Complete
UK-92	OL	6.25-400	All	48	Complete
UK-98	OL	12.5-400	All	48	Complete
UK-102	OL	6.25-700	All	52	Complete
UK-123	PC	1-15 mg/kg/d	Lennox-Gastaut	20	Complete
US-26	OL, Compass	6.25-700	All	156	Complete
US-40	PC	0.5-15 mg/kg/d	Partial	28-35	Complete
Monotherapy studies					
US-44	PC	0.5-15 mg/kg/d	Absence	9-23	Complete
UK-126	OL, AC (VPA)	2-10 mg/kg/d[a] 100-500[b]	General tonic-clonic	9-28	Ongoing
UK-136	OL, AC (CBZ)	2-15 mg/kg/d[a] 100-500[b]	Partial	9-28	Ongoing
Continuation studies					
US-41	OL	12.5-1000	All	≥52	Ongoing
UK-114	OL	12.5-700	All	120	Complete

a In patients aged 12 years and below.

b In patients aged more than 12 years.

AC = active-controlled; **CBZ** = carbamazepine; **Compass** = compassionate use; **OL** = open label; **PC** = placebo-controlled; **VPA** = valproic acid (sodium valproate).

ulations in the US, the Clinical Trials Certificate Exemption application in the United Kingdom, and corresponding arrangements in other countries) were observed. In particular, written informed consent was obtained from every patient's parent or guardian and from the patient whenever possible.

Adverse events were collected both as a result of spontaneous reports and direct questioning. An adverse event was regarded as 'treatment emergent' if it arose or worsened after the patient's enrolment into the clinical study. Adverse event reporting occurred regardless of what treatment had been administered and whether the test medication(s) was thought responsible. Investigators described the clinical severity of each adverse event as 'mild', 'moderate' or 'severe,' whether the adverse event led to withdrawal of the patient from the clinical trial, and whether they considered the event to be reasonably attributable to the study drug. The original adverse event terminology was standardised using a standard dictionary (Coding Symbols for a Thesaurus of Adverse Reactions Terms; COSTART). In 1 study (US-26, n = 415), adverse events were only recorded if they were 'serious' or led to withdrawal of the patient from the study. Serious adverse events were also analysed separately. The term serious adverse event included any experience that was fatal, life threatening, permanently disabling, or required or prolonged inpatient hospitalisation. Malignancies, overdoses of the study drug, or congenital anomalies (in offspring) were also reported as serious adverse events.

Safety assessments in most clinical trials included measurement of vital signs, clinical chemistry and haematology, urinalysis, and electrocardiograms. As these assessments have consistently failed to reveal any clinically significant changes with lamotrigine exposure,[15,20] they are not included in this review.

2. Demography and Baseline Characteristics

The number of unique lamotrigine-treated patients in the integrated database is 1096 (table II).

The add-on placebo-controlled studies (US-40 and UK-123) contributed data for 171 patients treated with placebo that serve as a comparator group in this review. In the other placebo-controlled study (US-44), patients were exposed to lamotrigine during the initial open-label, dose-ranging phase prior to randomisation to placebo (n = 14). In addition, a small number of patients in 2 open active-comparator studies were treated with valproic acid (sodium valproate) [n = 22] or carbamazepine (n = 18) monotherapy; because of the small number of patients, data from those patients receiving an active-comparator are not included in this review.

For all paediatric studies (n = 1096), 54% of patients were male and 46% were female. The majority of patients (56%) were 6 to 12 years of age, while 30% were 2 to 5 years, 12% were older than 12 years, and 2% were less than 2 years of age.

A variety of seizure types, classified according to the 1981 International Classification of Seizures,[21] were treated in the paediatric lamotrigine clinical studies (table I). In the placebo-controlled, lamotrigine monotherapy study US-44 (n = 45 lamotrigine recipients), patients had newly diagnosed typical absence seizures. The other 2 monotherapy studies enrolled newly-diagnosed paediatric patients with idiopathic generalised seizures (UK-126, n = 46 lamotrigine recipients) and partial seizures (UK-136, n = 42 lamotrigine recipients). For add-on studies (n = 959 lamotrigine recipients), the most prevalent seizure type was generalised seizures (39%), followed by multiple seizure types (33%), complex partial only (14%), and simple partial only (4%). Predominant seizure types varied across add-on trials; for instance, only patients with the generalised seizures of the Lennox-Gastaut syndrome were enrolled in UK-123 and only patients with partial simple and/or complex seizures, including secondarily generalised partial seizures, were enrolled in US-40.

