STEROID ANAESTHESIA: A CLINICAL TRIAL WITH 'PRESUREN' BRAND HYDROXYDIONE

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In 1941, while investigating many different steroid hormones, Selye[1] noticed that some of them had a sedative action on the central nervous system and produced anaesthesia in the laboratory animals on which he tested them. On further investigation of these steroids he found that those with the most powerful anaesthetic action were desoxycorticosterone, progesterone and pregnandione. The latter, however, was the only one that had no hormonal activity.[2, 3]

Laubach,[4] in 1955, systematically investigated a large number of steroids derived from these hormones for their anaesthetic or hypnotic action in animals. As a result, he suggested that a derivative of pregnandione, i.e. the sodium hemisuccinate of 21-hydroxypregnane-3,20-dione (known as hydroxydione) would be suitable for human anaesthesia He based his suggestion on a number of factors, viz. that it had a higher therapeutic index than thiopentone, was soluble in water, was non-carcinogenic, had no hormonal activity, and did not cause salt or water retention.

In 1955, Gordan *et al.*,[5, 6] and also Murphy,[7] first used hydroxydione, 'Viadral' brand, clinically in the USA. They reported favourably on its action. Since then it has been reported on by many others in Britain[8] and on the Continent,[9] and in South Africa by Kok and Knipe.[10] Initially used in solutions of strengths varying from 0·1% to 2·5%, several drawbacks to its use became apparent: The technique was cumbersome, involving the setting up of intravenous transfusions; a large volume of fluid was required; it produced a high incidence of thrombophlebitis in the veins through which it was introduced. Stedtfeld[9] increased the strength of the hydroxydione solution to 5 or 10%. Using warm saline as the solvent, and injecting the solution as rapidly as possible, he claimed the virtual elimination of thrombophlebitis.

The 'Presuren' brand hydroxydione used in this trial on 100 cases is the sodium hemisuccinate of 21-hydroxypregnane-3,20-dione. It is produced as a white powder in 1·0 g. and 0·5 g. rubber-stoppered bottles. It is soluble in water, saline and procaine, and can be administered as a 2·5, 5 or 10% solution.

The advantages of using these higher concentrations are mainly in the ease of administration. It can be given as a single injection. The necessity of setting up an intravenous drip is avoided and the tachycardia produced by the relatively large volume of fluid is eliminated. Painful thrombophlebitis is absent and the onset of anaesthesia is rapid compared with the period of 10 minutes or more which is usually required when the weaker solutions are used.

Presuren is miscible with thiopentone, gallamine, atropine,

neostigmine and methyl-amphetamine, but not with pethidine, d-tubocurarine or suxamethonium chloride.

DOSAGE AND ADMINISTRATION

Because of the previously described advantages of using a higher concentration of Presuren, 5% or 10% solutions were used as the anaesthetic in a series of 100 unselected patients ranging in age from 13 to 88 years. The 5% solution was administered to 41 patients and the 10% solution to 59. The 10% concentration produces a quicker and more powerful onset of anaesthetic action. The types of operation and the age distribution of the patients are indicated in Tables I and II.

TABLE I. TYPES OF OPERATIONS PERFORMED

Gastrectomy	4	Laryngectomy and block dissection of neck glands	3
Gastro-enterostomy	3	Fenestration	1
Biliary tract	7	Cranio-angiogram	1
Appendicectomy	9	Tonsillectomy	1
Herniorrhaphy	6	Caesarean section	14
Hemi-colectomy	2	Wertheim's hysterectomy	3
Abdomino-perineal resection of rectum	1	Abdominal hysterectomy	7
Repair of perforated duodenal ulcer	2	Vagina and perineum	17
Laparotomy for intestinal obstruction	4	Ovarian tumours	3
Mastectomy	3	Spinal fusion	1
Lumbar sympathectomy	1	Smith-Petersen pin and plate	2
Trendelenburg and stripping of varicose veins	4	Compound fractures femur and tibia	1
		Total	100

TABLE II. AGE DISTRIBUTION

10–20 years	7	51–60 years	12
21–30 years	19	61–70 years	18
31–40 years	14	71–80 years	12
41–50 years	16	81–90 years	2
		Total	100

Warm saline was the solvent used in all the cases. Recently Galley and Lerman[11] have published a report on the use of 0·25% procaine as the solvent, which, they state, prevents any pain on injection.

The patients were all premedicated with 1/3 gr. of omnopon and 1/150 gr. of scopolamine, or 50 mg. of pethidine and 1/100 gr. of atropine, depending on their age. Women undergoing Caesarean section were premedicated with atropine only.

