VIADRIL: A NEW STEROID ANAESTHETIC

PRELIMINARY COMMUNICATION

BY

L. H. LERMAN, M.R.C.S., D.A.

Consultant Anaesthetist, Moorfields, Westminster and
Central Eye Hospital

Ideal anaesthesia is seldom carried out to-day with only one agent. Like "all Gaul," such an anaesthetic consists of three parts: (1) a basal narcotic—for example, thiopentone sodium; (2) a muscle relaxant—D-tubocurarine chloride ("tubarine"), gallamine triethiodide, suxamethonium chloride, etc.; and (3) an analgesic mixture of nitrous oxide and oxygen with or without such adjuvants as trichlorethylene or pethidine.

"Viadril" (21-hydroxypregnane-3:20-dione sodium succinate) telescopes the narcotic and relaxant functions and requires only minimal nitrous oxide and oxygen to maintain anaesthesia. This substance is revolutionary in that it is a steroid. It bears no resemblance, therefore, to any group of drugs hitherto used or contemplated for the purpose. Viadril is a non-volatile crystalline solid, freely soluble in water, the solution having a pH of 7.8 to 10.2.

History

Selye (1941, 1942), investigating many different steroids in 1941, noted that some of these caused depression and anaesthesia in laboratory animals. Further work on the pharmacology of some of these compounds was carried out by Elliott and Gordan (1947). Laubach *et al.* (1955) investigated a large number of these compounds in animals and found 21-hydroxypregnane-3:20-dione sodium succinate to be the most satisfactory.

Viadril

It was found to have a wide margin of safety, the therapeutic index in mice being 11.1, as compared with 4.6 in thiopentone sodium. In anaesthetic doses it did not produce significant hormonal effects or cause salt retention. Gordan *et al.* (1955) studied its effects on cerebral metabolism in man, and reported changes identical with those of barbiturate anaesthesia. Thus emboldened, they used the drug together with nitrous oxide for a prefrontal leucotomy.

Murphy *et al.* (1955) described a series of 125 patients anaesthetized with viadril. The duration of anaesthesia varied from 1 to 10 hours.

The known disadvantages of viadril anaesthesia are the risk of venous thrombophlebitis and the slowness of induction.

Venous Thrombophlebitis.—This occurred in three of the cases described by Murphy *et al.* Their three patients, however, had severe pre-existing vascular disease. In an attempt to obviate this I injected the drug slowly into the giving-set tubing of a normal-saline drip, just below the inspection chamber. The drip was set to run at its fastest into a large vein of the arm. Two of the cases here

reported (Nos. 7 and 19) developed thrombophlebitis in spite of these precautions. In Case 7 on the day after operation the patient complained of a painful red swelling of the forearm and arm, which he did not regard as of major importance and which improved steadily day by day. A week later a cord-like thrombosis started at the site of injection in the cephalic vein at the wrist and extended by minor vessels on the volar aspect of the forearm to the basilic vein, which was thrombosed almost as far as the axilla. The veins were slightly tender throughout their length and there was some limitation of extension at the elbow due to tenderness.

Thrombophlebitis in the median basilic vein developed in Case 19. Five days later this could be felt as a solid cord from the elbow to the axilla, and was discoloured throughout this length. It was not, however, very painful or tender.

Slow Induction.—This is a marked feature of the drug and is something of a problem in the course of a busy operating session. Doubtless further chemical research on the compound will disclose a substance with a shorter time-lag. Gordan *et al.* (1955) suggest, in fact, that an intermediate metabolite of viadril is the cause of the anaesthesia. This would explain the delay in onset of unconsciousness. A search for this substance is being carried out.

Pharmacology

In many endocrine disorders disturbed mental or psychological function is seen. Myxoedema, hypoglycaemia, hypo- and hyper-parathyroidism, hypopituitarism, and Addison's and Cushing's diseases are examples which spring readily to mind. The use of cortisone and corticotrophin has familiarized many with the dramatic euphoria and psychoses which these agents provoke.

Merrymann *et al.* (1954), whilst investigating progesterone in psychiatric practice, found that several of their patients fell asleep. Woodbury (1952) studied the effect of steroids on electric convulsion therapy. He showed that deoxycortone is a powerful anticonvulsive agent.

The steroids exert a regulatory influence upon cerebral metabolism, as shown by the high rate of oxygen uptake of the brain of the castrate immature male rat. By administering various steroids this increased oxygen uptake can be reduced. The steroids with the androstene nucleus (including testosterone and 21-C steroids) can restore this "braking" action, which is normally exerted upon cerebral metabolism by the sex hormones.

