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Drugs, Memory, and Sedation

Specificity of Effects

THE history of drug research on memory is closely related to studies of anesthetics and research by anesthesiologists. This research focused almost exclusively on nitrous oxide until 1960.[1] In the 1960s, anesthesiologists became interested in the amnesic properties of drugs to be used as premedicants.[2,3] Thus the amnesic properties of the benzodiazepines and scopolamine were first recognized. Ghoneim, Mewaldt, and Hinrichs initiated studies in the 1970s that addressed theoretical questions and the mechanisms of actions of drugs on memory, and they were later joined by other research groups.[1]

Despite robust evidence that drugs such as the benzodiazepines, scopolamine, barbiturates, anesthetics, alcohol, and marijuana can impair memory, investigators have questioned whether these drugs affect memory directly or whether the observed amnesic effects may reflect impairments in attention, arousal, or mood rather than memory processes. Therefore, two questions need to be answered: How important are these concerns, and how can we dissociate the sedative and amnesic effects of these drugs?

Although it is important for practical reasons to quantify cognitive impairments, such as for the use of premedicants and anesthetics during surgery, or the use of drugs such as benzodiazepines during normal daily living, different agendas drive current research in cognitive psychopharmacology.[4] Drugs have been used as tools for modeling cognitive impairments in neuropsychiatric disorders. For example, the pattern of memory effects produced by scopolamine resembles that seen in Alzheimer's disease; similarly, the pattern of benzodiazepine-induced effects has been likened to that seen in Korsakoff's disease or postencephalitic amnesia.[5,6] Investigators have also used drugs to elucidate normal cognitive functioning mechanisms and to explore their neurobiologic substrates.[1,4] Again, one of the limitations to these pursuits is the issue of specificity of drug effects on memory systems and how to separate the amnesic effects from the other influences.

Investigators, studying primarily benzodiazepines and scopolamine, have used several methods to address the issue of specificity. One method is to use analysis of covariance to separate effects attributable to sedation. The main limitation of this statistical approach is that, as Curran[7] has noted, covariance assumes a linear relation between variate and covariate, and the relation between memory and sedation may be more complex than that. Another method, used with the benzodiazepines, is to try to reverse the sedative effects but not the amnesic effects. Use of small doses of flumazenil[8] or pretreatment with flumazenil before administration of the benzodiazepine[9] result in dissociation between sedation and memory impairment; *i.e.,* sedative effects of the benzodiazepines are alleviated without relief of a significant memory impairment.

Another method is to study two drugs that produce the same effects on sedation but different effects on memory. Thus Curran *et al.*[10] compared oxazepam and lorazepam in doses that produced similar levels of sedation but greater amnesic effects for lorazepam. Green *et al.*[11] compared chlorpromazine to lorazepam in doses that produced equal degrees of sedation but found that memory was impaired only by lorazepam. Because tests of sedation and memory may vary in difficulty, dissociations of this kind do not provide compelling evidence for independence between the two behaviors. One way to overcome this criticism is to show a double dissociation of sedative and amnesic effects; that is, drug X would produce impairment of sedation but not memory and drug Y would produce impairment of memory but not sedation. Unfortunately, no drug Y is currently available. Another method of demonstrating the specificity of the memory effects of benzodiazepines are studies in which participants receive repeated doses of these drugs, which results in disappearance of the sedative effects due to development of tolerance but persistence of memory impairments.[12]

The subject is complex for at least two reasons. First,

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memory and sedation can be measured in a variety of ways. Different tests of memory will lead to different conclusions about the degree of memory impairment produced by a particular drug. For example, one drug will impair performance on mental arithmetic and the Brown-Peterson tasks because of effects on short-term or working memory, whereas another drug does not. Another drug will impair priming tasks because of effects on implicit memory, whereas a fourth drug does not. A fifth and a sixth drug will impair the same tasks to different degrees. Similarly, different measures of sedation will yield different results, and there is no correlation between the various measures.[13] Second, there are differences across drugs, measures, and individual participants and their interactions. Thus separating memory and sedative effects of drugs will not be resolved with one or two studies. We will require converging evidence from multiple reliable sources to be convinced of the general pattern. Gradually we will be able to determine which measures are most effective, reliable, and cost-effective in separating memory effects from sedation.

