Estimation of Variance for Harmonic Mean Half-Lives

To the Editor:

The mean elimination half-life of a drug determined in a pharmacokinetic study can be presented in two ways. The common approach is to calculate the arithmetic mean of the half life ($\bar{t}_{1/2}$), determined for each subject under a given set of conditions. Alternatively, the mean half-life can be estimated by dividing ln 2 by the arithmetic mean elimination rate constant ($\bar{\beta}$) of the drug. The mean half-life computed by this latter method is equivalent to the harmonic mean of the half-lives ($\bar{H}_{t_{1/2}}$). A harmonic mean half-life can be determined from the relationship:

$$\frac{1}{\bar{H}_{t_{1/2}}} = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{t_{1/2,i}} \tag{1}$$

where n is the size of the sample. These two means, the arithmetic and the harmonic, are not equal, with the arithmetic mean always being greater than the harmonic mean. However, the harmonic mean half-life and the half-life obtained from the arithmetic mean elimination constant are always equal. The question must be asked, which mean half-life is more accurate and more precise in representing the mean of the population of half-life values?

In most pharmacokinetic studies the elimination half-life of a drug of a subject is calculated using:

$$t_{1/2,i} = \frac{\ln 2}{\beta_i} \tag{2}$$

where β_i is the elimination rate constant of the drug. This constant is usually estimated by fitting the log serum concentration–time data in the terminal elimination phase by linear regression or by applying nonlinear regression to all serum concentration–time data. Thus, it is the elimination rate constant and not the half-life which is determined experimentally. Because of this, it is more appropriate that the arithmetic mean of the β_i should be determined first and the mean elimination half-life computed using eq. 2. The harmonic mean rather than the arithmetic mean should, therefore, be employed to represent the mean of the half-lives in the population under investigation. However, the disadvantage of using the harmonic mean elimination half-life is that a measure of the variability (e.g., standard deviation) of the population half-lives can not be estimated by the conventional method. Conversely, if the arithmetic mean is used, the sample SD can be readily calculated using the relationship:

$$\mathrm{SD} = \sqrt{\frac{\sum_{i=1}^{n}(X_i - \bar{X})^2}{n-1}} \tag{3}$$

where $\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$. The ease of obtaining a standard deviation for the mean half-life is a possible reason for the common use of the arithmetic mean elimination half-life rather than the harmonic mean half-life.

The purposes of the present communication are to (*a*) call attention to a method for the estimation of the standard deviation of the harmonic mean elimination half-life; (*b*) further evaluate the appropriateness of the harmonic mean elimination half-life; and (*c*) determine the accuracy of the jackknife variance of the harmonic mean half-life as a measure of variability of the population.

The jackknife technique is a statistical tool found to be extremely useful in estimating any desired statistical parameters and their variances.[1,2] The principle of this method, when applied to means, is to determine the arithmetic mean for n − 1 values. This is repeated each time, omitting one value, and ultimately yielding n means.

Let $t_{1/2,1}$, $t_{1/2,2}$, . . . , and $t_{1/2,n}$ be a random sample of half-lives of sample size n. The harmonic mean half-life as given by eq. 1 can be expressed as:

$$\bar{H}_{t_{1/2}} = n \Big/ \left(\frac{1}{t_{1/2,1}} + \frac{1}{t_{1/2,2}} + \cdots + \frac{1}{t_{1/2,n}}\right) \tag{4}$$

The harmonic mean of n − 1 values, $\bar{H}_i$, would be given by the following relationship:

$$\bar{H}_i = (n-1) \Big/ \left(\frac{1}{t_{1/2,1}} + \frac{1}{t_{1/2,2}} + \cdots + \frac{1}{t_{1/2,i}-1} + \frac{1}{t_{1/2,i}+1} + \cdots + \frac{1}{t_{1/2,n}}\right) \tag{5}$$

where $t_{1/2,i}$ is deleted. This is repeated each time, deleting a different half-life value yielding n values of $\bar{H}_i$. Based on the generated values of $\bar{H}_i$, an approximate $(1-\alpha)100\%$ confidence interval for the harmonic mean can be determined and is:

$$\bar{H}_{t_{1/2}} \pm t_{n-1,\alpha/2}\sqrt{\frac{n-1}{n}\sum_{i=1}^{n}(\bar{H}_i - \bar{\bar{H}})^2} \tag{6}$$

where:

