CLINICAL INVESTIGATION OF VIADRIL*

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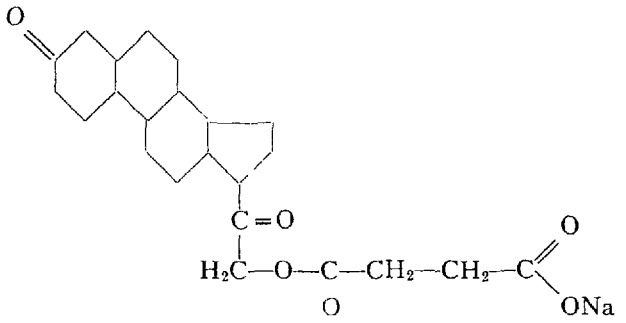
THE anaesthetic activity of steroid hormones in animals was reported by Selye in 1941 (1, 2). In 1942 the same author reported on the anaesthetic activity of 75 steroid compounds, and drew attention to the fact that Pregnanedione possessed anaesthetic activity but no hormonal activity (3, 4). In 1955 Laubach, P'an, and Rudel (5) suggested from animal studies that 21-hydroxypregnanedione sodium hemisuccinate (hydroxydione) might prove to be a satisfactory anaesthetic agent. The formula of this substance is shown below. This compound was prepared by the Pfizer Company under the trade name "Viadril,"[1] and clinical trials in 125 patients were reported by Murphy, Guadagni, and Debone in 1955 (6).



21-hydroxypregnanedione sodium hemisuccinate

The drug is supplied as a white powder which is readily soluble in water Since it is a soap, it tends to foam, and this characteristic can be a nuisance in the preparation of solutions It is irritating to tissues and tends to produce thromosis of veins.

METHODS

During the early phases of this investigation, and until we had familiarized ourselves with the characteristics of the drug, we confined its use to female patients undergoing uterine curettage. This selection had the advantages of short duration of anaesthesia, a standard surgical procedure which of itself caused no postoperative discomfort likely to produce restlessness or to require sedation, and a group of patients who were generally in good health. Following experience in these patients, we were able to develop a basis for adjustment of techniques

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[1]We wish to thank Pfizer Canada for making available to us the Viadril used in this study.

and dosage before proceeding to use the drug in operations requiring deeper and more prolonged anaesthesia

1. *Dosage and Techniques*

All patients in this series received a preoperative medication consisting of Demerol 100 mgm. or morphia gr.1/6 combined with Atropine gr.1/150 or gr 1/100. We commenced our investigation by giving a standard dose of 500 mgm. Viadril to each patient for the operation of dilatation and curettage. When the eyelid reflex had been lost, nitrous oxide and oxygen were administered in a high-flow semi-open system in a ratio of 75 to 25 per cent Shortly it became evident that the dosage scale must be adjusted on a weight basis, and analysis of our experience suggested an initial dosage of Viadril of 5 mgm. per pound body weight. This proved adequate for curettage when associated with nitrous oxide, but was inadequate for more painful operations An increase of the initial dosage to 7 5 mgm. per pound body weight was found adequate in all circumstances in which we employed the drug in this study.

Early in our experience we tried dilute solutions of 0 1 and 0 2 per cent of the drug in an intravenous drip infusion. This technique was abandoned because it prolonged the induction period unduly, did not improve controllability, and at the same time presented the necessity of giving large amounts of intravenous fluids.

The control of anaesthesia during more prolonged operations was a problem, because of the long latent period between injection of the drug and its maximum effect. It was apparent very early in this investigation that administration "on demand" was impracticable, because administration of additional Viadril when signs of a lightening of anaesthesia occurred was too late to stabilize the situation. Experience suggested that an additional dose should be given twenty minutes after the first, and further dosage each half hour The doses which proved satisfactory in most of the patients in this study were 50 per cent of the original dose twenty minutes after induction, and 25 per cent of the original dose subsequently. If signs of lightening anaesthesia occurred it was necessary to use another drug to stabilize the situation, and we used Demerol 50 mgm intravenously for this purpose In four cases Viadril was given as a continuous infusion during operation in solution in normal saline. In two cases this solution was 0 1 per cent in concentration and in the other two 0.2 per cent. In all other cases the drug was injected in a 2 per cent solution into the rubber tubing of a rapidly running intravenous infusion of normal saline or 5 per cent Glucose in distilled water. The rate of injection was such that the total initial dose was given within five minutes of commencement

Observations

We have used Viadril as an anaesthetic agent in this study in 100 patients undergoing a variety of surgical procedures. The nature of the operative procedure in these cases is indicated in Table I. The total dosage of Viadril varied from 500 mgm. to 3500 mgm.

