EVALUATION OF CARDIOVASCULAR, RESPIRATORY AND GENERAL PHARMACOLOGIC PROPERTIES OF HYDROXYDIONE

F. A. Montmorency, M.D., A. Chen, M.D., H. Rudel, M.D.
W. W. Glas, M.D., L. E. Lee, Jr., M.D.

Selye (1, 2) first reported the central depressant action of the steroids in 1941. However, little attention was given to the possible clinical use of steroid anesthesia until Laubach, P'an and Rudel (3, 4) reported the anesthetic properties of hydroxydione (21 hydroxypregnane-3, 20-dione sodium succinate) in 1955. Since that time, there have been numerous clinical studies evaluating the effects of hydroxydione. It was thought that further pharmacologic observations on the effect of this agent in man were warranted. This study was designed to quantitatively determine the cardiovascular-respiratory and general neuromuscular effects of hydroxydione in male humans under rigidly controlled conditions when used as the sole anesthetic agent. Prior to this study in human beings the methodology was standardized in mongrel dogs.

Methods

The subjects selected were all normal adult males requiring anesthesia for the performance of minor surgical procedures of short duration and not accompanied by significant blood loss. They showed no evidence of cardiovascular, respiratory, cerebral, hepatic, renal, hematologic, endocrine or metabolic disorders as judged by extensive clinical and laboratory examinations. The subjects were 39 to 55 years of age. Their surface areas varied from 1.70 to 1.99 square meters.

In all but the first 3 patients, an induction dose of 20 mg./kg. hydroxydione was administered intravenously as a 5 per cent solution in water. This dosage was given rapidly and followed by a 5 per cent glucose flush. In the first 3 patients, the 20 mg./kg. induction dose was given over an approximate ten minute period. Additional doses were given up to a maximum of 40 mg./kg if electroencephalographic level 4 narcosis was not obtained.

Cardiac output was determined by a modification of the Stewart dye dilution technique. Prior to the performance of each series of dye dilution cardiac output determinations an 8–10 ml. sample of heparinized arterial blood was obtained for the preparation of standard solutions. A modification of the precision pipette method of

Received from the Departments of Anesthesiology and Surgery, Wayne County General Hospital, Eloise, Michigan, and accepted for publication April 2, 1958. Dr. Glas is Director of Surgery, Wayne County General Hospital; Dr. Montmorency is in the Department of Surgery, Wayne State University College of Medicine, Detroit 7, Michigan; Dr. Rudel is at the Squibb Institute for Medical Research, New Brunswick, New Jersey, and Dr. Lee is on the staff of the Veterans Administration Hospital, Washington, D. C.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

Etsten (5) was employed for the injection of the dye. Evans blue dye was volumetrically diluted to permit the withdrawal and injection of 1–5 mg. from a previously calibrated 1 ml. volumetric pipette. The dye solution was prepared aseptically and injected directly into the right ventricle through the cardiac catheter and followed by a flush of 10 ml. of sterile saline. The exact concentration of the dye injected was rechecked by spectrophotometric determinations of the injected solution. The amount of dye remaining in the volumetric pipette was determined and subtracted from the original preparation in the final determinations.

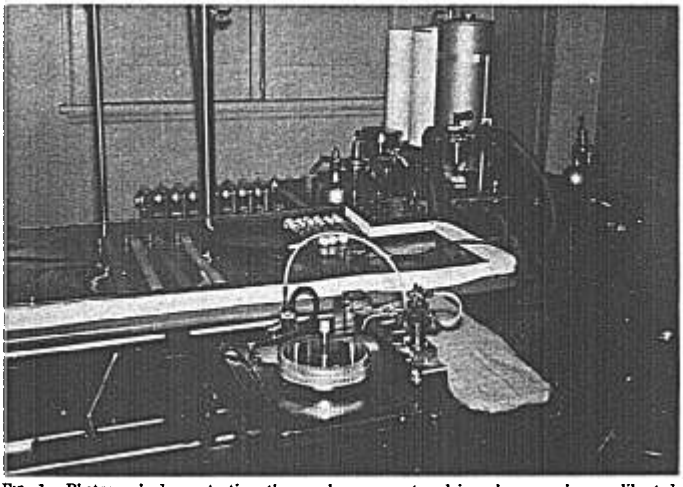

FIG. 1. Photograph demonstrating the synchronous motor driven kymograph precalibrated to collect samples at the rate of two per second.