$$\bar{\bar{H}} = \frac{1}{n}\sum_{i=1}^{n}\bar{H}_i \tag{7}$$

and $t_{n-1,\alpha/2}$ is the critical value obtained from a t table with n − 1 degrees of freedom and tail area $\alpha/2$. The $(1-\alpha)100\%$ confidence interval using the arithmetic mean would be:

$$\bar{t}_{1/2} \pm t_{n-1,\alpha/2}\cdot\frac{\mathrm{SD}}{\sqrt{n}} \tag{8}$$

where:

$$\bar{t}_{1/2} = \frac{1}{n}\sum_{i=1}^{n} t_{1/2,i} \tag{9}$$

and SD is the standard deviation. It can be deduced by comparing eqs. 6 and 8 that the quantity $\sqrt{(n-1)\sum_{i=1}^{n}(\bar{H}_i - \bar{\bar{H}})^2}$ in eq. 6 plays the same role as the standard deviation in eq. 8 which is given by:

$$\mathrm{SD} = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(t_{1/2,i} - \bar{t}_{1/2})^2} \tag{10}$$

The term $\sqrt{(n-1)\sum_{i=1}^{n}(\bar{H}_i - \bar{H})^2}$ is in fact the SD of the pseudo-values[1] $(n\bar{H}_{t_{1/2}} - (n-1)\bar{H}_i)$ that are generated by the

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jackknife technique, and therefore, we would prefer to refer to this term as the "pseudo standard deviation." The common practice is to report $\bar{t}_{1/2} \pm$ SD. An analogous expression using the harmonic mean would be:

$$\bar{H}_{t_{1/2}} \pm \sqrt{(n-1)\sum_{i=1}^{n}(\bar{H}_i - \bar{\bar{H}})^2} \qquad (11)$$

The jackknife technique can be illustrated using the results obtained in a recent relative bioavailability study of naproxen tablets.[3] The elimination half-lives of naproxen for eight healthy male volunteers after ingestion of 250-mg naproxen BP tablets were found to be 18.0, 15.9, 24.8, 19.7, 20.0, 12.4, 18.5, and 21.2 h. The harmonic mean half-life of naproxen determined using eq. 4 is given by:

$$\bar{H}_{t_{1/2}} = 8 \Big/ \left(\frac{1}{18.0} + \frac{1}{15.9} + \frac{1}{24.8} + \frac{1}{19.7} + \frac{1}{20.0} + \frac{1}{12.4} + \frac{1}{18.5} + \frac{1}{21.2}\right) = 18.12$$

Eight $\bar{H}_i$ values can then be generated from the naproxen half-lives using the jackknife technique, (i.e., eq. 5) where:

$$\bar{H}_1 = 7 \Big/ \left(\frac{1}{15.9} + \frac{1}{24.8} + \frac{1}{19.7} + \frac{1}{20.0} + \frac{1}{12.4} + \frac{1}{18.5} + \frac{1}{21.2}\right) = 18.14$$

$$\bar{H}_2 = \Big/ \left(\frac{1}{18.0} + \frac{1}{24.8} + \frac{1}{19.7} + \frac{1}{20.0} + \frac{1}{12.4} + \frac{1}{18.5} + \frac{1}{21.2}\right) = 18.49$$

and, subsequently, $\bar{H}_3 = 17.45$, $\bar{H}_4 = 17.92$, $\bar{H}_5 = 17.88$, $\bar{H}_6 = 19.40$, $\bar{H}_7 = 18.07$, and $\bar{H}_8 = 17.76$. The arithmetic mean of the $\bar{H}_i$, i.e., $\bar{\bar{H}}$, is found to be 18.14. The jackknife variance (V_j) of the harmonic mean half-life can then be determined using the equation:

$$V_j = \frac{n-1}{n}\sum_{i=1}^{n}(\bar{H}_i - \bar{\bar{H}})^2 \qquad (12)$$

which yields a value of V_j, in the present example, of 2.15. The pseudo standard deviation of the harmonic mean then equals $\sqrt{8 \times 2.15}$ or 4.15. Therefore, the mean half-life of naproxen and its pseudo standard deviation are 18.12 ± 4.15 h. This compares with an arithmetic mean half-life and standard deviation of 18.81 and 3.67, respectively. The coefficient of variation of the harmonic mean half-life in this example is 22.9%, which corresponds to a coefficient of variation of 22.1% for the average of the elimination rate constants.

