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Letters to the Editor

Comments on the isobole method for analysis of drug interactions

I am compelled to comment on the unfortunate juxtaposition of Tallarida's (1992) short review on analysis of drug interactions, which I commended in an accompanying editorial, with research reports in the same issue of *PAIN* by Miaskowski et al. (1992) and Plummer et al. (1992) claiming synergistic drug interactions. I suggested in my accompanying editorial that the isobolographic analysis described in Tallarida's review establishes for the journal a 'gold standard' for drug interactions. I characterize the printing of the two research reports in the same issue with Tallarida's review as unfortunate out of concern that the casual reader might assume, *incorrectly*, that the coincident printing constitutes an endorsement by the journal of the methods of analysis of drug interactions described in the two research reports.

Neither of the two research reports employs an isobolographic analysis and thus both fall short of this standard. Why should investigators of drug interactions adopt the isobole method as the standard? Are other approaches for analyzing drug interactions, such as described by Miaskowski et al. (1992) and Plummer et al. (1992), equally valid?

Concerns about analyzing interactions between biologically active substances have a long history. The most recent, comprehensive review to consider the problem is that by Berenbaum (1989), whom both Miaskowski et al. (1992) and Plummer et al. (1992) cite in their reports. Berenbaum (1989) discusses eight commonly used approaches for analysis of drug interactions, indicating that they are of varied status and that their coexistence has given rise to the inaccurate belief that all of the methods are equally valid. It is only the isobole method of analysis, however, which is a mechanism-free model, requires no assumptions about shapes of the agents' dose-response curves, and, *most importantly*, has been proven (mathematically) valid.

Thus, the isobole method is the 'gold standard' because it is the only model of analysis proven valid. Further, as emphasized by Tallarida (1992) in his review and by me in my editorial, this approach employs unbiased, objective, mathematical definitions of superadditivity (synergy), additivity (zero interaction) and subadditivity (antagonism). Approaches based on analyses of variance (i.e., the 'summation' model) as used by Miaskowski et al. (1992) and Plummer et al. (1992), according to Berenbaum (1989), suffer in that "... linearity of response is a basic assumption of this approach, in which interaction is *defined* (Berenbaum's emphasis) as departure from summation of effects". This 'definition' is inadequate and lacks the mathematical rigor required for unambiguous characterization of a drug interaction as superadditive.

Why does it matter whether Miaskowski et al. (1992) and Plummer et al. (1992) (or any authors) use the isobole method to analyze drug interactions they study? As I emphasized in my editorial, and as Miaskowski et al. (1992) and Plummer et al. (1992) suggest, appropriate drug combinations can be fruitfully employed clinically to achieve efficacious pain relief while minimizing undesirable side effects. If plans for clinical trials are based on results from non-human experimental studies which employed analyses that utilized faulty premises, there will be only harm to all. Thus, for reasons summarized here and reviewed by Berenbaum (1989), the isobole method is the gold

standard which investigators should adopt for analysis of drug interactions.

References

- Berenbaum, M.C., What is synergy?, *Pharmacol. Rev.*, 41 (1989) 93–141.
- Miaskowski, C., Sutters, K.A., Taiwa, Y. and Levine, J., Antinociceptive and motor effects of delta/mu and kappa/mu combinations of intrathecal opioid agonists, *Pain*, 49 (1992) 137–144.
- Plummer, J.L., Cmielewski, P.L., Gourlay, G.K., Owen, H. and Cousins, M.J., Antinociceptive and motor effects of intrathecal morphine combined with intrathecal clonidine, noradrenaline, carbachol and midazolam in rats, *Pain*, 49 (1992) 145–152.
- Tallarida, R., Statistical analysis of drug combinations for synergy, *Pain*, 49 (1992) 93–97.

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A further comment on testing for drug synergism

In a recent article (*PAIN*, 49 (1992) 137–144) Miaskowski et al. apply a 2-factor repeated-measures analysis of variance (ANOVA) to determine whether two drugs, used in combination, result in synergism. ANOVA is a standard statistical procedure that is well described in many standard textbooks on statistics such as those cited by these authors, as well as in my own book (*Manual of Pharmacologic Calculation*, Springer Verlag, 1987). However, they have failed to show its application to the problem at hand, namely, the demonstration that the two drug dosages are more (or less) than additive. The concept of additivity is well defined and the definition, which I quote and discuss in my review in that same issue of *PAIN* (49 (1992) 93–97), is quite simple, even though its demonstration requires statistical testing, also described in my review.

It is not clear why Miaskowski et al. use this well-known statistical procedure without first mathematically demonstrating its application. Surely they must know that mathematical results require mathematical proof, but they provide no proof. In fact, in their Methods section they present graphs to illustrate their application of ANOVA, and these graphs which they provide actually argue against their claim. Specifically, they show as an example of an additive interaction the parallel shift in drug A's dose-effect curve produced by a fixed dose of a second drug B. They build their illustration around the erroneous idea that this parallelism means simple additivity. This is simply not true! It is quite easy to show that a parallel shift (to the left), if sufficiently large, is superadditive. Moreover, a non-parallel