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Paediatric Postmarketing Pharmacovigilance Using Prescription-Event Monitoring

Comparison of the Adverse Event Profiles of Lamotrigine Prescribed to Children and Adults in England

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Abstract

Background: Using postmarketing pharmacovigilance data collected shortly after market authorization of lamotrigine in the UK, a study was conducted to compare the adverse event (AE) profiles of children and adults taking lamotrigine, using modified signal detection methods.

Methods: Data from the lamotrigine Prescription Event Monitoring (PEM) study, an observational cohort study, were stratified by age and examined using summary statistics for adverse drug reactions (ADRs), reasons for stopping treatment, deaths and follow-up information. Incidence densities of AEs in children (0–17 years) and adults (≥18 years) in the first month of treatment were compared with months 2–6 to examine whether the AE rates were different in these two periods. AE rates in children were compared with those in adults (proportional reporting ratio [PRR] and incidence rate ratios), to compare the AE profiles between these age groups.

Results: The cohort included 2457 children and 7379 adults. Differences in the AE profiles between children and adults were observed. Rash (PRR 1.2) and Stevens-Johnson syndrome (PRR 4.5) were more commonly reported in children, and confusion more frequently in adults (PRR 6.3). In children, 33% of ADRs were reported to the Regulatory Authority compared with 44% in adults. A higher proportion of children stopped treatment due to lack of effectiveness (45% vs 38%). No deaths were attributed to lamotrigine.

Conclusions: This study demonstrated that signal detection methods can be used to detect quantitative and qualitative differences in the AE profiles between the first children and adults taking a newly licensed drug.

Background

In the early 1960s the thalidomide disaster led to an increasing awareness of the issues surrounding drug safety. Many of these concerns affected children, who have often been excluded from drug safety and efficacy studies due to concerns about ethics, practicability and financial reasons. Summaries of product characteristics (SPCs) frequently include only limited paediatric drug safety information.

To address the issue of off-label and unlicensed prescribing in children, European regulations were issued to oblige pharmaceutical companies to submit a paediatric investigation plan for all new compounds, indications and formulations from January 2007 onwards.[1-3] Paediatric pharmacovigilance activities will have to be included in the benefit-risk management plan and other pharmacovigilance activities. Paediatric clinical trials of many new compounds could be delayed until more experience of the benefit-risk profile has been gained in adults, increasing the risk for off-label or unlicensed use of a newly licensed medicine in children. Furthermore, at the time of market authorization, less safety experience is usually available for children compared with adults. Therefore pharmacovigilance, particularly in the early phase after market authorization has been granted, will be particularly important for assessing paediatric drug safety.[4,5] Considering the differences – such as pharmacokinetics, pharmacodynamics, epidemiology and co-medication – between children and adults in general as well as between children of different age groups, the adverse event (AE) and adverse drug reaction (ADR) profiles may be different in children and adults. Pharmacovigilance tools may need to be adapted to the paediatric population.

The aim of this study was to use a modified analysis of a standard Prescription-Event Monitoring (PEM) study to explore possible differences in the AE profiles between children and adults, and identify possible differences between the proportions of AE reporting for children and adults and the AE signal profiles between these two age groups.

Methods

The methodology of PEM complies with international ethics guidelines for biomedical research involving human subjects.[6-8] PEM studies are postmarketing observational cohort studies conducted on newly marketed drugs.[9]

Patients

Patients are identified from dispensed National Health Service prescriptions issued by general practitioners (GPs) in England. These data are sent in confidence by the Prescription Pricing Division of the National Health Services Business Services Authority to the Drug Safety Research Unit (DSRU). In PEM there are no exclusion criteria, and patients are included in the study cohort irrespective of age, indication, dose or concomitant medications, provided they have been dispensed the drug of interest and a completed Green Form questionnaire is returned.

Green Forms were posted to the prescribing GP at least 6 months after the initial prescription for each individual patient was identified. The Green Forms requested demographic information, indication, dose, reason for stopping lamotrigine (if applicable), any events that had occurred since starting lamotrigine, whether any events were suspected to be ADRs and whether events were reported to the UK Regulatory Authority or manufacturer. An event was defined on the Green Form as ''any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any other complaint that was considered of sufficient importance to enter in the patient's notes.'' GPs provided information on the Green Form on an unpaid, voluntary basis.

All events reported on Green Forms were coded onto the DSRU database using a dictionary similar to the Medical Dictionary for Regulatory Activities.[9] The DSRU dictionary is hierarchical and arranged in a system-organ classification, grouping associated terminology used by the prescribing physician under 'lower level' event terms and related lower level terms under a

broader 'higher level' event term within the system-organ classifications. More than one AE may be entered for the same patient.