Table II. Lamotrigine or placebo exposures in clinical trials

Category	No. of trials	No. of unique patients	
		Lamotrigine	Placebo
All with paediatric or adolescent patients	13	1096	185
All primary add-on trials[a]	8	959	171
All primary monotherapy trials[a]	3	137	14[b]
Continuation trials	2		

a Includes patient numbers from the 2 continuation trials.

b These 14 patients received placebo after a period of treatment with open lamotrigine in US-44.

3. Treatment Duration and Dosage

Drug administration data were available for 1080 of the 1096 paediatric patients who were allocated to lamotrigine treatment. In add-on studies, the median exposure was 28 weeks. 18% of patients received the drug for less than 16 weeks; 31% were treated for at least 1 year, 17% for at least 2 years, and 4% for at least 3 years. In monotherapy studies, the median exposure was 22 weeks.

Maintenance dosage ranges of lamotrigine following initial dose escalation periods in each clinical trial are described in table I. The mean dosage was 2.93 mg/kg/day for lamotrigine monotherapy. In contrast, the mean dosage was 5.49 mg/kg/day and the dose varied dependent on concomitant anticonvulsants for patients in whom lamotrigine was used as add-on therapy. With enzyme-inducing anticonvulsants (e.g. phenytoin, carbamazepine, or barbiturates), daily lamotrigine doses typically ranged from 5 to 15 mg/kg after initial dose escalation. When combined with valproic acid, an inhibitor of lamotrigine metabolism, the range of lamotrigine dosages trended lower, 1 to 7 mg/kg/day. In add-on studies, 46% of patients were using concomitant valproic acid with or without other anticonvulsants, while 41% were using concomitant enzyme-inducing anticonvulsants alone.

The 13 studies summarised in this review used a variety of lamotrigine initial doses and dose escalation rates that were generally higher and faster than those of paediatric recommendations available at the time. Overall, only 29% of patients received the drug over the first 4 weeks according to those recommendations. The rest received higher initial doses and/or faster dose escalation rates than recommended. Of the patients using concomitant

Table III. Lamotrigine paediatric drug administration recommendations[17]

	Starting and escalation (maximum, mg/kg/d)			Maintenance (mg/kg/d)	MAD (mg/d)
			Increments		
Treatment week	1-2	3-4	Every 1-2 wks		
Concurrent therapy					
EIAED (with or without other AEDs, but no VPA)	0.6	1.2	1.2	5-15	400
VPA (with or without other AEDs)	0.15	0.3	0.3	1-5	200

AED = antiepileptic drug; **EIAED** = enzyme-inducing antiepileptic drugs(s); **VPA** = valproic acid (sodium valproate); **MAD** = maximum absolute dose.

valproic acid, only 3.5% received lamotrigine according to those recommendations, compared with 47% of patients not receiving valproic acid.

Revised guidelines for drug administration in paediatric patients based on pharmacokinetic modelling of serum concentration data from these trials have recently been released in several countries[17] (table III). These guidelines recommend lower starting doses and slower escalation of lamotrigine, particularly when administered with concurrent valproic acid.

4. Tolerability of Lamotrigine

4.1 Treatment Emergent Adverse Events: Add-On and Monotherapy Trials

Nonserious adverse events were not routinely recorded for US-26 unless they led to discontinuation of treatment. Adverse event rates from all other paediatric add-on studies (n = 544) and all monotherapy studies (n = 137) are summarised in table IV. In patients for whom intensity was recorded (n = 535 patients), most adverse events were of mild or moderate maximum intensity (80% in add-on studies and 91% in monotherapy studies). 51% of all patients experienced adverse events considered by the investigator to be reasonably attributable to study drug.

