INTRODUCTION

Epidemiology within Glaxo Wellcome (GW) has been used for quantifying medication safety issues for over a decade. Clearly, the collection and review of spontaneous reports from throughout the world is an important component of generating new safety signals. In this chapter we focus on the use of pharmacoepidemiology to address safety issues recognized during clinical development and through spontaneous reporting. Some issues addressed include:

- quantifying the expected background risk of adverse events related to an indicated condition for a new medication,
- quantifying the frequency of a serious adverse event known to be related to a new medication,
- assessing one component of the benefit–risk relationship by quantifying the frequency of a serious adverse event known to be related to some of the alternative therapies for a new medication,
- monitoring for the possibility of a new and unknown risk in pregnancies exposed to a new medication.

We illustrate these issues by describing the program of studies performed to quantify safety outcomes observed in people using lamotrigine in epilepsy. Lamotrigine was first available for epilepsy in the Republic of Ireland in 1991, and it was approved soon after within the United Kingdom. Its use spread throughout Europe shortly thereafter, and it was first available in the United States in 1995.

QUANITIFYING RISK AND RISK FACTORS FOR SERIOUS EVENTS ASSOCIATED WITH THE INDICATED CONDITION

Prior to the development and introduction of lamotrigine, there were case reports and a case series describing sudden death (SUD) in epilepsy.
Following the observation of a small number of cases of SUD co-occurring with lamotrigine therapy during the clinical development (Leestma et al., 1997), GW sponsored several cohort studies of the incidence of SUD in epilepsy. At the time, a literature search showed that there was little quantification of the frequency of these events in epilepsy. However, there were a number of case series from autopsies describing SUD in epilepsy. The new observational studies initiated by GW consisted of cohort studies of people with epilepsy and were performed in the large multipurpose administrative health care databases of Saskatchewan Health (Tennis et al., 1995), Group Health Cooperative (Jick et al., 1992), and General Practitioners Research Database (GPRD) (Derby et al., 1996). In all these studies, people with epilepsy were identified through their anticonvulsant prescriptions, and diagnoses or patterns of medication use were used to exclude people without epilepsy. The incidence of SUD ranged from 0.5 to 1.3 per 1000 person-years in all subjects with epilepsy. By stratifying on surrogate markers for refractory epilepsy, e.g. number of concomitant antiepileptic drugs, the Saskatchewan study showed that risk increased with the number of concomitant anticonvulsant medications, suggesting that people with refractory epilepsy had a higher incidence of SUD. Subsequent literature has confirmed the relatively high rate of SUD in people with refractory epilepsy (Nashef et al., 1995a; 1995b; Annegers et al., 1998).

To classify deaths, multiple types of records, including hospital discharge summaries, death certificates, and autopsy reports were requested so that the investigators could rule out explanatory causes of death. However, these records were inconsistently available and deaths could not always be well categorized. Therefore, deaths were classified as possible, probable or definite, and by including and excluding the less definite categories in the numerators, a range of rates could be calculated.

Another rare event spontaneously reported in patients on lamotrigine is multi-organ failure (MOF). These events occur so rarely that a study could not be designed to quantify the frequency of this event. MOF does not occur in isolation but represents a non-specific process associated with a number of severe illnesses including sepsis and status epilepticus. In addition, MOF may occur in the setting of severe allergic or hypersensitivity reactions to some drugs, including lamotrigine. Descriptions of MOF have been reported spontaneously for lamotrigine and are described in the product label. A literature review showed that such events were known to occur very rarely in people with seizures (Yuen and Bihari, 1992).