Most PEM studies collect data on at least 10 000 patients. It is estimated that a sample size of 10 000 patients should detect at least three AEs (higher level terms), with 85% power, if the AE occurs at a rate of at least 1 in 2000 and assuming the background rate is zero. However, it is recognized that the background rate of many AEs is often unknown. Similarly, if the sample size is 5000, at least three AEs should be detected if the AE occurs at a rate of 1 in 1000 (85% power).[10]

For this study, the data of the lamotrigine PEM study were stratified into three paediatric age groups (<2 years, 2–11 years, 12–17 years) and one adult group (≥18 years), and examined by using summary statistics for ADRs, reasons for stopping treatment and cause of death.[11] Patients for whom no age was specified were excluded from these analyses. Selected events of interest were followed up, mainly those that were medically serious and where causality was unclear from the information given on the Green Form or events highlighted by the GP as a suspected ADR and not listed in the SPC. Standardized causality assessments were made after follow-up information had been received.[12]

Incidence Densities

Incidence densities (IDs; number of first occurrences of an event/1000 patient-months of treatment) were calculated to examine whether the AE rate was different between the first month of treatment (ID_1) and the subsequent 5 months ($ID_{2–6}$) both in children (0–17 years) and in adults (≥18 years). The difference between ID_1 and $ID_{2–6}$ for all higher level term events was calculated for each higher level term event for children and adults. Statistical significance was determined by calculating a 99% confidence interval (CI) around the point estimate of the difference between ID_1 and $ID_{2–6}$. If this was positive and the CI did not include zero, it identified AEs occurring significantly more frequently in the first month of treatment (early onset) compared with months 2–6. AEs with a delayed onset, that is those presenting more frequently in months 2–6 compared with month 1, were identified if this difference was negative.[9]

Proportional Reporting Ratios and Incidence Rate Ratios

The calculation of proportional reporting ratios (PRRs) and incidence rate ratios (IRRs) was different to standard methods. Standard methods compare the proportion of an AE of interest in a drug of interest to the proportion of this same AE in all other drugs on the database. Differences between children and adults in pharmacodynamics, pharmacokinetics, morbidity and mortality, as well as differences in the disease and medication characteristics of the paediatric and adult cohorts on the DSRU database led to the decision to develop a modified calculation of the PRR and IRR for this study. To compare the risk of AEs between children and adults dispensed lamotrigine, PRRs and IRRs were calculated for children (age 0–17 years) and adults (age ≥18 years) for AE terms (higher level terms) with at least three reports in each age group in order to reduce the number of false positive signals. A statistically significant PRR or IRR indicated whether there were differences in the reporting frequency of AEs between children and adults.

The PRR was determined by dividing the proportion of AEs during the overall treatment period in children by the proportion of the same AE term in adults. The proportion of each AE, in children and adults, was calculated by dividing the number of AEs for each higher level term, for the respective age group, by the number of all AEs for the same age group.

A PRR >1 indicated that the AE was reported more frequently in children than adults. A proportional reporting ratio of 0–1 indicated that the AE was reported more frequently in adults. Statistical significance was determined using the Yates' correction for the Chi-squared statistic with one degree of freedom. A statistically significant p-value of 0.05 was indicated by a Chi-squared statistic above 4.[13]

IRRs were calculated for the first 30, 90 and 180 days of treatment for children and adults.

The incidence rate for each AE was calculated by dividing the number of AEs for the specified treatment period for each age group by the patient-years at risk in the respective age groups for the same treatment period. Then the incidence rate of the AE in children was divided by the incidence rate of this AE in adults during the specified time period.

An IRR >1 indicated that the AE was reported more often in children than adults. An IRR of 0–1 indicated that the AE was reported more frequently in adults than children. Statistical significance was determined by calculating the z-statistic, using the Poisson distribution. A statistically significant p-value was indicated by a z-statistic >1.6.[13]

To facilitate the comparison of the magnitude of the difference of the PRR or IRR in children and adults, the reciprocal of the adult PRR or IRR was calculated.

Adverse Event Signals

In this study, the term 'AE signal' was used for events reported as a suspected ADR, a reason for stopping or AEs assessed as possibly or probably related to lamotrigine after follow-up information had been received. In addition, AEs were considered 'AE signals' if they had reached statistical significance after the calculation of the incidence density difference, PRR, IRR or if a death had been attributed to the drug. It was possible for events to be identified as an AE signal by more than one criterion.