The intravenous injection of viadril causes loss of consciousness, analgesia, absent corneal reflex, and muscular relaxation, particularly of the larynx. It has no demonstrable hormone effects. No electrocardiographic changes have been observed. No haemolysis occurs with its use. There is no depression of respiration. Slight pain is sometimes noted in the recipient vein with dilutions higher than 2.5%. Hypotension commonly occurs, but small doses of pressor drugs soon restore the blood pressure. Nitrous oxide has a remarkable synergism with viadril. If necessary, relaxant drugs, pethidine, and the volatile anaesthetic agents can be given at the same time as viadril, though much smaller doses are needed.

Technique of Administration

Viadril was supplied for this clinical trial in bottles containing 500 mg. The addition of 19.8 ml. of normal saline results in a 2.5% solution. This is injected into the tubing of a giving-set, as already described. If the patient is engaged in conversation he will say he feels nothing. After a minute or two the creases in the face begin to smooth out. Blinking begins and finally the eyes close. Soft snoring supervenes a minute or two later. This process takes about five minutes. The observer cannot but be struck by its resemblance to the coming of ordinary sleep. The fact that viadril is a steroid promotes interesting speculation into the mechanism of normal sleep. Viadril induction is quite different from thiopentone induction. There is

no yawning or sighing. The patient has no feeling that "something is about to happen." There is no unpleasant smell or taste.

After the patient has fallen asleep, quite naturally as it were, he remains peacefully in that condition. There is no stertor. The colour remains pink and the pulse is unchanged. The patient is now allowed to breathe 20-30 breaths of a nitrous oxide and oxygen mixture in the proportion of 3 litres of the former to 1 litre of the latter. This dilute mixture can be given with the utmost confidence, owing to the remarkable synergistic effect of nitrous oxide and viadril.

At the end of this induction it will be found that the laryngeal reflex has been obtunded and intubation with a cuffed tube can now be carried out. The patient may "buck" slightly but soon settles down. With the doses that I have used breathing continues normally and hyperpnoea may occur, but in spite of this there is very little resistance to assisted respiration and the patient's breathing can be "taken over" almost at once. Relaxation is good, though not comparable to that of gallamine triethiodide or suxamethonium. Bleeding is usually much reduced. The blood pressure may fall, but it responds very quickly to small doses of vasopressors. Throughout, the colour of the skin is pink. At the end of operation the nitrous oxide is cut off and coughing begins, quickly followed by grimacing. On return to the ward the patient lies in an apparently normal sleep. After a short period he can be roused. At the end of an hour or so he is fully awake, and in reply to questions will say he feels well *and is in no pain*. Euphoria is a distinct feature of this agent. Vomiting occurred in only one of the cases here reported.

At all times my supplies were restricted, and it will be seen that only one patient received as large an amount as 1,250 mg. of viadril (Case 6).

American workers report the use of other adjuvants, pethidine, gallamine triethiodide, and suxamethonium being used. It must be remembered, however, that the duration of their operations much exceeds common British practice. Analysis of one American series (personal communication) of 57 cases in which viadril was given yields the following figures. Of the 28 cases in which the duration is mentioned

the average time was 3½ hours, the individual times ranging between half an hour (one case) to 8½ hours (one case). The average dose of viadril was 1,301 mg., ranging from 500 (one case) to 3,000 mg. (one case). Of these cases, 18 received pethidine, the average dose being 66.6 mg., ranging from 15 (one case) to 210 mg. (one case). The other adjuvants mentioned were thiopentone, 175 mg.; 2 ml. of D-tubocurarine chloride and suxamethonium chloride for the peritoneal closure; D-tubocurarine chloride, 5½ ml.; D-tubocurarine chloride, 4½ ml.; "small amounts of suxamethonium"; and "a suxamethonium drip" (no total mentioned).

In my series of 19 cases the average time was 26 minutes, ranging from 8 (one case) to 90 minutes (two cases). The average dose of viadril was 824 mg., ranging from 500 (two cases) to 1,250 mg. (one case). All except three were premedicated with "omnupon," ½ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.). In Case 4 morphine, ½ gr. (22 mg.), and atropine, 1/100 gr. (0.65 mg.), and in Case 8 morphine, ½ gr. (11 mg.), and atropine, 1/100 gr. (0.65 mg.), were given; another had pethidine, 100 mg., and atropine, 1/100 gr. (0.65 mg.). None received pethidine during the operation. Case 6 (see below) required 80 mg. of gallamine triethiodide and Case 8 50 mg. of suxamethonium. Local infiltration of lignocaine and adrenaline to obviate bleeding was used as routine in three cases (two thyroidectomies and one dacryocystorhinostomy). Chlorpromazine was used in Case 1. No significant reaction was noted.

