Epilepsy or Anesthesia with Ketamine

The implication that all anesthetics induce CNS depression\(^1\) confuses our thinking about the anesthetic state. Just comparing nitrous oxide and diethyl ether will demonstrate this. Diethyl ether induces four stages of “anesthesia.” Stage I is excitement; Stage II, delirium; Stage III, surgical anesthesia; Stage IV, medullary paralysis. In descriptions of the anesthetic effects of diethyl ether, it is usually implied that reference is being made specifically to Stage III, surgical anesthesia. However, descriptions of the anesthetic properties of nitrous oxide, which is not capable of inducing either Stage III or Stage IV at one atmosphere, refer to Stage II, delirium. It has been our experience\(^2\) that Stage II induced by nitrous oxide or diethyl ether is a state of hallucinosis and catalepsia, characterized in unrestrained subjects, by inappropriate behavior, bizarre fixed postures, accompanied by increased salivation, occasional emesis, mydriasis, and irregular respirations. Based on this behavior, the 2½-cps hypersynchronous epileptoid EEG activity, and the increase in reticular-formation neuronal activity, Stage I and Stage II anesthesia are characterized as stages of CNS excitation.\(^2\) Thus, “anesthesia” by nitrous oxide occurs during catalepsy and “anesthesia” by ether occurs during CNS depression.

The introduction of new anesthetic agents, namely gamma-hydroxybutyrate, phencyclidine (Sernylan), ketamine (Ketalar), and enflurane (Ethane) has made it even more necessary to re-evaluate the concepts of the various stages of anesthesia with respect to CNS physiology and clinical effects. In the United States both phencyclidine and gamma-hydroxybutyrate were tried as anesthetic agents and were rejected. In the course of studying these agents in comparison with halothane and barbiturates,\(^3\) it became clear that at least two distinct categories of agents were capable of immobilizing patients for operation. Agents of the first type, such as halothane, ultrashort-acting barbiturates, and diethyl ether at surgical levels, act by CNS depression (Stage III). Agents of the second type, such as nitrous oxide, phencyclidine, ketamine, enflurane, gamma-hydroxybutyrate, and trichloroethylene, act by a cataleptoid CNS excitation (Stage II). There is a tendency to assume that a reduction or lack of responsiveness is associated with depressed states only.\(^4,5\) The individual who is catatonic, hallucinatory, or convulsing has a reduction in responsiveness to stimuli and a loss of memory, but is in fact hyperexcited. Both types of agents used in anesthesia can induce a state of unresponsiveness and amnesia. Any agent or procedure, even asphyxiation, which meets these two criteria may find its way into use in anesthesia. Both excessively disorganized reticular-formation activity and reduced reticular-formation activity, as induced in Stages II and III, respectively, result in loss of the arousal response to stimuli and amnesia.\(^6,7\)

We have proposed the concept of a continuum of stages of CNS excitation and depression\(^5,8,9\) which incorporates this operational definition of anesthesia. Drugs which induce CNS excitation to Stage II have the curious ability to change direction and cause CNS depression (Stage III diethyl ether), to continue from Stage II to generalized convulsions (phencyclidine, enflurane, gamma-hydroxybutyrate), or to induce Stage II catalepsia only (nitrous oxide, ketamine, trichloroethylene). Differences among degrees of emergence delirium are related to differences in washout times. Nitrous oxide and trichloroethylene are
rapid, whereas ketamine is more prolonged; thus, ketamine has the longest emergence delirium.