TABLE I

OPERATIONS PERFORMED WITH VIADRIL

Dilatation and curettage	41
Laparotomies	9
Vaginal repair	4
Prostatectomy	2
Head and neck (major)	4
Bronchoscopy and oesophagoscopy	6
Operations on extremities	17
Other miscellaneous operations	11
Supplement for regional anaesthesia (includes 1 Caesarean)	6

In these patients we have studied the length of time from injection of the drug until the loss of the eyelid reflex occurred, the time required for response to calling of the name and for return of full consciousness after operation, the influence of Viadril on the cardiovascular function, respiration, and electroencephalogram records We have also noted the occurrence in the postoperative period of venous thrombosis, nausea and vomiting, headache, and pulmonary complications The urine of 20 patients was investigated for the presence of albumin and blood in the postoperative period.

1 *Induction*

The induction period is prolonged with Viadril All patients were asleep within five minutes of the beginning of the injection, where the injection was completed within five minutes. Eyelid reflex disappeared in every case before ten minutes had elapsed, and in some cases as early as six minutes from the beginning of the injection In four cases in which a continuous infusion of dilute solution of the drug was used, induction time was prolonged, the patient did not go to sleep for eight minutes to ten minutes, and the lid reflex was lost at about fifteen minutes from the beginning of the infusion.

In all cases the induction was extremely smooth. No patient complained of any vertigo, dizziness, or other unpleasant sensation. Three patients remarked that the room was turning green just before they went to sleep, and one had the same experience with red colour just before going to sleep. In no case did we encounter any excitement during the induction This induction, on the whole, appeared more to resemble the normal sleep process than that with any other drug to which we can compare it

The rate of injection of the 2 per cent solution of Viadril during induction appeared to be of some importance in relation to the production of venous thrombosis It was noted on several occasions when the injection was made at such a rate as to stop or almost stop the intravenous drip, that the patient complained of pain in the arm. Where the rate of injection was timed so that the rate of the drip of the infusion was not perceptibly or very little, slowed, there was no such complaint of pain.

2. *Recovery*

Nitrous oxide was used as an adjunct to Viadril in all cases. Patients who were given a dose of Viadril calculated on the weight basis previously described responded to name in about twenty minutes from the loss of the eyelid reflex, in each case. At this point the patient if left undisturbed would return to sleep. Full consciousness with complete orientation was usual at the end of thirty minutes. In other operations where the drug was used in conjunction with nitrous oxide, waking time in response to the patient's name after stopping nitrous oxide administration appeared to vary almost directly with the length of operation and the amount of the Viadril administered in the doses subsequent to the induction dose. In patients receiving a single dose for operations such as uterine curettage, response occurred from immediate y at the end of operation to ten minutes after the conclusion of the operation, the patients were wide awake and fully orientated in periods varying from ten minutes to forty-five minutes. The only factor which appeared significant in this variation in awakening time was age, but we could not determine statistically that there was a definite correlation. It would appear that patients show wide variations in respect to awakening time following administration of Viadril, as they do following the use of other anaesthetic agents.

Patients who had larger doses of Viadril (exceeding 1000 mgm.) required a longer period of time to respond after the conclusion of operation. Times for the initial response to the name in this group varied from five minutes to sixty minutes, the majority requiring from fifteen to twenty minutes for the first response. Awakening to full consciousness and orientation in this group was delayed from twenty-five to one hundred minutes, the majority requiring forty to forty-five minutes for complete recovery of orientation after the conclusion of operation. Here again a wide individual variation from patient to patient is evident.

3. *Cardiovascular System*

Pulse rate varied considerably during Viadril anaesthesia, the usual change from the state before induction being a slight increase, which was exaggerated by surgical stimulation in light anaesthesia. In no case was a large variation in pulse rate seen. No arrythmia occurred. Hypotension was rarely seen in the series. We have cast hypotension as a drop in systolic presure below 90 mm. of mercury systolic. A small decline in blood pressure was seen in almost every patient, but this was not considered significant. In the 100 patients in this study, hypotension below 90 mm. of mercury systolic was seen only in one during the operative period and in three during the postoperative period. All four responded promptly to small doses of vasopressor drugs, and the hypotension did not recur.

Electrocardiographic tracings were taken in five patients, and showed no variation from the normal record.

4. *Respiration*

Respiratory rate increased consistently in all patients receiving Viadril as an anaesthetic agent, while the tidal volume was decreased Respiratory records

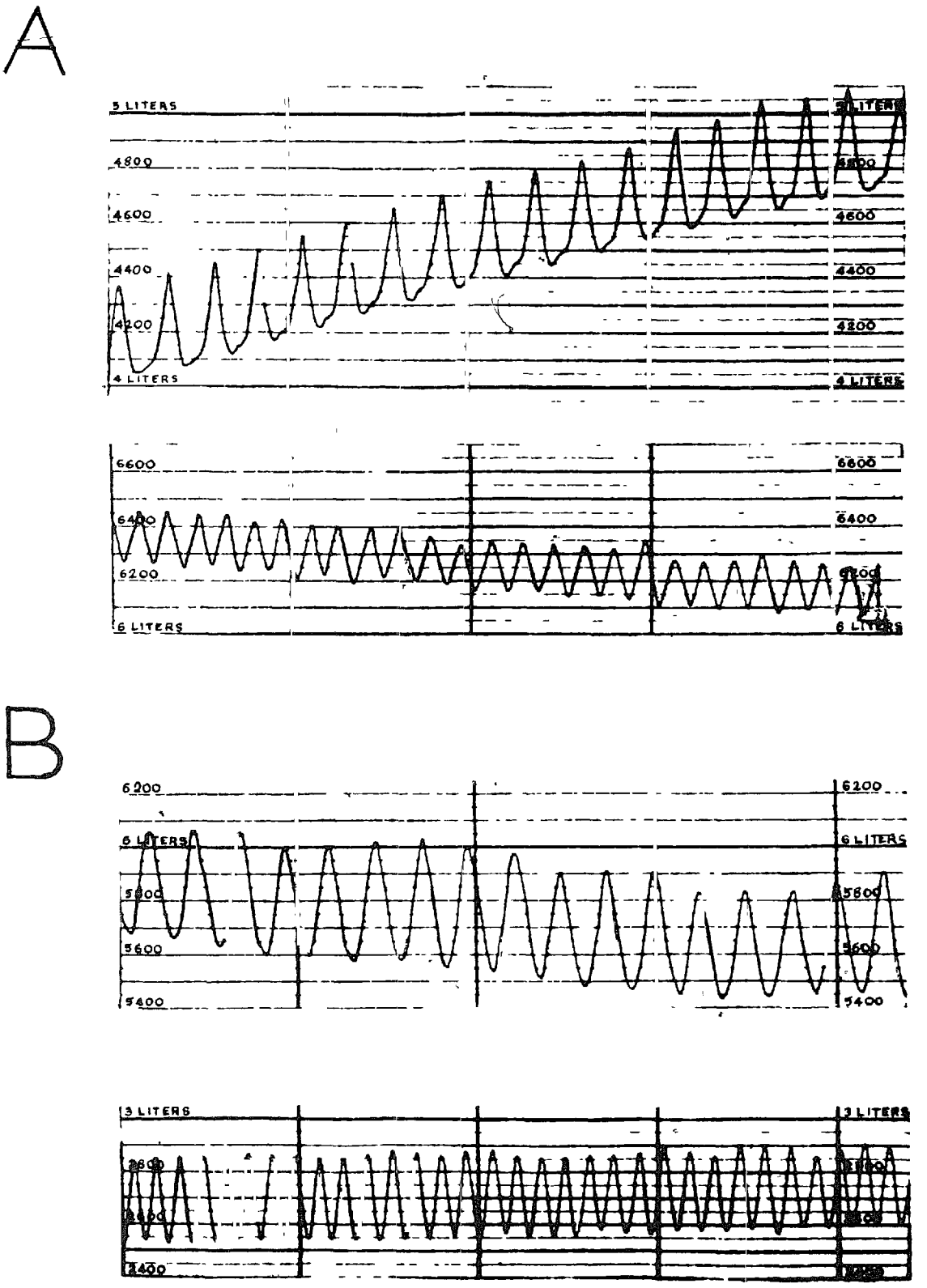

FIGURE 1. Respiratory records of two patients (*A* and *B*) during Viadril anaesthesia. The first line in each case is respiration at rest prior to induction, and the second a sample of the respiration at the deepest level obtained during the anaesthetic

