CORRELATION ANALYSIS FOR PHAMACOKINETICS (PK) CONCENTRATION BY USING A SCALIZATION METHOD

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Abstract - The ICH (International Conference on Harmonization) is to ensure that the drug approval regulations and guidelines are identical to those of patients in different regions of the world in order to rapidly deliver medicines. This has led many countries to comply with Food and Drug Administration (FDA) in the drug approval regulations.To prove the drug stability based on pharmacokinetics (PK) and pharmacodynamics (PD) in in-vivo experiments become significant issues. For this reason, the key motivation of this study is to investigate analysis methods of many different PK profiles associated with human and animal experiments. First, the characteristics of the PK profiles, which are time-oriented functions, for three different animals were analyzed by statistical distributional approaches. Second, the important criteria for the PK analysis, such as maximum of a PK curve (Cmax) and area under curve (AUC), were also compared by three animal PK profiles. Third, we then propose a scalization method for huge different scales of three different animal PK profiles. Fourth, after applying the proposed scalization method, a statistical time-oriented similarity test (i.e., paired t-test) was performed among three animal PK profiles. Finally, we performed a case study to demonstrate statistical similarities and differences of three animal PK profiles by using the proposed statistical distributional approach and paired t-test with the proposed scalization method for verification purposes.

Keywords - Pharmacokinetics(PK), Scalization, Paired t-test, Area under curve (AUC), Statistical distribution approach, Similarity analysis

I. INTRODUCTION

Many pharmaceutical companies have invested much money and time in order to develop chemical and bio new drugs. However, there have been many failures in drug development because enoughdrug stability could not be achieved. To address these problems, the Food and Drug Administration (FDA) proposed a number of possible ways to identify the drug stability and its associated factors at the early drug development stageto improve the probability of successful drug development [1]. Based on this FDA guideline, pharmacokinetic (PK) and pharmacodynamics (PD) data were used in drug product approval and renewal processes.

In the late 1990s, the International Conference on Harmonization (ICH) established a drug licensing regulations or guidelines in order to improve the quality of drug products. This has led many countries to comply with FDA drug approval requirements. In addition, many pharmaceutical companies around the world should begin to validate PK and PD data for a drug approval process. These kinds of new tighten regulations have resulted in a number of difficulties (i.e., CTD documentations, result validations, and experimental design methods) for approaching drug products to ICH member countries including U.S.A.,

Europe, Japan and so on [2]. For these reasons, PK and PD studies in drug development processes became a significantly important research area.

To this end, the key motivation of this study is to investigate analysis methods of many different PK profiles associated with human and animal experiments. First, the characteristics of the PK profiles, which are time-oriented functions,forthree different animals were analyzed by statistical distributional approaches.

The similarity of each time-oriented function (i.e., PK profile) was compared and evaluated by many existing statistical distributions (i.e., exponential, Weibull, gamma, lognormal distributions). Second, the important criteria for the PK analysis, such as maximum of a PK curve (Cmax) and area under curve (AUC), were also compared by three animal PK profiles. In many real-world industrial situations, the selection of an appropriate animal for a PK study may consider a critical issue in order to save in-vivo experimental time as well as to increase the possibility of a successful in-vivo experiment. Third, we then propose a scalization method for huge different scales of three different animal PK profiles. Without using this scalization approach, any statistical similarity test may not provide enough precision. Fourth, after applying the proposed scalization method, a statistical time-oriented similarity test (i.e., paired t-test) was performed among three animal PK profiles. Finally, we performed a case study to demonstrate statistical similarities and differences of three animal PK profiles by usingthe proposed statistical distributional approach and paired t-test with the proposed scalization method for verification purposes.

II. EXPERIMENT

This study collected PK data using the PK profile of the Shin (2016) study. Shin (2016) is research that proposed a method to search for the prediction model that is most similar to true PK profile.
Table 1 shows the PK concentration data of each animal by time-oriented, and the data collected in the PK profile are assumed to be animals A, B, and C.

