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Letters to the Editor

I Comment on the paper: A three-dimensional model to analyze drug-drug interactions. Prichard, M.N. and Shipman, C., Jr. (1990) Antiviral Res. 14, 181–206.

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Response surface modeling is a useful approach to analyzing effects of combined biologically active agents. The modeling procedure may be performed by fitting mathematical functions of the complete surface to experimental data (Gennings et al., 1990), using a piecewise fitting procedure with spline functions (Sühnel, 1990) or by simply connecting the data points with straight lines (Prichard and Shipman Jr., 1990). All these procedures have advantages and disadvantages but, in most cases, they will lead to similar results. Researchers involved in combination experiments are thus encouraged to apply any of these procedures.

There are several attempts to use response surface modeling not only for the representation of the response surface, but also for the evaluation of possible interactions between the agents under study (Greco et al., 1990; Prichard and Shipman Jr., 1990; Sühnel, 1990; Sühnel, submitted). The classical isobole approach can be easily interrelated with the response surfaces, as the contour plots of these surfaces represent nothing more than the corresponding isobolograms. If isobolograms do not display simple patterns, one would prefer to use approaches which directly indicate regions of synergism or antagonism in the dose range under study. To this end, so-called interaction functions and difference response surfaces were proposed (Baumgart et al., 1991; Sühnel, submitted). The latter approach is identical to the method suggested by Prichard and Shipman Jr. (1990) except for the definition of the case of no interaction.

Obviously, the results of any of these methods, and, of course, also of methods based on one-dimensional or two-dimensional analyses, depend critically on a definition of the case of no interaction. Unfortunately, there is so

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far no consensus concerning this point. Anybody involved in the evaluation of combination experiments should be aware of this fact. The two recent papers on the evaluation of interactions in this journal represent an additional example of this unfortunate situation (Sühnel, 1990; Prichard and Shipman Jr., 1990).

In our paper an attempt was made to take a step towards standardization following the lines of thought initiated by Berenbaum (1989), and references cited therein (Sühnel, 1990). According to this view the evaluation of any interaction should be performed independently of mechanistic information. This can be done by means of the isobole approach. Within this framework linear isoboles (provided the dose scale is linear) are the only and general criterion for the case of no interaction irrespective of the shapes of dose-response curves. If one is interested in relations between the combination effect and doses or effects of single agents, different dose-response relations of single agents lead to different expressions (Berenbaum, 1989; Sühnel, submitted). Following this reasoning the mathematical relations used by Prichard and Shipman Jr. (1990) are only correct for linear (SS eqn. 6) and exponential (DS eqn. 7) dose-response relations.

On the other hand, Prichard and Shipman Jr. claim in their paper that the SS and DS equations are generally correct for the case of no interaction, irrespective of the shapes of dose-response relation of single agents, even if they lead to non-linear isoboles.

It is beyond the scope of this short comment to compare the two approaches in more detail. The basic arguments can be found in the paper by Berenbaum (1989) and in our paper (Sühnel, 1990). Rather, the objective has been to point out the differences as clearly as possible and thus to avoid confusion. However, it should be noted that the claim of Prichard and Shipman Jr. on page 190 of their paper that 'Although isobolograms which predict additivity are typically not linear using the SS and DS assumptions they are nonetheless mathematically and theoretically valid' is not supported by any proof.

Finally, it should be noted that the approach by Greco et al. (1990) assumes a constant interaction over the whole dose range under study, which violates one of the basic tenets of the theory of interaction of biologically active agents.

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