

## CORRESPONDENCE

Anesthesiology

1998; 88:833

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### A Technique for Population Pharmacodynamic Analysis of Concentration-Binary Response Data\*

*To the Editor:*—I read with interest the article by Bailey and Gregg on population pharmacodynamic analysis.<sup>1</sup> They have presented a technique to analyze binary response data obtained from multiple patients with one data point per patient to distinguish between intra- and interpatient variability. However, an analysis of the mathematical basis on which the authors based their technique has revealed a fundamental flaw, which in my opinion invalidates the conclusions of their paper.

Basically, the parameters defining the intra- and interpatient variability are not both identifiable. To clarify this, let the concentration threshold above which there is a response to a certain stimulus be lognormally distributed so that

$$\ln C_{\text{threshold}} = \ln C50 + \epsilon \quad (1)$$

where  $C50$  is the median value for one patient and  $\epsilon$  has a normal distribution with mean zero and variance  $\alpha^2$ . To account for interpatient variability, assume that the  $C50$  is also lognormally distributed so that

$$\ln C_{\text{threshold}} = \ln \langle C50 \rangle + \epsilon + \delta \quad (2)$$

where  $\langle C50 \rangle$  is the median  $C50$  of the population and  $\delta$  has a normal distribution with median zero and variance  $\omega^2$ . Now the probability of a response can be shown to be equal to

$$P(\text{response}) = P\{C \geq C_{\text{threshold}}\} = \Phi \left[ \frac{\ln C - \ln \langle C50 \rangle}{\sqrt{\alpha^2 + \omega^2}} \right] \quad (3)$$

where  $\Phi$  denotes the cumulative standardized normal distribution.

\*Dr. Olofsen's letter demonstrates that the peer review process does not end at the moment of acceptance or publication, but continues long after. Dr. Bailey's response is a wonderful example of intellectual honesty and integrity. I thank them both. —MMT

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*In Reply:*—We agree that Mr. Olofsen has identified a fundamental flaw in the mathematical basis of our technique for analyzing binary data. We are surprised that our simulations did not reveal this flaw and can only conclude that we found local maxima to the log likelihood. We regret presenting a technique that did not have a sound mathematical basis. Although we agree with Olofsen that the technique we describe is invalid, we do not agree that all of the conclusions of this paper are invalid. We still contend that the measure of the steepness of the concentration-response curve,  $\gamma$ , frequently is underestimated because of the inability to distinguish intra- and interpatient variability. We believe our manuscript does identify the potential errors associated with naive pooled data analysis of binary response data, a problem that has not been explicitly identified in the literature and that is well illustrated by figures 1 and 4. We are hopeful that the technique presented by Sheiner<sup>1</sup> will be a means of

Notice that this equation is equivalent with eq.(A-5) in reference 1 when  $\alpha = 1/\gamma$  is substituted. The parameters  $\alpha$  and  $\omega$  are not both identifiable because there is an infinite number of combinations of values of  $\alpha$  and  $\omega$  for which  $\sqrt{\alpha^2 + \omega^2}$  has the same value. Only the total variance ( $\alpha^2 + \omega^2$ ) can be estimated.

The problem of the unidentifiable parameters originates from the fact that both  $\epsilon$  and  $\delta$  are assumed to be normally distributed, but this is a natural assumption. For other distributions, the parameters may be theoretically identifiable, but they probably will be poorly estimable. Moreover, the data analysis should not be critically dependent as to the assumptions on the distributions because their forms are unknown. Therefore, it appears to be imperative to acquire multiple measurements per patient to obtain information about the nature of the intrapatient variability.

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### Reference

1. Bailey JM, Gregg KM: A technique for population pharmacodynamic analysis of concentration—binary response data. *ANESTHESIOLOGY* 1997; 86:825-35

(Accepted for publication September 10, 1997.)

distinguishing the two sources of variability, but this must be confirmed by further study. However, given the flaws of our technique, we believe that our paper should be withdrawn.

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1. Sheiner LB: A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. *Clin Pharmacol Ther* 1994; 56:309-22

(Accepted for publication September 10, 1997.)