Interaction of Morphine and Clonidine on Gastrointestinal Transit in Mice

Drs. Puig, Pol, and Warner studied the interactive effect of morphine and clonidine on gastrointestinal transit. They determined the ED$_{90}$ to ED$_{90}$ of each drug separately and of mixtures of the two in three proportions: 1:1 (equal fractions of the ED$_{90}$ of each), 1:0.5:3, 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$_{90}$, ED$_{90}$, and ED$_{0}$ 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$_{90}$ 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 1:0.5:3 mixture, the ratios should be approximately (16/0.5) 1 = 48:1, in fact they are all about 2:1.

In the graph for ED$_{50}$ (their fig. 3), the coordinates of the "(1:1)" interaction point appear to be the ED$_{90}$ 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$_{90}$ 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$_{90}$ (their fig. 3) is correctly plotted, it shows a probably nonsignificant synergism. Also, in the graph for ED$_{50}$ (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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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$_{90}$s of the individual agents. The ED$_{90}$ 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
Visual Disturbance and Residual Paralysis

To the Editor:—It is with more than passing interest that I read the article on residual paralysis in volunteers by Kopman et al.¹ and the accompanied editorial by Brull.² The major significant finding was that visual changes (and subjective symptoms) persisted long after recovery of other functions. The authors are to be congratulated for observing and reporting this obviously common, yet always overlooked, phenomenon. As noted by Kopman et al., we performed a similar study examining the correlation between respiratory function and electromyography in volunteers during atracurium infusion.³ Our primary objective was to examine respiratory function and other clinical tests (hand-grip, head-lift, and so on) but not visual symptoms; therefore, we did not record them systematically nor did we report them. As one of the participants in the study, I remember I had to delay going home because I continued to have diplopia 60 min after the end of the study when all other musculoskeletal functions were normal. Moreover, I attempted to correct the diplopia by self-administering 2.5 mg of neostigmine and 1.2 mg of atropine intravenously, which produced severe abdominal pain, but no improvement in my diplopia. It was not until another 60 min had elapsed before I could drive home. As far as I know, the persistence of diplopia after reversal with anticholinesterase has neither been reported nor studied.

On a rhetorical note, why is the persistence of diplopia surprising? And is it important or necessary to have complete recovery of the eye functions before we discharge patients home?

We know that 3 mg of tubocurare (‘precursurization’ dose) would produce visual disturbance virtually in all patients, with preservation of respiratory and muscular functions in the majority of them. Is it surprising then that the visual disturbance persists after recovery of other muscle functions? The authors are correct in contending that train-of-four (TOF) during the onset of neuromuscular blockade cannot be equated to TOF during offset, but this does not detract from the previous observation because the visual symptoms occur not during the onset of muscular blockade but with a ‘nonparalyzing precursurization dose.’

As for the importance of visual symptoms, because we advise patients not to drive or otherwise engage in activities that require mental and intellectual capacity for 24 h and because the major complication of residual muscle paralysis is compromised respiratory function, why should we not be satisfied with complete recovery of respiratory function only? I would suggest that we warn the ambulatory patients about the persistent visual disturbances and not interpret this as ‘residual weakness.’

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the figures, the small magnitude of the bars (SEM) and the different scales used in ordinates and abscissae made graphic representation sometimes difficult: it is also possible that when drawing the isoboles, a few millimeters were misplaced. However, in table 3 we included the statistical evaluation of the results, which was obtained by comparing the doses that produced the expected effects (additivity) and the actual doses that produced the observed effects (experimental data). A P value < 0.05 was considered statistically significant.

We sincerely regret the errors, and appreciate the considerate comments of Drs Asai and Mapleson.

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