Table1: Animal PK concentration data with time-oriented

Time	Animal PK concentration data		
HR	Animal A	Animal B	Animal C
0	0.00	0.00	0.00
0.33	4.30	305.98	14.15
0.67	13.35	534.08	20.28
1.00	19.78	504.64	19.92
2.00	20.95	299.78	18.66
3.00	14.25	150.56	12.41
6.00	5.09	47.56	3.80
12.00	1.80	29.97	1.03
24.00	1.09	30.86	0.92
48.00	0.33	22.38	0.74
72.00	0.18	12.74	0.72
120.00	0.10	3.77	0.58
168.00	0.09	4.84	0.42
336.00	0.15	11.49	0.45
504.00	0.23	3.61	0.34
672.00	1.09	0.91	0.16

2.1. Statistical distributional approaches

We analysis of the characteristics of the PK profile, a time-oriented function for three animals, by statistical distribution approach. First, we investigate the probability plot and evaluate how closely the data points follow the appropriate distribution line.

If the fit of the theoretical distribution is satisfied, the points are arranged close to the straight line [3]. Using this hypothesis, the similarity of each time-oriented function as PK profile was compared and evaluated by many existing statistical distributions such as exponential, Weibull, gamma, lognormal distributions.

In this result, the null hypothesis is that the PK profile of the animal follows the distribution. If the null hypothesis is rejected, the PK profile of the animal does not follow that distribution. Conversely, if the null hypothesis is not rejected, we conclude that the PK profile of the animal has significance for that distribution.

2.2. Data Standardization

Since the scale of PK concentration varies from animal to animal, we have to reduce the variance of the data because there are many limitations to comparing PK concentrations. Therefore, we then propose a scalization method for huge different scales of PK profiles. Without using this scalization approach, statistical similarity test may not provide enough precision.

First, we divide PK concentration for all time zones into the Cmax value for each of the corresponding animal controls. The Cmax value indicates the highest value in the time zone PK concentration. Second, we multiply that by 100. This method is derived as follows.

$$\text{PK scalization data} = \frac{hr(n)}{Cmax(m)} * 100 \quad (1)$$
$$(\text{n} = \text{PK time}, \text{m} = \text{Cmax value})$$

The highest Cmax value becomes 100. Based on this, we then calculate the value of PK concentration per time zone according to the ratio.

2.3. Paired t-test

Paired t-test is a statistical technique used to test whether the difference in means between the two test variables within the same sample or group is statistically significant.To compare two population means when the samples are paired, we first translate the hypothesis of interest from one about the value of $\mu_1 - \mu_2$ to an equivalent one involvingμ_d [3]. Hence, the hypothesis can be written as

$$H_0: \mu_d = 0 \text{ versus } H_A: \mu_d \neq 0 \quad (2)$$
$$(\mu_1 - \mu_2 = \mu_d)$$

wegenerally use the significance level (α=0.05).If the null hypothesis is not rejected, it means that there is no sufficient basis for the difference between μ_1 and μ_2 since the p-value is higher than the significance level (α=0.05).On the other hand, If the null hypothesis is rejected, then there is difference between μ_1 and μ_2.
We used this statistical method to analyze similarities in PK concentration between animals.

2.4. Area under the curve (AUC)

The AUC measured after administration of a drug product is an important parameter in the comparison of drug products. the bioequivalence or bioavailability studies can be analyzed by comparing AUC values. Generally, it refers to the area under the curve (AUC) at 0-28days of steady state. In PK calculations, AUC is used as a reference, and AUC is calculated from the PK concentration-time curve graph as a trapezoidal rule. And AUC is useful for calculating the relative efficiency of different drug products.

III. RESULTS AND DISCUSSION

3.1. Scalization

Prior to analyzing their associated similarity by using statistical method, the animals PK concentration data are standardized as proposed method in this study.The PK concentration values of the time zone in Table 2, 3, and 4show that animal A and animal C are similar, but animal B is significantly different.

In order to effectively reduce the variance in PK concentration between animals, this study standardized the PK concentration data by each time zone, as shown in Tables 2, 3, and 4, using the scalization method.As the result, by using this scalization approach, statistical similarity test may provide enough precision.