were made in five patients using a recording device applied to the exterior of the thorax, but this proved unsatisfactory for any purpose other than the recording of respiratory rate. Records were made for two patients with the Collins Respirometer, and samples of the records of these two patients are shown in Figure 1. The samples from the records of these two patients are designated in the figure as *A* and *B*. The first line in each case is the record of respiration at rest prior to induction. The second line is a sample of the respiratory tracing in each case after the patient had been established for some time at the deepest level obtained during the operation with Viadril anaesthesia It will be noted in each case that the respiratory rate was sixteen per minute in the preinduction period, and the tidal volume 400 cc.

Minute respiratory volume was therefore 5400 cc. in each of these patients. Each patient showed a reduction in tidal volume and an increase in respiratory rate, the reduction in the first case being 50 per cent of the initial tidal volume, and in the second case 25 per cent It is interesting to note that in case *A* the minute volume of ventilation was decreased to 4800 cc per minute, while in case *B* it was greatly increased to 8400 cc. per minute. We are unable to explain this difference on the basis of the evidence available

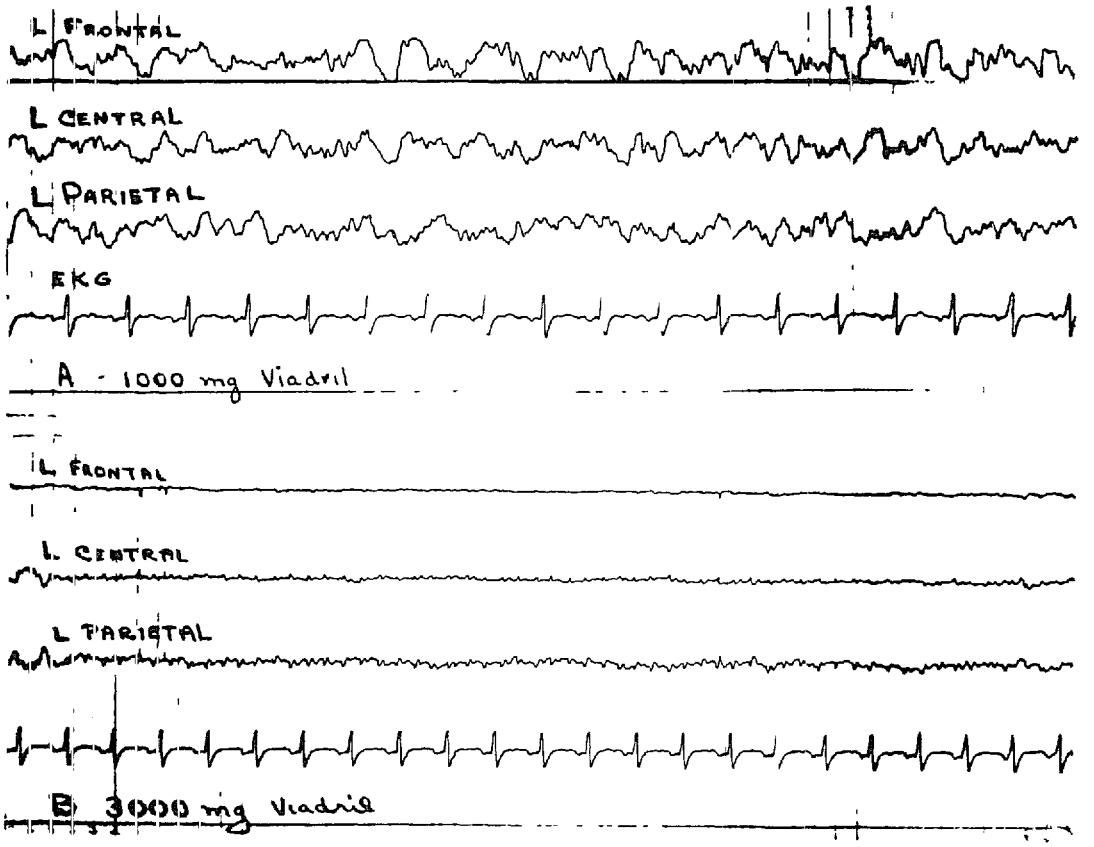

FIGURE 2. Electroencephalogram of a patient under Viadril anaesthesia The upper record was made when the eyelid reflex was lost after 1000 mgm of Viadril, the lower 50 minutes later after 3000 mgm. of Viadril.

