CORRESPONDENCE

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The Evidence That a Serotonergic Mechanism Plays an Important Role in Cryogenic Brain Injury: Are the Results Conclusive?

To the Editor:—Recently Archer *et al.*[1] described the influence of cryogenic brain injury on the pharmacodynamics of pentobarbital and the evidence for a serotonergic-mediated reduction of pentobarbital requirement following cryogenic brain injury. Although the study was well-designed and -executed, we believe that the results are not conclusive and that caution should be exercised in the interpretation of the data.

Based on two series of experiments in rats, one pretreated with the antiserotonergic p-chlorophenylalanine (PCPA) and the other without, Archer *et al.* observed that 1) the brain pentobarbital concentration required to prevent response to tail clamp (EC_{50}) was significantly decreased by cryogenic injury and 2) pretreatment with PCPA prevented this decrease, thus providing "support for a functional role for 5-hydroxytryptamine in the influence of cold injury on the pharmacodynamics of pentobarbital." Based on the results, we agreed with the first conclusion, but for the second conclusion to be valid, two additional conditions must be fulfilled: 1) PCPA pretreatment alone does not alter the EC_{50} of pentobarbital, and 2) a significant difference in EC_{50} exists between the untreated injured group and the PCPA-pretreated injured group (reduced in the former and unchanged in the latter). As shown in figure 2 of Archer *et al.*'s study, the second condition is not met. Although the authors demonstrated that there was no statistically significant difference in pentobarbital EC_{50} between the injured and uninjured animals following PCPA pretreatment, they did not establish that PCPA alone did not decrease the EC_{50} of pentobarbital (although this appears to be the case). More importantly, there was no apparent difference in pentobarbital EC_{50} between the untreated injured animal and the PCPA-pretreated injured animal. Thus, despite lower 5-hydroxytryptamine levels in the PCPA-pretreated animals, the EC_{50} was not significantly altered. Reanalysis with ANOVA for all four groups followed by a multiple comparison procedure may be more revealing. In addition, because the absence of difference is not proof of equality, β error analysis would also strengthen the arguments.

We recently completed a study[2] on the influence of closed-head injury on minimum alveolar concentration (MAC) of halothane. Although initial results suggest that MAC was decreased by head trauma, a more detailed examination reveals that, unless the rats were very severely injured with a neurologic score equivalent to Glasgow Coma Scale score of 5 in humans, it was not significantly affected by the injury.

Although in both studies brain injury was inflicted, the results are different. Possible explanations of this difference include the following. 1) The different timing: we studied the MAC for the first 48 h after injury, whereas Archer *et al.*[1] studied it 3 days after the trauma. 2) The different nature of injury: different models—head trauma with weight drop device *versus* cryogenic injury—were used. 3) Different drugs—halothane *versus* pentobarbital—were used. These differences highlight the importance of model and type of injury in both pharmacodynamic studies.

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In Reply:—The design of our experiment[1] was to compare the effects of cold injury on EC_{50} for pentobarbital in untreated animals and in animals pretreated with PCPA to block serotonin biosynthesis. We were advised by our statistical consultant* that the most appropriate statistical test for this design was two-way ANOVA. This test evaluated the effect of the cryogenic lesion on EC_{50} in each of the groups and *also* evaluated the effect of PCPA treatment (insignificant, $F = 0.013$, $P = 0.91$).

In addition, this analysis confirmed a significant difference of the effect of the lesion on EC_{50} between the untreated and the PCPA-treated groups ($F = 4.56$, $P = 0.04$). This method obviates the necessity of doing a power analysis on the EC_{50} data for the PCPA-treated group. We believe that these results provide support for a functional role of serotonin in the influence of cold injury on the pharmacodynamics of pentobarbital. We do not claim that the results are conclusive.

With regard to differences between the results reported by Shapira *et al.*[2] and our report, we suggest that the evaluation of anesthesia depth was very different. In a MAC study, the end-point usually is the abolishing of *purposeful* movement. In our study, the end-point was the abolishing of any, including reflex, movement. Differences in EC_{50}

* Brandt R: Personal communication.

between the normal and injured animals may increase at deeper levels of anesthesia. In other words, MAC and EC_{50} probably represent very different end-points. We are not surprised with the results of Shapira *et al.* because cryogenic injury produced in a fashion similar to the present report did not alter MAC for halothane in rats.† We have repeated our experiments with pentobarbital and confirmed the 30% decrease in EC_{50}. The pharmacodynamics of fentanyl also appear to be altered in this model.‡

We agree wholeheartedly that clear definition of model and type of injury are of great importance in the evaluation of these experimental results.

