

CLINICAL EXPERIENCES WITH VIADRIL®

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SOME ten to fifteen years ago it was the privilege of one of us (C. R. S.) to see Dr. Hans Selye inject into the peritoneal cavity of a rat a quantity of a steroid hormone. The animal promptly went to sleep, became limp, and did not react to potent stimuli. In about forty-five minutes he was fully awake and running about his cage again, apparently none the worse for his period of anesthesia. A drawback to this rather impressive demonstration was the probability that the steroid was stimulating the estrogenic or androgenic systems of the animal (1, 2).

Recently compounds of this type have been studied more intensively, and one has been isolated, 21-hydroxypregnanedione sodium succinate (Viadril®), which in animals possesses a wide margin of safety and appears to be devoid of estrogenic or androgenic stimulating properties (3).

It is the purpose of this paper to describe clinical experiences with the use of this drug as an anesthetic agent. One hundred and thirty-one patients undergoing operation have been administered doses varying between 500 and 2,800 mg. Forty-three patients were given 2,000 mg., while 64 received doses varying between 1,000 and 1,500 mg. The ages of the patients varied between 10 and 73 years. In 121 patients general anesthesia was maintained throughout operation and a variety of surgical procedures were performed (table 1). Spinal or epidural analgesia was employed in 10 patients, and Viadril was given merely to determine its hypnotic effect in combination with regional analgesia.

In addition to clinical observations, electroencephalographic studies were done on 11 patients who were either selected from the psychiatric service (9 patients) or were undergoing surgical procedures (2 patients).

METHODS OF ADMINISTRATION

Prior to administration of Viadril, all patients subjected to operations were administered premedication in the usual manner for this institution. A short acting barbiturate, two hours before operation, was followed by meperidine or morphine subcutaneously about one hour prior to surgery. Anticholinergic drugs also were given during the hour preceding induction of anesthesia.

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In all patients Viadril was injected in a 1 per cent solution, dissolved either in 5 per cent dextrose and water or normal saline. The drug was given intravenously rapidly over a period of 3 to 5 minutes. Following administration a 5 per cent dextrose and water solution was dripped into the vein as rapidly as possible for several minutes. Usually the predetermined dose was given all at once, but occasionally further quantities (300 to 500 mg.) were injected during the operation.

OBSERVATIONS DURING INDUCTION

Some patients (23.9 per cent) complained of a burning, aching pain near the site of injection as the solution was flowing in. This pain was not severe enough to cause attempts on the part of the patient to withdraw his arm. As the drug began to take effect, the patient's speech became slower and sometimes slurred. As with the administration of ultrashort acting barbiturates, nystagmus invariably occurred before loss of consciousness. Frequently patients would repeatedly deny feeling sleepy until they could no longer talk. As a

TABLE I
SURGICAL PROCEDURES IN PATIENTS RECEIVING VIADRIL®

Head and neck	27
Trunk	24
Extremities	23
Intra-abdominal	19
Genito-urinary	12
Gynecological-extraperitoneal	9
Intrathoracic	7
Total	121

rule unconsciousness intervened 5 to 8 minutes after beginning the Viadril infusion. In other words, the patient was asleep at the time or shortly after the injection was completed.

The apparent complete absence of fear or apprehension during induction prompted one of us (C. R. S.) to try a small dose of 500 mg. In this one experience there were no premonitions of impending unconsciousness; indeed, it was difficult for the subject to believe he had been asleep after he awakened. As one patient said, "It would be wonderful to go to sleep like that every night." Interrogation of patients postoperatively indicated that retrograde amnesia was present probably for a period of three to five minutes.

The full "anesthetic" effect of the drug did not appear to develop in patients until ten to fifteen minutes after the completion of the injection. The reason for this lag is unknown, although it has been suggested that the steroid may undergo some degree of metabolism in the body, with the consequent production of an effective hypnotic compound.



FIG. 1. Electroencephalographic pattern 1 during Viadril® anesthesia showing fast activity at frequencies of 10 to 30 cycles per second.