5. *Electroencephalogram Studies*

Electroencephalographic patterns during anaesthesia have been reported by previous workers (7, 8). Electroencephalographic records were made for six patients in this series. In each one recording was commenced before injection of Viadril was started, and continued throughout the operation. The records obtained from these patients are comparable in all significant respects, and a representative record from one of these patients is shown in Figure 2. The upper record was made when the patient had lost the eyelid reflex after 1000 mgm. of Viadril. This record shows slow waves superimposed upon faster waves. There is normal ten cycle per second alpha rhythm visible, which is not seen in a patient who is naturally asleep or anaesthetized This was the stage of anaesthesia which was found suitable in this series for operations such as uterine curettage.

As more Viadril was administered the total activity was decreased, and fifty minutes after the first record, when 3000 mgm. of Viadril had been given, and when the operation was well under way, there is a low voltage record which is shown in the lower record in Figure 3, with a fifteen cycle per second rhythm dominating. This is quite different from the records usually seen in surgical anaesthesia.

6 *Thrombosis of Veins*

Murphy *et al.* (6), Howland *et al.* (7), Taylor and Shearer (9), and others have reported the occurrence of venous reaction and venous thrombosis following the use of Viadril. Fourteen patients in this series showed venous thrombosis in the postoperative period, and six a perivenous reaction with no apparent occlusion of the vein. Two of the patients having postoperative venous thrombosis had received Viadril in a continuous infusion of 0.1 and 0.2 per cent respectively during rather prolonged operation. It would appear that other cases of postoperative venous thrombosis were associated with injection of the Viadril at such a rapid rate that the free flow of the intravenous infusion was impeded. In one case 2 per cent Viadril up to 1000 mgm. was injected into an intravenous drip running into a vein of the dorsum of the hand, with the intravenous tubing clamped off. This patient had a rapid development of thrombosis of the veins of the dorsum of hand, with a most severe oedematous reaction of the whole hand. In this case the circulation to the hand was so prejudiced that there was some fear that the patient might develop gangrene. It is of interest to note, however, that the hand appeared normal in all respects at the end of four days without treatment other than ice-bags in the immediate postoperative period, and at discharge from hospital at the end of ten days there was no evidence of venous thrombosis or reaction of any kind in the extremity.

In one patient who received a continuous infusion of Viadril 0.1 per cent in normal saline, a considerable quantity of the solution was injected into the subcutaneous tissues about the vein. This resulted in an immediate and severe reaction, having all the features of an acute inflammatory process. This reaction was completely dissipated by the interstitial infiltration of hyaluronidase solution,

and on the following day there was no evidence of perivascular reaction or thrombosis.

A number of patients complained of pain in the arm when the Viadril solution was injected somewhat rapidly. In the presence of a freely running intravenous infusion this pain disappeared promptly when the injection was slowed or discontinued. We have failed to establish any relationship between the occurrence of this pain during injection and the incidence of postoperative venous thrombosis.

7. *Postoperative Examination of Urine*

Since the occurrence of haematuria had previously been reported in dogs following the injection of Viadril (10), the urine of twenty patients who received Viadril for the operation of uterine curettage was examined after operation. In each case an indwelling catheter was placed in the bladder at the end of operation, and this was released at six hours and twelve hours. The urine samples obtained were examined for the presence of albumin and blood. In eight of these twenty patients a trace of albumin was found in the urine in the six-hour specimen. No patient had albumin in the twelve-hour specimen, and in no case was blood demonstrated in any specimen The trace of albumin in the early specimens was considered to be due probably to the presence of the indwelling catheter.

8. *Reflexes*

We have confirmed the observation of Murphy *et al* (6) and others (7, 9) that the pharyngeal reflexes are remarkably obtunded by Viadril in very light stages of anaesthesia. In many cases it was possible to insert a pharyngeal airway before loss of the eyelid reflex Under light anaesthesia the pharynx and larynx could be readily inspected through a laryngoscope without sign of resentment from the patient Stimulation of the larynx, however, or insertion of an endotracheal tube produced severe spasm One patient had severe respiratory spasm during the recovery period following bronchoscopy

9. *Endotracheal Intubation*

Intubation of the trachea may be readily accomplished under light Viadril anaesthesia when it is associated with adequate topical anaesthesia of the larynx and trachea. Sixteen patients in this series were so intubated, and we found relaxation of the jaws and pharynx to be quite adequate in each case The intubation was as easily performed as if a relaxant had been used.

