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INVESTIGATION PLANNING AND BIOEQUIVALENCE EVALUATION OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

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Results of a retrospective analysis of bioequivalence studies of generic angiotensin II receptor antagonists are presented. Losartan, valsartan, and telmisartan medicines can be considered highly variable with respect to the pharmacokinetic parameter for maximum blood-plasma concentration. Candesartan, irbesartan, and olmesartan medicines do not demonstrate high intra-individual variance in bioequivalence studies. Current regulatory recommendations and approaches to bioequivalence studies of highly variable medicines are discussed. Recommendations for the design and evaluation of test results of angiotensin II receptor antagonists are formulated.

Keywords: bioequivalence, intra-individual variance, angiotensin II receptor antagonists.

Bioequivalence studies of generic angiotensin II receptor antagonists demonstrated in many instances high intra-individual variance of the maximum concentration (C_{max}) and/or area under the concentration—time curve (*AUC*).

High intra-individual variance of pharmacokinetic parameters occurs when the coefficient of intra-individual variance exceeds 30% [1 – 3]. The coefficient of intra-individual variance is computed using an analysis of the variance (ANOVA) from the obtained mean-square error (MSE) [4, 5].

Currently, separate requirements apply to bioequivalence studies of highly variable medicines [6 – 8]. Studies with a repetitive crossover design, i.e., with three or four periods and the ability to scale the bioequivalence boundaries for C_{max} based on variance data of a reference drug, or with a "classical" simple two-period crossover design but without the possibility of scaling the recognized bioequivalence boundaries are recommended. The cohort size for the studies will differ significantly depending on the chosen study design because studies with a repetitive plan require smaller cohorts [9 – 11].

All studies to find an intra-individual variance coefficient were retrospectively analyzed to develop methodical recommendations for bioequivalence-study planning and evaluation.

EXPERIMENTAL PART

Results of 69 bioequivalence studies submitted to the SCEEMP, Ministry of Health of the RF, for registration during 2008 – 2017 were analyzed. Of these, 27 were studies of losartan; 18, valsartan; 10, candesartan; 7, telmisartan; 5, irbesartan; and 2, olmesartan. All studies were performed with a simple crossover design in two periods and two sequences with a single administration of the test and reference drugs.

Literature sources and data obtained by searching the internet (PubMed, Google, ResearchGate) were also analyzed to evaluate the intra-individual variance of olmesartan medicines because only two bioequivalence studies of olmesartan were submitted. The search terms were bioequivalence and olmesartan. If the source did not indicate the intra-individual variance coefficient, it was computed from data at the 90% confidence interval and cohort size in the completed studies.

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Data for 2308 subjects from 69 studies were retrospectively analyzed, i.e., the analysis included 9232 datasets for C_{max} and $AUC_{0\text{-}t}$. The quantity $AUC_{0\text{-}t}$ was computed by the trapezoidal rule. The pharmacokinetic parameters were transformed into logarithms and analyzed using ANOVA. The factors contributing to the observed variation that were included in the ANOVA were the sequence, subjects, period, and drug. The mean-square errors (MSEs) were used to compute coefficient CV_{intra} for C_{max} and $AUC_{0\text{-}t}$. The weighted average CV_{intra} of the study for each angiotensin II receptor blocker was computed. Pharmacokinetic parameters and CV_{intra} were computed using SSPS Statistics v. 25 and Microsoft Office Excel 2016 software.

TABLE 1. Intra-individual Coefficients of Variance of Losartan

No.	Number of subjects	CV_{intra} $AUC_{0\text{-}t}$, %	CV_{intra} C_{max}, %
1	24	6.63	7.39
2	24	6.46	7.28
3	40	18.39	**46.41**
4	18	9.29	**33.67**
5	18	8.80	10.16
6	24	27.38	**47.87**
7	26	26.65	**37.67**
8	44	13.18	**31.07**
9	72	16.00	**40.28**
10	30	14.25	28.11
11	18	9.09	**33.67**
12	56	20.19	**35.37**
13	36	16.85	**41.42**
14	24	12.62	23.07
15	48	13.14	**40.44**
16	24	5.46	7.02
17	18	10.38	19.51
18	24	20.56	23.38
19	24	8.41	6.84
20	18	8.46	8.59
21	24	7.20	23.03
22	24	22.84	28.26
23	54	12.87	**41.80**
24	18	18.20	**39.65**
25	24	11.15	22.71
26	24	18.34	**36.22**
27	24	18.84	25.43

Here and in Tables 2 – 7: $AUC_{0\text{-}t}$ is the area under the concentration—time curve in the time interval from 0 to the last blood sample collection time t; C_{max}, maximum blood concentration; CV_{intra}, intra-individual coefficient of variance.