MECHANISM OF ACTION

As with other drugs employed to produce unconsciousness and a degree of anesthesia, the mechanism of action of Viadril is unknown. In an effort to determine its effect on the cerebral cortex, the electroencephalographic studies noted above were undertaken. Recordings

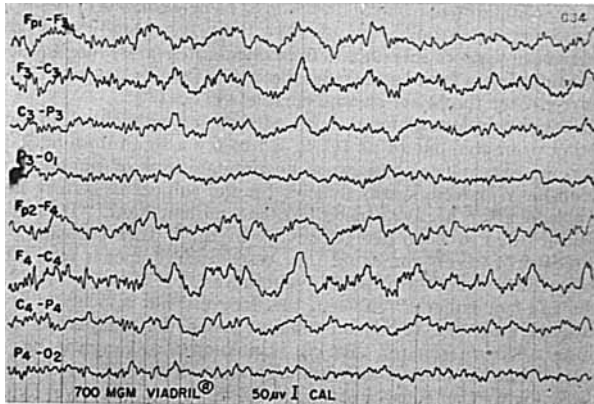


FIG. 2. Electroencephalographic pattern 2 during Viadril® anesthesia showing delta activity in frontal regions.

were done with silver chloride or needle electrodes, using a Grass III D, 8-channel electroencephalograph. Electrode positions were frontal, central, parietal, occipital, midtemporal, vertex, and ears. In one patient frontal polar electrodes were applied.

Electroencephalographic patterns were similar to those seen by Kiersey, Bickford, and Faulconer (4) during thiopental anesthesia. All patterns of change were seen, but it was found that the sensitivity of each patient to the drug varied.

In pattern 1 (fig. 1) there is the appearance of fast activity at frequencies of 10 to 30 cycles per second appearing maximally from the frontal and temporal regions. The occipital rhythms increase slightly in frequency. There is then a gradual slowing of all regions

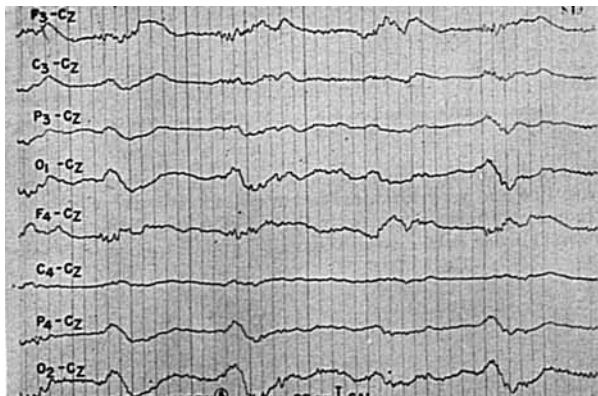


FIG. 3. Electroencephalographic pattern 3 during Viadril® anesthesia showing appearance of suppression burst activity.

with the appearance of slow activity of frequencies in the theta range at 4 to 7 cycles per second.

Pattern 2 (fig. 2) is characterized by the appearance of delta activity primarily in the frontal regions but spreading to all head regions. This is mixed with waves at faster frequencies, 6 to 12 cycles per second.

Patterns 3 and 4 (figs. 3 and 4) are characterized by the gradual appearance of suppression burst activity with the periods of suppression appearing first in the frontal region and being of short duration. With increasing doses of the anesthetic agent this becomes more generalized with the periods of suppression becoming longer and the bursts of fast activity decreasing in voltage.

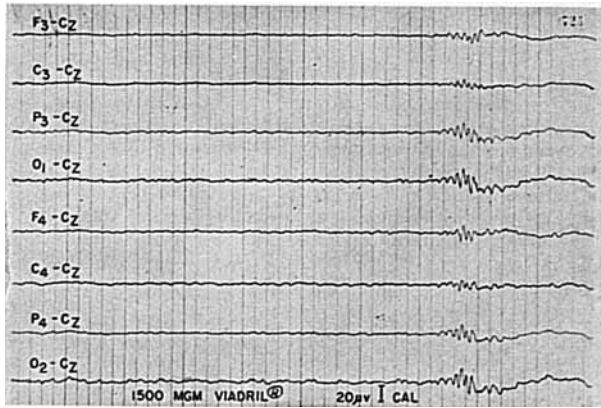


FIG. 4. Electroencephalogram pattern 4 during Viadril® anesthesia showing suppression burst activity with longer periods of suppression.

