Concentration-Effect Modelling of Blood-Pressure in Early Stage Trials

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Background

Drug-induced blood pressure (BP) increases in a patient population represents a health concern, particularly when the patient population is being treated on a chronic basis or has cardiovascular risk factors [1]. Sympathomimetics, corticosteroids and vasoconstrictors are examples of drug classes associated with increases in BP. Therefore assessment of a concentration-effect relationship for investigational medical products is valuable where vascular effects are possible. Scientific and regulatory efforts to raise awareness and better define approaches to assessment of BP during drug development have been made [1]. However, specific proposals for the design of clinical trials and data analysis were not yet provided for an overall approach to evaluation of blood pressure in early phase trials.

This study aimed to investigate the effect of a cholinomimetic agent (an oral IMP) being developed for use in Alzheimer's disease, on vital signs. Similar methods to those employed for ECG data were used [2,3]. Here we present a novel approach that aimed to establish a relationship between drug concentration and BP and HR effects, for a more definitive assessment of BP effect in early phase studies.

Methods

Study Design: A randomised study with 30 subjects (multiple dose and placebo-controlled) was conducted to assess the safety and PK of an oral IMP in healthy Japanese and Caucasian subjects.
Subjects received either IMP Dose 1 or matching placebo on Period 1 Day 1, daily for 5 days (5 doses in total) and IMP Dose 2 or matching placebo on Period 2 Day 1. Dose 2 was higher than Dose 1 by a factor of 1.7. Periods 1 and 2 were separated by a washout period of 14 days.

Vital signs: On Day 1 and Day 5 of both periods, vital signs were measured in supine position after the subject had rested comfortably for at least 5 minutes at -1.5, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 hours.

Statistical Analysis

To investigate dose dependency on vital signs and the appropriateness of a concentration-response model, the mean vital signs was adjusted for placebo effects. The placebo adjusted time course of vital signs was assessed and compared to mean drug plasma concentrations. Similar analysis was conducted with the metabolite. Three linear candidate models were evaluated: the one using both concentrations, the one using the concentration of the parent compound only and that using the concentration of the metabolite only. One with non-significant treatment effect and lowest Akaike Information Criterion (AIC) is to be selected as primary – the model with the parent only.

Results

The results shown in Figure 1 indicated that an exposure response model may be adequate for diastolic blood pressure and systolic blood pressure. The time effect on BP related to the concentration of the two moieties investigated (Figure 2).