In order to evaluate the relative merits of the harmonic mean compared with the arithmetic mean in estimating the true mean of the half-lives of a drug in a population, and also the appropriateness of the jackknife variance for the harmonic mean, a Monte Carlo study[4,5] was carried out. The model $C = C_0e^{-\beta t}$ was assumed. For each subject the data were simulated using a linear form of the model, i.e.:

$$\ln C_j = \alpha + \beta_i t_j + \varepsilon_j \qquad (13)$$

where C_j is the concentration, α is the intercept, and t_j is time. The error term ε_j and the individual elimination rate constant β_i were generated randomly. The error term ε_j was assumed to be normally distributed with the mean equal to zero and an assigned standard deviation (σ_1) of 0.05 or 0.1. These standard deviations were chosen because the error associated with the analysis of drug in biological fluids is normally <10%, and generally never exceeds 20%. Variation in analysis was assumed to be the major source of error. The value of β_i was generated

Table I—Relative Accuracy of the Arithmetic Mean and the Harmonic Mean in Estimating the Mean Elimination Half-life Using Computer Simulation

n	Observations[a]	Percentage Empirical Bias[b]	
		Arithmetic Mean	Harmonic Mean
		$\sigma_1 = 0.05$, $CV_2 = 20\%$	
6	3	4.28	0.24
	5	4.84	0.84
	10	4.59	0.73
8	3	4.80	0.64
	5	4.71	0.53
	10	4.79	0.60
12	3	4.75	0.34
	5	4.96	0.52
	10	4.43	0.21
		$\sigma_1 = 0.05$, $CV_2 = 30\%$	
6	3	13.26	0.82
	5	16.12	1.76
	10	17.05	1.59
8	3	13.42	1.42
	5	9.04	1.21
	10	13.60	1.27
12	3	11.54	0.75
	5	13.69	1.05
	10	14.25	0.60
		$\sigma_1 = 0.05$, $CV_2 = 40\%$	
6	3	21.40	2.46
	5	57.96	2.94
	10	32.52	2.83
8	3	21.69	2.53
	5	38.94	2.20
	10	9.10	1.79
12	3	15.04	1.35
	5	19.04	1.76
	10	26.01	1.18
		$\sigma_1 = 0.10$, $CV_2 = 20\%$	
6	3	5.01	0.56
	5	4.54	0.66
	10	4.25	0.51
8	3	5.22	0.60
	5	4.80	0.55
	10	4.80	0.59
12	3	5.27	0.48
	5	4.79	0.48
	10	4.72	0.39
		$\sigma_1 = 0.10$, $CV_2 = 30\%$	
6	3	14.76	0.91
	5	17.97	1.77
	10	23.18	1.60
8	3	11.81	0.84
	5	10.72	0.81
	10	12.88	0.92
12	3	14.25	0.95
	5	36.96	0.99
	10	14.14	0.87
		$\sigma_1 = 0.10$, $CV_2 = 40\%$	
6	3	30.69	2.53
	5	31.37	3.10
	10	37.41	2.84
8	3	27.24	1.74
	5	56.40	1.62
	10	25.38	1.77
12	3	8.11	1.61
	5	40.90	1.70
	10	38.28	1.53

[a] Number of observations in the terminal phase per subject. [b] Percentage empirical bias = $[(\bar{t}_{1/2})_E - (\bar{t}_{1/2})_T/(\bar{t}_{1/2})_T \times 100\%]$, where $(\bar{t}_{1/2})_E$ is the estimated average half-life from the simulated data, and $(\bar{t}_{1/2})_T$ is the true mean half-life.

Table II—Empirical Confidence Levels of the Harmonic Mean with the Jackknife Variance and the Arithmetic Mean using the Sample Variance