Pattern 5 (fig. 5) is characterized by only random variations of the base line and very low voltage bursts of faster frequencies.

Recovery patterns are usually the same as those seen in induction in reverse order. The record usually appears normal before the

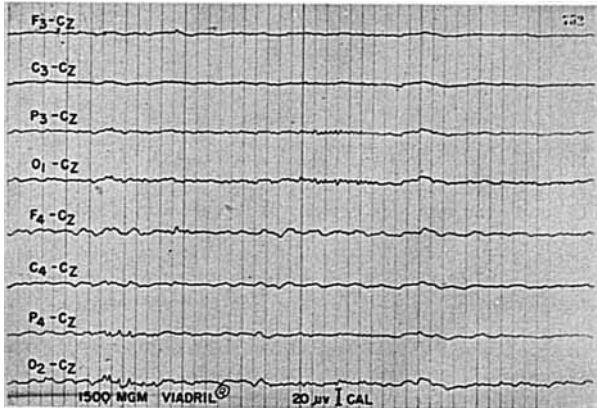


FIG. 5. Electroencephalographic pattern 5 during Viadril® anesthesia showing random variations of base line.

patient is awake with the exception of the frontal and temporal areas where fast activity tends to persist for long periods after the patient is awake.

MAINTENANCE OF ANESTHESIA

Observations from the electroencephalographic tracings would tend to indicate that the steroid acts in a manner similar to the ultrashort acting barbiturates. Clinical observations in patients have appeared to confirm that Viadril is primarily a hypnotic drug which confers analgesia only by virtue of the depth of hypnosis it produces. Table 2 indicates that in about two-thirds of the patients other drugs were required in addition to nitrous oxide or ethylene to maintain adequate operating conditions. Of course, in many instances the operation outlasted the duration of action of Viadril, which is believed to be about one to one and a half hours, and drugs were added simply because of the length of surgery. On the other hand, in numerous patients

TABLE 2
ANESTHETIC DRUGS USED IN COMBINATION WITH VIADRIL[®]*

Drugs	Patients
Nitrous oxide or ethylene	38
Nitrous oxide or ethylene plus thiobarbiturate	17
Nitrous oxide or ethylene plus meperidine drip	15
Nitrous oxide or ethylene plus muscle relaxant	14
Combinations of above drugs	17
Nitrous oxide or ethylene plus ethyl ether	11
Nitrous oxide plus trichloroethylene	6
Cyclopropane	3

* Nitrous oxide or ethylene was employed as basal analgesic in almost all patients.

movement at the time of incision indicated that the patient was "hypnotic" but not adequately "analgesic."

An outstanding difference between Viadril and the thiobarbiturate compounds is the marked depression of pharyngeal and laryngeal reflexes, accompanied by a variable degree of muscle relaxation, which appears with the steroid compound. This obtundation of reflexes obviates the fear of laryngospasm, allowing the early insertion of an oral airway or the introduction of ethyl ether into the anesthetic system without evidence of reflex irritation.

A particular advantage of this combination of reflex depression and muscular relaxation lies in the relative ease with which endotracheal intubation may be accomplished. Apart from third plane, third stage ether anesthesia, only Viadril "anesthesia," in our experience, allows one to intubate the trachea easily with the patient breathing regularly and spontaneously. It should be noted that if intubation is not accomplished on the first try, the potent stimuli elicited in the attempt may cause a partial return of muscle tone, making a second try more difficult. In this series endotracheal intubation was per-

formed in 58 patients. In 42 patients satisfactory hypnosis and relaxation for this procedure was obtained with Viadril alone. The other patients required the addition of muscle relaxant drugs to facilitate atraumatic placement of the endotracheal tube.

