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A quantitative approach for cardiovascular safety evaluation of a generic drug

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ORIGINAL ARTICLE

In generic drug development, comparative pharmacokinetic (PK) studies are conducted to assess equivalence in pharmacokinetics and safety profiles between test and reference formulations. However, there is no established quantitative approach available for safety assessment. This study aimed to propose a method for drug safety evaluation in generic drug development, as assessed by drug influence on blood pressure and heart rate change. Data were taken from a randomized, open label, 2-way cross-over comparative PK study for megestrol conducted in 39 healthy male volunteers. Vital signs of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured at 0 (pre-dose), 4, 8, 12, 24, 48, 72, 96 and 120 hours after the dose. Safety parameters used in the analysis were area under vital sign change versus time curve to the last measured time (AUVlast) and maximum vital sign change (Vmax). Considering highly variable nature of vital signs, the scaled bioequivalence approach developed by US FDA was adopted as a decision rule for safety evaluation between formulations. With the FDA scaled approach, 90% confidence intervals of geometric mean ratio for DBP, 0.7969~1.0377 for Vmax and 0.7304~1.0660 for AUVlast, were both included in the equivalence ranges of 0.7694~1.2997 and 0.6815~1.4674, respectively, and similarly, those for HR were included in their respective scaled equivalence limits, while SBP satisfied the conventional equivalence criterion of 0.8-1.25. These results illustrate the feasibility of applying the suggested approach in cardiovascular safety evaluation in a generic drug.

Introduction

In the development of a generic or an incrementally modified drug, which is the most common type of Phase 1 clinical trial in Korea,[1,2] comparative pharmacokinetic (PK) studies are conducted, the main objective of which is to assess equivalence of PK and safety in test and reference formulations. For PK comparison, the bioequivalence criterion of 80-125% is generally accepted worldwide.[3-6] However, unlike the bioequivalence criterion in PK assessment, there is no established criterion or guidance for safety assessment of a generic drug.

This study aimed to propose a method for establishing safety equivalence between formulations in generic drug development, with an application to cardiovascular safety evaluated by drug influence on blood pressure and heart rate change. To do so, megestrol acetate was used in the evaluation, which is a non-cardiovascular agent and was rarely reported to have cardiovascular adverse events.[7]

Methods

Subjects

Data were taken from a PK study, conducted as part of generic drug development at Severance Hospital in 2010. In that study, eligible subjects were healthy male volunteers between the ages of 20 and 55 and within 20% of their ideal body weight.

The study was designed as a randomized, open label, single dose, 2-way cross-over trial with a 14-day washout period to investigate PK and safety equivalence of two formulations of megestrol acetate, Megace® 800 mg/20 mL (Boryeong Pharmaceuticals, Korea) for reference formulation, and Apetrol ES 625 mg/5 mL (LG Life Sciences, Korea) for test formulation. This trial was registered on ClinicalTrials.gov (Identifier: NCT02446353).

After an overnight fast of 10 hours, subjects received the study medications and vital signs of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were measured at 0 (pre-dose), 4, 8, 12, 24, 48, 72, 96 and 120 hours after the dose, where measurements up to 24 hours were taken during hospitalization and those thereafter in an outpatient clinic. Blood pressure and heart rate were measured using the digital blood pressure devices placed over the brachial artery after subjects were relaxed at least for 5 minutes at sitting position. Safety markers measured other than blood pressure and heart rate included laboratory tests (hematology, blood chemistry, and urinalysis) and 12-lead Electrocardiography (ECG).

Analysis variable

The analysis variable used in this work for safety evaluation was defined as below:

$$V = Abs(V_{postdose} - V_{predose})$$

where V denotes vital sign change, Abs denotes the absolute value, and $V_{postdose}$ and $V_{predose}$ denote the vital signs measured post- and pre-dose, respectively. Then, for vital sign variables SBP, DBP, and HR, safety parameters were chosen as area under vital sign change versus time curve to the last measured time (AUV_{last}) and maximum vital sign change (V_{max}), which were obtained by non-compartmental method using Winnonlin 6.4 (Phoenix®, Pharsight, CA, USA).