In addition, this study proved through correlation that the information of existing PK concentration data is not lost when the scalization method is used. There is a strong positive correlation between the existing PK concentration data of each animal and the standardized PK concentration data (R-sq = 100%, p-value = 1.0). This is shown in Figures 1, 2, and 3.

Table2: Extraction of A-scalization data

A' Cmax	20.95	Scalization
hr (n)	Mean	$hr\ (n)/Animal\ A\ PK\ Cmax(20.95) * 100$
0.00	0.00	0.00
0.33	4.30	20.54
0.67	13.35	63.74
1.00	19.78	94.44
2.00	20.95	100.00
3.00	14.25	68.02
6.00	5.09	24.32
12.00	1.80	8.60
24.00	1.09	5.18
48.00	0.33	1.58
72.00	0.18	0.87
120.00	0.10	0.46
168.00	0.09	0.44
336.00	0.15	0.73
504.00	0.23	1.08
672.00	1.09	5.18

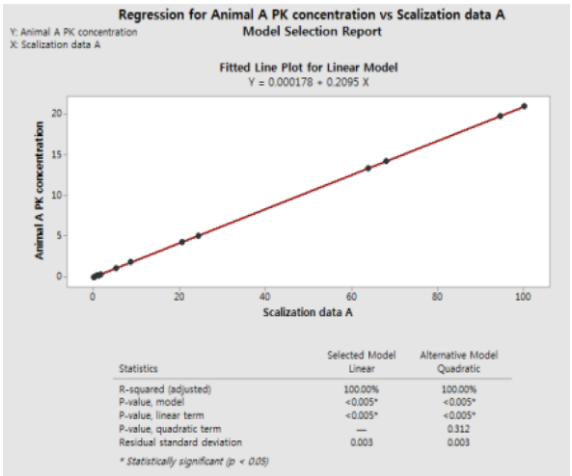


Fig.1. Regression analysis for animal A vs A' scalization data

Table3: Extraction of B-scalization data

B' Cmax	534.08	Scalization
hr (n)	Mean	$hr\ (n)/Animal\ A\ PK\ Cmax(534.08) * 100$
0.00	0.00	0.00
0.33	305.98	57.29
0.67	534.08	100.00
1.00	504.64	94.49
2.00	299.78	56.13
3.00	150.56	28.19
6.00	47.56	8.90
12.00	29.97	5.61
24.00	30.86	5.78
48.00	22.38	4.19
72.00	12.74	2.39
120.00	3.77	0.71
168.00	4.84	0.91
336.00	11.49	2.15
504.00	3.61	0.68
672.00	0.91	0.17

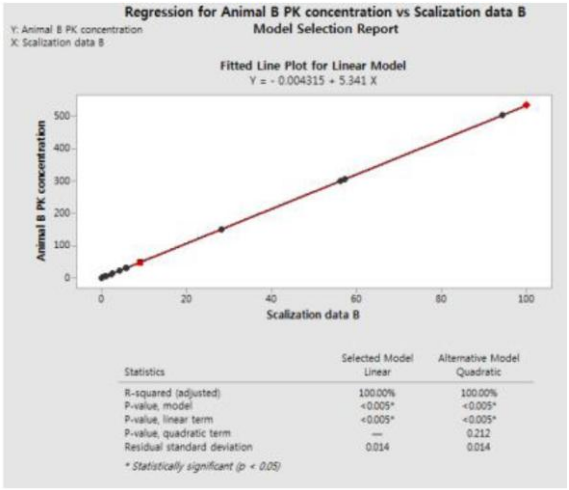


Fig.2. Regression analysis for animal B vs B' scalization data

Table4: Extraction of C-scalization data

C' Cmax	20.28	Scalization
hr (n)	Mean	$hr\ (n)/Animal\ A\ PK\ Cmax(20.28) * 100$
0.00	0.00	0.00
0.33	14.15	67.74
0.67	20.28	100.00
1.00	19.92	98.20
2.00	18.66	91.99
3.00	12.41	61.18
6.00	3.80	18.73
12.00	1.03	5.10
24.00	0.92	4.54
48.00	0.74	3.66
72.00	0.72	3.55
120.00	0.58	2.85
168.00	0.42	2.07
336.00	0.45	2.23
504.00	0.34	1.69
672.00	0.16	0.77