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† Todd MM: Unpublished data.
‡ Unpublished data.

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I. Factors Affecting Distribution of Catheter-injected Local Anesthetic

To the Editor:—In a recent article, Rigler and Drasner[1] reported that when intrathecal microbore catheters are injected at "clinically relevant rates," the 28-G catheter produces the greatest maldistribution of drug. They believe this is a function of the flow rate. However, we do not see how the data in the article support this conclusion.

Rigler and Drasner[1] determined the clinically relevant injection rates for 20-G (macrobore) and 28-G (microbore) catheters. They found that "normal injection rates" (NIR) with macrobore catheters (NIR = 12 s/ml) are faster than with microbore catheters (NIR = 53 s/ml). This difference in injection rate relates to the difference in the radius of the two catheters (flow rate is proportional to radius^4).

After determining NIRs, Rigler and Drasner[1] performed experiments with injection rates other than the NIR. Using Rigler and Drasner's data (their table 1), we interpolated the peak lidocaine concentration that can be expected with NIR (fig. 1). This figure shows the predicted maximum lidocaine concentrations with NIR for catheters in the lateral and central position. Figure 1 also shows: 1) the 28-G catheter produces a *lower peak* concentration than the 20-G multiport catheter, and 2) the 28 gauge catheter causes a peak concentration *similar* to the 20-G endport catheter.

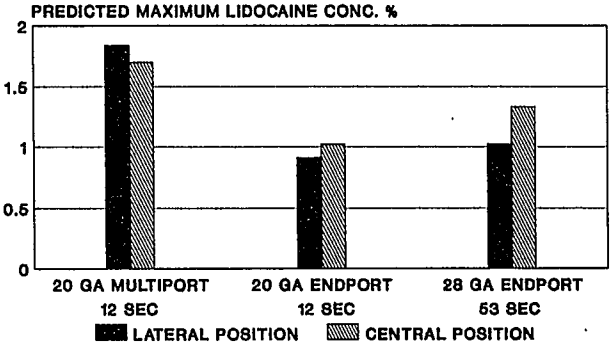

FIG. 1. Predicted maximum sacral lidocaine concentration (%) at "normal" injection rates for 20-G multiport, 20-G endport, and 28-G endport catheters. Data was extrapolated from Rigler *et al.*,[1], table 1, 50 mg 5% lidocaine with 7.5% glucose injected.

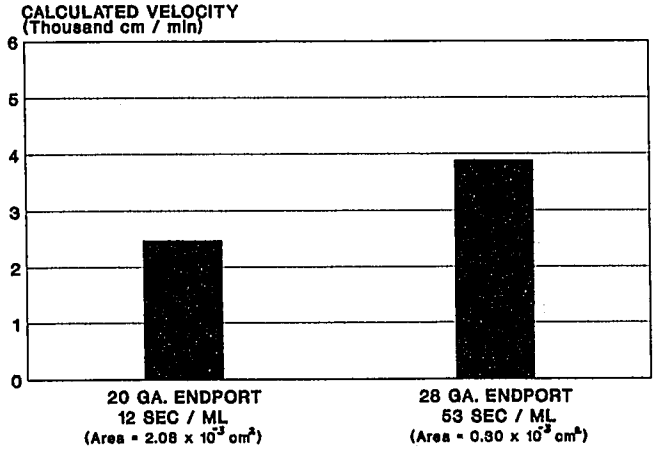

FIG. 2. Calculated velocity at "normal" injection rates for 20-G endport and 28-G endport catheters.

Figure 5 of the article by Rigler and Drasner shows the distribution profile of different catheters at various injection rates. *At NIRs,* the histograms illustrate that, while the multiport macrobore catheter distributes drug rostrally, the distribution with the 20-G endport and the 28-G catheter are *similar.* Neither catheter causes any appreciable amount of drug to flow rostrally. Furthermore, increasing the injection rate with the 28-G endport catheter to 30 s decreases lidocaine concentration levels.

Therefore, we do not agree with Rigler and Drasner's[1] conclusions 1) that microbore catheters produce the greatest maldistribution and 2) that distribution is primarily a function of flow rate. Rigler and Drasner[1] underestimate the importance of the microbore catheter's