Finally, event terms of undesirable effects added to the UK SPC up to 2009 were matched to higher level terms in the DSRU dictionary and compared with the AE signals identified in children and adults in this PEM study.[14,15]

Results

Patients

Patients were identified from dispensed lamotrigine prescriptions issued between December 1991 and February 1995 (lamotrigine was first licensed in the UK in October 1991). Of the 19 448 Green Form questionnaires sent, 13 196 (67.9%) were returned. Of these, 11 316 (58.2% of all Green Forms sent) contained clinical information.

Of this cohort, >20% (2457) of the patients were children (table I). The median observation period was 277 days for children (interquartile range 250–337 days) and 273 days for adults (interquartile range 248–331 days).

Indications

The indication was reported for 8991 (79.5%) patients. Indications not included in the label at the time, such as neuralgia or depression, were reported for 3.2% of patients (284/8991). It was noted that lamotrigine was prescribed for 88 children (3.6% of all children) under the age of 2 years, an age range for which it was not licensed at the start of this study.

Adverse Events

Incidence Densities

Differences between children and adults were identified for AEs that were reported significantly more frequently in the first month (ID_1) or in months 2–6 (ID_{2-6}) [table II]. For example, in children, but not adults, lack of effectiveness was reported significantly more frequently in months 2–6 compared with the first month of treatment. In adults, but not children, weight gain was reported significantly more frequently in months 2–6 compared with the first month of treatment.

Table I. Age and sex distribution of patients in the lamotrigine prescription-event monitoring study[a]

Sex	<2 y	2–11 y	12–17 y	**All children 0–17 y**	**Adults ≥18 y**	**Age not specified**	**Total**
Male	48 (54.6)	764 (56.1)	520 (51.6)	**1332 (54.2)**	**3580 (48.5)**	**734 (49.6)**	**5 646 (49.9)**
Female	39 (44.3)	590 (43.3)	486 (48.2)	**1115 (45.4)**	**3787 (51.3)**	**735 (49.7)**	**5 637 (49.8)**
Sex not specified	1 (1.1)	7 (0.5)	2 (0.2)	**10 (0.4)**	**12 (0.2)**	**11 (0.7)**	**33 (0.3)**
Total	88 (0.8)	1361 (12.0)	1008 (8.9)	**2457 (21.7)**	**7379 (65.2)**	**1480 (13.1)**	**11 316 (100.0)**

a Values are represented as number of patients (%).

Table II. Adverse events with a statistically significant difference in occurrence between month 1 and months 2–6 of treatment (incidence densities) in children and adults

Time to onset	Higher level term	Children [0–17 y]	Adults [≥18 y]
		ID_1–ID_{2-6} (99% CI)	ID_1–ID_{2-6} (99% CI)
Early onset[a]	Rash	24.8 (15.8, 33.9)	13.6 (9.4, 17.8)
	Convulsion	9.0 (0.8, 17.1)	9.0 (4.2, 13.9)
	Nausea, vomiting		6.4 (3.0, 9.7)
	Headache, migraine		5.1 (1.9, 8.2)
	Malaise, lassitude		4.3 (1.6, 7.0)
	Drowsiness, sedation		3.2 (0.5, 5.9)
Delayed onset[b]	Not effective	–4.5 (–7.9, –1.1)	
	Abdominal pain	–1.2 (–2.0, –0.3)	
	Acne	–1.1 (–1.9, –0.3)	
	Wart		–0.5 (–0.9, –0.2)
	Weight gain		–0.4 (–0.7, –0.1)
	Panic attack		–0.3 (–0.6, –0.1)

a Adverse events with a statistically significant higher occurrence in the first month compared with months 2–6 of treatment.

b Adverse events with a statistically significant higher occurrence in months 2–6 compared with the first month of treatment.

ID = incidence densities for months 1 and 2–6 as indicated.

Proportional Reporting Ratios and Incidence Rate Ratios

In children, overall 19 higher level terms were identified as being more commonly reported in children compared with adults, through a statistically significant PRR and/or IRR. Seventeen DSRU higher level terms reached statistical significance after calculation of the PRR and 16 after calculation of the IRR.

In children, four DSRU higher level terms described as undesirable effects in the UK SPC up to 2009 and identified by at least one signal detection method were reported significantly more frequently in children compared with adults (PRR; $p < 0.05$). Three were described in the first UK SPC for Lamictal® in 1991[15] – rash, Stevens-Johnson syndrome and fever; these also had a statistically significant IRR. One other DSRU higher level term was also more commonly reported in children compared with adults – upper respiratory tract infection – this may be related to the 1991 UK SPC term of flu-like illness. Lymphadenopathy was also identified as more commonly reported in children compared with adults and was not described in the first UK SPC, but included in the 2009 UK SPC.[14] In addition, children were more likely to change antiepileptic drug medication compared with adults (PRR, IRR).

