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Interaction of Morphine and Clonidine on Gastrointestinal Transit in Mice

Drs. Puig, Pol, and Warner[1] studied the interactive effect of morphine and clonidine on gastrointestinal transit. They determined the ED_{20} to ED_{80} of each drug separately and of mixtures of the two in three proportions: 1:1 (equal fractions of the ED_{50} of each), 1:0.33, and 1:3. They concluded that, with the 1:3 and 1:1 mixtures, the interaction between morphine and clonidine was synergistic at 20% and 50% inhibition but antagonistic at 60% and 80% inhibition. We congratulate the authors on the comprehensiveness of their experimental work, but we are disconcerted by the number of inconsistencies between the tables and figures - and even within a table.

In their figures 2 and 3, the SEMs on the ED_{20}, ED_{50}, and ED_{80} values for morphine and clonidine on their own are mostly much smaller than those given in their table 1, whereas the SEMs for the mixtures are sometimes smaller or sometimes larger than those in their table 2.

Table 2 also showed an internal anomaly: with the "1:1" mixture, the ratios of doses, morphine:clonidine, are fairly close to the 16:1 of the ED_{50} values of table 1. However, for the 1:3 mixture, the ratios should be approximately (16/3): = 5.3:1, whereas in the table, they range from 3.7:1 to 0.9:1. Similarly, for the 1:0.33 mixture, the ratios should be approximately (16/0.33):1 = 48:1; in fact they are all about 240:1.

In the graph for ED_{60} (their fig. 3), the coordinates of the "(1:1)" interaction point appear to be the ED_{60} values for morphine and clonidine individually, obtained by interpolation in their table 1. Correspondingly, the doses of morphine and clonidine at the ends of the ED_{60} isobole line appear to be derived, not by interpolation for each drug in table 1, but from the "1:1" mixture line in figure 1 (and the 16:1 ratio of actual doses from table 1). In other words, the authors appear to have swapped the two items of data.

When the graph for ED_{60} (their fig. 3) is correctly plotted, it shows a probably nonsignificant synergism. Also, in the graph for ED_{80} (their fig. 3), if the SEM for the clonidine in the 1:3 mixture is as large as given in their table 2 (0.35 mg/kg), the error bar will overlap the isobole line. Thus, even on their own, lenient criterion ("points were considered to differ significantly from additivity if their SEMs did not overlap [the isobole line]"), the authors do not appear to have demonstrated antagonism by the isobologram method.

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Reference

1. Puig MM, Pol O, Warner W: Interaction of morphine and clonidine on gastrointestinal transit in mice. ANESTHESIOLOGY 1996; 85:1403-12

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In Reply: — We appreciate Drs Asai and Mapleson remarks because they point out two inaccuracies in our paper that we sincerely regret: (1) a typing fault in the footnote of table 1, which instead of "SEM" should say "SD," and (2) an error in figure 3 *(upper panel)*, on the actual values that define the ED_{60}'s of the individual agents. The ED_{60} isobole was included to demonstrate that, at this level of effect, the 1:1 combination is antagonistic; this fact remains unaltered after correcting the data; the new isobole is included (fig. 1). Thus, the errors kindly pointed out by Drs. Asai and Mapleson do not alter the content nor the meaning of the published results.

However, we disagree with the calculation of the "dose ratios" and the "interpolation" of data performed by Drs. Asai and Mapleson. We could not find an "internal anomaly" in table 2 because values given in the table were experimentally obtained (observed data) and not predetermined. In these experiments, values cannot be calculated by a simple ratio or proportion (or "interpolated") as estimated by Drs Asai and Mapleson. When analyzing interactions, only actual doses of the individual agents that (when combined) produce a given level of effect are used. Similarly, we are not sure of what Drs. Asai and Mapleson mean by "interpolation," but in our study, responses at the different levels of effect (20%, 50%, 60%, 80%) were calculated by linear regression analysis of the dose-response relations after the equation:

$$\% \text{ response} = \text{slope} \times \log(\text{dose}) + \text{Y-intercept}.$$

Regarding the SEM of the MS:CL mixtures that are represented in

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