If gamma-hydroxybutyrate, pheynylcylidine, and enflurane induce "anesthesia" prior to seizures, then why can't pentylethenetrazol (Metrazol) likewise induce "anesthesia" at subconvulsant doses? First, a convulsant dose of Metrazol will induce a grand mal seizure in less than 3 minutes, whereas a drug like gamma-hydroxybutyric acid takes three to four hours to induce a seizure; thus, the time courses of action are different. Second, subconvulsant doses of gamma-hydroxybutyric acid last four to eight hours, whereas a subconvulsant dose of Metrazol lasts 5–20 minutes; thus, the durations of action are different. Attempting to maintain an anesthetic level with Metrazol by perfusion might result in accumulation of the drug to seizure-inducing levels. Third, the difference between a subconvulsant anesthetic dose and a convulsant dose is less with Metrazol than with gamma-hydroxybutyrate; that is, the therapeutic index is lower with Metrazol. Therefore, in a given subject, it is impossible to be sure that the administered dose of Metrazol will, in fact, be subconvulsant. Aside from these differences, Metrazol probably could be used for short operations either by using a subconvulsant dose or by using a convulsant dose and performing the operation immediately after the seizure. During both of these states the subject is unresponsive and amnestic. In fact, Metrazol is a drug of abuse in Rome, presumably because of its ability to induce Stage I excitation and Stage II delirium (aura) at subconvulsant doses (personal communication, 1970). Some users may even enjoy the occasional induced seizure. If it's a kick they want, Metrazol can give it to them. While the thought of using subconvulsant doses of Metrazol may seem ridiculous to anesthesiologists, they are in fact utilizing other agents with similar properties with relatively little concern.

Cats receiving ketamine manifest gross behavior and EEG patterns similar to those produced during Stage I and Stage II anesthesia induced by diethyl ether. At the lowest effective doses the subjects are initially ataxic, then lie in bizarre positions but respond to noxious stimuli. Higher doses induce shorter periods of ataxia, followed by about an hour of cataleptic behavior with no responsiveness to noxious stimuli. During the bizarre postures and catalepsia, epileptoid low-frequency hypersynchronous EEG-wave patterns are present and reticular neuronal activity is increased and disorganized.

There is a tendency among clinicians to consider studies performed in animal models to be irrelevant to man. We have examined the effects of ketamine in animal species from rats and cats to the higher primates and man and do not find any justification for suggesting that the excitatory effects in the cat differ from those in man. We agree with Kayama and Iwama about two major aspects of ketamine's action. First, we agree regarding the effects of ketamine on the EEG, evoked potentials, and single-unit activity in the cat. Studies like these add significantly to the basic understanding of the excitatory actions of ketamine. Second, Kayama and Iwama state that ketamine does not produce EEG dissociation between the activity of the limbic system and the thalamus. We are in complete agreement. Ketamine produces excitatory activity in both the thalamus and the limbic system, sometimes manifested by bursts of seizure activity in the hippocampus and amygdala. Often these limbic seizures occur without clinical evidence of a seizure. Only when this activity spreads to the thalamus and cortex are generalized convulsions seen.

Ketamine, a derivative of phenylcylidine, is claimed to have fewer psychiatric side-effects than phencyclidine. However, based on the other reports, there seems to be little difference between ketamine and phencyclidine except that ketamine produces a shorter duration of catalepsy and has less potency for inducing grand mal seizures. The introduction of ketamine initially in pediraphic and geriatric anesthesia made it difficult to evaluate postoperative psychiatric symptoms. Pediatric patients capable of describing their experiences do report an increased incidence of dreaming. The question of whether these are good dreams or bad dreams or, in fact, hallucinations, has been very difficult to evaluate on the basis of these reports and the ages of the
subjects. Clearly, the use of ketamine in human volunteers indicates that the emergence experience is hallucinatory and is extremely distressing to some individuals.

The question of whether ketamine is a CNS excitant or depressant is extremely important, since ketamine has been used for pediatric diagnostic procedures involving neurologic problems. It has been our experience and the experience of Kayama and Iwama that ketamine produces CNS excitation and EEG changes similar to those of epilepsy. The significance of these findings is, first, that the agent induces an epileptiform EEG which may be misinterpreted, and the patient may be incorrectly diagnosed as an epileptic. Second, faced with the emergency treatment of a patient who is convulsing, the physician might administer ketamine believing that it acts by CNS depression, when in fact this agent induces CNS excitation which could push the patient into status epilepticus.