Ten or 20 c.c. of sterile normal saline, according as whether 10% or 5% solution was used, was injected into a 1·0 g. bottle of Presuren. The stoppered bottle was then placed in a bowl of hot water at a temperature of 50° - 60°C and left there for 2 - 3 minutes. The warm solution was then drawn up into a glass syringe and immediately injected into the vein. Large veins in the antecubital fossa were used in preference to the veins on the dorsum of the hand, and all the same precautions were used as in the administration of thiopentone. The effects of accidental paravenous or intra-arterial injections of Presuren have been reported to be the same as with thiopentone.[12]

From previous reports it has seemed that pain and thrombophlebitis have been due to prolonged contact of the Presuren solution with the intima of the vein.[9] To counteract this, the dose of Presuren was injected as rapidly as possible, the time never exceeding 15 seconds. The needle was then withdrawn and the vein gently massaged in a proximal direction. The same vein was not used for subsequent injections of relaxants and adjuvant drugs. Care was taken to prevent over-abduction of the arm and over-extension of the elbow, since these positions are believed to delay the emptying time of the veins of the arm.[12]

None of the patients developed any post-operative thrombophlebitis, which was frequently reported where very dilute solutions were used. Slight pain in the arm radiating sometimes up to the shoulder was experienced in 18 cases. In no case was it severe and it always disappeared at the end of the injection.

The dosage of Presuren used to produce an adequate level of basal narcosis without respiratory depression was that suggested by Landau,[13] viz. 6 - 8 mg./lb., or a reduced dosage of 5 mg./lb. in aged, cachectic and under-weight patients. In practice, the initial injection in an average healthy adult did not exceed 1·0 g. The total amount of Presuren administered varied from 0·5 g. to 2·0 g. (in divided doses) in the longer operations. Sleep was induced with doses as low as 0·5 g.

The patients usually fell asleep within 2 or 3 minutes. An airway was then inserted, a mask placed on the face, and nitrous oxide and oxygen administered in the ratio of 5 : 2. Nitrous oxide shows a marked degree of synergism with Presuren and most of the operations were performed with these two only as the analgesic agents. The patient was usually sufficiently anaesthetized for the operation to begin about 8 or 10 minutes after the initial injection. Lightening of anaesthesia was indicated by slight movements, and supplementary injections of 0·2 - 0·3 g. of Presuren were then administered. In longer cases it was found that the initial injection lasted from 1½ to 2½ hours.

Trilene, ether, and cyclopropane were used to augment anaesthesia in a number of cases without any untoward effects.

Larynx. Presuren has a depressant effect on the pharyngeal and laryngeal reflexes as compared with thiopentone, which often stimulates them, causing laryngeal spasm. After the patient has been asleep for 3 - 4 minutes a laryngoscope could be gently introduced and an endotracheal tube could be passed through the open vocal cords. There was usually slight bucking as the tube was inserted, but this soon subsided. In cases where it was impossible to intubate in this manner 25 mg. of suxamethonium chloride was all that was needed to relax the cords. Because of its depressant effect on the laryngeal reflex it is unwise to use Presuren in operations of short duration, for there is the danger of sending the patient back to the ward with wide open vocal cords and all the possible consequences of this condition.

Respiration. With the dosage used, Presuren did not appear to have any noticeable effect on either rate or depth of respiration. This is a noticeable advantage over thiopentone with its ever-attendant dangers of possible respiratory depression. No bronchospasm was seen and it was well tolerated in patients with emphysema, chronic bronchitis and asthma.

Pulse rate and blood pressure. No alteration in the pulse rate was noticed, except in the cases where gallamine was used as the relaxant. No arrhythmias were seen in any patient. The normal systolic blood pressure usually dropped by 10—20 mm.Hg in the first 15 minutes after injection, but almost invariably returned to its normal level by the end of the operation. In 6 cases the systolic blood pressure dropped below 90 mm.Hg, but all responded to the injection of methyl-amphetamine. These cases were all in patients over the age of 60. In hypertensive patients the drop was more

pronounced, often dropping from about 180/120 mm.Hg to about 120/90. The return to their normal high level was generally slower.

Experimental work in cats suggests that hydroxydione causes hypotention by inhibition of the vasoconstrictor centre of the brain, with also a direct vasodilator action on the peripheral vessels.[14] Inhibition of the vasoconstrictor centre seems to be confirmed in man by the onset of hypotension with loss of conciousness, and the peripheral vasodilatation by the response to methyl-amphetamine.

Post-operative course. The time of waking after the end of the operation varies according to the dosage of Presuren administered. Where more than 1·0 g. was used, the return to consciousness often took up to an hour, although the cough reflex returned very soon after the end of the operation. The majority of the patients were awake within a few minutes after removal of the mask.

