Examination of International Normalised Ratio (INR) imprecision by comparison of exact and approximate formulas

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Abstract

Aim—To evaluate the accuracy of the approximate linear formula of International Normalised Ratio (INR) imprecision by formal mathematical analysis.

Methods—Using probability theory, an exact formula for the coefficient of variation (CV) of the INR was derived. The CV from the approximate formula was compared with the CV from the exact formula for INR determinations between 1.0 and 10.0 with International Sensitivity Indices (ISIs) between 1.0 and 3.0 and prothrombin time ratio CVs between 1.0 and 10.0%.

Results—When the ISI equals 1.0, the approximate formula and the exact formula are equal. When the ISI is more than 1.0, the approximate formula overestimates the exact CV, but by less than one hundredth of the exact CV in the parameter ranges studied. The approximate formula is most accurate when laboratories achieve excellent prothrombin time measurement precision and use sensitive thromboplastins.

Conclusions—The approximate formula provides a simple means for estimating the imprecision of the INR and is sufficiently accurate to warrant its use in clinical laboratories.

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The International Normalised Ratio (INR) has become the preferred measurement for monitoring patients stabilised with oral anticoagulants.^{1,2} Because thromboplastins are indexed to an international reference material, INR measurements can be more directly compared with one another in different laboratories.³ Therapeutic ranges have been established for the INR to permit better monitoring of patients taking oral anticoagulants.⁴ As with any laboratory test, proper interpretation of an INR determination requires an understanding of its imprecision. Taberner *et al* derived an approximate formula for the coefficient of variation (CV) of the INR, relating it to the CV of the prothrombin time ratio (PTR) and the International Sensitivity Index (ISI).⁵ A recent probability model for the INR has been derived and validated.⁶ We used this model to determine the accuracy of the approximate formula.

Methods

The INR is computed from the prothrombin time (PT) by the INR equation¹:

$$I = \left(\frac{P}{M} \right)^S, \quad (1)$$

where

I is the INR,

P is the PT,

M is the geometric mean of the reference range, and

S is the ISI.

An alternate form of the INR equation is:

$$I = R^x, \quad (2)$$

where *R* is the PTR and the other variables are as described before. Note that it can be shown that the CV of the PTR is identical with that of the PT.

APPROXIMATE FORMULA

Taberner *et al* derived an approximate formula for the CV of the INR from equation (2) using the first two terms of a Taylor series expansion—that is, method of differentials—see Appendix.⁵ The approximate formula of Taberner *et al* (Appendix, equation A8) is

$$CV_I \approx CV_R \cdot S, \quad (3)$$

where

CV_I is the CV of the INR,

CV_R is the CV of the PTR, and

S is the ISI.

EXACT FORMULA

We derived the probability density function of the INR with four parameters: the mean of the PT measurement; the standard deviation (SD) of the PT; the ISI; and the mean of the PT reference range.⁶ An equivalent three parameter equation is found by absorbing the geometric mean of the reference population (*m*, equation (1)) into the PTR, *R*:

$$f_I(i) = \frac{i^{1/S-1}}{s\sigma_R\sqrt{2\pi}} \exp \left[-\frac{(i^{1/S} - \mu_R)^2}{2\sigma_R^2} \right], \quad (4)$$

where

μ_R is the mean of the PT ratio measurement,

σ_R is the SD of the measurement error in the PTR,

S is the ISI, and

f_I(i) is the probability density of the INR evaluated at *I* = *i*.

From equation (4) the mean, *μ_I*, and SD, *σ_I*, of the INR distribution are:

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$$\mu_I = \int_{-\infty}^{\infty} if_I(i) di \quad (5)$$

and

$$\sigma_I = \sqrt{\int_{-\infty}^{\infty} (i - \mu_I)^2 f_I(i) di} \quad (6)$$

The exact formula for the CV of the INR is:

$$CV_I = \frac{\sigma_I}{\mu_I} \cdot 100\% \quad (7)$$

COMPARISON OF EXACT AND APPROXIMATE FORMULAS

The CV of the INR was calculated using the exact formula and the approximate formula for a spectrum of PTRs, PTR CVs, and ISIs. PTR CVs of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10% and ISIs of 1.0, 1.5, 2.0, 2.5, and 3.0 were evaluated. The PTRs selected for evaluation corresponded to integer INR values of 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, and 10.0.

The integrations required by equations (5) and (6) were performed by trapezoidal approximation using Excel (Microsoft Corp, Redmond, Washington, USA) as described before.⁶

Results

For fixed ISIs in the range of 1.0 to 3.0 and fixed PTR CVs in the range of 1.0 to 10.0%, both the approximate and exact INR CVs are constant for INRs between 1.0 and 10.0. In other words the INR CV is dependent only on the PTR CV and the ISI, not on the PTR level. Table 1 shows the exact and approximate CVs of the INR for selected combinations of ISI and PTR CV. When the ISI = 1.0, the exact and approximate CVs are

equal. When the ISI is more than 1.0, the approximate formula overestimates the exact CV, but by less than 1.0% of the exact CV in the parameter ranges studied.

