

Anesthesiology
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In Reply:—Dr. Sosis asks if our data might be consistent with a small degree of *retrograde* amnesia caused by midazolam. He comments that the mean pretreatment memory score was 3.4 of a possible 4 points on the memory scale as we defined it. First, each data point in figure 5 represents a *corrected* memory score; as stated in the section "Statistical Analyses," a covariance adjustment was applied to correct the post-treatment response for the pretreatment response. Second, if this imperfect recall of cards shown *prior* to drug administration were due to an effect of the drug, we would expect the effect to follow a similar pattern of dose-dependent inability to recall, as seen for those cards shown *after* drug administration. We found a clear dose-dependent diminution in memory score for cards shown *after* drug administration in all three drug treatment groups. These data confirm the well-described *anterograde* amnesic effect of midazolam and show that butorphanol also causes *anterograde* amnesia, albeit to a lesser degree. We found no dose-dependent effect on the memory scores for cards shown *before* drug administration in any of the three drug treatment groups, demonstrating that within the dose and time ranges we studied, neither butorphanol nor midazolam produces *retrograde* amnesia.

Dr. Kestin's criticism of our test for supraadditivity is valid in cases that resemble his example. However, if the effects for either single drug are about the same—and significantly less than the effect of the corresponding dose of the mixture—our test provides convincing evidence of supraadditivity. This is the case for the subject-rated somatic scales "not weak/very weak" and "not thinking clearly/thinking very clearly" and for the observer-rated measure "lid droop." For several other measures the effects (at the highest dose) of the two drugs differed, and supraadditivity cannot be established by this method. The more important message to be derived from these data is that the clinician should not *assume* that effects will be additive when these two drugs are combined.

The method we used for the determination of the presence of supraadditivity was essentially the same as the algebraic method described by Berenbaum,¹ which Dr. Kestin recommends in his letter. According to this method, if A_e and B_e are equieffective doses of drugs A and B, and A_c and B_c are doses of A and B that when used in combination cause the same magnitude of effect as A_e or B_e acting alone, then synergy occurs when

$$A_c/A_e + B_c/B_e < 1.$$

At the outset of our study, we had no information on the equieffective sedative doses of midazolam and butorphanol. Indeed, the determination of this information was one of the purposes of the study. For each dose group, the amount of midazolam and butorphanol in the

combination was exactly one half the amount of each drug when tested alone. Thus, for the measures referred to above, we may show supraadditivity of the combination by showing that the equieffective dose of the combination is less than $(\frac{1}{2}A_e + \frac{1}{2}B_e)$. This, however, is precisely what we have demonstrated by showing that the combination has a significantly larger effect than butorphanol or midazolam alone.

The t statistics referred to the t distribution with 24 degrees of freedom as indicated by the Satterthwaite approximation.² We considered isobolographic analysis but could not apply this method because only three doses were tested for each treatment, and this would not allow us to estimate the ED_{50} values with sufficient precision.

We think it was reasonable to focus our attention upon effects at the highest doses because supraadditivity is most easily detected where effects are large, and interactions at this dose level are most likely to be of clinical importance. The presence or absence of supraadditivity at lower dose levels would not fundamentally alter our conclusions.

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Pigtail Oximetry

To the Editor:—A variety of application sites for pulse oximeters has been described, including, most recently, the shaft of the penis.¹ Similar considerations apply to pulse oximetry in experimental anesthesiology, and such interest is likely to focus on the pig. As a consequence of animal protection legislation and public opinion, the experimental use of animals is currently shifting away from the classical models (cats, dogs, and primates) and toward food animals. In the United States, the dog is increasingly replaced by the pig;² in Europe, preferential

use of the pig model for experimental research was recently suggested by a working group of the *European Academy of Anaesthesiology*.³ The pig, however, does not readily lend its nose, "fingertips"—or penis—to sensor application. Based upon experience with greater than 200 pigs, we have found the tail to be a most appropriate monitoring site. Data (mean \pm standard deviation) were obtained from 64 consecutive experiments under defined conditions. Model: *Sus scrofa*, German landrace, 9 ± 1 weeks of age, body weight 25.9 ± 1.6 kg. Anesthesia: