Clinical Practice Data to Aid Narrow Therapeutic Index Drug Classification: Lamotrigine

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Background

- For drugs with a narrow therapeutic index (NTI), small differences in concentrations may lead to serious toxicities or therapeutic failures.
- Tighter bioequivalence standards are necessary for NTI drugs to ensure safety and improve prescriber confidence in generic drugs.
- Implementation of these new standards is challenging because some drugs do not have an established NTI classification, and objective criteria to classify NTI drugs are lacking.

Objective

- To develop a systematic approach to NTI drug classification that integrates clinical practice data from the public literature and electronic medical records with pharmacokinetic (PK)/pharmacodynamic (PD) modeling and simulation.

Methods

- We performed a systematic PubMed and Embase literature search (1985–2013) for lamotrigine PK, PD, efficacy, and safety data.
- We extracted medical record data from adults with seizures and at least one LTG level admitted to Duke Hospital (Figure 1).
- We selected an LTG population PK model from the literature that was appropriate for the medical record data.
- We fit our medical record data using the selected model and evaluated the model using predictive performance measures and normalized prediction distribution errors (NPDE) in NONMEM.
- We simulated LTG exposures (trough, maximum, and average concentrations) on the day of identified outcomes (efficacy and safety) and explored the exposure-response relationship.
- Efficacy and safety outcomes we evaluated included presence of seizures, multiple seizures, anemia, thrombocytopenia, leukopenia, and any adverse events resulting in dose reduction or discontinuation, as well as number of seizures, platelet count, hematocrit, and white blood cell count.

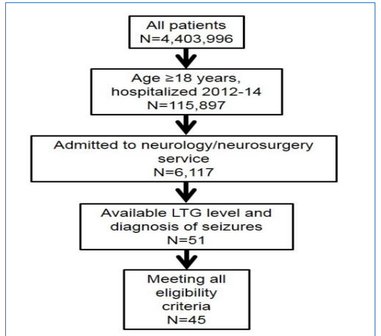

Figure 1. Identification of hospitalized seizure patients taking lamotrigine from Duke medical record.

Results

- Systematic literature search: The medical literature search identified 571 total articles; data were ultimately extracted from 77 relevant papers (Table 1).
- The LTG therapeutic index from the literature data was 1.3–20.
- Medical record data extraction: Demographic characteristics for 45 patients whose data were extracted from the medical record are shown in Table 2.
- Population PK/PD modeling: The medical literature population PK model predicted the medical record data well (Figure 2). A ratio of observed/predicted concentrations was 0.92 (95% CI: 0.75–1.14), and a mean NPDE was -0.076 (p-value = 0.77).
- The distribution of simulated LTG exposures associated with efficacy and toxicity overlapped (Figure 3). Only a weak relationship between hematocrit and LTG level was observed (Figure 4).

Table 1. Literature search summary for lamotrigine.

Stage of literature review	Number
PubMed abstracts identified and reviewed	384
Embase abstracts identified and reviewed	187
Manuscripts reviewed	132
Manuscripts with extracted data	77

Table 2. Demographics of LTG patients with data extracted from the Duke medical record (N = 45).

Variable	Median [25–75th percentile] Mean (range)
Male/female	23/22
Age (y)	43 [31–50] 41.8 (20–74)
Body weight (kg)	78.5 [65.8–99.3] 85.3 (46–175)
White/non-white	29/16
# of LTG levels	53
Mean # levels/subject	1.2

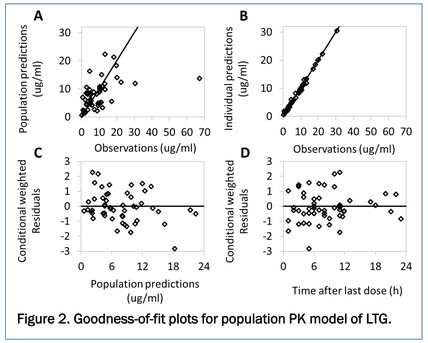

Figure 2. Goodness-of-fit plots for population PK model of LTG.

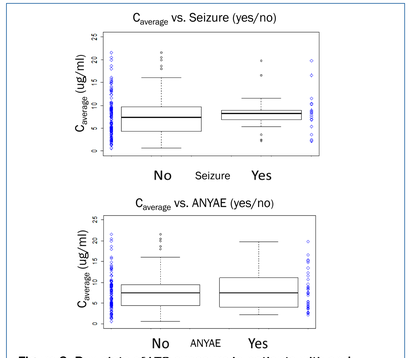

Figure 3. Box plots of LTG exposure in patients with and without seizures or adverse events (ANYAE).

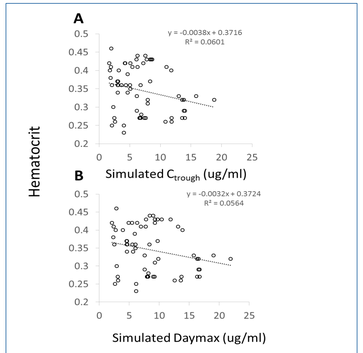

Figure 4. Relationship between hematocrit and simulated LTG levels.

Conclusions

- The use of clinical practice data to aid in classification of drugs with NTI is a promising approach.
- Validating this approach by correctly classifying a drug with a known NTI may be useful.
- Before universal implementation of this methodology, limitations in sample size and accurate characterization of the concentration-response relationship need to be overcome.

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