Because there were no databases judged to be large enough to quantify the frequency of this event in people with epilepsy, a case–control study of MOF and multi-organ dysfunction (MOD) following status epilepticus or aborted status epilepticus was initiated. This study was designed to better understand the risk factors for MOF following uninterrupted seizures. Ramesh Sachdeva and J.F. Annegers conducted this case–control study, and cases and controls were identified from two hospital admissions databases in a large US city. Controls were also identified from these databases and these had experienced status epilepticus or aborted status epilepticus but had not experienced MOF or MOD. The strongest and most consistent risk factor was the duration of status epilepticus (Sachdeva, 1996). These observations were consistent with the hypothesis that most cases of MOF in patients on lamotrigine were likely to be related to rare sequelae of seizures. Although the numbers of cases exposed to individual antiepileptic drugs (AEDs) were small, there was no indication that MOF or dysfunction were related to any specific AEDs.

**QUANTIFYING THE RISK OF AND RISK FACTORS FOR SERIOUS ADVERSE EVENTS ASSOCIATED WITH A MEDICATION**

Early in the postmarketing phase of lamotrigine development, it was evident that some patients using lamotrigine developed serious cutaneous reactions. As almost all of these reactions occurred during the first eight weeks of therapy, the at-risk period was limited to the initiation of lamotrigine. Lamotrigine is initiated through a dose escalation phase which lasts a minimum of six weeks. A
program of epidemiologic studies was launched in order to ask the following:

1. What is the risk of serious cutaneous reactions in patients initiating lamotrigine?
2. What is the risk of serious cutaneous reactions during initiation of alternative anticonvulsant therapies?
3. Are there factors that increase the risk of having a serious cutaneous reaction in patients initiating lamotrigine therapy?

The classification of cutaneous reactions can be problematic without photographic evidence. Therefore, most of the epidemiologic studies of rash in lamotrigine focused on rash associated with hospitalization during therapy initiation. Use of this definition may overestimate the seriousness of rash since some patients with epilepsy are hospitalized for seizure control when an anticonvulsant medication is withdrawn. By including all serious rash, however, the full impact of cutaneous adverse events could be assessed.

In most European countries and in the United States the first approved indication for lamotrigine was adjunctive therapy in adults with partial seizures, with or without secondary generalization. Since the initial approval of use in adults, lamotrigine has become available in >50 countries for children with epilepsy. At the time of first availability of lamotrigine, two cohort studies were initiated to quantify the adverse event profile in general clinical practice: Prescription–Event Monitoring (PEM) was initiated in the United Kingdom in 1991 and a large prospective US cohort study was initiated in 1995. In addition a retrospective cohort study was performed in the GPRD.

Over time, experienced clinicians found that the frequency of common, non-serious rash associated with lamotrigine could be reduced by slowing the dose escalation schedule, and dose escalation packs were developed by the manufacturer to facilitate appropriate dosing. Pediatric approvals came later to most countries, and in some countries children were initially prescribed lamotrigine without availability of pediatric formulations. Epidemiologic observational studies were initiated to quantify the safety profile of lamotrigine, and results suggested that children experienced higher rates of serious rash than adults. One hypothesis generated to explain this observation involved higher than recommended dosing in children because of lack of an available pediatric formulation. There was also some evidence that co-medication with valproic acid, which inhibits the metabolism of lamotrigine, might be a risk factor for serious rash in people using lamotrigine, and children could be using valproic acid more often. The recommended dosing escalation for lamotrigine in children was slowed in 1998, and lamotrigine was subsequently initiated at lower doses than originally recommended. As dose escalation practices changed, observational data could provide some indication of the role of lamotrigine dose as a risk factor for serious cutaneous reactions.

The PEM study of lamotrigine users was conducted by the Drug Safety Research Unit (DSRU) at the University of Southampton, UK (Mackay et al., 1997). All first-time users of lamotrigine between December 1991 and February 1995 were identified through General Practitioner (GP) prescriptions from the national British Prescription Pricing Authority. Six months after the first lamotrigine prescription, a follow-up form was sent to each prescribing GP. On this form the GP listed any adverse event, regardless of cause, occurring since the first lamotrigine prescription. For any significant medical event, such as hospitalization for rash or reported Stevens–Johnson Syndrome (SJS), the DSRU followed up for more information. Lamotrigine was not licensed for use in pediatric patients in the United Kingdom before May 1994, and neither pediatric dosing guidelines nor the formulation (5 mg tablets) of lamotrigine needed to dose many children accurately were available prior to licensing for use in pediatric patients. If serious rash is associated with dosing in children, then it is likely that the frequency of serious rash observed in this study was higher than that for children who use the currently recommended slower dose escalation schedule.

