

Clinical Trial Simulation of Nicardipine versus Labetalol for Management of Hypertensive Emergencies in the Emergency Department Setting

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Abstract

Objective: To perform clinical trial simulation in facilitating trial design decisions for a Phase 4, randomized clinical trial comparing nicardipine and labetalol in patients with hypertensive (HT) urgency or emergency.

Methods: The primary clinical endpoint is defined as the success rate of patients with systolic blood pressure (SBP) drop >15% and heart rate (HR) increase <20% at 30 minutes. Trial simulations were conducted based on the following PK/PD models and simulation scenarios of nicardipine and labetalol. For nicardipine, WinBUGS hierarchical power models were built for SBP and HR effect in relation to concentration change based on NDA data from 21 severe HT patients without end organ damage. Simulations were performed for 500-1250 subjects based upon the dosing regimen of 5, 7.5, 10, and 12.5 mg/h IV infusion each for 5 min sequentially, and 15 mg/hr for the final 10 min or until therapeutic response was reached. For labetalol, SBP and HR change were modeled as a function of time, group (pretreated, or untreated within 24 hours), and total dose based on published data from 59 severe HT or HT crisis patients. Simulations were performed based upon an initial IV bolus injection of 20 mg, followed by 20-80 mg every 10 minutes until therapeutic response or a total of 300 mg was reached.

Results: The fraction of patients receiving nicardipine with SBP drop >15% is projected to be ~61% and ~46% by 30 minutes without and with consideration of HR increase by <20%, respectively. Simulation also demonstrated that higher nicardipine infusion rates (>12.5 mg/h) will likely cause higher heart rate increases and hence unlikely gain any further benefit in improving the success rate. In contrast, the projected success rate of patients receiving labetalol with SBP drop >15% is 14-19% by 30 minutes while none is expected to have the SBP drop by >25% or HR increase >20%.

Conclusion: Per modeling and simulations based on available data/models, nicardipine is projected to yield >15% drop in SBP within 30 minutes in 45-61% subjects, much more than Labetalol (14-19%). This result is specific for the outlined study design and primary endpoints.

Background

- Hypertensive emergencies are estimated to occur in <1% of the 50 million people diagnosed with hypertension, characterized by severe elevations in blood pressure (BP) (systolic BP [SBP] >180 mmHg or diastolic BP [DBP] >120 mmHg) in the presence of impending or progressive end-organ damage.
- Both IV nicardipine and IV labetalol are commonly used in emergency settings to lower BP safely. As IV nicardipine is not a β -adrenergic blocker, it can be used in patients with obstructive airway, while IV labetalol requires less nursing time and may be preferred in patients when elevations in heart rate are a concern.
- Comparative trials of IV nicardipine and labetalol have only been performed in very select populations. It is unknown if one has tangible advantages over the other, specifically in terms of the time to achieve goal BP in emergency settings.
- Computer-simulated trials is a powerful tool that may provide valuable insights prior to embarking on a clinical study.
- Simulations can address concerns about the likely trial success rate, optimal dosing regimen, expected range of response, and impact of poor compliance or concomitant disease.
- Such a scientific- and integrated knowledge-based approach to optimize clinical study design has been long recognized and accepted by supervising regulatory agencies.

Objective

Clinical trial simulations were conducted to explore the optimal design for a comparative study of IV nicardipine versus IV labetalol in patients with severe hypertension. The objective was to assess the proportion of patients achieving predefined levels of BP response within 30 minutes under the proposed regimens.

Methods

- IV NICARDIPINE**
- Nicardipine BPHR data were taken from a study of 21 patients with severe hypertension but without progressive end-organ damage. Both BP and HR were modeled as a function of nicardipine concentration.
 - Six plasma concentration observations were available to validate established PK model, a 3-compartment, weight-normalized model estimated using nonlinear mixed-effects modeling (NONMEM) based on data from another study consisting of 37 patients with mild-to-moderate chronic stable essential hypertension.
 - A joint normal model of SBP/DBP was then estimated as a function of Nicardipine concentration, using WinBUGS (Bayesian Updating with Gibbs Sampling) with interindividual variability.
 - Simulations were made for 500 patients on each of the following 5 infusion scenarios in consistent with IV nicardipine label:
 - Starting at 5 mg/hr and remaining constant for 30 min
 - Starting at 5 mg/hr for 5 min, and 7.5 mg/hr for 25 min
 - Starting at 5 and 7.5 mg/hr for 5 min, and 10 mg/hr for 20 min
 - Starting at 5, 7.5, and 10 mg/hr for 5 min, and 12.5 mg/hr for 15 min
 - Starting at 5, 7.5, 10, and 12.5 mg/hr for 5 min, and 15 mg/hr for 10 min
 - For each patient, baseline SBP/HR, slope, power of concentration, and weight were drawn at random. Total number of patients reaching an efficacy target of both >15% SBP drop and <20% HR increase was counted to determine success rate in each regimen.