In studies of lamotrigine add-on treatment, 82% of patients experienced adverse events (table IV). The most common adverse events included somnolence, infection, rash, vomiting, increased seizures, pharyngitis, and fever. In monotherapy studies, 67% of patients experienced adverse events (table IV). The most common adverse events included infection, headache, rash, pharyngitis, and fever. The incidence of many adverse events was lower among patients receiving monotherapy compared with add-on therapy (somnolence 2.9 vs 17.8%, vomiting 8.8 vs 15.8%, increased seizures 2.9 vs 14.2%, ataxia 0.7 vs 9.0%, dizziness 3.6 vs 8.1%, nausea 2.9 vs 6.6%, diarrhoea 1.5 vs 5.9%).

4.2 Adverse Events Leading to Discontinuation of Treatment

Of the 1096 patients treated with lamotrigine, 106 (9.7%) discontinued treatment due to adverse events; 38% of those patients experienced events of severe intensity and 44% of moderate intensity. A total of 97 out of 959 (10.1%) lamotrigine recipients discontinued lamotrigine treatment due to adverse events in add-on studies. The most common events leading to discontinuation in add-on studies were rash (5.0%) and increased seizures (1.5%). A total of 9 out of 137 (6.6%) patients discontinued lamotrigine due to adverse events in monotherapy studies. The most common events leading to discontinuation in monotherapy studies were also rash (2.9%) and increased seizures (2.2%). The rate of discontinuation of lamotrigine due to adverse events was similar for paediatric patients to that previously observed in adult patients with add-on treatment (10.1 and 11%,[17] respectively) or monotherapy treatment (6.6 and 10%,[17] respectively).

4.3 Treatment-Emergent Adverse Events and Adverse Events Leading to Discontinuation of Treatment: Placebo-Controlled Trials

In 2 of the 13 studies (UK-123 and US-40), there was a parallel-group comparison between lamotri-

gine and placebo add-on therapies (see table I). Table V presents pooled adverse event data from 171 placebo recipients and 168 lamotrigine recipients enrolled in these 2 studies. Overall, 85% of the lamotrigine recipients and 83% of the placebo recipients experienced a treatment-emergent adverse event. The incidence of the most common adverse events was similar between placebo and lamotrigine treatment groups. The adverse events which occurred statistically more frequently in lamotrigine recipients versus placebo recipients were: dizziness (13.7 *vs* 3.5%), ataxia (10.7 *vs* 2.9%), tremor (9.5 *vs* 1.2%), nausea (9.5 *vs* 1.8%), diplopia (5.4 *vs* 0.6%), and urinary tract infection (3.0 *vs* 0%). Of those adverse events associated with add-on lamotrigine use in placebo-controlled studies in children, only abdominal pain (9.5 *vs* 5%[17]) and tremor (9.5 *vs* 4%[17]) were observed more frequently in children than in similar placebo-controlled trials in adults.

Table IV. Most common (≥5%) adverse events in paediatric patients treated with lamotrigine

Adverse event	Add-on studies [n = 544][a] (%)	Monotherapy studies [n = 137] (%)
No. of patients with ≥1 adverse event	445 (81.8)	92 (67.2)
Somnolence	97 (17.8)	4 (2.9)
Infection	96 (17.6)	25 (18.2)
Rash	92 (16.9)	20 (14.6)
Vomiting	86 (15.8)	12 (8.8)
Increased seizures	77 (14.2)	4 (2.9)
Pharyngitis	66 (12.1)	16 (11.7)
Fever	66 (12.1)	14 (10.2)
Headache	49 (9.0)	21 (15.3)
Ataxia	49 (9.0)	1 (0.7)
Rhinitis	49 (9.0)	13 (9.5)
Dizziness	44 (8.1)	5 (3.6)
Accidental injury	39 (7.2)	4 (2.9)
Nausea	36 (6.6)	4 (2.9)
Unevaluable reaction	35 (6.4)	3 (2.2)
Tremor	35 (6.4)	5 (3.6)
Asthenia	33 (6.1)	7 (5.1)
Diarrhoea	32 (5.9)	2 (1.5)
Dyspnea	30 (5.5)	0
Otitis media	30 (5.5)	3 (2.2)
Abdominal pain	29 (5.3)	7 (5.1)
Bronchitis	28 (5.1)	3 (2.2)
Cough	22 (4.0)	7 (5.1)

a Excludes patients from US-26 wherein data were not collected.