Of 19 448 six-month green forms posted during this study, follow-up data on 11 316 patients were collected. There were 12 events reported as SJS and 10 involved hospitalization. There were an additional two hospitalizations for cutaneous
reactions not reported as SJS (personal communication). In adults, the observed risk was seven events in 10,741 adults (1.1 per 1000), and in children <12 years of age the observed risk was five in 1598 children (3.1 per 1000).

These rates are consistent with those observed during the early clinical development program, including the higher rate of reported SJS in children (Messenheimer et al., 1998, 2000). All clinical and observational data on adults and on children have consistently shown that the frequency of serious rash in children initiating lamotrigine is three times higher than in adults.

Valproic acid is known to be a risk factor for common non-serious rash in people initiating lamotrigine therapy. However, because of the small numbers of events in any individual study, the relationship between lamotrigine serious rash and valproic acid use is difficult to assess. In this study, four of the seven adult cases and five of the five of the pediatric cases were on valproic acid. Data from the GPRD have shown that concomitant valproic acid use was ∼40% in lamotrigine users in the United Kingdom (Drug Research Unit, Lexington MA, USA, personal communication). Although these data are consistent with the hypothesis that valproic acid is a risk factor for serious rash in patients initiating lamotrigine, the number of cases is too small to assess this relationship.

The GPRD was used to supplement the time period covered by the PEM study. All individuals receiving lamotrigine prescriptions were identified, and hospitalizations for possibly drug-related events and all deaths within 60 days of a lamotrigine prescription were identified. Each prescribing GP was contacted to confirm the event, to obtain anonymized medical records about a possibly drug-related serious adverse event for review, and to obtain information on whether the GP was the first prescriber of lamotrigine for that individual. A total of 1722 individuals were identified, 279 were aged 12 years or younger, and 117 were aged 60 years or older. On the basis of earlier surveys of GPs listed in the GPRD about lamotrigine prescribing, it was estimated that 150 of the 279 children initiated their lamotrigine therapy through the GP. In these children, there were two mentions of rash, and none was associated with hospitalization.

In the United Kingdom, patients frequently start lamotrigine through a specialist and prescribing is then transferred to the GP. Because PEM and GPRD are GP-based, these studies cannot capture the initial period of drug exposure for some patients and may not capture some adverse events occurring prior to the transfer of prescribing to the GP. Unpublished GPRD data have shown that 31%–38% of GPRD lamotrigine users in 1993–1994 (predominantly adults) initiated lamotrigine therapy through non-GPs (Drug Research Unit, personal communication). Given the durations of non-GP prescribing, it was estimated that PEM or GPRD might not include up to 20%–27% of events leading to discontinuation within seven days of therapy in new lamotrigine users of all ages. A more recent analysis showed that 61% of children aged <12 years initiated lamotrigine therapy through a non-GP (Drug Research Unit, personal communication) in 1995.

Of the 876 adults in the GPRD estimated to have gotten their first prescription through the GP, none had a rash involving hospitalization and discontinuation. There was one patient with an unknown source of first lamotrigine prescription who had SJS while taking concomitant sodium valproate and had a gradual recovery.