10 *Vomiting*

Postoperative vomiting was a very rare occurrence in this series No patient vomited during the return of consciousness. Six vomited once during the first twelve postoperative hours. Of these one patient had acute appendicitis and had been vomiting for three days before operation; one had a post-traumatic cerebral syndrome associated with headache and vomiting, of many months' duration; one had a period of severe anoxia due to spasm following bronchoscopy, and one a similar episode following intubation at the end of a curettage, which was undertaken early in our series because we were unable to resist the tempta-

tion presented by the open relaxed larynx under light Viadril anaesthesia. Of the six patients who vomited, three did so only after taking food in the immediate postoperative period. No patient vomited more than once, and none after the first twelve hours.

11. *Headache*

Only four headaches were recorded in the postoperative period, and none of these were serious or significant. We believe that this incidence is probably no greater than it might be in a random sample of the same type of individuals who had had no anaesthetic or operation.

12. *Patient Reaction*

After operation, all patients in this series were entirely happy about their anaesthetic, despite the incidence of venous thrombosis. Many patients with experience of previous anaesthetics were definitely enthusiastic. The feature of their experience which appeared to impress the enthusiasts was the absence of diplopia, dizziness, or any sensation other than drowsiness during induction and recovery. Some patients who had previously experienced induction with a barbiturate agent were worried by the delay in going to sleep after the injection of the drug, but this was apparently forgotten after the operation.

Discussion and Conclusions

This study has demonstrated that Viadril produces satisfactory anaesthesia for a wide range of surgical procedures when combined with nitrous oxide and relaxants where these are indicated. In this respect it may be compared with the short-acting barbiturates and narcotics such as Demerol. Its tissue-irritating qualities and the slowness of induction tend to make it somewhat more cumbersome in practice than these other drugs. However, the extremely low incidence of complications other than venous thrombosis and the favourable patient reaction to the drug are factors which must demand serious consideration. It would appear from the experience of this study that Viadril may prove of value as a basal anaesthetic substance in some situations, such as the supplementation of regional anaesthesia, or for induction, but that the difficulty of control because of the long latent period between administration and maximum effect will make it less practical as an agent for general use throughout prolonged operations than other agents presently available to us.

Résumé

Les auteurs ont étudié, chez 100 malades, l'usage clinique du viadril (21-hydroxypregnanedione hemisuccinate de sodium) Le médicament est un stéroïde, fourni par la compagnie Pfizer, sous forme d'une poudre blanche instantanément soluble dans l'eau. Le produit est irritant pour les tissus et peut occasionner la thrombose des veines.

Au cours de cette étude, tous les malades ont reçu, en médication préopératoire, Demerol 100 mgm ou Morphine 1/6 gr. avec de l'atropine 1/150 ou 1/100 Le protoxyde d'azote et de l'oxygène, chez tous les malades, ont été administrés durant l'opération. Pour un curettage utérin, un dosage de viadril

de 5 mgm par livre de poids a suffi, mais, pour des opérations plus douloureuses, il a fallu donner 7.5 mgm par livre de poids. La liste des différentes opérations où le viadril a été employé comme anesthésique pour faire cette étude apparait en table I.

Avec le viadril, l'induction est lente. Le médicament doit être introduit lentement dans la tubulure d'une infusion intraveineuse au point de ne pas ralentir le rythme de l'infusion Au cours de cette étude, la concentration de la solution de viadril était de 2 pour cent. Quand toute la dose de viadril est injectée en deçà de 5 minutes, le malade s'endort à peu près dans le même délai et ses réflexes palpébraux disparaissent en deça de dix minutes après le début de l'injection. Chez les malades où il fallait prolonger l'anesthésie, il a été difficile de maintenir une anesthésie égale à cause de cette période de latance entre l'injection du médicament et son effet maximum; toutefois, les auteurs ont trouvé que, si une dose égale à 50 pour cent de la dose initiale était injectée de nouveau au bout de 20 minutes et un dose égale à 25 pour cent de la dose initiale injectée à toutes les demi-heures par la suite, l'anesthésie était suffisante à condition d'y ajouter du protoxyde et, au cours des opérations où le relâchement musculaire est requis, des substances curarisantes Au cours de l'induction, on n'a pas observé d'excitation, de vertiges, d'étourdissements ou aucun autre incident.