Withdrawals associated with adverse events were uncommon (4.5% of lamotrigine recipients and 6.8% of placebo recipients) with the exception of rash; 3.6% of lamotrigine recipients were discontinued from treatment because of rash compared with 0.6% of placebo recipients.

4.4 Deaths and Serious Adverse Events: All Trials

Nine paediatric patients treated with lamotrigine died during these clinical trials. None of the deaths was considered attributable to study drug. Four deaths were attributed to sudden unexplained death in epilepsy, 2 were related to seizure activity, and 1 each to the following causes: pneumonia, aspiration, and infection. The percentage of lamotrigine recipients reporting serious adverse events was 10.9% in add-on trials and 8.8% in monotherapy trials. In all paediatric trials, 117 out of 1096 (10.7%) lamotrigine recipients experienced a serious adverse event; 4.7% experienced a serious adverse event considered by the investigator to be study drug-related. The most frequently reported serious adverse event was increased seizures (3.1% of patients). In placebo-controlled studies, 14 out of 168 (8.3%) lamotrigine recipients experienced a serious adverse event compared with 8 out of 171 (4.7%) placebo recipients.

5. Skin Rash

5.1 Rash in Paediatric Trials

A range of cutaneous reactions was reported associated with lamotrigine treatment. However, there are no distinguishing factors between lamotrigine-associated rash and rashes associated with other anticonvulsants. These reactions most frequently included simple morbilliform rashes that were not associated with systemic symptoms. Less frequently, more severe rashes occurred in clinical trials, some of which were reported by the investigator as possible Stevens-Johnson syndrome (SJS). Toxic epidermal necrolysis did not occur in the clinical

Table V. Comparison of rate of common adverse events (≥5%) occurring more frequently with lamotrigine treatment and withdrawals due to adverse events between lamotrigine and placebo in add-on, placebo-controlled studies (US-40 and UK-123)

	Adverse events		Withdrawals	
Adverse event	Placebo [n = 171] (%)	Lamotrigine [n = 168] (%)	Placebo [n = 171] (%)	Lamotrigine [n = 168] (%)
Infection	17.0	20.2	0	0
Vomiting	16.4	19.6	0	0
Somnolence	14.6	16.7	0	0.6
Rash	14.6	14.9	0.6	3.6
Fever	14.0	14.9	0	0.6
Pharyngitis	11.1	13.7	0	0
Accidental injury	12.3	14.3	0	0
Dizziness	3.5	13.7*	0	0
Diarrhoea	8.8	11.3	0	0
Ataxia	2.9	10.7*	0	0
Nausea	1.8	9.5*	0	0
Abdominal pain	4.7	9.5	0	0
Tremor	1.2	9.5*	0.6	0
Asthenia	4.1	7.7	0	0
Flu	5.8	7.1	0	0
Bronchitis	4.7	7.1	0	0
Cough	6.4	7.1	0	0
Diplopia	0.6	5.4*	0	0

***** p<0.05 *vs* placebo.

trials in paediatric patients nor did severe forms of hypersensitivity associated with multiorgan failure. However, these latter conditions have appeared in postmarketing reports.

5.2 Paediatric versus Adult Rash Incidence

Table VI summarises the incidence of rash, rash leading to the discontinuation of lamotrigine, and serious rash (defined as rash associated with hospitalisation and the discontinuation of lamotrigine or rash reported as possible SJS) in the 13 paediatric clinical trials and compares the incidence to that in adult clinical trials.[18] Paediatric patients had a slightly higher incidence of rash (12.6 *vs* 10.7%, respectively) and rash leading to discontinuation (4.8 *vs* 3.5%, respectively) compared with adult patients. Although the actual number of cases is small, there was a 3-fold difference between paediatric and adult patients in the incidence of rash associated with hospitalisation or reported as SJS (1.0 *vs* 0.3%, respectively). The mean duration of lamotrigine treatment prior to discontinuation due to rash in paediatric patients was 25.4 days, consistent with the adult data.[19]

Important differences in concomitant anticonvulsant use between the paediatric and adult clinical trials may have contributed to the higher risk of rash among paediatric patients in add-on trials. Table VII summarises the concomitant anticonvulsants used in the paediatric versus adult trials[19] and their association with the occurrence of rash. Both adult and paediatric patients using lamotrigine in combination with valproic acid only or valproic acid and nonenzyme-inducing anticonvulsants were more likely to experience rash than other combinations of therapy (approximately 20 *vs* 5 to 15%, respectively). The concomitant use of valproic acid was limited in the adult clinical trials (15% of patients) compared with paediatric trials (41% of patients).