In adults, overall 27 higher level terms were identified as being more commonly reported in adults compared with children, through a statistically significant PRR and/or IRR. Twenty-seven DSRU higher level terms reached statistical significance after the calculation of the PRR and 13 after the calculation of the IRR.

For adults, nine DSRU higher level terms described as undesirable effects in the UK SPC up to 2009 were reported significantly more frequently in adults compared with children (PRR, $p < 0.05$). Six of these concerned effects described in the first UK SPC (1991): visual defect (including blurred vision and diplopia), headache, dizziness, unsteadiness, gastrointestinal effects and malaise/lassitude (including tiredness). However, three DSRU higher level terms – nausea/vomiting, confusion and the higher level term of oedema (which includes the lower level term of facial oedema) – were not included in the first UK SPC, but were described in the 2009 SPC. All but unsteadiness had a statistically significant IRR (table III).

A small number of AEs likely related to background disease or natural occurrence in each age group were reported significantly more frequently in children or adults, e.g. gastroenteritis or molluscum contagiosum in children and earwax

Table III. Examples of proportional reporting ratios (PRRs) and incidence rate ratios (IRRs) reported significantly[a] more frequently in children and adults

System organ class higher level term	Children (0–17 y)				Adults (≥18 y)			
	PRR (Chi-squared)	IRR (z-statistic)			1/PRR (Chi-squared)	1/IRR (z-statistic)		
		30 days	90 days	180 days		30 days	90 days	180 days
Psychiatric								
Confusion[b]					6.3 (11.8)		3.5 (2.0)	4.8 (2.7)
Anxiety					4.6 (12.3)	5.9 (1.7)	5.0 (2.2)	5.0 (2.8)
Depression					3.7 (19.0)		4.0 (2.8)	4.0 (3.7)
Abnormal behaviour	2.6 (18.3)		8.3 (3.4)	4.0 (4.2)				
Malaise, lassitude[c]					2.0 (12.5)	3.1 (2.8)	2.6 (3.6)	2.1 (3.4)
Skin								
Stevens-Johnson syndrome[c]	4.5 (4.8)	5.0 (2.0)	4.5 (2.2)	4.4 (2.2)				
Pruritus					3.1 (8.5)		3.0 (2.0)	4.4 (2.9)
Rash[c]	1.2 (4.1)	1.6 (3.0)	1.3 (2.0)	1.2 (1.9)				
Ocular								
Visual defect[c,d]					4.2 (41.3)	8.3 (3.4)	4.0 (4.2)	4.2 (5.5)
Conjunctivitis[b]	2.5 (13.1)	9.0 (2.9)	3.7 (2.7)	3.0 (3.7)				
Gastrointestinal[e]								
Gastroenteritis[c]	2.4 (5.7)		3.5 (2.1)	2.9 (2.4)				
Dyspepsia[c]					2.1 (4.4)			
Abdominal pain[c]					1.6 (4.1)			
Nausea, vomiting[b]					1.4 (5.2)	1.7 (2.1)	1.5 (2.1)	1.5 (2.4)

a $p < 0.05$.

b Described in the 2009 UK SPC,[14] but not in the 1991 UK SPC.[15]

c Described in the 1991 UK SPC.[15]

d Includes event terms of visual disturbance and diplopia.

e Described in the 1991 UK SPC[15] as 'gastrointestinal disturbance'.

SPC = Summary of Product Characteristics.

or non-malignant tumour in adults. However, these events had not been identified by any signal detection method such as ADR or reason for stopping and thus were considered unlikely to be related to treatment.

Reasons for Stopping and Reported Adverse Drug Reactions

A smaller proportion of children (18.8% [462/2457]) stopped treatment compared with 24.7% of adults (1823/7379). For 59.5% of children (275/462), 325 reasons for stopping were given and for 51.8% of adults (945/1823), 1236 reasons for stopping were given. For 40.5% (187/462) of children and 48.2% (878/1823) of adults who stopped treatment, no reason was given. Lack of effectiveness was the most commonly reported reason for stopping, affecting more children (44.7% [123/275]) than adults (38.0% [359/945]).