This steroid compound appears to potentiate the effect of other drugs used in anesthesia without any obvious synergistic action. It has been employed without incident with the various compounds noted in table 2. Relatively small quantities or concentrations of these drugs are required to produce the desired hypnotic, analgesic, or relaxant effects when Viadril has preceded them.

COMPLICATIONS OF ADMINISTRATION

Untoward effects have resulted from the administration of Viadril, but in no patient was it believed that complications were critical enough to endanger the patient's life. The predictability of action of the several dosages used has been difficult. To some extent this was related to age, as patients in the older age group react more pro-

TABLE 3
COMPLICATIONS IN ADMINISTRATION OF VIADRIL®

	Number	Per Cent
Thrombosis or thrombophlebitis (107 cases followed)	83	77.5
Hypotension, 10 mm. Hg or more	76	62.8
Increase in respiratory rate	35	28.9
Pain during injection	29	23.9
Apnea	27	22.3
Total Cases	121	—

foundly to smaller dosages. Our own inexperience with the drug probably also accounts for variations in results. It is believed that some of the side effects noted in table 3 could have been avoided had the original dosage of drug been chosen more judiciously.

Respiratory depression leading to cessation of spontaneous respirations was seen in 22.3 per cent of patients. The depression was one of decreased tidal volume rather than decreased rate of respiration. The apnea could be related to central depression of the respiratory center, to a peripheral myoneural blocking action, or to a combination of both factors. Usually there was diminished intercostal activity for several minutes and then diaphragmatic activity persisted after intercostal paralysis was complete. The picture did not resemble the central respiratory depression seen with large doses of thiobarbiturates. It was somewhat similar to that seen with the muscle relaxant drug succinylcholine. When the respirations became depressed, controlled respiration could be established easily by rhythmic manual compression of the reservoir bag. The administration of ethyl ether in moderate amounts did not enhance the decreased tidal volume which might

be present. Apnea might persist for as long as an hour. It was probably prolonged by hyperventilation.

Some degree of tachypnea occurred in 28.9 per cent of the patients. The cause of this increase in respiratory rate was unknown. It could be due to sensory stimulation resulting from inadequate analgesia. However, tachypnea developed in some patients when sensory stimulation was minimal. A disturbance in the Hering-Breuer reflex mechanism could be postulated as an explanation.

The principal cardiovascular reaction seen with Viadril administration was hypotension. Sometimes this was associated with tachy-

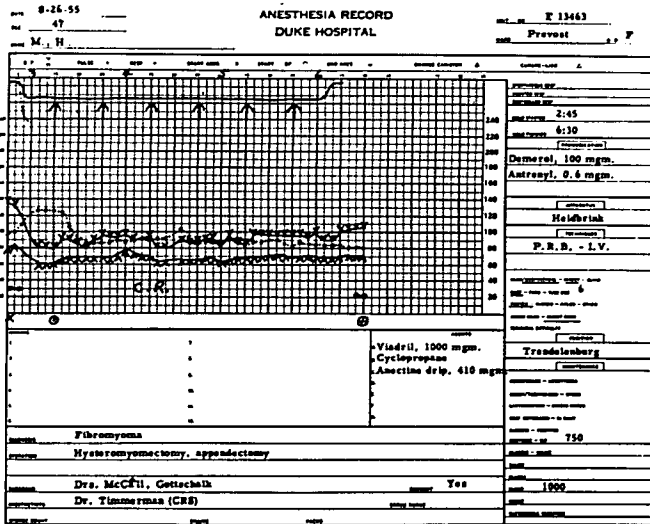


Fig. 6. Anesthetic record of a 47-year-old patient showing fall in blood pressure from 134/80 to 80/60 after administration of Viadril®, 1,000 mg.

cardia. Some reduction in blood pressure was observed in 62.8 per cent of patients. In only 9 patients was the fall in pressure profound enough to warrant injection of a vasopressor drug. The response to vasopressors was prompt and adequate. Figure 6 is the anesthetic record of a 47-year-old patient who demonstrates this hypotension and associated tachycardia. The etiology of the hypotension was obscure, but could result from generalized peripheral vasodilatation. Selye (1) noticed in animals a warming and vascular dilatation of the extremities after the injection of steroid hormones. In the patients who developed

hypotension in this series the extremities were warm and dry and the veins were not collapsed. Arrhythmias associated with administration of Viadril were not noted with the exception of one patient who developed extrasystoles shortly after induction. An irregular, rapid pulse persisted for the duration of a three hour operation.