5.3 Rash Leading to Hospitalisation or Stevens-Johnson Syndrome

A total of 11 paediatric patients experienced a rash associated with hospitalisation and the discon-

Table VI. Incidence of rash in paediatric versus adult patients

Type of rash	No. of patients ≥16 years old[18] (%) [total no. 3348]	No. of patients <16 years old (%) [total no. 1096
Rash	359 (10.7)	138 (12.6)
Rash leading to discontinuation	118 (3.5)	52 (4.7)
Rash associated with hospitalisation	11 (0.3)	10 (0.9)
Possible SJS	4 (0.1)	5 (0.5)
Possible SJS or hospitalised	11 (0.3)	11 (1.0)

SJS = Stevens-Johnson syndrome.

tinuation of lamotrigine or a rash reported as possible SJS (1 patient reported with SJS was not hospitalised), as shown in table VI. Five of the 11 cases were receiving concomitant valproic acid. Of the 5 possible cases of SJS, 4 were receiving concomitant valproic acid. Eight of these 11 cases received starting doses or dose escalations of lamotrigine that exceeded drug dose recommendations in place at the time.

The range in days to onset of rash in 10 of these 11 patients was 10 to 59 (mean = 29.8) days. The remaining patient received lamotrigine 200 days without event but developed a rash 6 weeks after phenytoin was added. The patient was admitted to the hospital because of the rash and an increase in seizures to 9 to 10 per day. Lamotrigine was discontinued. The mean number of days to onset of rash for all 11 patients was 45.3 days.

6. Discussion

In the 13 paediatric clinical trials, 1096 children were exposed to lamotrigine, the majority for at least 6 months. Investigators reported all adverse events regardless of the perceived relationship to lamotrigine therapy. In most of these trials, lamotrigine was given in combination with other anticonvulsants that are known to be associated with certain adverse events. About 50% of the children in add-on trials were using concomitant valproic acid and about 50% were using enzyme-inducing anticonvulsants alone (e.g. phenytoin and carbamazepine); these drugs are associated with a risk of neurotoxicity and gastrointestinal effects.[22-26] In general, adverse event reporting rates are higher in clinical studies (with protocol-mandated probing for adverse events and fixed dosing schedules) than for spontaneous, postmarketing reporting systems. Therefore, the incidence estimates reported here for lamotrigine may be higher than normally observed.

Placebo-controlled comparisons from the paediatric clinical trials showed that adverse effects associated with lamotrigine use as add-on therapy included dizziness, ataxia, tremor, nausea, diplopia, and urinary tract infections. Another observation was that lamotrigine monotherapy had lower incidences of most adverse events than lamotrigine add-on therapy. Several adverse events were observed more frequently in add-on than in monotherapy studies, particularly those of the central nervous system (e.g. somnolence, increased seizures, ataxia, dizziness) and gastrointestinal system (e.g. vomiting, nausea, diarrhoea). Of the adverse events that were significantly more common with lamotrigine treatment than with placebo treatment in add-on trials, only abdominal pain (5.1%) and asthenia (5.1%) were observed frequently (≥5%) in monotherapy trials. These data suggest that the adverse effects of concurrent anticonvulsant therapy or combination therapy of lamotrigine and other anticonvulsants were a risk factor above that of lamotrigine alone.