Post-operative vomiting occurred in 10 cases and a marked feature of the immediate post-operative period was the feeling of well-being experienced by most of the patients.

TYPES OF OPERATION

(*a*) *Head and neck.* Presuren appears to be an ideal anaesthetic for long operations in this region, e.g. laryngectomy and block dissection of neck glands. The depression of the laryngeal reflex is a distinct advantage and obviates the need for relaxants to obtund this reflex. Supplementary injections of Presuren were usually only required after the operation had been in progress for 2 hours and the patients tolerated doses of up to 2 g. very well.

(*b*) *Abdominal operations.* Varying degrees of relaxation of the muscles of the abdominal wall were produced by Presuren. For most lower abdominal operations, e.g. appendicectomy and ovarian cystectomy, no relaxant at all was required. In upper abdominal operations half the normal dose of relaxant was all that was needed to produce adequate relaxation. Controlled respiration could be initiated with relatively reduced amounts of relaxants.

(*c*) *Caesarean section.* In the 14 Caesarean sections that were performed under Presuren, the hydroxydione did not appear to cross the placental barrier in appreciable amounts.[15] After induction with 1·0 g. of Presuren, anaesthesia was maintained with nitrous oxide and oxygen only. Occasionally a small dose of suxamethonium chloride was needed when the peritoneum was closed. All the babies delivered, except 2, cried either immediately or within a minute or two. The 2 exceptions weighed 5 lb. and 4 lb. and were delivered from patients who were undergoing Caesarean section for pre-eclamptic toxaemia at 34 and 32 weeks respectively. Both these babies cried only an hour after delivery and died within 48 hours. Because of their prematurity it was felt that Presuren was not a contributing factor. In none of the 14 cases did any vomiting occur during anaesthesia.

(*d*) *Operations in the elderly.* Presuren was used without mishap in the 32 patients whose age was over 60. Doses of up to 1·0 g. were well tolerated, but in patients in poor condition the dose was reduced to 0·5 g. Two octogenarians with fractured necks of femur were anaesthetized for the insertion of Smith-Petersen pins and plates. They showed no untoward effects whatever.

(*e*) *Operations in bad-risk patients.* As Presuren has no effect on respiration and only slight effect on the blood pressure the risks of anoxia and severe hypotension are reduced and for this reason Presuren is an ideal anaesthetic for bad-risk patients. It was used satisfactorily in 4 bad cases who were undergoing laparotomy for intestinal obstruction. Regurgitation of stomach contents during or after induction was not a feature in any of them. It was also used in a patient suffering from porphyria, and in this condition, in which barbiturates are contra-indicated, it seems to be the anaesthetic of choice.

(*f*) In the *other operations* (Table I), e.g. mastectomy, Trendelenburg, etc., Presuren with nitrous oxide and oxygen was found to produce satisfactory, uneventful anaesthesia.

In Table III the dose of Presuren and of supplementary drugs is shown for certain illustrative operations. The duration of the operations is also shown.

TABLE III. TYPES OF OPERATIONS SHOWING DOSAGE OF PRESUREN AND OF SUPPLEMENTARY DRUGS

Operation	*Age*	*Total Dose of Presuren (mg.)*	*Dose of Relaxant (mg.)*	*Dose of Analgesic (mg.)*	*Operating time (minutes)*
Partial gastrectomy ..	71	1,000	G.80 S.25	—	95
Laryngectomy and block dissection of glands of neck	62	2,000	—	P.50	300
Appendicectomy	17	1,000	—	—	29
Caesarean section	24	1,000	—	—	50
Laparotomy (freeing of adhesions causing volvulus)	68	500	G.60 S.25	—	23
Abdominal hysterectomy	37	1,000	G.40	—	90
Cholecystectomy	76	1,000	G.80	—	51
Smith-Petersen pin and plate	88	500	—	—	35

G. = Gallamine triethiodide. S. = Suxamethonium chloride. P. = Pethidine.

SUMMARY AND CONCLUSIONS

A steroid, Presuren brand hydroxydione, was used as a basal anaesthetic in 100 patients. It was used as a 5% or 10% solution, with warm saline as the solvent. Induction is smooth and pleasant. Nitrous oxide has a synergistic action, and reducer doses of relaxants produce adequate relaxation.

Provided care is taken with the injection, post-operative thrombophlebitis should not occur; no evidence of this was seen in any of the patients in this series.

Respiration was unaffected and lowering of blood pressure slight. Where hypotension did occur it could be easily corrected with methyl-amphetamine. Presuren has a depressant effect on the laryngeal reflex. In Caesarean sections it does not appear to cross the placental barrier.

Presuren has a wide safety margin. It can be used for most operations and can be given with confidence in elderly and poor-risk patients.

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