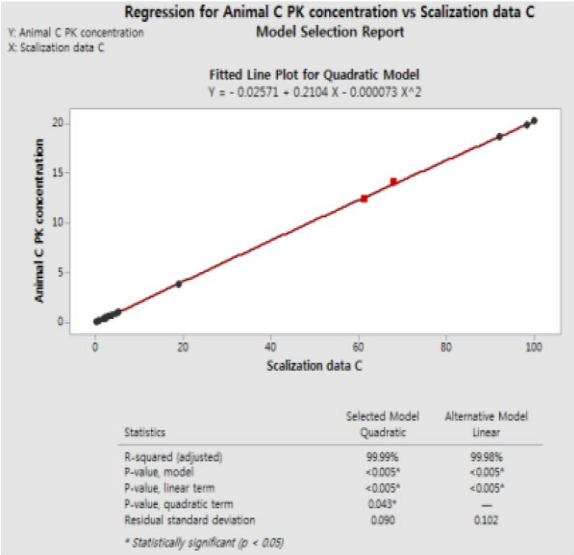


Fig.3. Regression analysis for animal C vs C' scalization data

3.2. Statistical distribution approach similar to each animal PK profile

We investigated the probability plot and estimated how closely the data points follow the appropriate distribution line by using the statistical software Minitab 18.

First, as shown in figure4, animal A was derived to have an exponential (p-value=0.003), gamma (p-value=0.175), weibull (p-value=0.230) and lognormal distribution (p-value=0.428). Second, as shown in figure5, animal B was derived values of exponential (p-value=0.003), gamma (p-value=0.250), weibull (p-value=0.250) and lognormal distribution (p-value=0.235). Finally, as shown in figure6, animal C was derived the values of exponential (p-value=0.003), gamma (p-value=0.018), weibull (p-value=0.023) and lognormal distribution (p-value=0.085). Based on these results, lognormal distribution was determined to be similar to each animal.