A précis of the anaesthetic case histories is given in the Table, and three fuller histories are given to bring out various points.

Illustrative Cases

Bad Risk: Case 8.—Man aged 76. General condition very poor, ears cyanosed, tongue very dry and furred. Emaciated. Ill for six weeks with "stomach trouble." Very deaf; extremely difficult to take history. Barium enema previous week showed "large filling defect" of stomach. Perforated eight hours previously. Premedication: morphine, ½ gr. (11 mg.), and atropine, 1/100 gr. (0.65 mg.). Temperature 102° F. (38.9° C.), pulse 112, B.P. 160/100. At 11.33 viadril, 400 mg., injected into drip. 11.38: patient

Summary of Anaesthetic Case Reports

Case No.	Sex and Age	Operation	Pre-operative Condition	Pre-medication	Viadril (mg.)	Conduct of Operation	Length of Op. (min.)	Post-operative Condition*	Vomiting
1	M 73	Cystoscopy; extravesical prostatectomy; bilateral vasectomy	Very good; has large scrotal hernia. B.P. 140/80	Omnupon, ½ gr.; scopolamine 1/150 gr.	750	Excellent relaxation. Hypotension relieved by methylamphetamine 30 mg. Chlorpromazine 50 mg. intramuscularly*	60	After ½ hour could be roused; said, "I feel all right." Eight hours later was reading newspaper. Developed thrombophlebitis	No
2	M 55	Cystoscopy; extravesical prostatectomy; bilateral vasectomy	Excellent. B.P. 120/70	Omnupon ½ gr.; scopolamine 1/150 gr.	750	"Some fullness" in arm during induction. Relaxation excellent. Patient almost "apnoeic at will"—i.e., breathing can be easily taken over. B.P. fell to 155/90	62	1½ hours later: excellent condition, says he has no pain	"
3	M 73	Transvesical prostatectomy; bilateral vasectomy	Fair. Was admitted 4 days earlier for emergency suprapubic cystostomy for retention. 84 fl. oz. urine evacuated from bladder. Haemoglobin 69%; blood urea, 105 mg./ml. B.P. 170/80	Omnupon ½ gr.; scopolamine 1/150 gr.	750	Patient coughed once or twice. When N ₂ O/O ₂ mixture was raised from 3/1 to 6/1 patient relaxed. B.P. fell from 170/80 to 95/50, but methylamphetamine 15 mg. restored this to 150/80	40	Patient answered to his name ½ hr. later. Four hours later was in excellent condition and free from pain	"
4	M 80	Partial thyroidectomy	Good. Deviation of trachea. B.P. 210/100	Morphine ½ gr.; atropine 1/100 gr.	500	Local infiltration of lignocaine and adrenaline. Excellent anaesthesia. B.P. fell to 120/70. Surgeon says, "practically no bleeding"	33	Twenty minutes later was rousable. One hour later: sitting up; says he is "dry"	"
5	M 47	L. Keller's operation	Good	Omnupon ½ gr.; scopolamine 1/150 gr.	750	Very satisfactory	30	75 minutes later patient dozing. On being roused says "feels fine"	"

* Routine: This surgeon uses adrenaline 0.1 mg. in 60 ml. water as a prostatic capsule haemostatic. The chlorpromazine is here used as a prophylactic against pressor effects. B.P. fell steadily until unreadable, though pulse good. Methylamphetamine 30 mg. restored B.P. to 120/70 immediately.

Summary of Anaesthetic Case Reports.—Contd.

