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BRIEF COMMUNICATION

Lamotrigine and Severe Skin Eruptions

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SUMMARY

Lamotrigine is an important new addition to the drugs used to treat people with seizure disorders, but disconcerting are reports of a higher than expected incidence of severe skin reaction among children. Using automated data from three HMOs, we conducted a retrospective investigation of children (<15 years) exposed to lamotrigine from 1 January 1995 to 30 June 1997. The outcome of interest was hospitalization for a severe skin reaction (e.g. erythema multiforme). Lamotrigine was dispensed to 124 children (56% female, mean age 8.7 years); the mean number of dispensings per person was 10. Of those exposed, 59 (47%) were hospitalized at least once during the study period, mainly for convulsions and epilepsy. There were no hospitalizations for or with a diagnosis of severe skin reactions. Our investigation revealed no evidence to support a causal relationship between lamotrigine and severe skin reactions. However, because our sample size was small we had power to detect only a very strong association between lamotrigine and severe skin disease. Taken alone, our study does not establish the risks of lamotrigine. These results should be viewed as a contribution to the totality of evidence that will be used to assess the safety of lamotrigine. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — lamotrigine; anticonvulsant; adverse reaction; skin disease

INTRODUCTION

Lamotrigine, an antiepileptic drug of the phenyltriazine class, received Food and Drug Administration (FDA) approval in late 1994 for use in persons 16 years and older. Lamotrigine is recommended for use as adjunctive therapy for refractory partial seizures not satisfactorily controlled with conventional anticonvulsants.[1] The 1998 PDR includes warnings about severe, potentially life-threatening rashes occurring at a rate of about 1 in 1000 among adults, and at a much higher rate among children (e.g. 1/50–1/100).[1,2] A number of clinical trials and other reports have implicated lamotrigine as the cause of a high rate of adverse skin reactions (3–19%), some of which were severe (e.g. Stevens-Johnson syndrome).[3–6] While the rashes were rarely severe enough to warrant hospitalization, they were generally one of the more common reasons for discontinuation of therapy. Furthermore, a summary of lamotrigine clinical trials reported that the risk of skin rash requiring hospitalization was similar to that of carbamazepine (0.1–1.4%), and that children experienced higher rates than adults.[7]

Because the FDA was evaluating a New Drug Application that would have approved the use of lamotrigine in children and because there was some evidence to indicate that children were at increased risk of severe skin rashes, we conducted an exploratory, retrospective investigation to

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determine the association of lamotrigine and severe skin reactions that required hospitalization.

METHODS

The investigation was conducted using the Joint Pharmacoepidemiology Program which comprises the populations and pharmacoepidemiology resources from three Health Maintenance Organizations (HMOs): Fallon Community Health Plan (Worcester, MA), Harvard Pilgrim Health Care (Boston, MA), and HealthPartners (Minneapolis, MN). In general, each HMO works with its own data to create summary data or analysis files using a common study protocol. The combined current membership of the Joint Program is approximately 2 million persons; 300,000 members are less than 10 years old.

The exposed cohort was comprised of children less than 15 years old with one or more dispensings of lamotrigine during the study period, 1 January 1995 to 30 June 1997. Individuals dispensed lamotrigine (both the original prescription and refills) were identified by searching the automated pharmacy databases of each of the HMOs.

The outcome of interest was primary hospitalization for a severe skin reaction. These were identified by first extracting from the automated claims files all ICD9 codes representing hospitalizations during the study period for any diagnosis. The hospitalization lists were then screened for the following severe skin reactions: dermatitis due to drugs/medicines (693.0), toxic erythema (695.0), erythema multiforme (695.1), other specified erythematous condition (695.89). Hospital and outpatient records were available for review to confirm the diagnosis of hospitalization and determine whether there was an appropriate temporal association with lamotrigine dispensing.

RESULTS

From January 1995 through June 1997, a total of 124 children less than 15 years old (56% girls, mean age 8.7 years) were dispensed lamotrigine at the three HMOs (Table 1). The mean number of dispensings per person was nearly 10 and ranged from 1 to 35. The 25 mg tablet formulation accounted for the majority of drug dispensed.