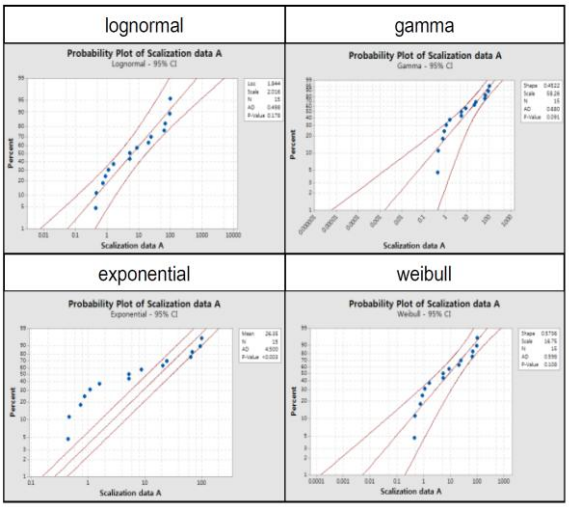


Fig.4. Statistical distribution approach based on probability plot of animal A

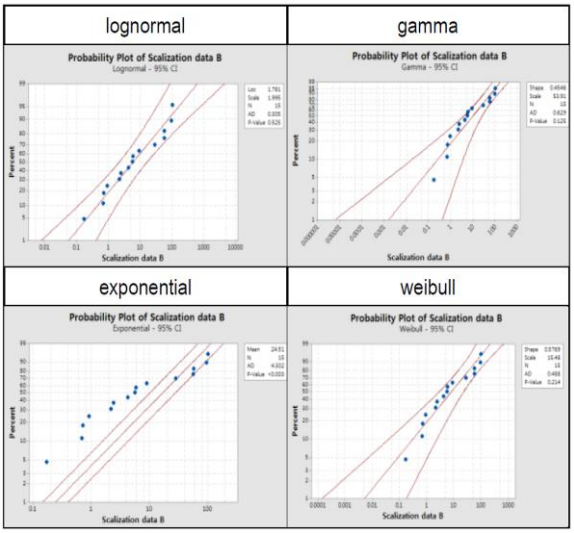


Fig.5. Statistical distribution approach based on probability plot of animal B

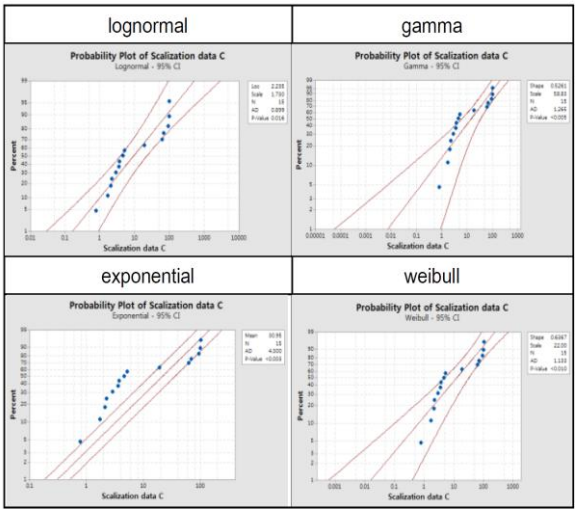


Fig.6. Statistical distribution approach based on probability plot of animal C

3.3. Comparison of paired t-test according toscalization

Before using the scalization method, animal A vs animal B, animal A vs animal C, animal B vs animal C were analyzed for a statistical similarity test using the paired t-test.As the result, First, no similarity exists between A vs B (p-value=0.019). Second, A vs C has similar time zone PK concentration (p-value=0.363). Lastly, no similarity exists between B vs C (p-value=0.018). Before using the scalization method, the paired t-test results for PK concentration in animals A vs B, and B vs C were not significant.

Table 4 shows the analysis results.And the results of this analysis may be noticed this result easily in shown in Figures 7, 8, and 9.

After using the scalization method,as the result, first, the p-value of A vs B increased from 0.019 to 0.783 after using the scalization method and became similar time zone PK concentration. Second, A vs C still has similar time zone PK concentration. In addition, the p-value of B vs C increased from 0.018 to 0.052 after

using the scalization method and became similar time zone PK concentration. After using the scalization method, the paired t-test results for PK concentration in animals A vs B, A vs C, and B vs C were significantly derived.

Table 5 shows the analysis results. And figure 10, 11, and 12, it can be easily noticed that the variance of PK concentration data between animals is lower than that of Figures 4, 5, and 6.

Table4: Paired t-test about A, B, C before scalization.