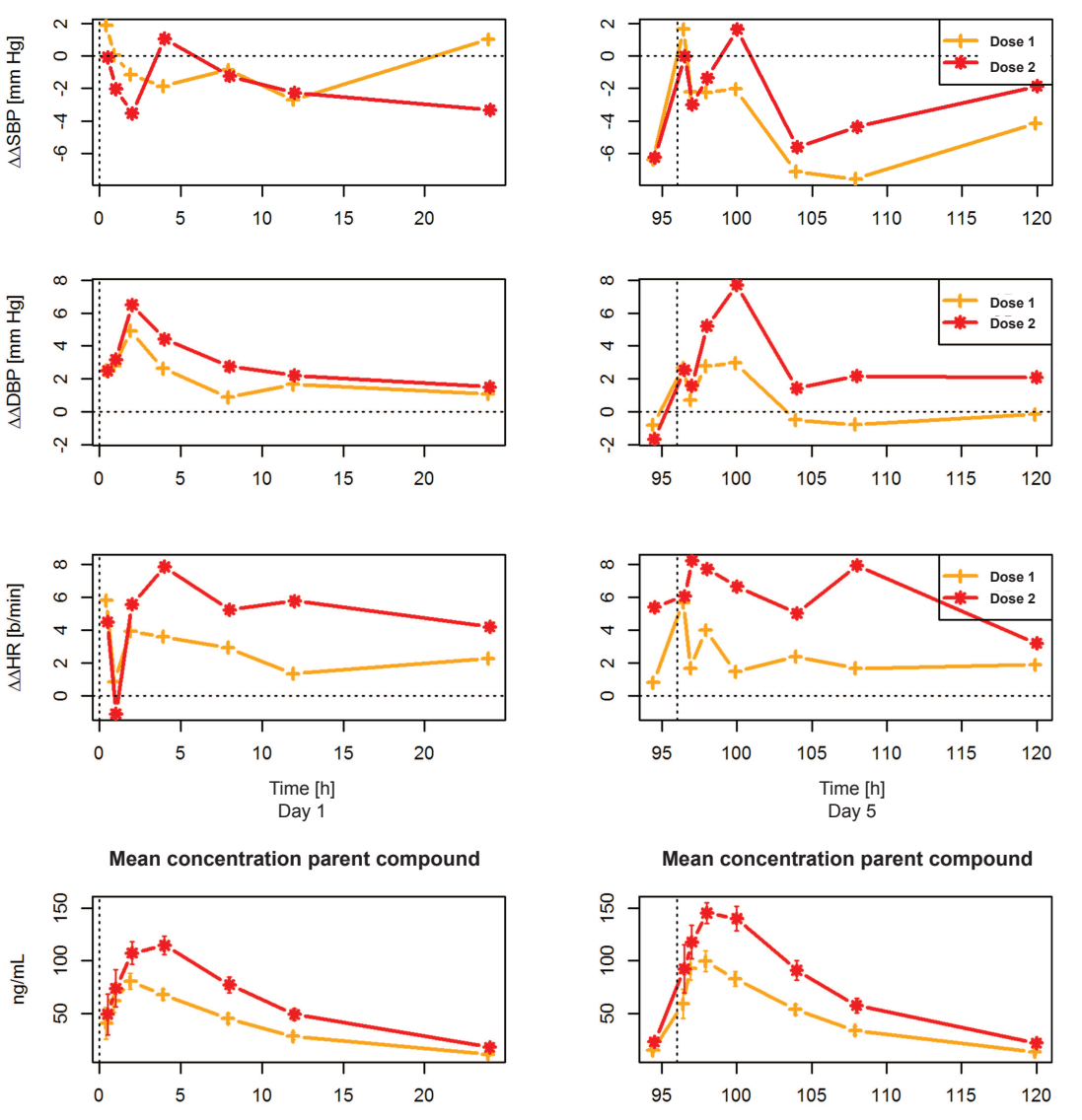
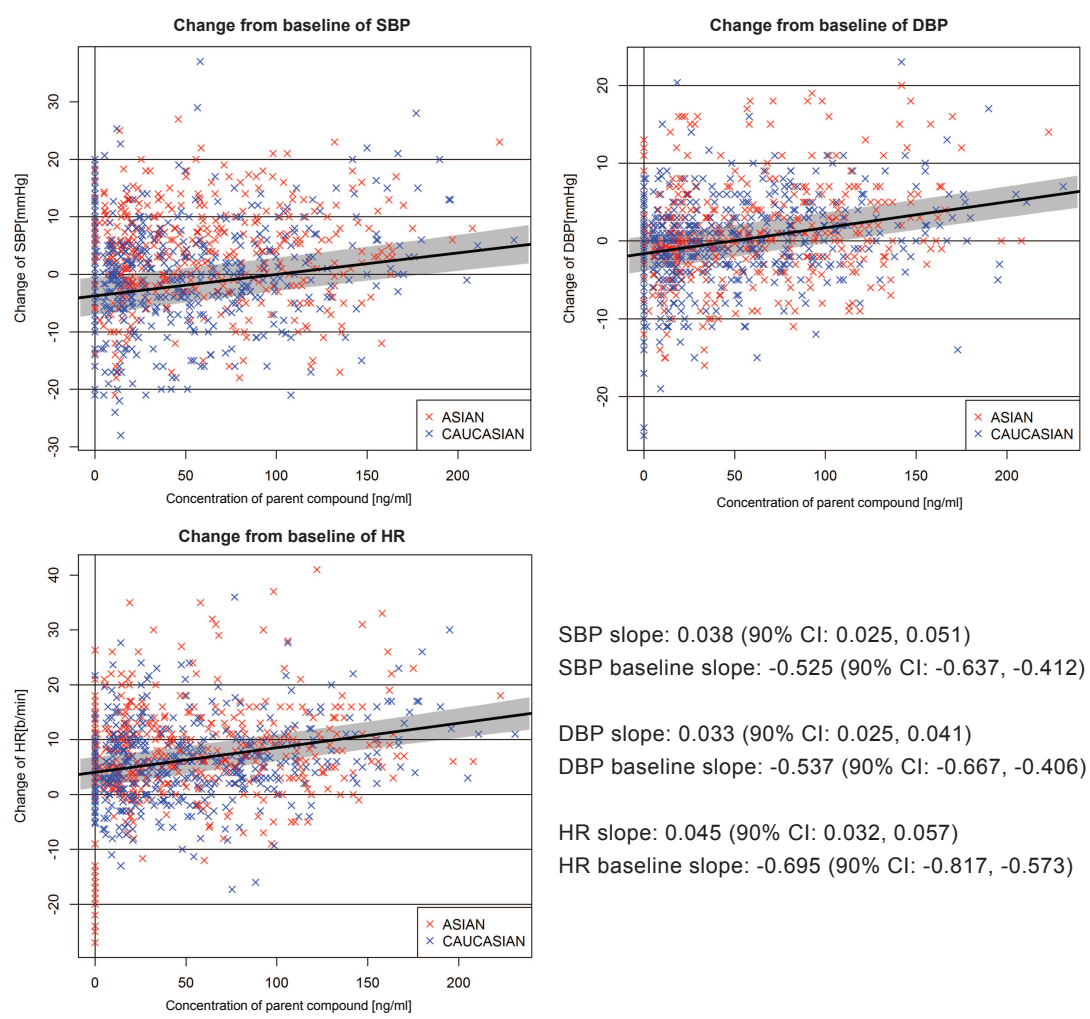