RESULTS AND DISCUSSION

Losartan. Tables 1 and 2 present results of a retrospective analysis of C_{max} and $AUC_{0\text{-}t}$ for losartan and its active metabolite aimed at determining their intra-individual variance. High intra-individual variance of C_{max} of the starting compound was found in 13 of the studies. Thus, losartan demonstrated with high frequency (48%) high variance for the starting compound. An analysis of the intra-individual variance of the active metabolite did not reveal instances of high variance.

The upper limit of the confidence interval of the mean intra-individual variance coefficient ("pooled" CV_{intra} value) was recommended to compute the cohort size for analyzing data from several bioequivalence studies.

TABLE 2. Intra-individual Coefficients of Variance of Losartan Active Metabolite

No.	CV_{intra} $AUC_{0\text{-}t}$, %	CV_{intra} C_{max}, %
1	–	–
2	–	–
3	14.16	14.63
4	19.37	33.00
5	9.46	11.22
6	–	–
7	19.41	21.33
8	9.23	14.83
9	9.21	16.42
10	14.51	11.96
11	9.08	16.51
12	–	–
13	17.54	20.95
14	11.11	12.35
15	7.93	13.42
16	–	–
17	–	–
18	15.98	24.62
19	18.02	8.75
20	5.77	17.55
21	6.98	17.15
22	21.43	27.18
23	–	–
24	–	–
25	10.08	15.79
26	16.71	21.55
27	16.90	18.45

"–", only starting compound evaluated in these studies.

TABLE 3. Intra-individual Coefficients of Variance of Valsartan

No.	Number of subjects	CV_{intra} AUC_{0-t}, %	CV_{intra} C_{max}, %
1	18	24.09	12.79
2	70	27.22	**32.61**
3	39	27.62	**35.65**
4	56	**33.43**	**38.41**
5	53	**33.47**	**36.04**
6	38	23.78	24.65
7	44	**37.28**	**31.51**
8	36	**30.51**	**44.09**
9	40	5.44	8.07
10	40	9.19	7.54
11	18	18.52	24.01
12	24	**30.06**	**30.54**
13	40	29.67	**34.60**
14	28	28.42	**33.02**
15	34	**30.53**	28.83
16	34	**30.66**	**33.86**
17	44	26.13	**30.73**
18	45	32.88	**35.79**

Evaluations of the weighted average CV_{intra} from 27 studies of the starting compound showed that CV_{pooled} of C_{max} was 0.327 (upper limit of the confidence interval, 0.334) and CV_{pooled} of AUC_{0-t}, 0.157 (upper limit of confidence interval, 0.160). The corresponding values for losartan active metabolite were 0.179 (upper limit of confidence interval, 0.182) and 0.135 (upper limit of confidence interval, 0.138).

Thus, the starting compound was considered to demonstrate high variance of C_{max} in many studies [the weighted average intra-individual coefficient of variance in all studies was 0.33 (33%)]. The variance of losartan active metabolite was significantly less. However, bioequivalence should be confirmed using the starting compound according to applicable requirements. The cohort size should be computed based on an intra-individual variance coefficient of 33%.

TABLE 4. Intra-individual Coefficients of Variance of Candesartan

No.	Number of subjects	CV_{intra} AUC_{0-t}, %	CV_{intra} C_{max}, %
1	40	15.83	24.91
2	35	13.20	16.98
3	18	9.91	7.92
4	30	16.51	15.85
5	24	15.76	23.14
6	18	12.59	18.45
7	24	21.42	22.87
8	24	19.16	25.37
9	18	4.85	7.24
10	37	19.43	**30.14**

TABLE 5. Intra-individual Coefficients of Variance of Telmisartan

No.	Number of subjects	CV_{intra} AUC_{0-t}, %	CV_{intra} C_{max}, %
1	85	21.94	**43.27**
2	36	21.86	**32.72**
3	40	27.79	**33.67**
4	59	25.24	**48.35**
5	60	**35.29**	**49.45**
6	50	14.78	**34.12**
7	40	**37.28**	**31.51**

Valsartan. Table 3 evaluates the intra-individual variance of C_{max} and AUC_{0-t} for valsartan. High intra-individual variance of C_{max} was found in 12 studies. The frequency of occurrence of high variance for valsartan was 67%.

Pooled data from 18 studies of valsartan showed that CV_{pooled} of C_{max} was 0.314 (upper limit of confidence interval, 0.320) and CV_{pooled} of AUC_{0-t} was 0.282 (upper limit of confidence interval, 0.288). This argued in favor of high intra-individual variance for valsartan. The coefficient of intra-individual variance of 32% was used as a benchmark for computing the cohort size.

Candesartan. Table 4 presents the intra-individual variance for candesartan. High intra-individual variance was found in only one study.