	Paired t-test	SE of Mean
A vs B	0.019	44.6
A vs C	0.363	0.788
B vs C	0.018	44.2

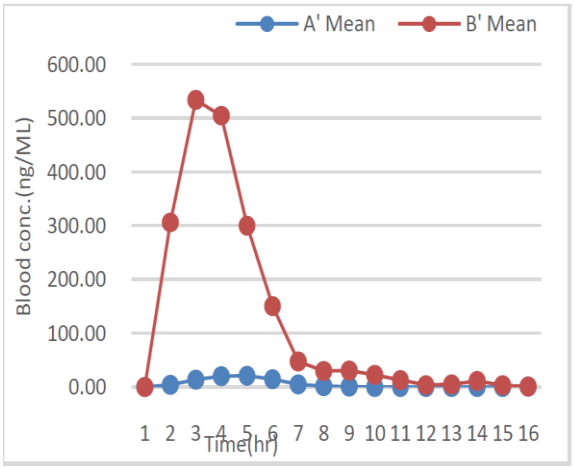


Fig.7. Comparison of A and B Data plot before the scalization

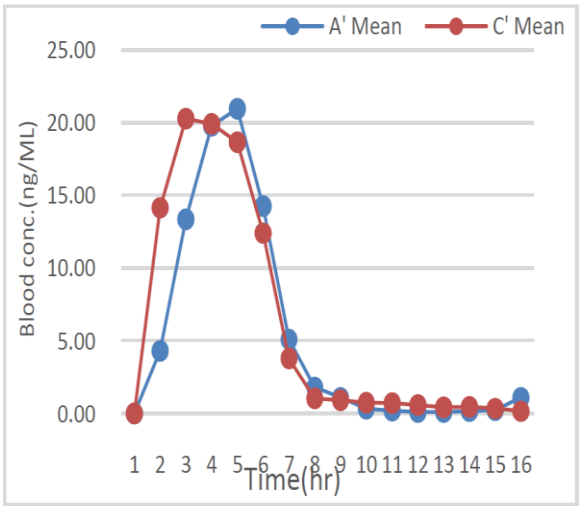


Fig.8. Comparison of A and C Data plot before the scalization

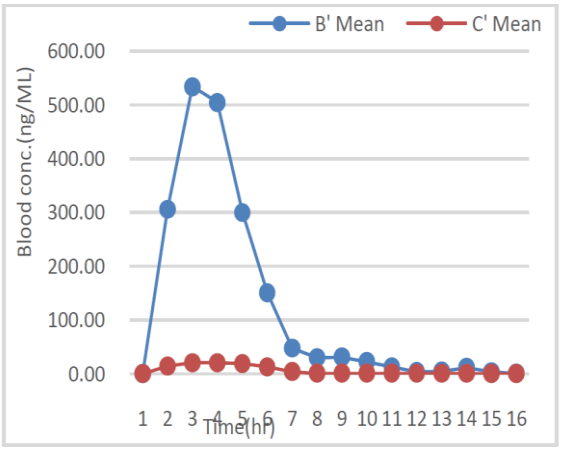


Fig.9. Comparison of B and C Data plot before the scalization

Table5: Paired t-test about A, B, C afterscalization

	Paired t-test	SE of Mean
A vs B	0.783	5.17
A vs C	0.271	3.89
B vs C	0.052	2.92

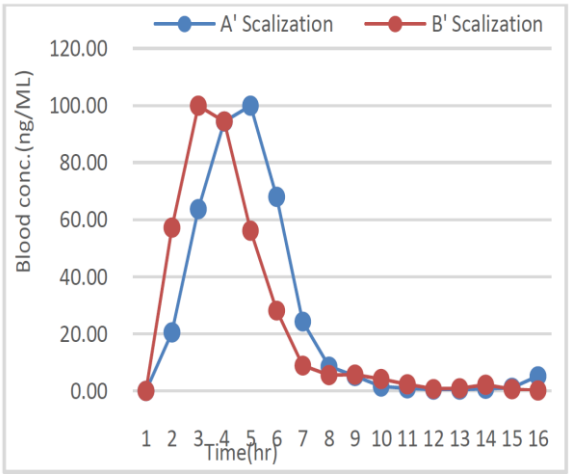


Fig.10. Comparison of A and B Data plot after the scalization

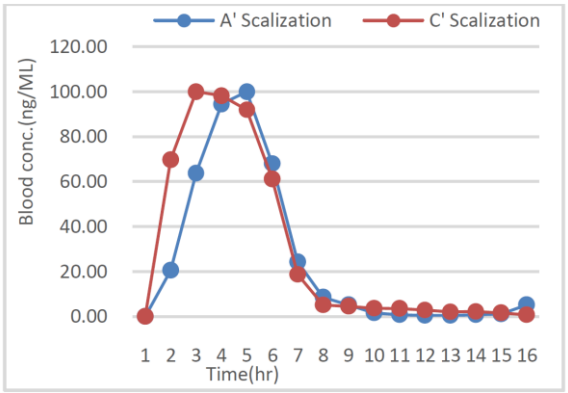


Fig.11. Comparison of A and C Data plot after the scalization

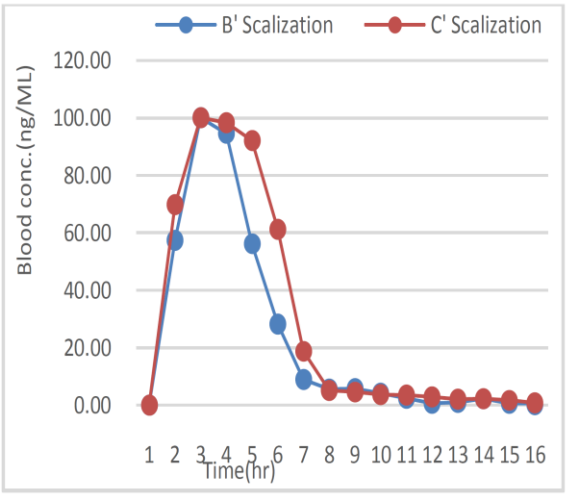


Fig.12. Comparison of B and C Data plot after the scalization

3.4. Area under the curve (AUC) value comparison among animals

The important criteria for the PK analysis, as area under the curve (AUC), was also compared by three animal PK profiles.