Figure 1: Time courses of mean concentration of IMP and metabolite and placebo adjusted mean SBP, DBP and HR. The effects of meals were removed by subtracting the placebo data.

Concentration effect-modelling



SBP slope: 0.038 (90% CI: 0.025, 0.051)
SBP baseline slope: -0.525 (90% CI: -0.637, -0.412)

DBP slope: 0.033 (90% CI: 0.025, 0.041)
DBP baseline slope: -0.537 (90% CI: -0.667, -0.406)

HR slope: 0.045 (90% CI: 0.032, 0.057)
HR baseline slope: -0.695 (90% CI: -0.817, -0.573)

Figure 2: Change from baseline (Δ) of SBP, DBP and HR for the model with parent only. Zero concentrations are given by the placebo data.

Predictions

Table 1: Predictions for the model with parent only.

Dose	Conc [ng/ml]	Prediction					
		Prediction	SE	df	T-value	90% CI [ms]	
				SBP			
Dose 1	110	1.0	1.38	43.5	0.73	-1.3	3.3 NS
Dose 2	162	3.0	1.55	56.1	1.92	**0.4**	**5.6***
				DBP			
Dose 1	110	3.6	0.89	36.9	4.06	**2.1**	**5.1***
Dose 2	162	5.4	0.98	56.7	5.45	**3.7**	**7.0***
				HR			
Dose 1	110	5.6	1.13	33.2	4.94	**3.7**	**7.5***
Dose 2	162	7.9	1.34	45.1	5.92	**5.7**	**10.2***

Conclusions

- Concentration-effect analysis suggests dependence of BP on the drug concentration, consistent with the mode of action of the IMP.
- Some subjects had isolated abnormal vital signs during the study; however, these were not prolonged and none were judged to be clinically significant.
- This study supports the use of concentration-effect modelling to identify BP effects during Phase I trials.
- Placebo data is important to eliminate the diurnal variability on the changes in vital signs, evaluate and reduce the non–drug-related sources of BP variability in a clinical trial.
- The outcome of this approach would identify the presence of an important BP effect sufficiently early in drug development. However to classify the risk of a long therapy an extended study would be necessary.
- To determine the level of risk associated with BP increases of the magnitude found in this study, more data on other compounds with adverse outcomes is required.

References

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