Using serial patient data to prospectively and continuously assess analyzer imprecision: dealing with the disappearance of reference sample quality control

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Abstract

Introduction: Over the last decade, regulators of in vitro diagnostic systems have been reducing the requirements for external quality control predicated on the analysis of internal standards. Prompted by puzzling patient results arising from specific exempted blood gas analyzers (BGA) operated in tandem, we now recommend two different, complimentary approaches to verify analytic goodness when external reference sample quality control is unavailable or infrequent or considered optional or non-value added.
Methods and Material: Our approaches are based on the analysis of laboratory data contained in large health system repositories. Based on today's excessive daily patient repeated testing, we developed a highly specific average of deltas (AoD) that can verify the morning accuracy of hospital chemistry and hematology analyzers. In addition, we have developed a calculus for transforming serial intrapatient results into a measure that we call PAAN™, a combined measure of PreAnalytic variation including biologic variation as well as ANalytical variation (PAAN). As preanalytical error is assumed to be sample-dependent, PAAN generally represents a mixture of biologic variation and analytic variation. As biologic variation of most laboratory tests is relatively constant, increases in PAAN can usually be attributed to increases in analytic variation and, occasionally, to preanalytic variation. Given today's high repeat testing rates, PAAN can be determined for virtually all hospital analyzers and even for specific analytical periods.
Results: Based on general chemistry testing at Hitchcock, using AoD to demonstrate an analytical problem in a morning's run, the minimum numbers of repeated patient observations (N) follow: albumin (9), ALP (22), ALT(30), AST(25), HCO3(14), UN(32), calcium(22), glucose(22). We are now implementing AoD at Hitchcock Medical Center. With reference to PAAN, we have just validated the PAAN calculation for glucose determinations in two different blood gas analyzers
Conclusion: As reference sample quality control continues to be de-emphasized by the regulator and the laboratory industry, there is a growing need for serial patient data algorithms to fill the quality measurement and quality control vacuum.

Introduction

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AoD: Introduction

Cervinski has previously shown that moving averages (MA), a patient based real time quality control technique, can rapidly detect systematic error (SE).
However the ability of the MA to detect SE for some analytes such as albumin, alanine aminotransferase and alkaline phosphatase is limited.
The ability of the MA to detect SE in inpatient populations is also typically poorer than in ambulatory populations.
In an effort to improve the ability to rapidly and reliably detect SE we have developed the Average of Deltas (AoD) strategy that monitors the mean intra-individual delta on consecutively collected patient results.
For each assay in this study the average number of patient deltas to detection (ANPDD) was calculated in response to induced SE.
We also compare the performance of the AoD to the MA for the detection of induced SE.

AoD: Methods and Materials

A database of 4.2 million patient results spanning 638 days was analyzed for this study.
The effectiveness of AoD to detect SE was investigated for albumin, ALT, ALP, amylase, AST, bicarbonate, bilirubin, BUN, calcium, chloride, creatinine, lipase, sodium, phosphorus, total protein and magnesium.
MatLab (Mathworks, Natick, MA) was used to generate analyte specific arrays containing pairs of patient results collected within 20-28 hours of each other.
The number of patient pairs of results to average (Np) and truncation limits to remove large delta values from the AoD were selected using a simulated annealing algorithm in MatLab.
To calculate ANPDD for each assay, MatLab was used to add positive or negative simulated SE at fixed intervals to arrays of within patient delta results.
The control limits for each protocol were set to 2.5 times the standard deviation of the delta values at 24 hours.
To standardize reporting we report the ANPDD for each assay at the predetermined control limits, or the amount of SE tolerable for each protocol.

AoD: Results and Conclusions

The AoD rapidly detected induced SE equal to assay control limits.
The best AoD was for total protein where an error equal to 0.75 g/dL was detected with ANPDD = 6.9 result pairs.
The largest ANPDD in our study was for alanine aminotransferase where an error equal to 15 U/L was detected with an ANPDD of 31.6 result pairs.
The AoD detected SE more rapidly than our MA protocols. However one limitation of this comparison is that for the AoD the number reflects the number of paired results, while the moving average represents consecutive results within the protocol inclusion limits.
The AoD strategy relies on monitoring the average intra-individual difference of pairs of patient results collected within 20 - 28 hours of each other. This strategy will benefit institutions with a significant inpatient populations but has limited value for reference and outpatient laboratories. We are now implementing AoD at Hitchcock Medical Center.

Average Number of Deltas to Error Detection and Protocol Parameters

Analyte	Control Limits	ANPDD (SD)	Parameters (N/TLu/TLl)	Pairs Per Day
Albumin (g/dL)	+0.5 -0.5	7.6(3.5) 8.9(4.7)	6/1.5/-9.8	6
ALP (U/L)	+26 -26	13.6(10.0) 22.5(17.2)	10/109.1/-78.4	6
ALT (U/L)	+15 -15	30.6(40.3) 9.9(6.2)	5/52.0/-23.7	6
AST (U/L)	+17.5 -17.5	21.8(16.3) 25.3(18.8)	11/56.1/-53.5	6
CO2 (mmol/L)	+5 -5	9.1(7.5) 13.7(13.0)	6/19.9/-19.1	66
BUN (mg/dL)	+7.3 -7.3	31.1(30.0) 12.6(4.7)	12/79.2/-24.9	69
DBIL (mg/dL)	+0.15 -0.15	22.4(15.8)) 28.0(19.1)	12/0.56/-0.56	6
TBIL (mg/dL)	+0.4 -0.4	32(28) 19(14)	5/0.5/-0.7	6
Ca (mg/dL)	+0.75 -0.75	11.6(7.8) 22.1(20)	8/2.29/-1.34	66
Cl (mmol/L)	+5 -5	10(8) 10(8)	6/10/-28	62
Creat (mg/dL)	+0.32 -0.32	13(8.1) 16(12.7)	9/1.02/-1.01	69
Gluc (mg/dL)	+25 -25	29.4(22.6) 29.7(20.2)	15/52/-98.6	69
Lipase (U/L)	+22.5 -22.5	6.0(1.4) 8.5(3.5)	5/58.8/-50.8	0.5
Mag (mmol/L)	+0.125 -0.125	13.7(7.7) 15.7(8.6)	11/1.94/-19.96	19
PO4 (mg/dL)	+1.0 -1.0	13.7(6.8) 18.8(11.6)	12/13.4/-12.9	13
K (mmol/L)	+0.675 -0.675	14.1(9.6) 10.1(6.1)	8/4.2/-3.2	62
Na (mmol/L)	+4 -4	17.7(13.1) 19.7(16.0)	12/14/-14	64
TP (mg/dL)	+0.75 -0.75	8.8(5.4) 6.9(3.6)	5/2.9/-1.5	6