Discussion

Taberner *et al* reported an approximate formula, equation (3), for calculating the CV of the INR, using the linear terms of the Taylor series expansion of equation (2) (see Appendix).⁵ This approximate formula was stated to be valid when the ISI is between 1.0 and 2.6 and the PTR CV is between 5% and 15%, and data were presented to illustrate the empirical validity of the formula. We recently validated a mathematical characterisation of the imprecision of the INR based on probability theory,⁶ from which we derived an exact formula for calculating the CV of the INR. In this study we have used our exact formula to ascertain, from a theoretical mathematical standpoint, the accuracy of the approximate formula of Taberner *et al*. If shown to be sufficiently accurate, the simplicity of the approximate formula provides any laboratory with an effortless method for estimating the precision of the INR based on its analytical technique and PT data. Prothrombin time measurements have been shown to be Gaussian distributed.⁶ Starting with these observations, the exact formula permits complete examination and a full explanation of the behavior of the INR transformation on a Gaussian distributed variable.

We compared the CVs calculated by the approximate formula with the exact CVs when the ISI was between 1.0 and 3.0 and the CV of the PTR was between 1.0% and 10.0%. These ranges for the ISI and PTR CV

Table 1 Exact and approximate CVs of the INR*

PTR CV, %	INR CV, %		
	Exact†	Approximate†	Difference, %††
<i>ISI = 1.0</i>			
1.00	1.00	1.00	0.00
2.50	2.50	2.50	0.00
5.00	5.00	5.00	0.00
7.50	7.50	7.50	0.00
10.00	10.00	10.00	0.00
<i>ISI = 1.5</i>			
1.00	1.50	1.50	0.00
2.50	3.75	3.75	0.03
5.00	7.49	7.50	0.11
7.50	11.22	11.25	0.25
10.00	14.93	15.00	0.44
<i>ISI = 2.0</i>			
1.00	2.00	2.00	0.01
2.50	5.00	5.00	0.05
5.00	9.98	10.00	0.19
7.50	14.94	15.00	0.42
10.00	19.85	20.00	0.75
<i>ISI = 2.5</i>			
1.00	2.50	2.50	0.01
2.50	6.25	6.25	0.06
5.00	12.47	12.50	0.23
7.50	18.65	18.75	0.53
10.00	24.77	25.00	0.93
<i>ISI = 3.0</i>			
1.00	3.00	3.00	0.01
2.50	7.50	7.50	0.06
5.00	14.96	15.00	0.25
7.50	22.37	22.50	0.56
10.00	29.71	30.00	0.99

*Conditions: INR between 1.0 and 10.0.

†Values rounded for presentation but not for computation.

††Difference = (Approximate - Exact)/Exact × 100%

Figure 1 Illustration of approximate v exact INR CVs as a function of the INR in a community hospital. PTR determinations were made on an MLA 900 using a thromboplastin with an ISI of 1.93. The PTR CV profile is shown for comparison.

Table 2 Exact and approximate parameters of selected INR distributions

		INR distribution parameters			
		Mean		CV, %	
PTR*	ISI	Exact	Approximate	Exact	Approximate
PTR CV = 2.0%					
3.0000	1.0	3.0000	3.0000	2.0000	2.0000
1.7321	2.0	3.0012	3.0000	3.9988	4.0000
1.4422	3.0	3.0036	3.0000	5.9976	6.0000
PTR CV = 5.0%					
3.0000	1.0	3.0000	3.0000	5.0000	5.0000
1.7321	2.0	3.0075	3.0000	9.9813	10.0000
1.4422	3.0	3.0225	3.0000	14.9627	15.0000

* Prothrombin time ratio

Figure 2 Approximate v exact distributions of the INR at PT ratios yielding an INR of 3.0 when the CV of the PT ratio is 2.0% and the ISI is 1.0 (highest pair of curves), 2.0 (middle pair of curves), and 3.0 (lowest pair of curves). Note that the approximate and exact distributions are identical when the ISI is 1.0.

for this study were selected to encompass values that are commonly seen in clinical laboratories performing automated PT determinations. As shown in table 1, the approximate formula overestimates the CV of the INR when the ISI is above 1.0; however, the magnitude of the overestimation is minimal,

Figure 3 Approximate v exact distributions of the INR at PTRs yielding an INR of 3.0 when the CV of the PTR is 5.0% and the ISI is 1.0 (highest pair of curves), 2.0 (middle pair of curves), and 3.0 (lowest pair of curves). Note the increased spread of the distributions compared with fig 2.

reaching a maximum difference of less than 1.0 % of the exact CV at the upper limits of ranges of the ISI and the PTR CV. When the ISI equals 1.0, the approximate formula and the exact formula produce identical CVs. These results lend theoretical validity to the approximate formula of Taberner *et al* and extend their work to a lower range of the PTR CV.