Analysis method

If within-individual coefficient of variation (CV) of maximum concentration (C_{max}) or area under the concentration-time curve (AUC) of a drug is greater than or equal to 30%, the drug is regarded as a highly variable drug in PK. When different formulations of a highly variable drug are tested for bioequivalence, instead of the traditionally used bioequivalence limit of 0.8 to 1.25, wider equivalence limits have been proposed, including the one suggested by US FDA, which is called a reference scaled average bioequivalence approach.[5,6,9-12]

The bioequivalence limits suggested by the FDA scaled approach are defined as

$$\text{Upper/lower limits} = \exp\left(\pm \text{In}\,(1.25) \cdot \frac{s_{WR}}{s_{W0}}\right) \quad \text{(Equation 1)}$$

where s_{WR} is standard deviation corresponding to within-subject variability of the reference product and s_{W0} is a constant referring to regulatory standardized variation. According to the FDA guideline, s_{W0} is set at 0.25, and CV_{wR}, coefficient of variation corresponding to s_{WR}, can be approximated as

$$CV_{wR}\,(\%) \fallingdotseq \sqrt{residual\ \ variance}\ \text{X}\ 100\,(\%) \quad \text{(Equation 2)}$$

where residual variance is obtained from analysis of variance (ANOVA) result derived from average bioequivalence test.

Considering that vital signs are in general highly variable, we adopted the scaled average bioequivalence approach suggested by FDA described above as a criterion for assessing safety equivalence between the formulations.

Results

Study Population

A total of 40 healthy male subjects were enrolled in the study, randomized into 2 groups. Mean age, weight and height of the subjects were 25.1 year, 71.6 kg and 176.4 cm for group 1, and 27.1 years, 67.3 kg and 175.0 cm for group 2. Among 40 subjects

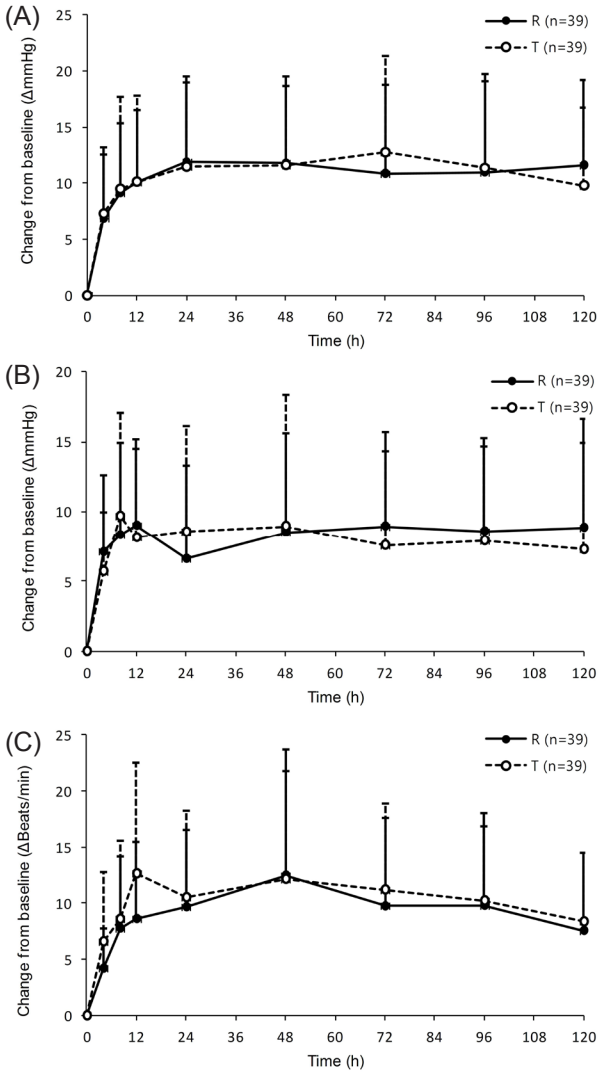

Figure 1. Mean (SD) vital sign change versus time profiles of (A) systolic blood pressure, (B) diastolic blood pressure and (C) heart rate for reference (R) and test formulation (T).

enrolled, 39 completed the study, with 1 withdrawing consent in the wash-out period (group 1). Demographic characteristics of enrolled subjects were presented in Table 1.

