SHORT COMMUNICATION

Drug Saf 2010; 33 (8): 653-658
0114-5916/10/0008-0653/$49.95/0

Alopecia in Association with Lamotrigine Use

An Analysis of Individual Case Safety Reports in a Global Database

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Abstract

Background: The WHO Programme for International Drug Monitoring, maintained by the Uppsala Monitoring Centre (UMC), has more than 90 member countries contributing individual case safety reports (ICSRs) from their existing national pharmacovigilance systems; these reports are stored in the WHO global ICSR database, VigiBase. A continuous increase of ICSRs of alopecia in suspected connection to lamotrigine use has been observed in VigiBase; however, only limited information has been published on this topic.

Objective: To examine in greater detail the association between lamotrigine and alopecia by outlining the characteristics of the accumulated reports in VigiBase.

Method: An analysis of all reports in VigiBase, up to 1 April 2009, where lamotrigine was suspected of having caused alopecia.

Results: Lamotrigine was suspected of being involved in the development of alopecia in 337 patients, reported from 19 countries. The age of the patients ranged between 5 months and 84 years (mean 36 years), with a predominance (58%) of patients <40 years of age. 272 patients were female. In 291 reports, lamotrigine was the only drug suspected by the reporter, and in 112 reports, lamotrigine was the sole reported drug. Commonly co-reported drugs were other antiepileptic drugs. For 217 patients, alopecia was reported as the single event. In 11 patients, the reaction abated on cessation of lamotrigine. One patient was reported to have had a recurrence of alopecia on re-administration of lamotrigine.

Conclusions: The UMC continues to receive reports of alopecia associated with the use of lamotrigine. Although alopecia may not be regarded as serious from a regulatory perspective, this adverse reaction has the potential to affect compliance, resulting in decreased efficacy of the treatment regimen and detrimental effects on patient health outcomes.

Background

A continuous increase of individual case safety reports (ICSR) of alopecia in suspected connection to lamotrigine use have been observed in the WHO global ICSR database, VigiBase; however, only three published case reports[1-3] and a case review performed by the Netherlands Pharmacovigilance Centre in November 2007[4] are publicly available on this topic. This triggered a review of all reports received internationally by the Uppsala Monitoring Centre (UMC).

The WHO Programme for International Drug Monitoring, maintained by UMC, has more than 90 member countries. The countries contribute ICSRs from their existing national pharmacovigilance systems, and these reports are stored in VigiBase. The reports contain divergent data with respect to country of report origin, reporter type, amount of data and quality of data. The reports represent a varying degree of suspicion, and as with all spontaneous reporting data the results must be interpreted with caution. One of the main tasks for the UMC is to issue international signals of previously unknown drug safety concerns arising from the data, and case summaries are regularly distributed to the national centres of the member countries.[5]

Lamotrigine, a phenyltriazine compound, is an antiepileptic medicine used as monotherapy or as an adjunct to treatment with other antiepileptic drugs, e.g. valproic acid, carbamazepine, clonazepam, phenytoin, topiramate.[6-8] It is used as a first-line treatment for several types of epilepsy, such as primary generalized tonic-clonic, partial seizures, and atypical absence, myoclonic, and atonic seizures.[8] Skin rash and serious skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [which can cause scarring alopecia[3]], are known adverse drug reactions (ADRs) for lamotrigine.[6]

An initial evaluation of cases with lamotrigine and alopecia was undertaken by the UMC in 2004 following a request from the Swedish Medical Products Agency. The review indicated that alopecia could be another, although less serious, skin problem associated with lamotrigine use. The assessment, based on 98 reports, was distributed among the members of the WHO programme, via the restricted document SIGNAL (unpublished data).[9]

In April 2009, when a follow-up of the topic was performed, alopecia was not listed as an ADR for lamotrigine in Martindale,[6] the UK and Swedish Summary of Product Characteristics (SPC)[7,10] or Drugdex.[11] In the Physician's Desk Reference (PDR),[12] alopecia was stated to have been infrequently reported as an adverse event in clinical trials.