The practical value of the close agreement of the approximate formula with the exact formula is illustrated in fig 1. Although the difference between the approximate and exact INR CVs increases with increasing INR, the magnitude of the difference is trivial. The differences between the approximate and exact CVs are a result of differences in the approximate and exact distributions of the INR. The approximate formula implicitly assumes that the imprecision in the PTR measurements is distributed Gaussian and that the imprecision in the INR is also Gaussian. The exact formula shows that if the PTR is Gaussian, the INR is non-Gaussian if the ISI is more than 1.0, and is Gaussian if the ISI equals 1.0.⁶ Thus the moments such as mean and SD of the exact INR distribution do not equal those of the approximate Gaussian distribution unless the ISI equals 1.0, as illustrated in table 2. Within the parameter ranges of this study, the means, SDs, and distributions of the exact and approximate distributions are not identical but are remarkably similar (figs 2 and 3).

The striking similarities are a direct result of the mathematics of the INR. The exponential transformation is a smooth, well behaved function whose infinite Taylor series expansion is well approximated by the first two terms of the expansion (see Appendix). The exact formula shows that the Gaussian approximation of Taberner *et al* is robust for a wide range of ISI and PT distribution values.

The clinical importance of INR imprecision is illustrated in figs 2 and 3. For any level of PTR imprecision, the imprecision of the INR is dramatically greater with high ISI thromboplastins compared with low ISI thromboplastins. Excessive imprecision in the INR muddles the clinical interpretation of INR measurements and increases the likelihood of inappropriate therapeutic decisions. This is particularly worrisome in North America where thromboplastin ISIs are typically in the range of 2.0 to 3.0.

We conclude that the approximate formula is mathematically substantiated on theoretical grounds and is adequate for characterising the imprecision of the INR when the ISI is between 1.0 and 3.0 and the PTR CV is between 1.0% and 10.0%. The approximate formula offers the advantage of being computationally simpler than the exact formula, making it more appropriate for use in clinical laboratories.

Appendix: the method of differentials applied to the INR

The method of differentials for estimating the precision of a random variable involves a Taylor series expansion of a function about a

value, a^7 :

$$g(x) = \sum_{k=0}^{\infty} g^{(k)}(x-a)^k \quad (\text{A1})$$

$$= g(a) + \frac{g'(a)}{1!} (x-a) + \frac{g''(a)}{2!} (x-a)^2 + \dots,$$

where

g is the function of x , and
 a is the point about which the function is expanded.

For the third, fourth, and terms beyond in equation (A1), the sum is:

$$\begin{aligned} \varepsilon &= \sum_{k=2}^{\infty} \frac{g^{(k)}(a)}{k!} (x-a)^k \\ &= \frac{g''(a)}{2!} (x-a)^2 + \frac{g'''(a)}{3!} (x-a)^3 + \\ &\quad \frac{g^{(4)}(a)}{4!} (x-a)^4 + \dots + \frac{g^{(n)}(a)}{n!} (x-a)^n + \dots \end{aligned} \quad (\text{A2})$$

For the INR, the function is approximated by the first two terms as:

$$i(r) \approx i(a) + \frac{i'(a)}{1!} (r-a)^1, \quad (\text{A3})$$

where

i is the INR function,
 r is the PT ratio (PTR), and
the error of approximation is ε as above.

If ε is small, the the first two terms of the series are a good approximation of the function.

The variance of the INR, $\text{var}[I]$, can be computed from equation (A3), recognising that (1) the variance of a sum is the sum of variances for independent random variables, (2) the variance of a constant is zero, (3) the variance of a random variable plus a constant is the variance of the random variable alone, and (4) the variance of a constant times a random variable is the square of the constant times the variance of the random variable alone⁸:

$$\begin{aligned} \text{var}(I) &= \sigma_I^2 = \text{var}\left[g(a) + \frac{g'(a)}{1!} (r-a)\right] \\ &= 0 + [g'(a)]^2 \cdot \text{var}[r-a] \\ &= 0 + [g'(a)]^2 \cdot \text{var}[r] \end{aligned} \quad (\text{A4})$$

$$= [g'(a)]^2 \cdot \sigma_R^2.$$

Since

$$i(r) = r^s, \quad (\text{A5})$$

then

$$i'(r) = s \cdot r^{s-1}. \quad (\text{A6})$$

Assuming that the mean of the INR is approximately equal to the transformation of the mean of the PTR:

$$\mu_I \cong i(\mu_R) = \mu_R^s. \quad (\text{A7})$$

With algebraic rearrangement, the relation of the approximation of the INR CV to the PTR CV emerges as:

$$\begin{aligned} \sigma_I &= \frac{dr}{di} \sigma_R = s \cdot r^{s-1} \sigma_R \\ &= s \cdot \mu_R^{s-1} \sigma_R = s \cdot \frac{\mu_R^s}{\mu_R} \sigma_R \\ &\cong s \cdot \frac{\mu_I}{\mu_R} \sigma_R \\ &\Rightarrow \frac{\sigma_I}{\mu_I} \approx s \cdot \frac{\sigma_R}{\mu_R} \\ &\Rightarrow CV_I \approx s \cdot CV_R. \end{aligned} \quad (\text{A8})$$

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