Deacon's Challenge

No 162 - Answer

Current guidelines indicate that a patient with Familial Hypercholesterolaemia who fails to achieve a 50% reduction in LDL-cholesterol concentration compared to the pre-treatment value should be referred for specialist management. In your laboratory, LDL-cholesterol is calculated using the Friedewald equation and the results of total cholesterol, triglycerides and HDL-cholesterol.

A patient has a pre-treatment LDL-cholesterol of 12.2 mmol/L. Calculate the value following treatment that would allow you to confirm a 50% fall in the true value with greater than 95% probability.

Current IQC performance shows CVs of: total cholesterol 2.9% at 7.0 mmol/L, HDL cholesterol 2.7% at 1.5 mmol/L, and triglycerides 2.5% at 1.6 mmol/L.

Table of z-distribution:

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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First calculate the SD for LDL measurement using the individual SDs for total chol, HDL-Chol and TG. As only CVs are given these are first converted to SDs at the concentrations in the QC samples assuming that the SD will be the same at the concentrations in the patient's second sample.

$$\text{SD (mmol/L)} = \frac{\text{CV (\%) x Concentration (mmol/L)}}{100}$$

For total chol, $SD = \frac{2.9 \times 7.0}{100} = 0.203$ mmol/L

For HDL-Chol, $SD = \frac{2.7 \times 1.5}{100} = 0.0405$ mmol/L

For TG, $SD = \frac{2.5 \times 1.6}{100} = 0.040$ mmol/L

The Friedewald equation is $\text{LDL-Chol} = \text{Total-Chol} - \text{HDL-Chol} - \frac{TG}{2.2}$

$$SD_{LDL\text{-}Chol} = \sqrt{\{SD_{Total\text{-}Chol}^2 + SD_{HDL\text{-}Chol}^2 + (SD_{TG}/2.2)^2\}}$$
$$= \sqrt{\{0.203^2 + 0.0405^2 + (0.040/2.2)^2\}}$$
$$= \sqrt{(0.041209 + 0.001640 + 0.000331)}$$
$$= \sqrt{0.04318}$$
$$= 0.208 \text{ mmol/L (to 3 sig figs)}$$

Both the initial and post-treatment measurements are subject to analytical error. However, the guidelines say that the post-treatment value should be half of the pre-treatment value – not the "true" pre-treatment value. Therefore analytical variation in the pre-treatment result can be ignored. The expected LDL-Chol value, if it is reduced by exactly 50% will be 12.2/2 = 6.1 with an SD of 0.208. We need to find a decision level, which, taking analytical variation into account, will be lower than 6.1 mmol/L 95% of the time i.e. greater than 6.1 mmol/L 5% of the time. The difference between 6.1 and this cut off point will be normally distributed. A *z*-value can be defined with the appropriate probability value:

$$z = \frac{(6.1 - \text{Cut-off})}{SD}$$

z = 1.65 (90% value) since we are only interested in a decrease in LDL-Chol (95% of results will be less than the cut-off).

Substituting these values:

$$1.65 = \frac{6.1 - \text{Cut-off}}{0.208}$$

$$1.65 \times 0.208 = 0.343 = 6.1 - \text{Cut-off}$$

$$\text{Cut-off} = 6.1 - 0.343 = \mathbf{5.8\ mmol/L} \text{ (to 2 sig figs)}$$

Notes:

1. If analytical variation of the pre-treatment value is to be considered then the above calculations would be performed using the ratio of pre- to post-treatment result (assuming the same SD at both concentrations) so that the ratio becomes 2.125 instead of 2 yielding a decision level of 5.7 mmol/L.
2. Intra-individual biological variation should also be considered.
3. Depending upon exactly how data was used to develop the guidelines it is possible that analytical (and biological) variation has already been taken into account and the above calculations may be unnecessary.

Question 163

Calculate the loading dose of intravenous aminophylline required to achieve a plasma theophylline concentration of 15 mg/L in a 65 kg man, given that the volume of distribution of theophylline is 0.5 L/kg and that aminophylline is 80% w/w theophylline. What infusion rate would be required to maintain this concentration if the half-life is 8 hours?

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