GPs reported at least one ADR for similar proportions (1.1%) of children (27/2457) and adults (81/7379). Some patients experienced more than one ADR (46 ADRs reported in 27 children; 128 ADRs in 81 adults). The most commonly reported ADRs in children were those affecting the skin (12/46 [26.1%]), whereas neurological ADRs (28/128 [21.9%]) were most commonly reported in adults.

A smaller proportion of suspected ADRs in children (32.6% [15/46]) were notified to the UK Regulatory Authority compared with those in adults (43.8% [56/128]). None of these events was reported to the manufacturer.

The type and order of ranking by frequency of the five SOCs with the highest number of clinical reasons for stopping were the same both in the

children and in the adult cohorts – neurological, followed by skin, psychiatric, gastrointestinal and ocular SOCs. However, for ADRs, a difference between children and adults was observed for the type and ranking by frequency of SOCs. In children, the most commonly reported SOCs were skin, followed by neurological, gastrointestinal, ocular and haematological, whereas for adults these were neurological, followed by skin, psychiatric, gastrointestinal and haematological.

Furthermore, there were differences in the frequencies of reasons for stopping and ADRs reported for children and adults. For example, in adults a similar proportion of psychiatric ADRs and reasons for stopping were reported: 13.3% (17/128) and 12.3% (152/1236), respectively. In contrast, only 4.4% (2/46) of all ADRs reported in children were psychiatric ADRs, but 10.8% (35/325) of all reasons for stopping in children were related to a psychiatric AE (table IV).

Follow-Up Information

After follow-up information was received, 38 AEs were assessed as possibly related to and two (abnormal liver function test and leucopenia) as probably related to lamotrigine treatment. Fourteen cases concerned children, 24 were reported for adults and no age was specified for two.

Co-medication was specified for 12 children and 17 adults whose AEs were assessed as possibly or probably related to treatment after follow-up information was received. Two children and three adults were prescribed lamotrigine as monotherapy (off-label use at the time). Nine children (75.0% [9/12]) and nine adults (52.9% [9/17]) were taking valproate with or without other antiepileptic medicines.

No case of antiepileptic hypersensitivity syndrome (most common signs are fever, rash, lymphadenopathy and hepatitis) was reported in this cohort. However, AEs such as lymphadenopathy and fever were reported as reasons for stopping and as ADRs in either children or adults.

Deaths

During this study 124 (1.1%) patients died. The age was reported for 81 patients (10 children [0.4%] and 71 adults [1.0%]); for 43 patients the age was not known. None of the deaths were attributed to lamotrigine by the reporting GP.

Three children and 11 adults were found dead; three of these adults experienced a sudden death, of which two were witnessed. Information on the actual cause of death of these three children and 11 adults was not available.

The most commonly reported cause of death both in children (four patients) and in adults (33 patients) was epilepsy; nine of these adults died due to status epilepticus. The second most commonly reported cause of death in children was pneumonia (two patients). For adults it was motor neuron disease (14 patients) followed by cardiovascular disease (ten patients). Four adults drowned and one committed suicide.

DSRU Higher Level Terms Matching UK SPC Terms and Adverse Event Signals

Between 1991 and 2009, 36 undesirable effects were added to the UK SPC for lamotrigine. 32 of these SPC terms matched to 27 DSRU higher level terms. In children, 51.9% (14/27) were identified by at least one signal detection method compared with 66.7% (18/27) in adults. Table V shows the differences in signal pattern between children and adults; this was particularly notable in the psychiatric SOC (tables III and IV). In children, the majority (eight terms) of new SPC terms were identified by just one signal detection method whereas in adults the majority (13 terms) were identified by two or more methods. In children, a smaller proportion of SPC terms added up until 2009 were identified as ADRs compared with adults (5 terms vs 13 terms).

For 13 higher level terms in children and 9 in adults, no signal was identified for undesirable effects added to the UK SPC up until 2009. All these were described as rare or very rare, or had only been observed during a clinical development programme for bipolar disorder, an indication not included in the UK SPC at the time of data collection.