PAAN: Introduction

We developed a calculus for transforming serial intrapatient results into a measure that we call PAAN™, a combined measure of PreAnalytic variation including biologic variation as well as ANalytical variation (PAAN). As preanalytical error is assumed to be sample-dependent, PAAN generally represents a mixture of biologic variation and analytic variation. As biologic variation of most laboratory tests is relatively constant, increases in PAAN can usually be attributed to increases in analytic variation and, occasionally, to preanalytic variation. Given today's high repeat testing rates, PAAN can be determined for virtually all hospital analyzers and even for specific analytical periods.
PAAN is calculated from serial intra-patient differences that are transformed by the standard deviation of differences.
For increasing time interval between the repeated test, the standard deviation of differences (SDD) is calculated for all the intrapatient test pairs within that interval, (x_1,x_2), (x_3, x_4) … $(x_{2i-1}\, x_{2i})$

$$SDD = \sqrt{\frac{\sum (x_{2i-1} - x_{2i})^2}{2n}}$$

The SDD vs timeline is generally linear and if the SDD is regressed against the midpoints of the time intervals, the y intercept (y_0) represents the square root of the sum of the PreAnalytic error including the intra-patient biologic variance (s_b^2) and the ANalytic variance (s_a^2) now referred as PAAN™ .

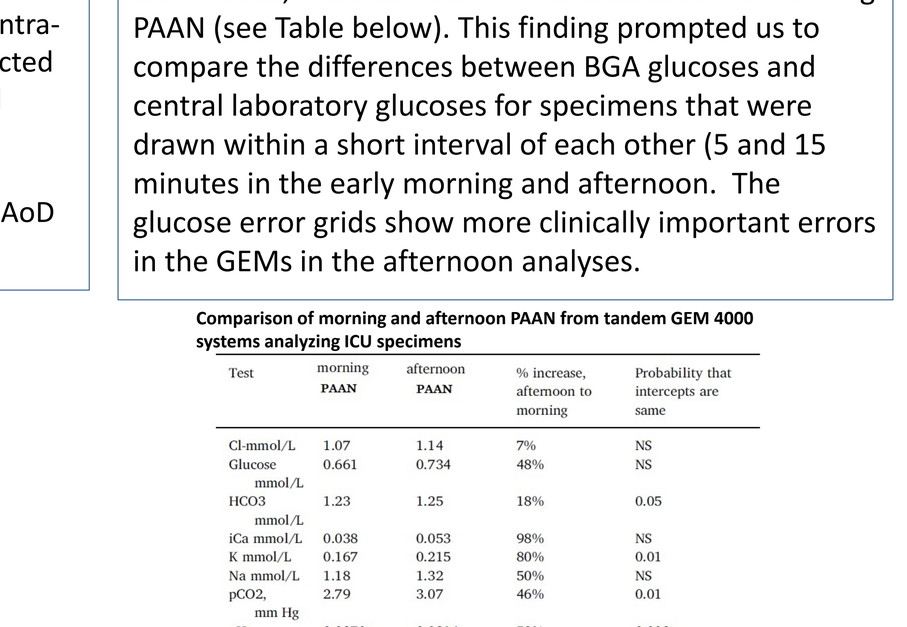
PAAN: Methods and Results

We discovered that the PAAN of tandem GEM 4000s operated at the Foothills Hospital General ICU was consistently higher for all blood gas analytes compared to the PAAN of tandem Radiometer ABL 800s operated at the University of Alberta Hospital general ICU. For the GEM 4000s, the afternoon PAANs exceeded the morning PAAN (see Table below). This finding prompted us to compare the differences between BGA glucoses and central laboratory glucoses for specimens that were drawn within a short interval of each other (5 and 15 minutes in the early morning and afternoon. The glucose error grids show more clinically important errors in the GEMs in the afternoon analyses.

Comparison of morning and afternoon PAAN from tandem GEM 4000 systems analyzing ICU specimens

Test	morning PAAN	afternoon PAAN	% increase, afternoon to morning	Probability that intercepts are same
Cl-mmol/L	1.07	1.14	7%	NS
Glucose mmol/L	0.661	0.734	48%	NS
HCO3 mmol/L	1.23	1.25	18%	0.05
iCa mmol/L	0.038	0.053	98%	NS
K mmol/L	0.167	0.215	80%	0.01
Na mmol/L	1.18	1.32	50%	NS
pCO2, mm Hg	2.79	3.07	46%	0.01
pH	0.0270	0.0314	59%	0.003
pO2, mm Hg	14.0	15.5	48%	NS

Use of Klonoff Surveillance Error Grid to demonstrate clinically important glucose errors (red zone). x axis shows the glucose measured in the central laboratory and y axis shows either tandem GEM 4000s or ABL 800s



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