The overall mean interval from enrollment to first lamotrigine dispensing was 1002 days and ranged from 1 day to over 10 years; the median interval at each HMO was at least 500 days and the 25th percentile was more than 180 days. Thus, it is likely that most children were incident users of lamotrigine during the study period.

Of the 124 exposed children, 59 (47%) were hospitalized at least once during the study period. Convulsions and epilepsy were the most frequent reason for hospitalization; diagnoses from these two groups accounted for 69% (100/145) of all hospitalizations. There were no hospitalizations for or with a diagnosis of severe skin reactions (ICD9 693, 695) during the study period. However, one male infant (7 months old) who was hospitalized for convulsions was also diagnosed with nonspecific skin eruptions (ICD9 782.1). Overall, he received six prescriptions (480 25 mg tablets)

Table 1 — Characteristics of lamotrigine dispensing to children less than 15 years old who were members of one of three HMOs

	HMO A	HMO B	HMO C	Total
Base population < 15 years	38,632	138,401	201,379	378,412
Persons exposed	19	46	59	124
Age (mean years)	9.3	9.3	7.9	8.7
Females	47%	59%	61%	56%
Lamotrigine dispensings				
Total	181	547	486	1214
Mean	9.5	11.9	8.2	9.8
Range	1–22	1–35	1–31	1–35
Days supply (total)	5647*	17,071	15,132	37,850*
Interval from enrollment to first dispensing (mean days)	1193	1409	623	1002

*Days supply was estimated by multiplying average days supply from the other two sites (31) and number of dispensings.

during the 3 months preceding the hospitalization, the most recent being 29 days prior to the hospitalization at which time he was dispensed 180 tablets of lamotrigine (25 mg). He was also dispensed valproic acid, a drug known to inhibit the metabolism of lamotrigine, during the 3 weeks prior to hospitalization, but we have not determined if the patient was on combination therapy. In the 8 months after hospitalization, the patient was dispensed felbamate and topiramate several times each, but received no lamotrigine or valproic acid.

Given that 124 patients were exposed to lamotrigine and assuming the rate of severe skin reactions in children is the same as in adults (0.1%),[7] we would have a 12% probability of finding one or more cases of severe skin reactions, and a 71% probability if the risk were as high as 1/100.[1] The 95% upper limit of our observed point estimate (0 adverse events) is 3, assuming that the distribution of the adverse event is Poisson.

CONCLUSIONS

Severe skin reactions subsequent to lamotrigine therapy have been reported; estimates from most of the clinical trials are unstable because their study samples were small in number.[2,4,7] Our investigation revealed no evidence to support a causal relationship between lamotrigine and severe skin reactions. However, despite investigating populations of three HMOs using a standard study protocol, we had limited power to detect all but a very strong association between lamotrigine and severe skin disease. An additional limitation is that we identified only those reactions that resulted in a hospitalization. While an examination of less severe skin rash would be informative, case ascertainment and validity would still be dubious unless performed with a more expensive and time-consuming longitudinal study of a large number of patients.

Generally, it is difficult to quantify the degree of safety because in addition to the objective element of risk measurement, it depends on the subjective acceptability of risk.[8] The provider and patient must consider a number of factors that, in part, determine the extent to which a given level of risk is acceptable. Such factors include aspects of the exposure, such as the necessity of treatment and availability of alternatives, and aspects of the adverse outcome, such as severity, reversibility, and frequency. Lamotrigine is considered an important addition to the relatively small armamentarium of antiepileptic drugs, because it has shown promise in the treatment of seizure disorders resistant to other therapies. Clearly, uncontrolled seizures subject the patient to unacceptable suffering and may even be fatal. While skin rash in patients taking lamotrigine was shown to be relatively common in pre-marketing clinical trials, severe reactions were infrequent. Taken alone, our study does not establish the risks of lamotrigine. Instead, these results should be viewed as a contribution to the totality of evidence from clinical trials and other studies that will be used to assess the safety of lamotrigine.

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