Deacon's Challenge

No 132 - Answer

Recent NICE guidelines for the use of newer agents in the treatment of Type 2 Diabetes have recommended that glucagon-like peptide 1 (GLP-1) agonist drugs such as exenatide should only be continued if their introduction results in a reduction in HbA1c of at least 8 mmol/mol Hb.
If the biological within-subject variance is 0.1, what analytical precision must the assay achieve in order to be able to detect a true fall of 8 mmol/mol with greater than 95% certainty?
Values of the normal deviate (z-score) and P are:

P(%)	10	5	2	1	0.2	0.1
z	1.65	1.96	2.33	2.58	3.09	3.29

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If x_1 is the initial HbA1c result, x_2 the result after treatment and s_1 and s_2 their respective standard deviations then the differences between the two results $(x_1 - x_2)$ can be considered as a normally distributed variable with mean $m_{1\text{-}2}$ and standard deviation of their differences $s_{1,2}$.
If x_1 and x_2 are not significantly different then measured differences $(x_1 - x_2)$ would belong to a distribution with a mean of zero and combined standard deviation of $s_{1,2}$. A z-score can be calculated for any value of $(x_1 - x_2)$ in order to determine the likelihood that this value is significantly different from $m_{1\text{-}2}$ at any desired level of probability:

$$z = \frac{(x_1 - x_2) - m_{1\text{-}2}}{s_{1,2}}$$

If a *z*-score of 1.96 is used and there is no real change in *x* (i.e. the difference between their means is zero) then on 95% of occasions these differences would fall within the mean ± $1.96s_{1,2}$ range with 2.5% of results less than the mean - $1.96s_{1,2}$ and 2.5% greater than the mean + $1.96s_{1,2}$. However, since we only wish to detect a fall in HbA1c only the negative side of the curve is used and we instead adopt a *z*-score of 1.65 so that the mean ± $1.65s_{1,2}$ range includes 90% of results with 5% less than the mean - $1.65s_{1,2}$ (and 5% greater than the mean + $1.65s_{1,2}$) so that any value less than the mean - $1.65s_{1,2}$ would indicate a fall in HbA1c with at least 95% certainty.

Therefore substitute $(x_1 - x_2)$ = 8 mmol/mol, $m_{1\text{-}2} = 0$ and $z = 1.65$ and solve for $s_{1,2}$:

$$1.65 = \frac{8 - 0}{s_{1,2}}$$

$$s_{1,2} = \frac{8}{1.65} = 4.85 \text{ mmol/mol}$$

The combined variance for two results ($s_{1,2}$) which are added (or subtracted) is the sum of their individual variances:

$$s_{1,2}^2 = s_1^2 + s_2^2$$

Since the same assay was used to obtain two measurements from the same individual it follows that $s_1 = s_2$ and $s_{1,2}^2 = 2s^2$ where *s* is the total standard deviation of each measurement.

Taking square roots: $s_{1,2} = \sqrt{2} \times s = 1.414\,s$

Substituting $s_{1,2} = 4.85$ and solving for *s*:

$$4.85 = 1.414s$$

$$s = \frac{4.85}{1.414} = 3.43 \text{ mmol/mol}$$

This is the total standard deviation which is made up of intra-individual biological and analytical components:

$$s_{\text{Total}}^2 = s_{\text{Analytical}}^2 + s_{\text{Biological}}^2$$

Substituting s_{Total} = 3.43 mmol/mol and $s_{\text{Biological}}^2$ = 0.1 mmol/mol then solving for $s_{\text{Analytical}}$:

$$3.43^2 = s_{\text{Analytical}}^2 + 0.1$$

$$s_{\text{Analytical}}^2 = 3.43^2 - 0.1 = 11.76 - 0.1 = 11.65$$

$$s_{\text{Analytical}} = \sqrt{11.65} = \mathbf{3.4\ mmol/mol} \quad \text{(2 sig figs)}$$

N.B. The biological variation is small compared to the analytical variation and makes little difference to the overall variation.

Question 133

A 14-year old boy was admitted in an intoxicated state having been suspected to have consumed an unknown quantity of methylated spirit (a mixture of ethanol and methanol). He weighed 55 Kg. The following laboratory results were obtained on a blood sample taken within 15 minutes of admission:

Urea	3.7	mmol/L
Sodium	136	mmol/L
Potassium	4.2	mmol/L
Glucose	3.2	mmol/L
Osmolality	342	mmol/Kg
Ethanol	190	mg/dL

Estimate his serum methanol concentration in mg/dL and the volume of methanol he consumed (volume of distribution 0.6 L/Kg, density 0.791 g/mL), stating any assumptions you make or limitations of this approach.

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