This historical perspective and review of the issue of specificity of amnesic effects of drugs introduce us to the important contribution of Veselis *et al.* in this issue of ANESTHESIOLOGY.[14] With sophisticated statistical analysis, the authors demonstrate a dissociation between memory impairments and levels of sedation for some drugs. The authors varied the concentration of several drugs with different sedative properties, thereby manipulating (while repeatedly measuring) the subjective level of sedation. Much later, after the subjects have largely recovered from all effects of the drugs, they are tested on their memory for information presented during various levels of sedation. The authors then fit functions relating serum concentration for each drug to memory performance and level of sedation. (Actually, two different fitting functions are used for sedation, one assuming equivalent sedation for each drug [Emax] and one based on a fixed level of subjective sedation [LR]. Because it is difficult to determine whether individuals' reported level of sedation is attributable to differences in reactions to the drug or in use of the scales, it can be argued that the LR fit is preferred when between-group comparisons are made.) Setting criteria for memory impairment and sedation (Cp_{50}) then permits comparison of the probability that normalized serum concentrations will meet the two criteria. Their figure 4 shows that the tested drugs exhibit very different sedation and amnesia relations for the same criteria of felt sedation and memory impairment. For example, propofol at low serum concentrations shows a high likelihood of exceeding the criterion of memory impairment well before it meets the criterion of sedation; in contrast, fentanyl exceeds the sedation criteria and shows low probability of amnesia for the same concentration range. Because the comparisons use several statistical scaling procedures, normalization of concentration levels, and arbitrary standards of performance, it is not easy to communicate the results simply. However, the methods are robust and lend themselves to wide application so that further comparisons and replications will eventually make the procedures familiar.

Considering the complexity of the subject and the desirability of future replication of Veselis *et al.*'s methods with different assessment tools and drugs, some cautionary remarks about their study are needed. Some of the points just raised also apply to their study, such as task sensitivity and possible interactions across drugs and individual subjects. Further, the authors used only one method to assess sedation. Considering that several groups of investigators[15–17] have found that persons treated with benzodiazepines may be unable to estimate how sedated they are and usually underestimate it, other drugs may have different sedative effects, depending on the measure. Perhaps, the authors also should have used psychomotor tasks as evidence of "objective" sedation, such as a digit cancellation task assessing attention, a tapping task as an index of motor sedation, and so on. Nevertheless, Veselis *et al.* report an excellent study that adds another methodologic tool for investigating the complicated relations between memory and sedation. It is also gratifying to continue the tradition of contributions by anesthesiologists and the studies of sedative-hypnotics and anesthetics to drug research on memory and cognition.

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Methylnaltrexone

Reversing the Gastrointestinal Effects of Opioids

SOMETIMES the effects of opioids on the gastrointestinal tract are therapeutic, but more often they are problematic and undesirable. All of the commonly used opioid agonists, such as morphine, meperidine, and fentanyl, can produce spasm of gastrointestinal smooth muscle. This may cause various side effects, including constipation, biliary colic, and delayed gastric emptying. Constipation occurs when intestinal transit time is increased due to a loss of normal peristalsis and increased sphincter tone. It can be a particularly debilitating problem in patients who require chronic opioid treatment because very little tolerance develops to this stimulant effect. Increased biliary pressure occurs when the gall bladder contracts against a closed or narrowed sphincter of Oddi. Passage of gastric contents into the proximal duodenum is delayed because there is increased tone at the gastroduodenal junction. This last effect is particularly important for anesthesiologists because analgesic premedication may increase the risk of aspiration or delay the absorption of orally administered drugs. All of these effects may be reversed or prevented with naloxone, but this is usually undesirable because the analgesic effects also will be antagonized.

The article by Murphy *et al.* in this issue of ANESTHESIOLOGY[1] shows that selectively antagonizing the peripheral effects of morphine can prevent nearly all of the decrease in gastric emptying. The study design is simple and concise: Morphine is given to volunteers, either alone or with N-methyl naltrexone, a permanently charged competitive antagonist that cannot cross the blood–brain barrier. The rate of emptying is then measured with two validated techniques, bioimpedance and acetaminophen absorption. It should be clear that the existence of a peripheral opioid effect was never really in doubt because animal studies have long suggested that central nervous system and peripheral mechanisms

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