Discussion

This study showed that there were differences in the AE profiles between children and adults

Table IV. Reasons for stopping treatment in four most commonly reported System Organ Classes and reported adverse drug reactions (ADRs) in children and adults taking lamotrigine[a]

Higher level term	Children (0–17 y) [n = 2457]		Adults (≥18 y) [n = 7379]	
	reasons for stopping (n)	ADRs (n)	reasons for stopping (n)	ADRs (n)
Total no. of reports	**325**[b]	**46**[c]	**1236**[d]	**128**[e]
Neurological total	**62**	**11**	**284**	**28**
Convulsion, epilepsy			62	1
Drowsiness, sedation	14		57	2
Dizziness	6	1	48	8
Headache, migraine	5	3	50	10
Ataxia	5	2	23	3
Tremor			11	1
Unsteadiness			9	1
Aphasia, dysphasia			5	
Other	32	5	19	2
Skin total	**57**	**12**	**156**	**26**
Rash	48	8	131	19
Stevens-Johnson syndrome	5	1	4	1
Pruritus			10	
Other	4	3	11	6
Psychiatric total	**35**	**2**	**152**	**17**
Abnormal behaviour	9		6	
Irritability	6	2	9	1
Aggression	5		18	1
Malaise, lassitude	5		40	3
Depression			18	3
Confusion			14	1
Anxiety			7	1
Insomnia			6	
Agitation			5	1
Hallucination			5	1
Mood swings			4	
Other	10		20	5
Gastrointestinal total	**18**	**5**	**99**	**16**
Nausea, vomiting	11	4	70	11
Anorexia			4	
Diarrhoea	3		4	1
Dyspepsia	1		4	
Other	3	1	17	4

a More than three reasons for stopping reported per higher level term in children or adults; not all ADRs reported were also reported as reasons for stopping and not all events reported as reasons for stopping were identified as ADRs.

b Reported in 275 patients.

c Reported in 27 patients.

d Reported in 945 patients.

e Reported in 81 patients.

taking lamotrigine. In addition, differences were observed in the proportion of ADRs reported to the UK Regulatory Authority for children and adults.

PEM studies are observational cohort studies conducted in general practice and therefore differ from clinical trials with regard to the type of patients included and methods of data collection.

In contrast to the exclusion criteria applied in clinical trials, PEM studies aim to capture drug usage as it occurs in clinical practice; for example, they include off-label use. The aim of the present study was to investigate possible differences between the proportions of AE reporting for children and adults and the AE signal profiles between these two age groups for lamotrigine.

The response rate of 68% in this study was above the average for PEM studies (56%).[9] In PEM, the most common reason for GPs not responding was that they were too busy to fill out the questionnaire.[16] At the time of the PEM study, lamotrigine belonged to a relatively new class of antiepileptic drugs and knowledge about the drug class was limited. Initially, it was only licensed for add-on treatment.[15] This may have increased the risk of patients experiencing an AE through a selection bias towards patients with difficult-to-treat epilepsy, other medical problems and patients taking a number of antiepileptic drugs. The proportion of AEs may have been underestimated in this study if GPs were more reluctant to fill out questionnaires for patients with complex medical histories. This could have affected the calculation of incidence densities, PRRs and IRRs. Also, more serious AEs may have been more likely to be reported compared with events that were thought to be trivial, which may lead to reporting bias. Clarity of the causal relationship and pre-existing knowledge about the ADR profile of the drug may have influenced reporting. It is possible that GPs differ from hospital specialists such as neurologists in the way they report AEs or ADRs, and this may influence signal detection. Furthermore, reporting may be different in children and adults because, in the case of children, this often depends on adults observing children and interpreting their symptoms. In addition, data capture depends on the patient reporting the event, and the doctor entering the event into the patient's notes and then reporting it to the DSRU. When comparing AE signals from this study with those described in the UK SPC it is important to remember that this PEM study, an observational cohort study, focused on AEs rather than ADRs and that the AE data may not have been complete, whereas undesirable effects added to the UK SPC may be based on a variety of data, e.g. clinical trial data and spontaneous ADR reports.

The main strengths of this study were that it included the first patients being prescribed a newly licensed drug under 'real-life' conditions in general practice, leading to a wide variety of patients being included.[9,17] The collection of AE rather than ADR data in a large cohort enables PEM to detect AE signals, which none of the prescribing GPs had suspected to have been possibly due to lamotrigine. Selection bias was minimized by the observational character of PEM and because patients were identified from dispensed prescriptions, i.e. after GPs had decided to prescribe lamotrigine.

Table V. UK Summary of Product Characteristics (SPC) terms added up to 2009 and matching Drug Safety Research Unit higher level terms identified by at least one signal detection method (SDM) in children or adults

Parameter	Children				Adults			
	no. of matching SPC terms identified	RSs	ADRs	other (ID, PRR, IRR, FU)	**no. of matching SPC terms identified**	RSs	ADRs	other (ID, PRR, IRR, FU)
≥3 SDMs	**1**	1	1	1	**6**	6	6	6
2 SDMs	**5**	5	4	1	**7**	7	7	
1 SDM	**8**	7		1	**5**	4		1
Total no. (%) of matching SPC terms identified by ≥1 SDM	**14/27 (51.9)**	13	5	3	**18/27 (66.7)**	17	13	11
No. (%) with no signal for matching SPC terms	**13/27 (48.2)**				**9/27 (33.3)**			

ADRs = adverse drug reactions; **FU** = assessed as possibly or probably related to treatment after follow-up information was received; **ID** = difference in incidence density (early or late onset); **IRR** = incidence rate ratio; **PRR** = proportional reporting ratio; **RSs** = reasons for stopping.

