Correspondence

Antagonism of Diazepam by Physostigmine

To the Editor: — I read with interest the article by Bidwai et al. 1 Although I commend the authors on their well-planned and well-executed study, I beg to differ regarding the purpose and the conclusions of their investigation.

Diazepam action is probably mediated through a facilitation of the GABA-ergic transmission 2 and through specific receptor sites in the brain. 3 Physostigmine, an inhibitor of acetylcholinesterase, acts through the cholinergic pathways, and if it antagonizes diazepam, it would probably be through a general arousal effect. This is not unexpected, since it has been found that the distribution of acetylcholinesterase neurons closely corresponds to the location of the reticular activating system. 4 The drug arouses subjects from normal sleep 5 and from stupor due to a variety of drugs and conditions. I suggest that the reversal of diazepam somnolence by physostigmine could have also been achieved by a wide variety of central nervous system stimulants, e.g., mephedrine, strychnine, and picROTOXIN. The practice of using analeptics to counteract intoxication from general depressants and to hasten recovery from general anesthesia has been discredited by an understanding of the supportive care needed for the unconscious patient.

As is true with all central nervous system stimulants, the actions of physostigmine are dose-dependent and produce marked variability in responses among subjects. In one study, physostigmine, 1.5 to 2 mg, intravenously, produced decreased speech, slurred thoughts, and mild sedation. 6 It also impaired memory. A similar dose given to volunteers after diazepam did not counteract the memory deficit produced by diazepam, and the subjects felt more sedated than before receiving the physostigmine. 7 However, physostigmine, 1 mg, given alone, enhanced the storage of information into long-term memory. 8 It is possible that the actions of the drug may vary with the subject’s baseline level of central cholinergic activity.

Finally, if one can avoid the use of a long-acting drug such as diazepam, whose average half-life is 31 hours, for an operation such as dilatation and curettage, the need to use a drug such as physostigmine is unlikely to occur.

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References


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In reply: — We would like to thank Dr. Ghoneim for his comments. We agree that the mechanisms by which physostigmine antagonizes the depressant actions of diazepam and other central nervous system depressants could be through a general arousal rather than through actions at specific receptor sites in the brain. It was neither possible nor was it the purpose of our study to define the mechanism by which physostigmine works, but simply to evaluate whether the drug is effective as an antagonist to CNS depression following diazepam–N O anesthesia. The object of our study was not to advocate diaze-
pam-N₂O anesthesia for dilatation and curettage operations nor the routine reversal of CNS depression following this or any other anesthetic technique. There are, however, some patients for whom diazepam-N₂O anesthesia does provide some advantages, and others who could benefit from rapid antagonism of postanesthetic somnolence. It is important to appreciate that in those patients, certain doses of physostigmine can effectively reverse diazepam-induced postanesthetic somnolence with a minimum of side effects.

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Is the Rate–Pressure Product a Misleading Guide?

To the Editor:—In the study of Sonntag et al., 1 poor correlation between myocardial oxygen consumption (mVO₂) and heart rate–blood pressure product index (RPP) was found during halothane anesthesia in man. This finding merits special attention, since RPP is recommended as a guide to the prevention of intraoperative myocardial ischemic injury.2 For the patient with coronary-artery disease, a proposed goal is not to exceed a RPP level of 12,000.∗

The RPP was introduced as an index of mVO₂ by Gerola and associates in 1957, on the basis of their experiments with hypoxemic dogs.3 Since then, this correlation was reported as valid for a number of conditions in animals and in man, including operations for coronary-artery bypass.4 However, Sonntag and associates have shown that RPP cannot always be an adequate index of mVO₂.

We would like to draw attention to the other side of this problem. In our opinion, it may be dangerous to make the seemingly logical step from RPP—index of mVO₂—to RPP—predictor of impending ischemia—since the components of this index—heart rate (HR) and blood pressure (BP)—have opposite effects on myocardial blood supply which, in balance with mVO₂, determine the severity of ischemia. When, for example, the BP is reduced and HR increases, it is possible to have a RPP below the suggested safe level during myocardial ischemia. Thus, a low RPP caused by low BP could lead to a false sense of security. The use of RPP as a guide for ischemia was motivated by the work of Robinson,5 who demonstrated that exercise of various types and severity induced pain in patients with angina pectoris at similar levels of RPP. But the author also stated the following, "... in the


![Graph](image)

Fig. 1. Effects of heart rate and blood pressure on electrocardiographic (ECG) ischemic changes in the myocardial area perfused by the constricted coronary artery.

In pentobarbital-anesthetized open-chest dogs, the left anterior descending coronary artery was constricted until the epicardial ECG, recorded from the myocardial zone supplied by the constricted artery, was just at the verge of normal. Various levels of mean arterial pressure (MAP) were provided by constricting the descending aorta. At each level of MAP, the heart rate was increased by pacing until profound ischemic S–T segment deviations in epicardial ECG appeared in the jeopardized area.

Notice that at low MAP, ischemic changes appeared at lower HR (and RPP) than at higher MAP. As a result, RPP did not correlate with ischemia.

experiments reported there were only small changes in arterial pressure; it might be expected that larger variations in arterial pressure would lead to changes in coronary flow and so cause alterations in the level of myocardial work required to provoke pain."