These results on risk of serious rash were similar to what was observed in a US observational study of adults initiating lamotrigine therapy before starter packs were available (Tennis et al., 1996). In this study, there were two cases of rash (one also on valproic acid) associated with hospitalization and without sequelae in 767 adults. Because of the small number of cases, risk factors for serious cutaneous reactions could not be evaluated. Although all of the risk estimates for serious rash are based on small numerators, and the issue of neurologist prescribing in the United Kingdom generates some questions about underestimation of serious rash, the risk of serious rash in adults was consistently close to 1/1000. Because of the recent revision of the dosing recommendations in children, it is not yet feasible to quantify the risk of serious rash in children initiating lamotrigine under current prescribing conditions in general clinical practice.
AT-RISK PERIOD FOR SERIOUS RASH

Without knowledge of the risk associated with the initiation of alternative anticonvulsant therapies, the benefit–risk assessment for lamotrigine was not definable. National registries had published rates of SJS and toxic epidermal necrolysis (TEN) associated with alternative therapies. However, these estimates were based on total defined daily doses in the denominator (Roujeau et al., 1990; Schöpf et al., 1991). Given that the at-risk period was likely to be limited to the first few weeks, it seemed likely that denominators based on the total population exposed to an individual therapy would underestimate those at risk by using a denominator which was too large. Therefore, several retrospective cohort studies were initiated to measure the risk of serious cutaneous reactions in new users of older alternative antiepileptic medications associated with serious cutaneous reactions.

RECORD LINKAGE STUDIES OF ADVERSE EVENTS RISK ASSOCIATED WITH ALTERNATIVE THERAPIES

In two North American databases (Saskatchewan Health and Medicaid), studies were initiated by different investigators. New users were identified as anyone with at least a two-year history in the insurance plan at the time of the first prescription of one of three anticonvulsant drugs. Hospitalizations for cutaneous conditions during the first 60 days of drug exposure were identified, and anonymized medical records were reviewed by dermatologic experts to substantiate the discharge diagnosis. The specific case definitions were left to the discretion of each investigator, but the basic study designs were similar. The Saskatchewan study showed that the risk associated with phenytoin initiation was 1/1000 (Tennis and Stern, 1997) and the risk associated with initiation of carbamazepine was 0.6 per 1000. In the two Medicaid states (US), the risks associated with two alternative therapies ranged from 0.3 to 1.6 per 1000 (Judith Jones, personal communication). Although based on small numbers of cases, these results suggested that the overall risk of serious cutaneous reactions in patients initiating lamotrigine was not dissimilar from that in patients initiating some alternative therapies. However, because of the very small numbers of events, the real-world risk of serious rash in children has not yet been well defined for these other anticonvulsant therapies.

When the International Case–Control Study on Severe Cutaneous Adverse Reactions published data on the association of anticonvulsant therapies with SJS and TEN (Rzany et al., 1999) it appeared that the risk associated with lamotrigine was similar to that of other anticonvulsants (Table E.1). However, the number of cases using lamotrigine was small.

This study shows how case–control studies can be useful for detecting the role of medications as risk factors for an outcome. However, case–control studies alone cannot quantify the frequency of an event.

The German population-based registry of severe skin reactions was extremely useful for understanding SJS or TEN associated with lamotrigine.

Table E.1. Relative risks associated with initiation (<8 weeks of use) of anticonvulsant medications reported by the International Case–Control Study of SJS and TEN (Rzany et al., 1999).