Lamotrigine was initially (in 1991) only licensed for adults and children >12 years of age. It was not until May 1994 that the drug was licensed for children ≥2 years; however, lamotrigine was prescribed off-label in relation to age for children under the age of 2 years. Unlicensed use (e.g. crushing a tablet) may have affected most children aged less than about 7 years because most would not have been able to swallow a tablet, which was the only licensed preparation available when lamotrigine was initially licensed.[15] Towards the end of our study, in 1994, dispersible lamotrigine tablets became available.[18] At the time of the lamotrigine PEM study no information about the formulation used was requested, thus the true proportion of children taking an unlicensed formulation is not known. Unlicensed and off-label drug use in children has been associated with an increased risk of ADRs.[19] However, licensing status may have had little influence on the prescribing practice of paediatricians.[20]

Lack of effectiveness was a signal raised in children for which the incidence density was significantly higher in months 2–6 compared with the first month of treatment. This was supported by a higher frequency of this event as a reason for stopping treatment in children compared with adults. In addition, a change of antiepileptic drug was more frequently reported in children compared with adults (PRR, IRR). Possible explanations are differences between children and adults in the type of epilepsy, co-medications and treatment options, as well as under-dosing and the formulation available to children.[19,21,22]

Differences between children and adults in the frequency and type of AEs were detected, e.g. in both the dermatological and the psychiatric system organ classes. Children developed a rash or Stevens-Johnson syndrome more frequently compared with adults (PRR, IRR). Explanations for these differences may be a higher incidence of infections associated with a rash during childhood, differences in hepatic drug metabolism, or co-medication, such as valproate.[21,23,24] In clinical trials, more children (41%) than adults (15%) had valproate prescribed as co-medication.[25] Reports in the literature regarding these risk factors only began to emerge from 1993 onwards.[26] However, the relatively small number of ADR reports of rash is surprising considering that this study was conducted soon after marketing authorization in the UK, when warnings regarding dosing and co-medication may not have been as well recognized as they are today. Notably during this study, only 2 of the 11 cases of Stevens-Johnson syndrome (one concerning an adolescent and one an adult) were reported to the UK Regulatory Authority. In the 2009 UK SPC for Lamictal®, Stevens-Johnson syndrome was described as a rare event in patients >12 years of age, and hospital admission due to Stevens-Johnson syndrome or rash was described as more common in children (1%) than in adults (0.3%).[14] However, many paediatric departments have a low threshold for admitting children with a rash, particularly when they present out of hours or if they are young children.[21]

From the data reported in this study it was not possible to ascertain whether any patients had experienced antiepileptic hypersensitivity syndrome.[27] Antiepileptic hypersensitivity syndrome can be difficult to diagnose and few diagnostic criteria have been published, thus it was difficult to judge if any cases had occurred. In addition, the cohort size of this PEM study may have been too small to detect an event that occurs so rarely. The incidence of antiepileptic hypersensitivity syndrome has been estimated to be between 1 in 1000 and 1 in 10 000 exposures to aromatic antiepileptic drugs (e.g. carbamazepine).[27,28] Antiepileptic hypersensitivity syndrome has also been associated with lamotrigine and valproate, both non-aromatic antiepileptic drugs.[29-31]

However, AEs such as lymphadenopathy and fever were reported as reasons for stopping and as ADRs in the lamotrigine cohort but not in a similar PEM study in patients dispensed vigabatrin (vigabatrin PEM study [unpublished data]: 3196 children; 6007 adults).