In several patients jerky, clonic-like movements occurred in the extremities during the induction period following loss of consciousness. These abnormal movements, sometimes quite pronounced, appeared to bear some relationship to stimulation. The arms and legs were stiff at the time of their occurrence. The movements gradually ceased spontaneously, to be replaced by relaxed extremities. Respirations were not interfered with during these episodes. The electroencephalogram showed no changes in pattern during these clonic movements.

Hiccups developed in several patients after the full effect of Viadril was present. Usually some intercostal paresis was present at the time. In most of these patients there was an associated stimulus of the gastrointestinal tract.

Probably the most serious complication associated with Viadril administration was the thrombophlebitis and thrombosis which developed in 77.5 per cent of patients during the postoperative period. Pain about the site of injection and extending upwards into the arm, redness, localized swelling, and tenderness were the immediate signs and symptoms which became evident within forty-eight hours. In 2 patients these symptoms persisted for a week and delayed discharge from hospital. Usually these acute manifestations were followed by a thrombosis of the involved vein. In one patient seen four months after administration, a marked thrombosis of the vein persisted from the midforearm to as high in the axilla as one could feel. Abscess formation, sloughs, or other permanent damage have not been seen. In 2 patients extravascular infiltration occurred, but did not cause more irritation than that seen following intravenous injections.

Venous irritation is to be suspected when pain is felt during injection of Viadril solution. Stasis of the solution in the extremity appears to bear some relationship to the severity of thrombophlebitis. When the drug was injected into the arm which had a blood pressure cuff on it, postoperative sequelae were more severe. The worst case of phlebitis seen, in which nearly all the veins of the forearm and arm were involved, occurred in a patient who had had a radical mastectomy two years previously on the involved side. In this patient both lymphatic and venous drainage were markedly impaired. In an effort to overcome stasis it was our practice to "wash out" the injected solution by allowing 5 per cent dextrose and water to run in rapidly following the Viadril injection. This procedure, however, did not prevent thrombophlebitis from occurring.

Apart from thrombophlebitis and thrombosis, the immediate postoperative course of patients receiving this steroid compound was rela-

tively benign. Nausea and vomiting were rare, but when vomiting did occur, retching was persistent for several hours. The awakening period was devoid of excitement or other unusual manifestations.

DISCUSSION

The introduction of a new drug into anesthetic practice often is associated with opinions of optimism. This reaction is natural because anesthesiologists are cognizant of the limitations inherent in the present array of compounds. The hope is that each new drug will fill the void. However, time and experience are necessary before any true evaluation can be made.

The production of anesthesia by the injection of a steroid compound is a fascinating thought. An entirely new vista is opened up for exploration. The use of drugs for anesthesia which are similar chemically to compounds elaborated physiologically in the body is perhaps a step towards solving the enigma of the narcotic state. We should learn as much about compounds of this type as possible.

From the practical viewpoint, it seems doubtful at the moment that Viadril represents the utopian anesthetic compound. The ideal drug would be safe over a wide range of error, be easily reversible in its action, nonexplosive, confer adequate hypnosis, analgesia, and relaxation, and have minimal side effects.

It is questionable if Viadril is safe physiologically over a wide range of error. It can provide, however, good operating conditions in some patients with relatively little in the way of supplementation (fig. 7). But the effect of any given dosage is unpredictable in our experience and may lead to marked alterations in the respiratory and cardiovascular systems.

In its manner of present use the effects of Viadril administration are not easily reversible. The actions of the injected compound must run their course, even though we do exercise control over the respirations of the patient and can reverse a developing hypotension.