The aim of this study is to communicate greater detail on the association between lamotrigine and drug-induced alopecia to a broader audience by outlining the characteristics of the accumulated reports in VigiBase. Although alopecia from a regulatory perspective is not an ADR of serious character, it may have negative consequences on the compliance of the antiepileptic medicine use and thereby cause patient harm.

Method

A search was made in VigiBase for reports, up to 1 April 2009, where lamotrigine was suspected to have caused alopecia (WHO Adverse Reaction Terminology [WHO-ART] preferred term). Cases were reviewed and descriptive data analysed.

Results

As of 1 April 2009 the number of ICSRs in VigiBase where lamotrigine was suspected of being involved in the development of alopecia was 337, received since 1994 and reported from 19 countries. Alopecia was reported disproportionately more often for lamotrigine compared with the overall reporting of alopecia in VigiBase, with an Information Component (IC) value of 1.66 and IC_{025} (lower limit of the 95% credibility interval for the IC) of 1.50.[13,14] A combination of automated[15] and manual screening for suspected duplicates revealed only two suspected duplicates among the reports. At the time of the study,

Table I. Patient age for lamotrigine and alopecia reports

Age range (y)	No. of patients
<12	16
12–17	26
18–39	99
40–65	89
>65	14
Not specified	93

VigiBase contained a total of 16 750 reports of lamotrigine with any reported ADR.

Patient demographics for the reports showed that 272 (81%) patients were female, 50 were male and 15 reports lacked information about sex. Among the reports that included age (244 reports), the average age was 36 years, with a range of between 5 months and 84 years. The distribution is presented in table I.

Although 19 countries had reported alopecia in suspected connection to lamotrigine use, a majority of the reports came from the US (n = 205), while 13 European countries had contributed 109 reports. There were also a wide variety of reporters, as seen in table II.

Reported Term

WHO-ART terminology groups similar terms, and each report may contain a more detailed term. Specifics of the reported lower level alopecia terms are provided in table III. One report can include more than one term.

Co-Reported Drugs

In 291 reports lamotrigine was the only drug suspected by the reporter, and in 112 reports lamotrigine was the only reported drug. 225 reports included co-reported concomitant or suspected drugs (each report can contain several co-reported drugs). The most frequently co-reported drugs (as either suspected, interacting or concomitant), each appearing in more than ten reports, are displayed in table IV. Five of the top co-reported drugs are antiepileptic drugs commonly used together with lamotrigine.

Co-Reported Events

For 217 patients, alopecia was reported as the single event, 111 patients had 2–9 reported events, and nine patients had between 14–60 reported events. The ten most frequently co-reported adverse reactions are displayed in table V.

Apart from alopecia, a few reports also included other hair-related terms, such as hair discolouration (n = 2), hair disorder (n = 2) and hair texture abnormal (n = 3). The majority of the co-reported skin reactions (80 events in 51 reports) were non-serious, such as rash (19 events, 18 reports), dry skin (3 events, 3 reports) and pruritus (9 events, 8 reports). The only co-reported skin reactions of a more serious nature (those on the WHO-ART critical terms list) are listed in table VI.

Twenty-two reports included co-reported drugs/events indicating illnesses that could result in alopecia: lupus erythematosus systemic (n = 1), thyroid disorder (n = 3), levothyroxine (n = 14), iron preparations (n = 3) and anorexia (n = 3).[8,17,18]

Time to Onset

Details on time from lamotrigine start to onset of alopecia were available and categorized in 110 cases (see table VII).

Doses of Lamotrigine

Dosage information was available in 109 reports. For 32 patients a dosage above 200 mg/day was recorded, of which five reports included a dosage above 500 mg daily (the usual maintenance

Table II. Primary reporter for lamotrigine and alopecia reports

Reporter type	No. of reports
Consumer/non-health professional	166
General practitioner/physician/hospital	78
Other[a]/unknown	68
Pharmacist	12
Other health professional	11
Literature	2

a Reports with 'other' reporter have been reported according to a previous report format specified as 'not physician or dentist', i.e. this group can include consumer reports and various types of other health professionals.