Psychiatric AEs were more commonly reported in adults compared with children, and the type of AEs reported appeared to be more specific in adults (PRR, IRR). It is possible that children in general are less prone to experience psychiatric ADRs with antiepileptic medications.[32] Alternatively, it could reflect difficulties in diagnosing

psychiatric disease in children, which could be due to differences in their ability of expression. Psychiatric events in patients taking antiepileptic drugs may be confounded by the underlying condition, the release phenomenon and a higher risk of developing psychiatric disease.[33,34] Lamotrigine has been associated with beneficial effects on mood. In children, treatment of epilepsy with antiepileptic drugs has a beneficial effect on their development,[33] although concerns remain about long-term effects of antiepileptic drugs (e.g. on cognition).[35]

Comparison of death rates reported in the literature with those in this PEM study was difficult because in this PEM study data on risk factors were incomplete, and also because PEM studies are observational cohort studies conducted in the primary-care setting. The overall standardized mortality ratios reported in the literature for children and adults with epilepsy were 7.5 (95% CI 4.4, 13.0) and 3.6 (95% CI 3.5, 3.7), respectively.[36,37] In this study, the most frequently reported cause of death for children and adults was epilepsy, which is in keeping with the literature.[36,37] It was noted that no case of sudden unexpected death in epilepsy was reported. In the literature, 2–18% of all deaths in epileptic patients were reported to be due to sudden unexpected death in epilepsy.[37,38] We were concerned to learn that four adults drowned. Better education of patients and their carers may have prevented some of these deaths. Only one adult was reported to have committed suicide. Patients with epilepsy are thought to be at increased risk of psychiatric disorders and suicide.[39]

Overall comparison of AE signals and undesirable effects added to the UK SPC up to 2009 showed that many added undesirable effects could be identified as AE signals in the early postmarketing phase of this PEM study if a combination of signal detection methods was used. Only a few rare events had no signal, which in part may be explained by diagnostic difficulties for these conditions.

Most AE signals detected in this PEM study are included in the 2009 UK SPC as undesirable effects,[14] though some of these were not included in the first UK SPC.[15] Overall, more signals were detected in adults compared with children. Differences between children and adults in the signal detection patterns were also noted. Most signals for SPC terms added up to 2009 were identified by only one signal detection method in children, whereas most signals in adults for these SPC terms were identified by two or more signal detection methods. Both in children and adults, most terms were reported as reasons for stopping. Notably fewer terms were reported as ADRs in children compared with adults.

The calculation of PRRs or IRRs was useful for gaining more insight into the reporting frequency of those DSRU higher level terms identified by two or more signal detection methods. However, a number of higher level terms not identified by any signal detection method reached statistical significance after the calculation of PRRs or IRRs, and these events were generally likely to be related to background diseases specific to children or adults and assessed as unlikely to be related to treatment.

Events identified as AE signals in children were more likely to be reported as reasons for stopping rather than ADRs, whereas for adults more events identified as AE signals were reported as both ADRs and reasons for stopping. A possible explanation could be that describing an event as a reason for stopping may seem more objective, as it reflects something that actually happened and does not require a causality assessment. In addition, less suspected ADRs in children (33%) were reported to the UK Regulatory Authority compared with adults (44%).

Spontaneous ADR reporting in children was lower than in adults. Therefore, signal detection for children using spontaneous reporting databases may benefit from the addition of signal detection using databases that capture AEs and reasons for stopping in addition to ADRs. Examining the use of large healthcare databases for signal detection should be explored.

In summary, in this study the frequency and nature of AEs reported in children and adults prescribed lamotrigine during its immediate postmarketing period were examined. The observed quantitative and qualitative differences in the AE profile between children and adults may be

explained by differences in pharmacodynamics,[40] pharmacokinetics,[24] morbidity, mortality, psychomotor development[21] and differential reporting rates in the two age groups.[41] Also, the difference may have been a reflection of the ways that the product was given to children when it was not licensed for them, e.g. inappropriate dosing, giving children crushed adult tablets. This PEM study and its modified methods of analysis of comparing data in the paediatric population with that of adults, contributes to the tools available for assessing paediatric drug safety. It supports the conduct of pharmacovigilance studies in children in the immediate postmarketing period of newly licensed drugs.

Conclusions

This study demonstrated that a combination of various quantitative signal detection methods and evaluation of follow-up information can be used to identify possible differences in the AE profile between children and adults, and to detect AE signals in both age groups early in the postmarketing period. Quantitative and qualitative differences between children and adults were observed. These can often be explained by differences in pharmacokinetics, pharmacodynamics and other developmental differences between children and adults, which should be taken into consideration when conducting pharmacovigilance studies in children. Collecting AE data may be more suitable for identifying AE signals in children early in the postmarketing period than spontaneous reports because the reporting rate of ADRs in children may be lower compared with adults. Signal thresholds may need to be different for children and adults to compensate for possible reporting differences between children and adults. Larger cohorts of studies in children should stratify by age group and sex to examine these findings further. Finally, we feel that further research is needed to better understand how and why the AE profile of lamotrigine is different in children compared with adults.

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