With the increasing use of the cautery and electronic recording devices in modern surgery and anesthesia, the nonexplosiveness of anesthetic drugs is assuming great importance. This desirable attribute is present in Viadril.

The electroencephalographic studies above corroborate the work of Howland, Boyan and Kuo-Chen Wang (5) and show that the effects of Viadril on cortical activity are exactly the same as those described previously for thiopental. Like the thiobarbiturates, this steroid clinically is a good hypnotic. Its method of action is exceedingly pleasant for the patient, and such an attribute is demanded in the practice of modern medicine.

The analgesic action of Viadril in our clinical experience does not measure up to the hypnotic effect. Certainly response to painful

stimuli is diminished, but perhaps to a large extent owing to the depth of hypnosis achieved. When pain stimuli are blocked, as in regional analgesia, a pleasant, uninterrupted sleep is provided by Viadril in relatively small doses (500 mg.).

The muscular relaxation provided by this compound is a most intriguing property. It is sufficient to allow rapid, expert intubation, and in some patients it has provided satisfactory operating conditions for upper as well as lower abdominal surgery. It can abolish the fear of acute, intractable laryngospasm during induction, and it minimizes

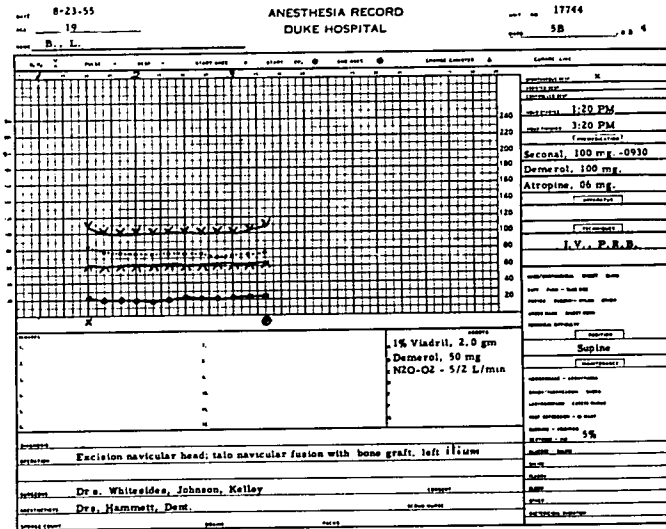


Fig. 7. Anesthetic record showing smooth course of anesthesia with Viadril®, 2,000 mg., in 19 year-old patient undergoing orthopedic procedure.

undesirable reflex activity in head and neck surgery. One can hypothesize on the possible relationship between the jerky, clonic-like movements seen in some patients and the sometimes violent movements associated with rapid injections of succinylcholine. Muscular relaxation follows both events. Perhaps a depolarizing action at the myoneural junction is associated with Viadril injection, and this is an explanation for the muscular relaxation which occurs. When succinylcholine is given by rapid administration following adequate steroid administration, we have not seen fasciculatory movements in the patient.

As the properties of Viadril become more evident with experience, it appears that its immediate competition is the thiobarbiturates. In comparing these two types of compounds, the disadvantage of the steroid compound is the thrombophlebitis and thrombosis seen in the postoperative period. One cannot routinely inflict the possibility of such a side effect on patients when the thiobarbiturates do give a satisfactory hypnosis without these residual manifestations.

SUMMARY

A steroid compound, 21-hydroxypregnanedione sodium succinate (Viadril), was administered intravenously as an anesthetic drug to 131 patients undergoing a variety of surgical procedures. Electroencephalograms recorded in 11 patients were similar to those described for ultrashort acting barbiturates. Clinical observations indicated that Viadril exerted primarily a hypnotic effect, differing from thiobarbiturate compounds by the additional production of marked depression of pharyngeal and laryngeal reflexes and also a variable degree of muscular relaxation. Complications of Viadril administration included thrombophlebitis and thrombosis of veins near the site of injection, tachypnea, respiratory depression, hypotension, clonic-like movements of extremities, and hiccups.

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