Case No.	Sex and Age	Operation	Pre-operative Condition	Pre-medication	Viadril (mg.)	Conduct of Operation	Length of Op. (min.)	Post-operative Condition	Vomiting
6	M 75	See text							
7	M 53	Excision of hydrocele	Good	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Some hyperpnoea, but soon abolished by raising N_2O/O_2 mixture from 3/1 to 5/1	18	Two hours and a half later: dozing—says "feels fine" Developed thrombophlebitis	No
8	M 76	Laparotomy	See text						
9	M 29	Trendelenburg. Stripping of veins of lower limb	Good. Is a eunuch (post-mumps)	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	750	Patient "bucked" on tube a good deal. Owing to shortage of supply only 750 mg. viadril given. Would have been better with 1,000 mg. B.P. pre-op. 100/60; during operation 120/60	30	Patient dozing in ward an hour later but easily roused	No
10	F 50	Local excision of tumour of breast	Good. B.P. 135/80	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Very relaxed throughout. Very satisfactory result. B.P. fell to 85/60	25	Two hours later patient sitting up in bed	"
11	M 20	Right inguinal herniotomy	Good. B.P. 145/75	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Good anaesthesia. Surgeon complained at beginning of operation that muscles were tonic, but assisted respiration obviated this	21	Two hours later patient sitting up in bed	"
12	F 32	See text							
13	F 17	Right lateral rectus resection and recession	Excellent. B.P. 130/65	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	750	Very quiet smooth anaesthesia. B.P. rose to 150/100 (? CO_2 retention) then fell to 115/70	11	Quickly recovered	No
14	F 39	Rt. dacryocystorhinostomy	Good. Apprehensive. B.P. 110/70	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Asleep under five minutes. Nose packed with gauze soaked in 0.2 ml. cocaine hydrochloride 15% containing 0.5 ml. adrenaline (1:1,000). Local infiltration of eyelids with lignocaine containing 1:80,000 adrenaline. After intubation nasopharynx packed. B.P. rose to 135/80. Excellent anaesthesia. Colour pink, bleeding minimal, quiet respirations; B.P. 85/60. Pulse 80	70	Forty minutes later patient says she feels fine; "eve does not hurt"	Yes
15	M 50	(1) Right inguinal herniotomy. (2) Appendectomy	Good. Fat man; looks old. Thyroidectomy 20 years previously (? myxoedema)	Omnopon $\frac{1}{2}$ gr.	750	B.P. fell steadily from 100/80 to 60/50 at 42nd minute. Pulse 70. Methylamphetamine, 15 gr., had no effect. On repeating dose B.P. rose to 130/80. Two hours later in ward, sitting up, delighted to have had operation. Surgeon's comment: "Certainly does not look like man who had an operation two hours ago"			No
16	F 35	Local excision of tumour of breast	Excellent. B.P. 130/100	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	750	Asleep in five minutes. Easily intubated under N_2O/O_2 3/1	20	Seen by surgeon 3½ hours later. Patient sitting up in bed complaining of slight headache	"
17	M 53	Dilatation of urethra	Good	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	500	No nitrous oxide. Slept peacefully throughout procedure. Jaw not relaxed. Breathing quiet; B.P. fell from 195/100 to 130/80, with pulse 66	8	Excellent. Rapid recovery	"
18†	F 50	Radical mastectomy	"	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Very satisfactory anaesthesia. Bleeding very troublesome. This was due at first to slight respiratory obstruction due to kinking of endotracheal tube. Excessive bleeding persisted after this had been dealt with and in spite of fall in B.P. from 160/90 to 115/105 and very quiet respiration; transfused with 1 pint of blood during operation	90	Fair. Coughing at end of operation but appears shocked. P. 110. Contents of re-breathing-bag show CO_2 content = 0.3%. Collapsed after return to ward and required further pint of blood to restore her condition	"
19	F 28	Partial thyroidectomy	Good, thin; was toxic 3 months previously but not now; has been treated medically	Omnopon $\frac{1}{2}$ gr.; scopolamine 1/150 gr.	1,000	Local infiltration with lignocaine and adrenaline. Breathing quiet and shallow. Occasionally "bucked" slightly when trachea was disturbed, but assisted respiration overcame this within 3 or 4 breaths. Very satisfactory anaesthesia	90	Excellent. Coughed as soon as tube was removed and nodded head when spoken to. 80 minutes later patient conscious in ward; had slightly sore throat when swallowing. Developed thrombophlebitis	"

† This is the same patient as Case 10.

sleeping lightly; viadril, 250 mg. (total, 650 mg.); ears now pink. N_2O/O_2 (3/1) begun; patient intubated. 11.45: on table, almost apnoeic; B.P. 170/70, pulse 120. 11.50: abdomen opened; fluid in peritoneum (stomach contents); carcinoma of stomach found with many secondaries in liver; B.P. 150/80, pulse 150. 12.05: operation very difficult on account of secondary involvement of mesentery, peritoneum, colon, etc., and adhesions between all these organs. Blood transfusion begun. The perforation could not be found. Three pints (1.7 litres) of fluid were aspirated from the peritoneum and the heart began to fibrillate (B.P. 100/60, pulse 118, respirations 36). Methylamphetamine hydrochloride, 30 mg., restored the B.P. to 120/80. At 12.30, the perforation not having been found, the peritoneum was closed. One-half was sutured with ease. The patient now began to tighten up. Suxamethonium, 50 mg., relaxed him at once. The operation was completed at 12.40; the patient was then pale, but pink, with a dry skin. The pulse was of good volume but fibrillating. Death occurred on the fifth post-operative day.

