be usefully applied to whichever of the three values is entered or modified last:

SD: upper limit = $\sqrt{N} \times \text{mean}$

mean: lower limit = SD/$\sqrt{N}$

N: lower limit = $(\text{SD/mean})^2$ rounded up to an integer, or 2 (whichever is larger)

Returning to the example above, initial entries of $N = 10$ and mean = 1.0 would restrict SD to a maximum of $\sqrt{10} \times 1.0$, or 3.162. Alternatively, mean = 1.0 and SD = 10 000 would require $N \approx 10^8$ (which would probably be flagged as too large).

These rules are easily incorporated into computer programs that require $N$, mean, and SD as input data. They cannot prevent all errors (or experimentation), but they do confine data to internally consistent combinations. Laboratory analysts might also be comforted to know that poor reproducibility does have a physical upper limit!

Maximum observable SD. The usual computational formula for the SD of a set of observations, $x_i$, $i = 1, 2, \ldots, N$, is

$$SD = \left( \frac{\sum_{i=1}^{N} x_i^2 - (\sum_{i=1}^{N} x_i)^2}{N} \right)^{1/2}$$

Expanding $(\sum_{i=1}^{N} x_i^2)^2$ yields

$$= \left( \sum_{i=1}^{N} x_i \right)^2 = (x_1 + x_2 + \ldots + x_N)^2$$

contains the cross-product elements. Substituting

$$= N \sum_{i=1}^{N} x_i^2 + C$$

where $C = 2 \sum_{i=1}^{N} \sum_{j=1}^{N} x_i x_j$ (i ≠ j)

N

$$\sum_{i=1}^{N} x_i^2 = \left( \sum_{i=1}^{N} x_i \right)^2 - C,$$

into Eq. 1 and rearranging yields

$$SD = \left[ \frac{\sum_{i=1}^{N} x_i^2}{N - C/(N - 1)} \right]^{1/2}$$

$$= \left[ N \sum_{i=1}^{N} x_i^2 - C \right]^{1/2}/(N - 1)!$$

where $\bar{x}$ is the mean of the set. The particular case, all $x_i = 0$ (typical of virtually all types of medical laboratory results), implies that all cross-product elements in $C$ are $\approx 0$, and therefore the maximum observable SD is $\sqrt{N} \times \bar{x}$ when $C = 0$. There are two cases where $C = 0$: all $x_i = 0$ (trivial case), and all but one $x_i = 0$; i.e., the largest SD of N observations ($\approx 0$) distributed about a mean $\bar{x}$, occurs when $(N - 1)$ observations are 0 and the single non-0 observation has the value $N\bar{x}$. It also follows that the largest observable CV for any set of N observations ($\approx 0$) is $100\sqrt{N}$, which could be used to formulate consistency rules for $N$, mean, and CV.

Reference


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FPIA and EMIT Methods Compared for Cyclosporine Monitoring in Heart Transplant Patients

To the Editor:

Rejection after heart transplantation, especially in the early posttransplant period, is associated with high morbidity and mortality rates. Cyclosporine (CsA) has been widely used in combination with azathioprine and prednisone as immunosuppressants. Besides its narrow therapeutic range, CsA evokes marked inter- and intra-individual differences in bioavailability and pharmacokinetics [1, 2]. Therefore, reliable monitoring assays and adequate CsA concentrations are crucial. The aim of this study was to compare two different immunoassays for CsA monitoring in heart transplant patients. We used both an enzyme-multiplied immunoassay technique (EMIT; Behring) and a monoclonal fluorescence polarization immunoassay (mFPIA; Abbott) to assay in parallel 163 EDTA-anticoagulated blood samples from 87 heart transplant patients.

Our results show a linear correlation between both assays for CsA trough concentrations, with mFPIA values averaging 45% more than EMIT concentrations (mean ± 2 SD: 173.8 ± 106.1 vs 119.7 ± 78.8 μg/L, respectively; Fig. 1). Assay interference from CsA metabolites may be particularly high immediately after heart or liver transplantation or in the presence of renal failure [3].

EMIT reportedly shows no significant interference from the CsA metabolites AM1, AM19, and AM4 N and only a slight cross-reactivity for metabolite AM9 [4]. The mFPIA, however, reportedly shows significant interference from AM1 and AM9 [5]. Our results show an even greater discrepancy between both assays and differ substantially from published data for liver and kidney recipients. LeGatt et al. [6] showed that FPIA-derived CsA concentrations averaged 14.2% more than those obtained with EMIT in kidney recipients. Dias et al. [7] obtained from renal, liver, and heart transplant patients CsA trough FPIA values averaging 32% more than the EMIT results. Dusci et al. [5] reported differences (mFPIA vs EMIT) of 43% and 27% for liver and renal transplant recipients, respectively.

EMIT data on CsA in heart transplantation are sparse. In line with our results are the findings of Seydoux and Goy [8] for a series of 66 CsA measurements in 28 heart transplant patients; the mFPIA values were 50% greater than the EMIT values.

From our results we cannot explain the overt discrepancies between mFPIA and EMIT in renal and cardiac recipients. We speculate that during the immediate posttransplant
period, higher concentrations of CsA metabolites can arise from a slower rate of metabolism because of temporary liver congestion.

In conclusion we found EMIT to be a rapid, viable, and specific assay for measuring CsA concentrations in transplant recipients. Obviously, however, an adjustment of the CsA therapeutic range for the EMIT is necessary.

References

Availability of Assays for Definitive Diagnosis of Primary Hyperoxaluria Types 1 and 2

To the Editor:

We read with interest the paper by Dietzen et al. [1] on improving the extraction and therefore the quantification of urinary glycerate and glycolate. Since this paper went to press, there have been further developments in the field of primary hyperoxaluria (PH) that may be of interest to your readers. Dietzen et al. correctly state that normal glycolate excretion does not exclude PH1. However, we now know that increased glycolate excretion cannot always confirm a diagnosis of this disease [2] and personal observations, so measurement of urinary metabolites cannot be conclusive. In addition, although l-glycerate is a marker of PH2, most methods cannot distinguish between the D and L isomers and, because of the small numbers studied, we do not yet know whether excretion of the L-isomer is unequivocally increased in all cases of PH2.

There is therefore a requirement for definitive diagnosis of these diseases by measurement of enzyme activity—not only because of the implications for treatment (hepatic vs renal transplantation) but also for counseling of families with respect to risk of recurrence. Methods are now available for the measurement of the relevant enzymes for PH1 and PH2 in a single needle liver biopsy [3, 4].

References