IV LABETALOL

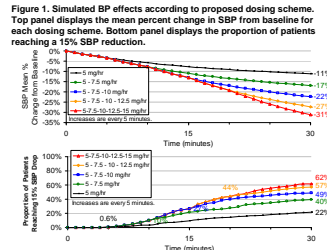
- Labetalol BP and HR data were taken from Wilson et al (Am J Med 1983;75:95-102) of 59 patients with severe hypertension stratified based on prior treatment with antihypertensives in previous 24 hours.
- Consistent with drug label, these patients received an initial 20-mg IV injection, followed by repeated 20-80 mg at 10-min intervals to achieve a supine DBP <95 mmHg or decrease in DBP >30 mmHg.
- Plasma concentrations were not modeled as they did not correlate with acute effect on BP. Instead, BP and HR were related directly to total dose and time.
- SBP and HR relationships with labetalol dose and time were estimated from simulated patient data. Models were established using S-PLUS 8.0 (Insightful Corp) and fitted to data that were linear in time, total dose, and the product of these two, and also stratified by pre-treatment.
- These models fit data well, and hence used to predict SBP and HR by patient and time, repeatedly for 200 datasets of the simulated individual data. The frequency distributions of SBP and HR percent change from baseline were then calculated.
- The total number of patients reaching an efficacy target of >15% SBP drop was then counted to determine the success rate.
- As no clinically relevant HR effect was observed, the contribution of HR effect on the success rate were negligible.

Results

IV NICARDIPINE SIMULATIONS

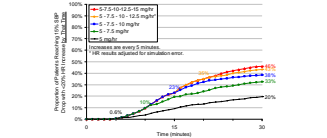
- The PK model predicted concentrations were similar to the actual observed concentrations.
- A longitudinal joint model of SBP/DBP responses was created with a series of models of increasing complexity tested. Optimal model predicted BP is linear in concentration raised to a power jointly
- Patients staying at constant 5 mg/hr are predicted an average SBP drop of 11% by 30 minutes, and patients titrated to 15 mg/hr are predicted an average SBP drop of 31% by 30 minutes (Figure 1).
- In the clinical setting, however, once clinical endpoint is reached, dose would not further increase, but either stabilize or reduce.
- Since there was no time-delay effect, patients are unlikely to have a SBP drop substantially more than 15% in any regimen simulated once the dose is stabilized or reduced.
- In the primary analysis, 62% of patients titrated to 15 mg/hr would reach a >15% SBP drop within 30 minutes, as opposed to 22% of patients staying at 5 mg/hr (Figure 1).

Figure 1. Simulated BP effects according to proposed dosing scheme. Top panel displays the mean percent change in SBP from baseline for each dosing scheme. Bottom panel displays the proportion of patients reaching a 15% SBP reduction.



- When <20% HR increase was also considered, 46% of patients when drug titrated to 15 mg/hr met both endpoint criteria (BP and HR) within 30 minutes, and 20% of patients when drug stayed constant at 5 mg/hr met both endpoints within 30 minutes (Figure 2).

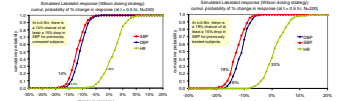
Figure 2. Proportion of patients with > 15% SBP reduction and <20% HR increase. Results are calculated by summing proportion first reaching >15% SBP drop and <20% HR increase over time to each timepoint.



IV LABETALOL SIMULATIONS

- Mean predicted baseline BP was similar to results from Wilson et al, suggesting the labetalol models described the observed data well.
- The PK model predicted concentrations were similar to the actual observed concentrations.
- HR changes were generally within $\pm 10\%$ from the baseline and hence is not a clinical concern for labetalol.
- As IV labetalol bolus can cause excessive BP drop, attempts were made to exclude patients exhibiting SBP drop by >25%. The steepness of cumulative probability suggested small horizontal shifts resulted in big probability shifts and may not yield reliable outcome (Figure 3).
- These patients were still included in the overall success rate evaluation, and may hence overestimate the success rate of IV labetalol.

Figure 3. Simulated probability of patients (N=200) treated with labetalol achieving a 15% reduction in BPHR within 30 minutes in (Left) previously untreated subjects and (Right) previously treated subjects.



Discussion and Conclusions

- Developed BP and HR models of IV nicardipine predict the observed data well, hence validated these optimal models.
- A higher proportion of IV nicardipine-treated patients (46%, even when limiting the HR increase to <20%) than IV labetalol-treated patients (14-19%, even without factoring the possibility of excessive BP drop) is predicted to achieve target BP reduction within 30 min.
- Based on these simulation results, a phase IV trial to differentiate the efficacy of IV nicardipine and IV labetalol for the emergency treatment of hypertension is warranted.
- This trial simulation based upon available, existing data provided a likely projection of PK/PD data into a "real-time," although virtual, clinical interface.
- The ability to refine clinical study designs based on stepwise evaluation of preliminary data may assist with protocol optimization prior to actual patient recruitment, allowing trials to be conducted in a more time- and cost-efficient manner.
- This Simulation should be evaluated considering following limitations: The BP and HR models for nicardipine was based on data from only 21 severe hypertensive patients. Uncertainties are high for labetalol as the model was constructed based on a single literature study, and individual subject data by timepoint were lacking, the weakest link in the analysis.

Reference: Wilson DJ, Wallin JD, Vlachakis ND, et al. Intravenous labetalol in the treatment of severe hypertension and hypertensive emergencies. Am J Med. 1983;75:95-102.