Table III. Reported alopecia terms[a]

Reported term	No. of reports[b]
Alopecia	311
Hair loss	16
Alopecia areata	8
Hair thinning	3
Hair loss aggravated	1
Alopecia effluvium	1

a Reported terms are listed as originally coded on the report either by WHO Adverse Reaction Terminology included terms or by Medical Dictionary for Regulatory Activities lowest level terms.

b One report can contain more than one term.

dosage is 100–200 mg daily. Some patients have required up to 500 mg daily.[6])

Reports with Information on Dechallenge and Rechallenge

In 11 patients the reaction abated on cessation of lamotrigine. For 39 patients the drug was withdrawn, but the outcome of that action was unknown, and in one patient withdrawal of lamotrigine did not result in any observed effect. In 13 patients dechallenge information was given as 'dose reduced', for 113 of the patients the dose was not changed, and in 4 cases the lamotrigine dose was increased. There was no information on the outcome of these actions. One patient was reported to have recurrence of alopecia on rechallenge with lamotrigine, and that was the only patient who was reported to have been readministered the drug.

Adverse Reaction Outcome Information

Where outcome information was available (204 reports), 30 patients recovered, 12 patients were recovering at the time of the report, 6 patients recovered with sequelae, and 156 patients were recorded not to have recovered at the time of report.

Discussion

Since 1994 alopecia has been reported in suspected connection to lamotrigine use from 19 countries in the WHO Programme for International Drug Monitoring. In the majority of these cases, the reporter had listed lamotrigine to be the single suspected drug.

About half of the ICSRs were reported by consumers or non-health professionals, which implies that alopecia is a concern felt strongly enough by the patient that they report their ADR, but which health professionals may overlook or be insufficiently motivated to report. Reports were also received from doctors, pharmacists and other health professionals indicating that these events were also regarded as significant by healthcare professionals. The review of patient demographics shows that alopecia is reported for patients of all ages, but with a predominance (58%) of patients <40 years of age.

A majority of the reports concerned females (81%). Drug-induced hair loss seems to occur more often in women than men, and the patients generally do not have other co-occurring symptoms.[17] Alopecia was reported as the only term in about two-thirds of the cases, and in very few of the patients was a serious event reported in addition to alopecia.

Drug-induced hair-loss is usually reversible after discontinuation of treatment. The incidence and severity depend on the drug and individual predisposition.[17-19] In general, a causal association between a drug and a suspected adverse reaction is strengthened if there is improvement after withdrawing the drug (dechallenge).[17] The causal association is further strengthened if hair

Table IV. Most frequently co-reported drugs for lamotrigine and alopecia reports

Co-reported drug	No. of reports	Alopecia/hair loss labelled in Summary of Product Characteristics?[16]
Valproic acid	40	Yes
Clonazepam	24	Yes
Bupropion	23	No
Lithium	19	Yes
Quetiapine	17	No
Carbamazepine	16	Yes
Levothyroxine	14	No
Venlafaxine	14	Yes
Escitalopram	11	Yes
Phenytoin	11	No
Topiramate	11	Yes

Table V. The ten most frequently co-reported adverse reactions by WHO Adverse Reaction Terminology preferred term for lamotrigine and alopecia reports

Co-reported reaction	No. of reports[a]
Rash	18
Vision abnormal	10
Weight increase	9
Pruritus	8
Convulsions grand mal	8
Nausea	7
Fever	7
Depression	7
Anxiety	7
Amnesia	7

a One report can contain more than one term.

loss again occurs after the same drug is restarted (rechallenge).[18] Among the reports in this study, information on dechallenge/rechallenge actions and outcomes were quite limited. For 11 patients, the reaction abated when stopping lamotrigine, and in only one of these patients was lamotrigine re-introduced with a subsequent recurrence of alopecia. However, as concluded by Mercke et al.,[18] the patient and physician need to discuss the risks and benefits of continuing or changing the dose of an effective treatment that is causing alopecia. This could be reflected by the fact that about one-third of the patients continued their treatment without any reported dose adjustments.