In Figure 1, the time courses of vital sign change for SBP (A), DBP (B) and HR (C) are depicted for reference and test formulations. Except for a few time points, overall, the figure shows time courses of the change are similar in the 2 formulations

Table 1. Demographic characteristics of the subjects

Characteristics	Group 1 (n = 20)	Group 2 (n = 20)
Age, yr		
Mean (SD)	25.1 (1.9)	27.1 (3.9)
Range	23–31	23–40
Weight, kg		
Mean (SD)	71.6 (7.9)	67.3 (8.5)
Range	60.9–90.7	55.7–83.7
Height, cm		
Mean (SD)	176.4 (5.8)	175.0 (4.4)
Range	164.8–186.4	165.8–181.5
Smoking, no. (%)		
Smoker	6 (30)	9 (45)
Nonsmoker	14 (70)	11 (55)
Alcohol drinking, no. (%)		
Drinker	14 (70)	13 (65)
Nondrinker	6 (30)	7 (35)

Equivalence limits

Table 2 reports the scaled bioequivalence limits imposed by the FDA approach for a range of within-subject CVs. While Equation 1 allows to set the equivalence limit for each CV value, this table implies that the process can be simplified in such a way that for a drug with 30% ≤ CV < 35% the equivalence limit can be chosen as 0.7694 to 1.2997, for a drug with 35% ≤ CV < 40% it can be chosen as 0.7382 to 1.3547, and so on. In this regard, the analysis in this work was based on the equivalence range listed in Table 2.

Safety assessment

When the usual bioequivalence criterion was applied, for SBP, both V_{max} and AUV_{last} satisfied the criteria, yielding 90% confidence interval (CI) of the geometric mean ratios (GMRs) of 0.8804~1.1200 and 0.8551~1.1643, respectively, both of which

Table 2. Scaled bioequivalence limits for highly variable drugs imposed by the FDA approach

Within-subject CV (%)	Lower limit*	Upper limit*
30	0.7694	1.2997
35	0.7382	1.3547
40	0.7089	1.4106
45	0.6815	1.4674
50	0.6558	1.5248

*These limits were obtained from the relationship that upper/lower limits = $\exp(\pm \mathrm{In}(1.25) \cdot \frac{s_{wR}}{s_{w0}})$ where s_{wR} is standard deviation corresponding to within-subject variability of the reference product and s_{w0} is set at 0.25. See text for details.

Table 3. Comparison of safety parameters (AUV_{last} and V_{max}) in reference and test formulations

Parameter*	Geometric Mean		Geometric Mean Ratio Test/Reference		P-value†	Residual variance	CV_{wR} (%)	Scaled bioequivalence limit
	Test (n= 39)	Reference (n= 39)	Ratio	90% CI				
SBP								
V_{max}	19.65	19.78	0.9930	0.8804~1.1200	0.9218	0.0992	31.49	0.7694~1.2997
AUV_{last}	1201.1	1204.8	0.9978	0.8551~1.1643	0.9809	0.1631	40.39	0.7089~1.4106
DBP								
V_{max}	15.32	16.85	0.9094	0.7969~1.0377	0.2323	0.1193	34.53	0.7694~1.2997
AUV_{last}	784.8	889.4	0.8824	0.7304~1.0660	0.2714	0.2446	49.46	0.6815~1.4674
HR								
V_{max}	18.77	17.34	1.0923	0.9274~1.2632	0.2833	0.1634	40.43	0.7089~1.4106
AUV_{last}	1098.6	968.4	1.1335	0.9335~1.3763	0.3932	0.2580	50.79	0.6558~1.5248