n	Observations*	Arithmetic Mean (Usual Variance)		Harmonic Mean (Jackknife Variance)	
		$\sigma_1 = 0.05$, $CV_2 = 20\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.913	0.958	0.906	0.957
	5	0.909	0.954	0.910	0.959
	10	0.911	0.953	0.902	0.949
8	3	0.884	0.957	0.895	0.949
	5	0.890	0.948	0.905	0.945
	10	0.915	0.959	0.908	0.957
12	3	0.902	0.953	0.909	0.951
	5	0.879	0.943	0.891	0.943
	10	0.864	0.937	0.888	0.943
		$\sigma_1 = 0.05$, $CV_2 = 30\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.916	0.964	0.907	0.953
	5	0.915	0.958	0.916	0.954
	10	0.913	0.959	0.908	0.947
8	3	0.888	0.959	0.893	0.950
	5	0.895	0.950	0.904	0.944
	10	0.916	0.965	0.907	0.956
12	3	0.879	0.952	0.910	0.955
	5	0.869	0.942	0.891	0.942
	10	0.866	0.939	0.893	0.942
		$\sigma_1 = 0.05$, $CV_2 = 40\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.915	0.951	0.889	0.945
	5	0.933	0.978	0.908	0.962
	10	0.921	0.963	0.909	0.944
8	3	0.898	0.965	0.895	0.947
	5	0.909	0.961	0.905	0.943
	10	0.921	0.966	0.910	0.945
12	3	0.885	0.961	0.909	0.953
	5	0.878	0.947	0.894	0.942
	10	0.879	0.957	0.896	0.941
		$\sigma_1 = 0.10$, $CV_2 = 20\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.919	0.957	0.911	0.951
	5	0.888	0.951	0.889	0.943
	10	0.896	0.952	0.895	0.945
8	3	0.887	0.959	0.899	0.952
	5	0.889	0.952	0.903	0.949
	10	0.915	0.962	0.913	0.959
12	3	0.870	0.951	0.896	0.946
	5	0.864	0.946	0.890	0.954
	10	0.873	0.938	0.893	0.941
		$\sigma_1 = 0.10$, $CV_2 = 30\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.915	0.962	0.905	0.954
	5	0.912	0.957	0.914	0.956
	10	0.914	0.958	0.909	0.948
8	3	0.903	0.956	0.897	0.951
	5	0.894	0.964	0.894	0.949
	10	0.924	0.971	0.920	0.959
12	3	0.865	0.951	0.903	0.947
	5	0.859	0.953	0.900	0.949
	10	0.864	0.936	0.898	0.942
		$\sigma_1 = 0.10$, $CV_2 = 40\%$			
		$1 - \alpha = 0.90$	0.95	0.90	0.95
6	3	0.913	0.960	0.894	0.946
	5	0.923	0.958	0.915	0.954
	10	0.922	0.962	0.910	0.947
8	3	0.913	0.961	0.902	0.944
	5	0.905	0.967	0.898	0.944
	10	0.920	0.964	0.907	0.945
12	3	0.886	0.951	0.901	0.942
	5	0.867	0.954	0.905	0.952
	10	0.868	0.952	0.897	0.943

* Number of observations in the terminal phase per subject.

using the model:

$$\beta_i = \bar{\beta} + \delta_i \tag{14}$$

where $\bar{\beta}$ is the true population mean of the half-lives and δ_i accounts for the interindividual variation. The term δ_i was also assumed to be normally distributed with the mean of zero and standard deviation of σ_2. The standard deviation, σ_2, and the coefficient of variation, CV_2, of β_i are related by the following equation:

$$\sigma_2 = \bar{\beta} \times CV_2 \tag{15}$$

To generate δ_i, the value of CV_2 was fixed at 20, 30, or 40%. These values of CV_2 provided data with a 2.33-, 4-, or 9-fold range in β_i values, respectively. After data were generated for each subject using eqs. 13 and 14, least-squares were employed to compute the estimated β_i. The corresponding half-life was then calculated using eq. 2. This procedure was performed for 6, 8, and 12 subjects with 3, 5, and 10 concentration time points in the terminal elimination phase per subject. One thousand mean half-lives were generated for each of the 54 combinations.

Table I shows the percentage empirical bias for the above 54 cases. In every case the bias of the arithmetic mean is much larger (6–30 times) than that of the harmonic mean. The bias of the harmonic mean ranges from 0.2 to 3.1%, which is relatively insignificant. However, for the arithmetic mean, the bias ranges from 4.25 to 57.96%. Such variations cannot be ignored, especially when CV_2 is large.

Two confidence intervals, 90 and 95%, were calculated for the harmonic mean using the jackknife variance and for the arithmetic mean using the usual sample variance as demonstrated in eqs. 6 and 8. The results are presented in Table II. In most cases, the empirical confidence level of the harmonic mean is closer to the true levels, i.e., 0.9 or 0.95, than that of the arithmetic mean.

In conclusion, the harmonic mean is significantly better than the arithmetic mean in representing the true mean of the population. In addition, jackknife variance of the harmonic mean performs extremely well using the t distribution. Therefore, in estimating the mean elimination half-life of a drug in pharmacokinetic studies, the harmonic mean and pseudo standard deviation are recommended in lieu of the arithmetic mean and the usual sample standard deviation.

References and Notes

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