Depending on the type of alopecia, hair loss usually becomes evident within a few days to weeks, up to 5 months, of starting treatment.[17] In these reports, time to onset, which is important in establishing a causal relationship, could be calculated and categorized in 110 reports where the highest proportion of cases reported alopecia starting between 1 and 6 months after the introduction of lamotrigine.

Analysis of the alopecia diagnosis is limited by not having scrutinized the original case reports in this case series, and also by the fact that WHO-ART terminology does not include all the various types of alopecia, e.g. alopecia androgenetica, instead assigning reports to more general terms.

In 112 of these reports lamotrigine was the only reported drug, although this is no guarantee that no other drugs were used. Some of the reports had co-reported drugs that are known to cause alopecia, and there were also some reports where the co-reported drugs/events indicated illnesses that could result in alopecia. However, there was no consistent pattern of events/drugs, apart from lamotrigine, that could serve as an explanation for alopecia.

VigiBase contains more than 300 reports of alopecia in suspected connection to lamotrigine use and, in addition to these spontaneous reports, there are three published case reports.[1-3] This is consistent with the findings of Pillans and Woods,[17] who, in 1994, found eight published cases of fluoxetine and alopecia, while the corresponding number of reports in VigiBase at the time was 526. Given these experiences it appears that alopecia is an ADR that is overlooked in the literature, and the publication of information from a spontaneous reporting system may provide additional knowledge.

Lamotrigine is already known to cause serious skin reactions. Although it was found that new information had been entered in DrugDex[11] (August 2009) referring to a placebo-controlled clinical trial in which lamotrigine as an adjunctive treatment (n = 118) had induced alopecia in 2% (n = 2) of the patients, compared with 1% in the placebo group (n = 120), there is still very limited information or no labelling in the product information.[6-7,10-12] Even though alopecia is a much less severe skin reaction compared with, for example, SJS and TEN, it is important from the patient perspective to know of such a possible ADR. Hair loss can be devastating for the concerned individual, and could potentially decrease compliance to taking the medication.[18] While hair loss is usually reversible when stopping the medicine, cessation of the treatment is not always

Table VI. Co-reported serious skin reactions according to WHO Adverse Reaction Terminology critical preferred terms for lamotrigine and alopecia reports

Co-reported serious skin reaction	No. of reports
Stevens Johnson syndrome	4
Dermatitis exfoliative	3
Epidermal necrolysis	2
Photosensitivity reaction	1
Skin exfoliation	1

Table VII. Reported time to onset for lamotrigine and alopecia reports

Time to onset category	No. of reports[a]	No. of reports where lamotrigine was the sole-suspected drug[b]
<1 mo	22	17
1–6 mo	50	48
≥6 mo	38	31

a Time to onset information was available and categorized in 110 cases.

b Time to onset information was available and categorized in 96 reports where lamotrigine was the sole-suspected drug.

possible. The advantages and disadvantages of continuing on the drug must be reviewed, considering the hair loss severity, its emotional impact and status of the disease treated.[18]

Conclusions

The continuing increase in spontaneous reports and published case reports may provide sufficient support to include alopecia consistently in the product labelling for lamotrigine in all countries where it is marketed. We believe it is important to increase awareness among physicians and patients since this adverse reaction has the potential to affect compliance, resulting in decreased efficacy of the treatment regimen and detrimental effects on patient safety.

Acknowledgements

The authors are indebted to the national centres contributing data to the WHO Programme for International Drug Monitoring. The opinions and conclusions, however, are not necessarily those of either the various centres or the WHO. The authors would also like to acknowledge Professor Ralph Edwards for editing assistance, and Mr Anders Viklund for assistance in data collection, both of whom work at the UMC.

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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