As shown in table 6, after scalization of animal PK concentration data, AUC were derived based on the trapezoidal method. In view of the drug delivery capacity, late-time PK concentration and AUC are important, which is considered to be more significant than early time.

As shown in table 7, Thedifference between animals A and C is less than that of other animals.

Table6: Derive AUC based on trapezoid rule

AUC	Animal PK concentration data		
day-day	Animal A	Animal B	Animal C
AUC (0-1)	1288.47	881.31	1167.47
AUC(0-2)	1480.34	1191.32	1368.25
AUC(0-3)	1549.96	1391.39	1545.23
AUC(0-5)	1625.44	1577.93	1870.18
AUC(0-7)	1676.08	1674.02	2134.79
AUC(0-14)	1908.27	2490.19	3186.03
AUC(0-21)	2268.62	3071.91	4158.14
AUC(0-28)	3512.18	3270.87	4780.31
AUC(7-14)	232.19	816.17	1051.24
AUC(7-21)	592.53	1397.89	2023.36
AUC(7-28)	1836.09	1596.85	2645.52
AUC(14-21)	360.34	581.72	972.12
AUC(14-28)	1603.90	780.68	1594.28
AUC(21-28)	1243.56	198.96	656.86

Table7: Comparison of AUC among animals by time-oriented

AUC	Animal PK concentration data		
day-day	Animal (A-B)	Animal (A-C)	Animal (B-C)
AUC(0-1)	407.16	121.00	286.16
AUC(0-2)	289.03	112.10	176.93
AUC(0-3)	158.56	4.73	153.84
AUC(0-5)	47.51	244.75	292.26
AUC(0-7)	2.07	458.70	460.77
AUC(0-14)	581.91	1277.75	695.84
AUC(0-21)	803.29	1889.53	1086.24
AUC(0-28)	241.31	1268.13	1509.44
AUC(7-14)	583.98	819.05	235.07
AUC(7-21)	805.36	1430.83	625.47
AUC(7-28)	239.24	809.43	1048.67
AUC(14-21)	221.38	611.78	390.40
AUC(14-28)	823.22	9.62	813.60
AUC(21-28)	1044.60	586.70	457.90

CONCLUSTIONS

One of the pharmacokinetic differences between animals and humans is that small animals have faster antibiotic removal rates and shorter half-lives (Lee, 2018). For this reason, the key motivation of this study need to standardize the PK profile of each animals. Therefore, we propose a scalization method for huge different scales of PK profiles. Without using this scalization approach, statistical similarity test may not provide enough precision. The major conclusions before and after the scalization method are as follows:

1. Before using the scalization method, the paired t-test results for PK concentration in animals A vs B, and B vs C were not significant.On the other hand, the paired t-test result of PK concentration of animal A vs C was significant
2. After using the scalization method, the paired t-test results for PK concentration in animals A vs B, A vs C, and B vs C were significantly derived.
3. This study proved through correlation that the information of existing PK concentration data is not lost when the scalization method is used.
4. Using a statistical distribution approach similar to each animal PK profile, we determined that all animals were significant with lognormal distribution
5. Critical criteria for PK analysis, such as under-curve area (AUC), were also compared by the three animal PK profiles, concluding that animals A and C are the most similar animals

By using the scalization method and the paired t-test, the selection of an appropriate animal for a PK study may save in-vivo experimental time as well as increase the possibility of a successful in-vivo experi-

ment. However, it may be difficult to provide enough precision for animal similarity analysis only by this statistical method. This study will use more statistical methods such as Sum of square (SS) and Root mean square error (RMSE) for the PK profile after using the scaling method to obtain more accurate reliability.

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