*Parameter units are ΔmmHg for V_{max} and ΔmmHg*h for AUV_{last} for SBP and DBP, and ΔBeats/min for V_{max} and ΔBeats/min*h for AUV_{last} for HR. †P-values were obtained using WinNonlin bioequivalence test with significance level of 0.05. AUV_{last}: area under vital sign change versus time curve to the last measured time. V_{max}: maximum vital sign change. CV_{wR} (%): coefficient of variation for within subject variability of the reference product, which was approximated as $\sqrt{residual\ variance}$ x 100 (%), in this work.

lied within the conventional equivalence range of 0.8-1.25. However, for DBP and HR, 90% CIs of GMR were not included in this conventional range, with the lower bound of 90% CI being below 0.8 for DBP and the upper bound being above 1.25 for HR, in both V_{max} and AUV_{last} as listed in Table 3. In contrast, when the FDA scaled approach was used, the equivalence range for V_{max} and AUV_{last} became as wide as 0.7694~1.2997 and 0.6815~1.4674 for DBP and 0.7089~1.4106 and 0.6558~1.5248 for HR, resulting in 90% CI of V_{max} and AUV_{last} falling within the equivalence range in both DBP and HR, which indicates the feasibility of applying the suggested approach in evaluating the safety equivalence between formulations in generic drug development.

Discussion

Drug safety evaluation is essential in clinical drug development and drug influence on vital signs, including SBP, DBP and HR, is one of the key safety indices to be examined. Noting the importance of cardiac safety in drug development, the Cardiac Safety Research Consortium (CSRC) was launched in 2006 by FDA to support researches in the evaluation of cardiac safety of medicines.[13,14] The consortium focused on the evaluation of drug's influence on cardiovascular system, providing general requirements for the evaluation of influence of non-cardiovascular drugs on blood pressure changes.[15] However, the consortium did not clarify what kind of analysis or criteria should be needed to quantitatively assess drug-induced cardiovascular safety.[16,17] Similarly for generic drugs, no guidance is currently available for the quantitative assessment of drug safety.

With this background, this work was conducted to propose a quantitative approach for evaluating drug safety in generic drug development with an application to vital sign changes in blood pressure and heart rate. By choosing safety parameters as area under vital sign change versus time curve and maximum vital sign change and by noting the highly variable nature of vital signs, the proposed approach was based on the FDA scaled bioequivalence criterion, which was originally developed for assessing PK equivalence in highly variable drugs. The area under curve based approach to assess drug safety similar to ours is also found in a previous study [8], where the area under the adverse event curve above a pre-defined threshold was used as a safety index to take into account the time course of a safety marker and its duration.

When the FDA scaled approach was used, equivalence limits ranged from 0.6558~1.5248 for AUV_{last} of HR to 0.7694~1.2997 for V_{max} of DBP, both being wider than the conventional range of 0.8~1.25. These wider ranges resulted in 90% CIs of GMR for AUV_{last} and V_{max} falling within their respective equivalence limits in all of the safety parameters examined, enabling to support that the 2 formulations have equivalent safety profiles in vital signs.

When the FDA scaled bioequivalence approach was used in this work, within-subject variability of the reference product s_{WR} was approximated as residual variance obtained using ANOVA result derived from WinNonlin's average bioequivalence test because in our study replicated design was not used for reference product and thus s_{WR} was not attainable.[9] The FDA scaled approach requires as the secondary constraint that the point GMR estimate should be within the range of 0.8~1.25,[6] and our data satisfied this criterion.

The European Medicines Agency (EMA) also proposed an approach that can be used for assessing bioequivalence of highly variable drugs. However, the EMA approach is of limited use because it can only be applied for assessing Cmax,[6] whereas the FDA approach can be used for assessing both AUC and C_{max}.

Noting that no general criterion is available for drug safety evaluation, taking the vital sign change as an example, this paper suggested the FDA's scaled approach as a potential solution. When tested for data from another comparative PK study, the suggested method yielded a reasonable result also (not shown). Further studies will be needed to validate the suggested approach as a standard tool for testing safety equivalence in generic drug development

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Conflict of interest

The all authors declare that there are no conflicts of interest.

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