The induction of CNS excitation, especially in the young developing nervous system, has not been systematically evaluated. A critical question is the relationship between the drug-induced electrical seizure activity and the development of brain damage. We have no clear-cut answers to this in man. A study we have in progress, however, indicates that mature rats receiving daily subcataleptic and cataleptic doses of ketamine for 1, 2, or 3 months developed spontaneous epileptiform brain-wave patterns. This should be kept in mind when this agent is given repeatedly to young subjects for long periods, for example, in the treatment of extensive burns.

Another point worth noting is that the Stage II, delusional-type, action of ketamine is like that of LSD, mescaline, and phencyclidine (known on the streets as “PCP”, “peace,” “angel’s dust” or “hooch”)—all major drugs of abuse. When used in less than cataleptic doses, phencyclidine is a potent hallucinogen. With the increased medical and veterinary use of ketamine, it will probably become a popular hallucinogenic street drug, as recently reported by Reier. It is vital that those using this agent be aware of its potential hazards, both from the medicolegal standpoint and with regard to the patient and the community. It is worth keeping in mind when using this agent in children that the action of ketamine, i.e., cataleptic anesthesia, is not unlike the action of notorious street drugs. If this analogy becomes widely known, many parents may object to the elective use of this agent for their children or themselves for routine procedures.

I do not imply that ketamine does not have clinical usefulness. The purpose of these critical comments is to emphasize the necessity for those who use agents such as ketamine to be aware of the mechanism of their action so they can use them more skillfully and wisely. Obviously, the anesthesiologist must evaluate indications critically in deciding which patients will benefit from the use of such drugs. By the same token, it is his responsibility to weigh the consequences of their use.

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References
6. Winters WD, Spooner CE: A neurophysiological comparison of gamma hydroxybu-
CAVAL THROMBOSIS AND CONGENITAL HEART DISEASE  This article reports the cases of seven children with cyanotic congenital heart disease who developed thrombosis of the inferior vena cava. Unilateral lower-extremity edema occurred in five, with the edema being bilateral in three. Hematuria was present in three of the patients. All had undergone cardiac catheterization and had received radiopaque contrast material in amounts greater than 1 ml/kg body weight. Results of coagulation studies done prior to catheterization were normal. The diagnosis of inferior vena cava thrombosis was confirmed by subsequent catheterization, angiography, surgery, or autopsy. Three patients died, two as a result of extension of the thrombosis to involve both the renal and adrenal veins. Common factors related to the development of thrombosis of the inferior vena cava included cardiac catheterization and an indwelling venous catheter. Polyethylene catheters were placed in the deep veins draining into the inferior vena cava in five of the seven patients for periods exceeding 24 hours. The authors note that polyethylene is a thrombogenic material, more so than other prosthetic materials. Hypercoagulability and hyperviscosity associated with polycythemia probably abet the high incidence of thrombosis. Contrast material injected during catheterization may precipitate intravascular clotting secondary to the diuresis it initiates, with attendant hemocoagulation and sludging in the peripheral venous system. Surgery was performed in all the patients described, and blood loss, hypotension, or hypoxemia during anesthesia may increase the propensity to thrombosis. The authors conclude that patients susceptible to this complication should be properly hydrated and blood viscosity should be lowered prior to and during catheterization or surgery. Adequate oxygenation and strict sepsis should be maintained, and whenever possible trauma to the inferior vena cava during catheter manipulation should be avoided. Only minimal amounts of contrast material should be used, and use of indwelling catheters following the procedure should be avoided whenever possible. The article stresses the importance of avoiding this complication rather than its diagnosis. (Kuehl, K. S., Perry, L. W., and Scott, L. P.: Thrombosis of the Inferior Vena Cava in Patients with Cyanotic Congenital Heart Disease, Pediatrics 79: 430-435, 1971.)