In general, the adverse event profile observed in children treated with lamotrigine was similar to that observed in adults. The types of adverse events reported in these paediatric trials were similar to those reported in adult clinical trials.[19] The incidence of adverse events was also similar; among the adverse events associated with add-on lamotrigine treatment in placebo-controlled trials, only abdominal pain and tremor were observed more frequently in children than in adults.[17] Furthermore, the discontinuation rate due to adverse events was similar to or lower in paediatric patients than in adult patients treated with lamotrigine.[17]

Skin rash was reported in paediatric lamotrigine trials, as has been reported with a number of anticonvulsants.[27-31] Although the general incidence of rash was similar to that reported for adults, the incidence of rash associated with hospitalisation

Table VII. Paediatric and adult rash rates with different concomitant anticonvulsant drugs

Therapy	Total no. of patients	All rash (%)	DC rash (%)[a]	Hosp/SJS rash (%)[b]
Paediatric (<16 years)				
LTG + EIAED	394	9.6	4.1	0.8
LTG + VPA + EIAED	155	4.5	0	0
LTG + VPA only	145	20.0	9.0	1.4
LTG +VPA + NEIAED	145	21.4	10.3	1.4
LTG + other	60	11.7	3.3	0
LTG monotherapy	192	13.5	3.1	1.6
Adult (≥ 16 years)[19]				
LTG + EIAED	2240	6.7	2.0	0.1
LTG + VPA + EIAED	303	7.6	3.3	0.7
LTG + VPA only	205	19.5	12.2	2.0
LTG + VPA + NEIAED	10	20.0	10.0	0
LTG + other	195	10.3	5.1	0.5
LTG + monotherapy	420	14.5	6.0	0

a Rash leading to treatment discontinuation (DC).

b Rash leading to hospitalisation or Stevens-Johnson syndrome (SJS).

EIAED = enzyme-inducing antiepileptic drug(s); **LTG** = lamotirgine; **NEIAED** = nonenzyme-inducting antiepileptic drug(s); **VPA** = valproic acid (sodium valproate).

and the discontinuation of lamotrigine or rash reported as possible SJS was higher in paediatric patients than in adults. One factor in the higher incidence of serious rash in children may be the more frequent use of concomitant valproic acid in the paediatric clinical trials. Rash occurred more frequently with the concomitant use of valproic acid, both in children and adults, probably because valproic acid markedly increases the half-life of lamotrigine.[32-34] Another factor may be the higher initial doses and faster dose escalation of lamotrigine used in these paediatric trials compared with recently approved paediatric dosing guidelines; analyses in adults have recently demonstrated the positive relationship of dose with the incidence of rash.[18] Paediatric patients in these trials achieved higher lamotrigine plasma concentrations at a faster rate than adult patients, according to a recently conducted population pharmacokinetic analysis.[35] The new recommendations for use of lower lamotrigine dosages in paediatric patients are expected to result in serum concentrations of lamotrigine that are very similar for adult and paediatric patients throughout the dose titration period and are expected to result in a reduced incidence of rash for paediatric patients.

Currently, the mechanism for rash is unknown, but it is under active investigation. However, risk factors for lamotrigine-associated rash include concomitant valproic acid, age, dose and dose escalation. The best prevention against the occurrence of lamotrigine-associated rash is to follow the drug dosage guidelines. Nevertheless, if rash occurs, lamotrigine should be immediately discontinued unless the rash is clearly not drug-related.

7. Conclusion

This review presents a summary of safety data in 1096 paediatric patients who participated in all centrally conducted and monitored paediatric clinical trials with lamotrigine. The principal adverse effects associated with lamotrigine were dizziness, tremor, ataxia, nausea, diplopia, and urinary tract infections. Almost all of these events were mild to moderate in intensity and did not require discontinuation of lamotrigine. There was a higher incidence of rash associated with hospitalisation and the discontinuation of lamotrigine or rash reported as SJS in children compared with adults. This may be associated with the higher incidence of risk factors (concurrent valproate, high initial dose, and rapid dose escalation). Lamotrigine is a well tolerated broad spectrum anticonvulsant with qualitatively similar adverse events in paediatric and adult patients.

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Correspondence and offprints: Dr *John Messenheimer*, Neurology and Psychiatry Clinical Research, GlaxoWellcome Research Institute, 5 Moore Drive, Research Triangle Park, NC, 27709, USA.
E-mail: jam40606@glaxowellcome.com