Pooling of results from 10 studies of candesartan showed that the CV_{pooled} of C_{max} was 0.230 (upper limit of confidence interval, 0.238) and CV_{pooled} of AUC_{0-t} was 0.164 (upper limit of confidence interval, 0.170). Thus, candesartan medicines demonstrated low intra-individual variance. The cohort size was computed using the coefficient of intra-individual variance of 24% as a benchmark.

Telmisartan demonstrated high intra-individual variance of C_{max} in each of seven studies, i.e., with 100% incidence. Table 5 present the intra-individual variance data.

TABLE 6. Intra-individual Coefficients of Variance of Irbesartan

No.	Number of subjects	CV_{intra} AUC_{0-t}, %	CV_{intra} C_{max}, %
1	27	17.80	20.20
2	32	20.66	24.67
3	18	11.73	25.12
4	22	23.17	15.38
5	24	11.98	15.56

TABLE 7. Intra-individual Coefficients of Variance of Olmesartan

Source	Number of subjects	CV_{intra} AUC_{0-t}, %	CV_{intra} C_{max}, %
Pharmacokinetic and bioequivalence of two olmesartan medicines, 20 mg [12]	39	15.17	15.24
Public assessment report of Netherlands regulator with evaluation of olmesartan bioequivalence study NL/H/3128/001-003/DC [13]	39	19.00	25.00
Pharmacokinetic characteristics and bioequivalence of olmesartan medoxomil/hydrochlorothiazide in healthy Korean volunteers [14]	40	14.90	19.62
Public assessment report of Danish regulator with evaluation of bioequivalence study of olmesartan, DK/H/2520/001-003/DC [15]	30	10.89	13.14
Public assessment report of Spanish regulator with evaluation of bioequivalence study of olmesartan, ES/H/0322/001-004/DC [16]	36	16.44	18.81

Pooling data from seven studies of telmisartan showed that the CV_{pooled} of C_{max} was 0.435 (upper limit of confidence interval, 0.448) and the CV_{pooled} of AUC_{0-t} was 0.263 (upper limit of confidence interval, 0.271). This was indicative of high intra-individual variance for telmisartan. The coefficient of intra-individual variance of 45% was used as a benchmark to compute the cohort size.

Irbesartan did not demonstrate high intra-individual variance in any of the analyzed studies (Table 6).

Pooling results of five studies of irbesartan showed that the CV_{pooled} of C_{max} was 0.207 (upper limit of confidence interval, 0.217) and the CV_{pooled} of AUC_{0-t} was 0.180 (upper limit of confidence interval, 0.189). This was consistent with low intra-individual variance. The cohort size was computed using the coefficient of intra-individual variance of 22% as a benchmark.

Olmesartan. A retrospective analysis included data for two studies of olmesartan medoxomil generics. The number of subjects in the studies were 24 in one and 20 in the other. The *CVs* of C_{max} were 8.83 and 14.38%; AUC_{0-t}, 6.91 and 11.96%. Literature data for olmesartan medoxomil bioequivalence studies confirmed out supposition that olmesartan had low variance (Table 7).

Pooling the combined data from the two studies submitted to SCEEMP, Ministry of Health of the RF, and the five literature studies for olmesartan medoxomil demonstrated that the CV_{pooled} of C_{max} was 0.178 (upper limit of confidence interval, 0.185) and the CV_{pooled} of AUC_{0-t} was 0.147 (upper limit of confidence interval, 0.152). Thus, olmesartan medoxomil medicines can be considered to have low variance. The coefficient of intra-individual variance of 19% provided a benchmark for computing the cohort size.

Angiotensin II receptor antagonists include medicines demonstrating high intra-individual variance of C_{max} and AUC_{0-t}. A retrospective analysis of bioequivalence studies showed that losartan, valsartan, and telmisartan had high variance. Losartan and valsartan in bioequivalence studies showed moderately high variance. The pooled *CVs* were 32 – 33%. The variance of telmisartan was significantly higher with a pooled *CV* of 45%. According to the results, bioequivalence studies of losartan, valsartan, and telmisartan should be planned with the repetitive design and the possibility of scaling the boundaries with respect to the most variable parameter C_{max}, in compliance with point 2.10 of National Standard GOST R 57679–2017 "Drug bioequivalence studies" and points 105 – 110 of "Rules for drug bioequivalence studies in the Eurasian Economic Union" [6 – 7]. Conversely, about 44 – 46 subjects would be required for studies with the simple crossover design in two periods for losartan and valsartan. About 82 subjects would be required for telmisartan studies. The boundary of bioequivalence recognition in this instance should be 80.00 – 125.00% for C_{max} and AUC_{0-t}.

Candesartan, irbesartan, and olmesartan medoxomil medicines did not demonstrate high intra-individual variance in bioequivalence studies. Correspondingly, their studies should be planned according to common approaches for conducting bioequivalence studies.

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