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Risk of a lamotrigine-related skin rash: Current meta-analysis and postmarketing cohort analysis

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ABSTRACT

Purpose: We systematically reviewed studies to provide current evidence on the incidence and risk of skin rash in patients with LTG therapy.
Methods: PubMed and Scopus databases, up to 15 March 2014 were searched to identify relevant studies. Eligible studies included prospective studies, retrospective studies and postmarketing reports, which included data of skin rash in patients with LTG therapy.
Results: Forty-one articles met the entry criteria. A total of 4447 patients with LTG therapy from 26 prospective studies, 2977 patients from 8 retrospective studies, and 26,126 patients from 5/7 postmarketing reports were included. The overall incidence of skin rash with LTG therapy was 9.98% (444/4447) from prospective studies, 7.19% (214/2977) from retrospective studies, and 2.09% (547/26,126) from postmarketing reports. A meta-analysis of the risk of skin rash in 21 prospective studies, did not show a significant difference between patients with LTG and other drugs, including placebo, other ADEs or lithium (OR 0.99–2.41). In 6 respective studies, there was a significantly higher OR in patients with LTG compared with those with non-aromatic AEDs. However, there was no significant difference in rash risk between patients with LTG and aromatic AEDs.
Conclusions: Our study showed that LTG significantly increased the risk of developing a skin rash compared to non-aromatic AEDs. Our results support the need for large prospective population-based studies and clinical trials to determine whether LTG increases the risk of developing a skin rash than compared to other drugs.

1. Introduction

Lamotrigine (LTG) is the most commonly administered second-line antiepileptic-drugs (ADEs) and is also effective in the treatment of a variety of other abnormalities of neuronal excitability, including bipolar disorder [1,2], and neuropathic pain [3]. However, 10% of subjects in controlled trials are allergic to LTG and are susceptible to a wide spectrum of adverse cutaneous clinical manifestations including extremely painful and life-threatening conditions [4].

Skin reactions are a common side effect of antiepileptic drugs (AEDs) and a major cause of treatment discontinuation. The clinical spectrum of these reactions is wide. Most skin reactions are common and mild maculopapular rashes that disappear within a few days after discontinuing drug use. Benign rashes are relatively common with aromatic AEDs, such as carbamazepine (CBZ), phenytoin (PHT), and phenobarbital (PB), with a frequency ranging from 5 to 15% of treated individuals. Some of the newer drugs also frequently cause skin rashes, particularly lamotrigine (LTG), and oxcarbazepine (OXC).

The incidence of rash is now well recognized to be dose- and titration-dependent, and is related with concomitant therapy with valproic acid (VPA). Since the introduction of a gradual titration schedule in 1994, the rate of severe rashes with LTG has declined from 1 to 0.1–0.01 percent [5]. However, there was not a substantial reduction observed in the rate of benign rashes, which has still remained between 8 and 11 percent [6].

Although LTG has been used in everyday clinical practice for nearly 25 years and the possibility of rash is now routinely

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managed, it is still not clearly known whether LTG increases the risk of developing a skin rash compared to other drugs. Here, we systematically reviewed published studies to provide current evidence on the incidence of LTG related skin rashes and compared this risk with other drugs.

2. Methods

2.1. Search strategy

We searched the PubMed (data from 1990 to March 2014), and Scopus (up to March 2014) databases for relevant studies. The search terms used were: "lamotrigine", "lamictal", "rash", and "skin reaction". Studies were limited to human studies and were published in English.

A cutaneous adverse reaction was defined as any types of rash (erythematous, maculo-papular, papular, pustular or unspecified) that could only be caused by an antiepileptic drug effect and that resulted in contacting a physician.

2.2. Selection criteria

To determine the practical significance of the study, we evaluated the incidence and the risk of developing a skin rash in patients who received LTG therapy. Thus, we included multiple dose levels of LTG treatment. We included all prospective, retrospective and postmarketing studies reporting a skin rash with LTG therapy. Clinical trials that met the following criteria were included in the meta-analysis: (1) prospective randomized controlled trials or open-label trials of patients receiving LTG treatment and its presence with a control group; (2) retrospective study, which included the data of LTG related rashes and could be compared with other drugs.

