Dense Data - Methods to Handle Massive Data Sets without Compromise

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INTRODUCTION

Histamine is an important mediator in the pathogenesis of allergic disease and asthma and is responsible for a cascade of events in the allergic/inflammatory response. Histamine Iontophoresis with Laser Doppler monitoring (HILD) is a robust and dynamic surrogate for histamine microvasculature response. HILD has been shown to provide a dynamic and robust assessment of microvasculature blood flow in response to epicutaneous histamine application (Jones, et al. 2009).

This study aimed to characterize histamine pharmacodynamics in adult participants using HILD; however, several challenges emerged that required innovative solutions before data modelling could occur.

HILD data collection produces a rare situation for pharmacometricians -- an abundance of data that must be appropriately pared down to a useful and manageable size, while maintaining an accurate representation of the variability in histamine responses.

This study sought to develop methods for handling the dense data associated with Histamine Iontophoresis with Laser Doppler monitoring (HILD).

METHODS

HILD data were obtained from 16 adults as previously described (Jones, et al. 2009) in a convenience sample for the evaluation of HILD. Blood flow results were given in perfusion units (flux) and calculated by the software package provided by the manufacturer (Version 2, Moor Instruments Ltd, Devon, UK).

The data were aligned based upon application of a second derivative function to determine rise from baseline, maximal effect, and when possible, return to baseline. Data were sampled utilizing an averaging algorithm and data delays were removed to normalize initial parameters using Excel. The percent change from baseline was also determined.

Subsequently, a non-compartmental analysis and non-linear mixed-effects model with a linked effect PK/PD model were developed to provide estimates for the area under the effect curve (AUEC), maximal response over baseline (EffmaxNT), and time of EffmaxNT (Tmax) using Phoenix® WinNonlin version 6.2 (Pharsight, Mountain View, CA). Effect data (Eff_{maxNt} and time of Eff_{maxNt}; T_{max}) were initially evaluated by visualization of time vs. response relationships.

ANOVA and regression analyses were performed to compare the Characteristic Flux vs. Time Curves using R statistical software.

RESULTS

Distinct histamine response phenotypes were identified among the adult participants after data sampling. The need for this method of data handling arises as a result of the HILD technique itself that generates data at 40 Hz producing nearly 30,000 measurement/time data parings over the course of a maximum 2-hour run.

The instrument uses an internal clock to record each data point, rather than using an atomic date/time measurement, which complicated the process of aligning data across multiple subjects. Using a hierarchical model (**Flow Chart**), we performed iterative averaging of the data to simplify the analysis, while ensuring that intra-individual variability was maintained. This was determined to be successful through evaluations of the time-to-peak response **(Figures 1 and 2)**.

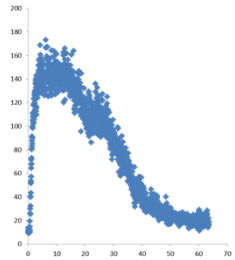


Figure: Example 1a - dense data

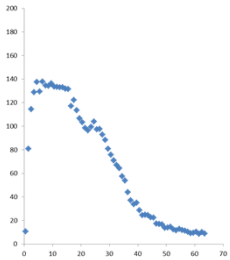


Figure: Example 1b – after data processing

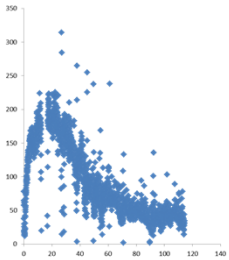


Figure: Example 2a - dense data

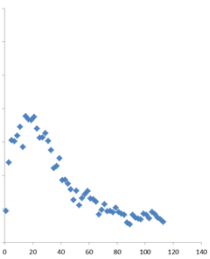
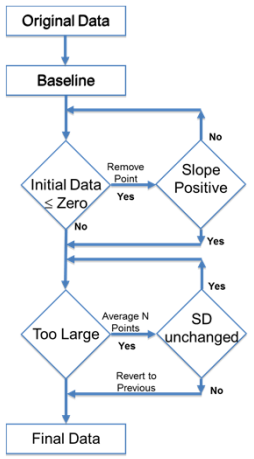


Figure: Example 2b – after data processing

Characteristic Flux vs. Time Curves Representative time (minutes) on *x-axis* vs. flux on *y-axis* of curves



Flow chart of the data processing

CONCLUSIONS

Data quality and integrity remain the most important considerations when assessing large datasets, although current modelling software programs have difficulty managing very large data sets as they were designed to handle far fewer observations per individual than techniques such as HILD generate.

The study successfully developed a method for handling dense HILD data without compromise to curve shape or loss of intra-individual variability. Automated processes that will allow adequate sampling and subsequent modelling are clearly needed.

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