Increased Risk of Cardiovascular Disease with Erythropoietin in Chronic Dialysis Patients

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Dear Sir,

The paper of Iseki et al. [1] purports to show that the death rate from stroke and acute myocardial infarction following the introduction of erythropoietin in April 1990 was statistically significantly higher than that before.

There are two major problems with this study. Firstly, the calculation of statistical significance is incorrect. Secondly, the study design does not allow for causal attribution of a difference even if it were statistically significant.

In comparing stroke rates, the authors state that in the two years (April 1988 to March 1990) the number of deaths of 25, with 1,279 patient-years of observation, is significantly lower than in the three years after the introduction of erythropoietin (61 deaths in 4,106 patient-years). The rate ratio (which is more sensible to use in these circumstances than the odds ratio) is 1.295.

Although this figure is higher than the odds ratio shown by the authors, it is by no means statistically significantly different from 1. The p value using Poisson methods is 0.28; the 95% confidence interval is from 0.81 to 2.1,

For acute myocardial infarction, the rate ratio is 2.12 ($p = 0.24$), with 95% confidence intervals of 0.6-7.5. The p values given by the authors of $p < 0.01$ in each instance are not correct.

Adjustment for age (which needs the original data) is likely to make the p values even less significant.

The individual rates of 11.5 and 14.9 have confidence intervals of 7.4-16.9 and 11.4-19.1, respectively. These overlap the estimated values in the other groups which also show that the difference between them is far from statistically significant.

The statistical methods used by the authors (Mantel-Haenszel) are in this instance incorrect, and it is not clear what they have done to obtain the quoted odds ratios. It seems likely that they have used the number of people who were alive in the two periods before and after erythropoietin.

This is incorrect because many people are double-counted since they were alive at some point in both of the two periods. It seems likely that the analyses in each time period were then stratified by age group.

Although many incorrect methods of analysis do not change the scientific interpretation, this error does have important consequences. Although the data are compatible with a rise in death rates after the introduction of erythropoietin, they provide at strongest only very weak evidence of such a rise and are definitely compatible with chance fluctuations in the rates.

The conclusion that 'this study provides epidemiological evidence that the risk of cardiovascular disease might be aggravated by the addition of erythropoietin' is not justified. The authors note that a retrospective study must be treated with caution.

Any change in the use of erythropoietin based on this paper alone would be severely mistaken. Wrong statistical analysis could damage patients' health.

Reference

Iseki K, Nishime K, Uehara H, Tokuyama K, Toma S, Yoshihara K, Kowatari T, Terukina S, Osawa A, Fukiyama K: Increased risk of cardiovascular disease with erythropoietin in chronic dialysis patients. *Nephron* 1996;72: 30-36.

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