<table>
<thead>
<tr>
<th>Anticonvulsant and duration of use (weeks)</th>
<th>No. of cases exposed to anticonvulsant (total no. of cases = 73)</th>
<th>No. of controls exposed to anticonvulsant (total no. of controls = 28)</th>
<th>Relative risk for new user of specific anticonvulsant, compared with population risk</th>
<th>Relative risk 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital, &lt;8 wks</td>
<td>23</td>
<td>2</td>
<td>57</td>
<td>16–360</td>
</tr>
<tr>
<td>Phenytoin, &lt;8 wks</td>
<td>14</td>
<td>0</td>
<td>91</td>
<td>26–∞</td>
</tr>
<tr>
<td>Carbamazepine, &lt;8 wks</td>
<td>18</td>
<td>0</td>
<td>120</td>
<td>34–∞</td>
</tr>
<tr>
<td>Lamotrigine, &lt;8 wks</td>
<td>3</td>
<td>0</td>
<td>25</td>
<td>5.6–∞</td>
</tr>
</tbody>
</table>
This registry is an observational registry collecting information on cases of SJS, TEN, and erythema multiforme with mucosal involvement throughout Germany. They make every effort to identify all hospitalized cases of SJS and TEN within the country, and they collect information on drug exposures prior to the event. Each possible case is reviewed by an expert group to assign a diagnosis. For estimation of rates, they utilize prescription data (defined daily doses, or DDDs) as a surrogate for the number of people exposed to each medication, and initially when lamotrigine was first marketed in Germany their data seemed to demonstrate that the rate based on DDD denominators for SJS or TEN in lamotrigine was substantially higher than other anticonvulsants. However, as the market matured and the percentage of total use which was new use declined, the ratio of the number of cases to the number of DDDs declined (Schlingmann, 2000). This observation is consistent with the concept that for mature medications the rates of SJS and TEN are substantially underestimated because the denominators are overestimated with the inclusion of long-term use. Nevertheless, given that the numbers of SJS or TEN cases failed to increase while the use of lamotrigine was increasing, it is likely that other factors, such as the reduction of the lamotrigine starting dose, may have also contributed to this decline in rate.

**LAMOTRIGINE PREGNANCY REGISTRY**

Pregnancy exposure registries, which are simple cohort studies, are useful for monitoring and quantifying the impact of medications on birth defect frequency. There are several factors which contribute to the decision to develop a pregnancy registry. These factors include the need for treatment of the indicated condition during pregnancy, a medication indication associated with birth defects, alternative therapies associated with birth defects, and background information about the medication itself (e.g. animal data).

As with many chronic conditions, epilepsy is treated chronically. Pregnancies in women with epilepsy are exposed to anticonvulsant medications from conception and throughout pregnancy. The literature shows that women with epilepsy and using anticonvulsant medications during pregnancy have an elevated risk of major birth defects compared with the general population (Samren, 1997; Canger et al., 1999), and some anticonvulsants have been associated with an elevated frequency of specific major malformations (Omtzigt et al., 1992; Dravet, 1992; Arpino et al., 2000). Although there was no pre-clinical evidence of teratogenicity for lamotrigine, the Lamotrigine Pregnancy Registry was initiated to monitor for the possible elevated risk of birth defects. With the entry of a number of new medications into the armamentarium for treating epilepsy, anticonvulsant exposure in pregnancy has become a growing issue. Prospective pregnancy exposure registries focusing on anticonvulsant exposures have been initiated in North America and in Europe with support from a number of pharmaceutical sponsors. Each registry enrolls exposures and follows the pregnancies prospectively to evaluate the pregnancy outcome, specifically major structural birth defects. Each registry is based on a different methodologic model. The North American Pregnancy Registry invites women with ongoing pregnancies to enroll themselves, and the European Anticonvulsant Registry works with epilepsy centers within multiple countries where clinicians enroll exposed pregnancies.

The Lamotrigine Pregnancy Registry, initiated in 1992, invites physicians throughout the world to enroll pregnancies exposed to lamotrigine. Physicians enroll exposed pregnancies anonymously before the outcome of the pregnancy is known. After the expected date of delivery, a follow-up form is sent to the physician requesting information on the pregnancy outcome. Birth defects are included if they meet the criteria for birth defects established by the Centre for Disease Control (CDC) in their birth defects monitoring program. An advisory committee consisting of independent experts in teratology, epidemiology and epilepsy semiannually review the data. As of September 2000, outcome data on 243 first-trimester exposures, 100 involving monotherapy, have been identified. The number of exposures is too small to make definitive conclusions about the risk of
birth defects following lamotrigine exposure during pregnancy. However, to date the frequency of birth defects following monotherapy exposures, 3.0% (95% confidence interval 0.8%–9.2%), does not suggest a signal for concern.