Les malades qui avaient reçu une seule dose de viadril pouvaient répondre à leur appel au bout de 20 minutes et après trente minutes, ils étaient tout-à-fait orientés. Chez les autres malades, de délai pour pouvoir marcher après l'arrêt du protoxyde d'azote a semblé varié de façon presque directement proportionnelle à la quantité de viadril donnée après la dose initiale.

Au cours de l'anesthésie au viadril, le rythme cardiaque s'est légèrement accéléré et, dans presque tous les cas, la tension artérielle s'est abaissée de façon peu marquée. Au cours de cette série de 100 malades, en une occasion seulement, la tension s'est abaissée au-dessous de 90 mm Hg au cours de l'opération et, en trois occasions, dans les suites post-opératoires.

Le rythme de la respiration s'est également accéléré de façon marquée chez tous les malades soumis au viadril, mais le volume de l'air courant diminuait. Des graphiques de la respiration de deux malades sont présentés en figure 2.

Les auteurs ont également fait des tracés électro-encéphalographiques chez six malades sous anesthésie au viadril. Chez les malades sous anesthésie légère au viadril, ils ont obtenu un rythme normal de 10 cycles par seconde, ce qui ne s'observe pas chez un malade dormant naturellement ou anesthésié avec d'autres agents. Chez les malades soumis à une anesthésie plus profonde (figure 3) le tracé est tout-à-fait différent de celui qu'on obtient habituellement au cours de l'anesthésie chirurgicale.

Au cours de cette série, quatorze malades ont souffert de thrombose veineuse et six autres de réaction periveineuse sans obstruction apparente de la veine. Il semblerait que l'apparition de la thrombose serait en fonction de la vitesse d'injection du viadril dans la tubulure de l'infusion, de sorte que l'infusion aurait été ralentie et même arrêtée. Un certain nombre de malades ont accusé des douleurs dans le bras lors de l'injection rapide du viadril.

Chez vingt malades qui avaient reçu du viadril pour subir un curettage utérin, les auteurs ont fait l'examen des urines au cours des suites opératoires. Chez huit

d'entre elles, ils ont trouvé des traces d'albumine dans l'échantillon prélevé par sonde six heures après mais aucune trace d'albumine dans l'échantillon prélevé 12 heures après l'anesthésie. Aucun malade n'a présenté du sang dans ses urines.

Sous anesthésie légère au viadril, les réflexes laryngés étaient abolis. Chez plusieurs malades, il a été possible de mettre en place un tube pharyngé avant même la disparition des réflexes palpébraux. Toutefois, une stimulation du larynx, à ce moment-à, provoquait un spasme laryngé. Chez 16 malades, l'intubation trachéale a été pratiquée facilement à l'aide de l'anesthésie locale du larynx et de la trachée.

Les vomissements post-opératoires ont été rares. Chez quatre malades, on a observé de la céphalée post-opératoire mais chez aucun d'eux elle n'a pris une certaine importance.

Au cours de cette étude, tous les malades ont manifesté, au cours des suites opératoires, une entière satisfaction au sujet de leur anesthésie; ceux qui avaient l'expérience d'anesthésies antérieures étaient réellement enthousiastes du manque de sensation au cours de l'induction. Les malades qui avaient l'expérience d'une induction antérieure aux barbituriques étaient parfois inquiets du retard à s'endormir.

Cette étude a démontré que le viadril peut produire une anesthésie satisfaisante pour une grande variété d'opérations si on l'associe au protoxyde d'azote et aux curarisants s'il y a lieu Ses propriétés irritantes pour les tissus et sa lenteur d'induction le rendent difficile à manier, mais il semblerait que le viadril peut s'avérer utile comme substance anesthésique de base en certaines circonstances telles que en complément d'une anesthésie régionale ou pour une induction; toutefois, la difficulté de contrôler l'anesthésie à cause de la longue période de latance entre l'injection et l'effet maximum rend le viadril moins pratique comme agent d'usage courant au cours d'opérations prolongées que ceux que nous pouvons obtenir actuellement.

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