Very Satisfactory Anaesthetic: Case 12.—Woman aged 32. Operation: medial rectus recession. Premedicated with omnopon, $\frac{1}{2}$ gr., and scopolamine, 1/150 gr. B.P. 110/70. At 9.59, viadril, 750 mg. (B.P. 130/65, pulse 120). 10.02, asleep. 10.04: N_2O/O_2 (3/1) begun. 10.06: intubated. 10.12: patient nearly apnoeic (B.P. 115/60). 10.20: breathing regular and of adequate volume. 10.25: operation completed, N_2O/O_2 stopped; coughed immediately. At 11.00 the patient was seen in the ward, sleeping. Easily aroused, she asked—although the conjunctival sac of the affected eye was filled with blood—“Have I been done?” and when reassured said, “Lovely; I’ve been asleep.”

Unsatisfactory Anaesthetic: Case 6.—Man aged 75. Operation: herniotomy and repair; orchidectomy. A very fit, well-built man who appeared younger than his years. B.P. 180/80. At 11.04, viadril, 750 mg. 11.12: patient was “just asleep,” N_2O/O_2 (5/1) begun. 11.17: not relaxing; viadril, 250 mg. 11.22: unable to intubate. 11.30: viadril, 250 mg. 11.35: intubated; still coughing. 11.40: relaxing (B.P. 100/60). 11.45: methylamphetamine hydrochloride, 20 mg. 11.48: patient still coughing (B.P. 110/70). 11.50, N_2O/O_2 still running at 5/1; patient resented cord being pulled. 11.53: orchidectomy complete; operation proceeding with difficulty. 12.10: gallamine triethiodide, 80 mg. 12.15: B.P. 120/80, pulse 100. 12.25: operation completed, neostigmine, 25 mg., atropine, 1/100 gr. (0.65 mg.), patient began to cough immediately. N_2O cut off.

On consideration of Case 6 it was thought that the viadril when being injected into the tubing of the drip was going up into the saline bottle. As a result the routine was instituted of closing off the tubing by means of a clamp whilst the injection was actually being given, a few millilitres at a time; stopping the injection; opening the clamp to dilute the viadril; then repeating the process as often as necessary until the full dose had been given.

Summary

A steroid, viadril (21-hydroxypregnane-3:20-dione sodium succinate), has been used as an anaesthetic in 19 cases. The pharmacology of the drug is discussed and the mode of administration described. Usually premedication was with omnopon and scopolamine, and maintenance by nitrous oxide and oxygen. In some cases relaxants were also given.

Viadril anaesthesia resembles normal sleep; relaxation is fairly good and bleeding usually much reduced. The patient is fully awake in an hour or so after operation, feeling well and without pain. Hormonal effects are absent and vomiting is rare.

Disadvantages are the slowness of induction and the risk of thrombophlebitis in the injected arm. Measures to combat these are suggested.

Details of the 19 cases are tabulated, and three case histories given to emphasize special points.

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FAMILIAL TUBEROUS SCLEROSIS

BY

W. M. JORDAN, B.M., B.Ch., D.Obst.R.C.O.G.
Late Senior House Officer, Solihull Hospital; Lately
Captain, R.A.M.C.

Tuberous sclerosis was first diagnosed in 1880 by Bourneville, who described the case of an epileptic imbecile who died of the disease; and the disease was named after the discoverer. The fully developed disease is manifested classically by infantile epilepsy, mental defect, and the characteristic facial eruption of adenoma sebaceum. It is a rare hereditary disorder of tissue growth, in which many different tissues may be affected and many varying clinical syndromes found. It may be familial, and such an afflicted family is described.

Family History

The composition of the family is shown in Fig. 1. The family is mainly domiciled in Malta, and is compounded of mixed Anglo-Maltese racial stock. The heredity is com-

FIG. 1.—Family tree, showing four members affected with tuberous sclerosis. The ages of living members examined are shown. The grandfather married his first wife's sister.

plicated by the two marriages of the grandfather, who married his deceased wife's sister. The four patients affected by tuberous sclerosis are all alike, showing the typical facies, and anxious family inquiry is made whenever a child is born into the family. All other members of the family are of normal facial appearance and are reputedly healthy.

Case 1

This young girl died in convulsions at the age of 14 years in 1935. Zahra Neumann (personal communication) states