CONCLUSIONS

In summary, pharmacoepidemiology is uniquely useful for quantifying the risks of adverse events and risk factors for adverse events within populations larger and more diverse than those exposed during clinical development. It is also useful for obtaining essential data to assess whether adverse events may be related to the background condition being treated. To be more specific, the data on the incidence of SUD in epilepsy were instrumental in addressing regulatory questions regarding the rate of this event during clinical trials and, during the early postmarketing phase, regarding reported deaths in people taking lamotrigine. These data, along with the demonstration that length of status epilepticus was a major risk factor for MOF, confirmed that serious events occurring in people with epilepsy can be related to seizures.

Serious rash in association with lamotrigine use has been of interest to GW and to regulatory bodies throughout the world. The first observation that the risk of serious rash was higher in children taking lamotrigine than in adults arose during the PEM study, and these results triggered hypothesis-generating to explain this pattern. Possible explanations included high dosing in children related to lack of available pediatric formulations. The PEM Study, the GPRD Study, the German Registry, and the International Case–Control Study consistently suggested together that the absolute risk to children in general clinical practice was not as high as that observed in the early clinical trials. These observational data were crucial for assessing the risk–benefit of lamotrigine when an early pediatric clinical trial yielded a single case of serious rash within a small number of children. The Saskatchewan and Medicaid studies, although sometimes criticized because of the difficulty of categorizing serious rash without photographs, demonstrated that the risk associated with the initiation of older anticonvulsant therapies was not as low as that previously estimated. In addition, these observational record linkage studies were consistent with the case–control study which demonstrated that the principal at-risk period for these medications is during the first eight weeks of therapy.

Clinicians and patients have been keenly interested in any information which can provide a perspective on expected risks in pregnancies involving lamotrigine exposures. The literature shows that women with epilepsy and using anticonvulsant medications during pregnancy have elevated risk of major birth defects compared with the general population (Samren, 1997; Canger et al., 1999), and some anticonvulsants have been associated with an elevated frequency of specific major malformations (DiLiberti et al., 1984; Ardinger et al., 1988; Dravet, 1992; Lindhout et al., 1992; Omtzigt et al., 1992; Arpino et al., 2000). Even without statistical power to compare medications, results have been crucial for providing to patients and clinicians information key to the management of pregnancies in women using this chronic medication. In addition, the results of other pregnancy registries will provide important information on all new anticonvulsant medications and updated information on older anticonvulsants.

In summary, pharmacoepidemiologic studies have been instrumental in addressing questions posed by regulatory bodies and clinicians. The funding of pharmacoepidemiologic efforts has been an integral part of the overall cost of drug development and continued safety surveillance. By providing quantitative real-world data on some risks related to epilepsy and the frequency of serious rash related to lamotrigine treatment and to some alternative treatments, the approach has provided regulatory bodies, clinicians and patients with the information needed to understand lamotrigine treatment in the world of diverse patients and clinician approaches.

ADDENDUM

Recently the risk of hospitalization with SJS or TEN in patients initiating lamotrigine was estimated. Sales of low-dose lamotrigine for initiation
of treatment were used to estimate numbers of new adult and pediatric users of lamotrigine in Germany. Numbers of cases identified by the German Registry of Severe Cutaneous Reactions were used as the numerator. Based on 1 pediatric case and 9 adult cases during 1998–2000, the risk was estimated as 1.5 in 10 000 adults and 2.1 in 10 000 children.

REFERENCES


Ardinger HH, Blackston JF, Elsas LJ, Clarren SK, Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell 1.5 in 10 000 adults and 2.1 in 10 000 children. Based on 1 pediatric case and 9 adult users of lamotrigine in Germany.

Canger R, Arpino C, Brescianini S, Robert E, Castilla EE, Cocchi et al