We excluded reviews, editorials, single cases and case series, studies published only as abstracts, letters, or commentaries and studies they were a part of duplicate populations. For the meta-analysis, on the basis of the inclusion and exclusion criteria, we identified a total of 21 prospective case-controlled studies (1 study involving Asian subjects and 20 involving European–Caucasian subjects) (Table 1), and 6 retrospective studies (2 studies involving Asian subjects and 4 studies involving European–Caucasian subjects) (Table 2).

2.3. Data extraction and quality assessment

We designed and piloted a standardized data abstraction form to capture all of the relevant study-level information required for analysis. Two independent investigators performed the data extraction (W.X.Q. and X.J.), and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was obtained: the author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, number of patients in the treatment and control groups when available, median age, median treatment duration, and adverse outcomes of interest (skin rash).

2.4. Statistical analysis

All of the analyses were performed using STATA 12.0 (StataCorp, College Station, Texas, USA). A p-value of less than 0.05 was considered statistically significant, and all of the tests were two-sided. The crude odds ratios (ORs) and 95% confidence intervals (CIs) were used to express the risk of skin rash with LTG therapy compared with other drugs. Forest plots were used to depict the visual representation of the meta-analysis results. Meta-analysis was performed using fixed-effects [7] or random-effects [8] models. Heterogeneity was tested using w^2-based Cochran's Q statistic [9] and I^2 metric statistics [10]. Random-effects models were used only when there was considerable heterogeneity ($P < 0.05$ or $I^2 > 50\%$ among the studies).

Studies were classified according to the study type (prospective study, retrospective study and postmarketing reports). In the first two group, all of the crude OR calculated by the original data were pooled. We performed the analyses on only the observed crude rate estimates, primarily because there was no study that reported adjusted estimates. We also performed the following specified subgroup analyses: different control groups (placebo, other antiepileptic drugs, or other antidepressive drugs), different groups of patients (epilepsy, bipolar or patients with neuropathic pain), prospective study, and retrospective study.

3. Results

3.1. Study selection and characteristics

Our search yielded 748 records describing the use of LTG and a skin rash from the Pubmed and Scopus databases. The selection process is summarized in Fig.1. After the exclusion of duplicate studies and a review of the abstracts, a total of 94 human clinical studies were identified with information on LTG therapy and benign rashes. Full-text articles were retrieved for these records and carefully studied. Finally, in the prospective studies, a total of 26 studies involving LTG-induced rash were used to evaluate rash incidence [11–36] and 21 articles with controls fulfilling the inclusion and exclusion criteria were identified for meta-analysis [11–31] (Fig.1 and Table 1). In this group, 4447 patients receiving LTG treatment were investigated, including a variety of diseases: epilepsy (13 trials) [15,16,23–30,33,34,36], dipolar disorder (9 trials) [17–22,31,32,35], and neuropathic pain (1 magraine [11], 1 multiple sclerosis [12], 1 HIV-related [13], and 1 diabetic [14]). The sample sizes were within the range of 20–958 patients with LTG. The median age of study participants was 9.6–77 years.

In the retrospective studies, 8 articles were used to evaluate rash incidence [37–44] and 6 studies fulfilling the inclusion criteria were identified for meta-analysis [37–42], which were all derived from epileptic studies (Fig.1 and Table 2). The sample sizes were within the range of 8–1037 patients treated with LTG. Two articles were pediatric studies, of which one study included all age groups and 5 studies included patients older than 12 years.

There were 5/7 postmarketing studies that provided data on the skin rash incidence of LTG [45–47,49,50] (Table 3). Four studies were performed in the U.K., which were performed by Prescription-Event Monitoring (PEM) to establish the safety of LTG and other drugs, in which the entire population of prescriptions issued was accessible [45–47,50]. One study was performed in Germany [49], where the data were obtained from a database of 208,401 psychiatric inpatients who were monitored by the Safety surveillance project Drug Safety in Psychiatry from 1993 to 2005, which surveys clinically relevant adverse reactions to all marketed psychotropic drugs. One report was performed in Sweden [51], which aimed to determine the extent of the spontaneous reporting of ADRs in children. One study was on the safety profile of antiepileptic drugs in Italy [48], from January 1988 to June 2005. Only 2/7 of these studies followed cohorts of more than 10,000 subjects [45,49].

3.2. Incidence of skin rash

The overall incidence of skin rash with LTG treatment was 9.98% (444/4447) from 26 prospective clinical trials, 7.19% (214/2977) from 8 retrospective studies, and 2.09% (547/26,126) from 5 postmarketing reports.