Following the intravenous injection of the dye, arterial blood samples were collected from the radial artery in sixty siliconed, heparinized one milliliter vials attached to a drum driven by a synchronous motor kymograph precalibrated to collect samples at a rate of two per second. This apparatus is illustrated in figure 1. The samples were immediately centrifuged and refrigerated until read. The plasma dye concentration was determined on the Beckman DU spectrophotometer using semimicro technique correcting each determination for hemolysis and glycolysis as recommended by Gibson (6). Dye concentrations were plotted on a semilogarithmic graph paper and cardiac output determined by extrapolation. A sample graph of five serial determinations of cardiac output obtained at one sitting is shown in figure 2.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

Blood gases were determined by the method of Van Slyke and Neill (7, 8). The venous samples were obtained from the pulmonary conus or pulmonary artery by cardiac catheterization.

Respiratory excursions were recorded on a 9 l. Benedict-Roth recording spirometer (Collins respirometer) attached to a double 90 liter nonrebreathing box-bag apparatus (9). Compressed air was used as the respiratory gas mixture at all times.

Electroencephalograms were obtained continuously from bilateral fronto-occipital leads and recorded on a Grass direct writing electroencephalograph.

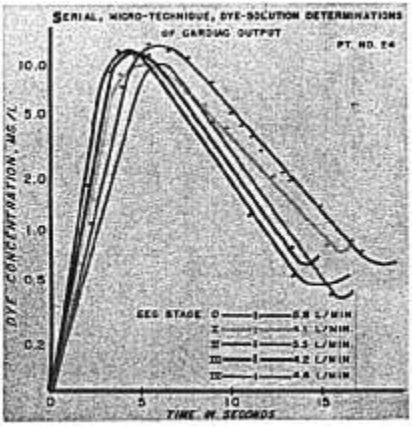

FIG. 2. A graph of five serial cardiac output determinations obtained at one sitting.

Intra-arterial blood pressure was obtained from the left radial artery by direct cannulization utilizing the Stratham Strain gauge and a Sanborn direct writing recorder.

The electrocardiographic standard lead 2 was monitored at all times on the Sanborn direct writing recorder.

RESULTS

Following the administration of the first initial dose of 20 mg./kg. of hydroxydione, there was an induction period which varied between three and eleven minutes. In all but one patient, electroencephalographic level 4 anesthesia was reached with the total dose administered. In this patient a total dose of 40 mg./kg. was administered and only electroencephalographic level 3 was obtained. The dose necessary to produce electroencephalographic level 4 narcosis varied from 14.7

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

TABLE 1

CORRELATION OF CARDIAC HEMODYNAMICS WITH DEPTH OF HYDROXYDIONE ANESTHESIA IN 10 HUMANS (DYE DILUTION METHOD)

Electrocardiographic Stage (*Number of Determinations*)	0 (4)	1 (1)	2 (7)	3 (5)	4 (4)
Heart rate	74	100	98	97	98
Stroke volume (cc.)	77	42	58	57	56
Cardiac output (l./minute)	5.7	4.2	5.6	5.4	5.5
Cardiac index (l./minute/m.²)	3.2	2.2	2.9	3.0	2.9
Change in cardiac index	—	−31%	−9%	−6%	−9%

to 40 mg./kg. These dosages were administered over a period of one to thirty-six minutes. With the induction dose of 20 mg./kg., all patients went to sleep but reached varying electroencephalographic levels of narcosis from stage 2 to 4.

The results of the cardiac output determinations are recorded in table 1 and illustrated in figure 3. Discounting stage one observations because of insufficient determinations, there was no significant change in cardiac index. However, there was a tachycardia in association with a decrease in the stroke volume. Stage 4 observations showed no greater decrease than was present at stage 2.

The results of intra-arterial pressure measurements are recorded in table 2 and further illustrated in figure 4. There is a moderate progressive reduction in pulse pressure of 37 per cent from normal to stage 4 narcosis. There is also a moderate progressive drop in both systolic and diastolic blood pressures of 23 and 14 per cent. Systolic pressures decreased somewhat more than did diastolic pressure resulting in a moderate narrowing of the pulse pressure. This is consistent with the reduction in stroke volume noted previously. The average maximum drop in mean pressure was 17 per cent.

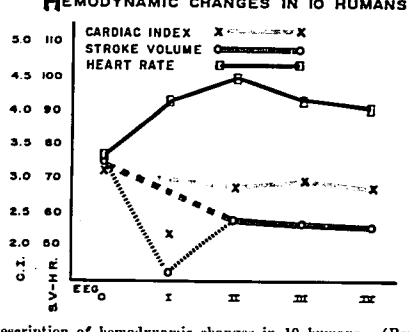

FIG. 3. Graphic description of hemodynamic changes in 10 humans. (Broken lines indicate an insignificant number of determinations of EEG stage 1.)

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

TABLE 2

TABULATION OF THE RESULTS OF INTRA-ARTERIAL PRESSURE MEASUREMENTS IN 10 HUMANS IN RELATION TO THE DEPTH OF ANESTHESIA (RADIAL ARTERY, MM. OF MERCURY)

Electroencephalographic Stage (*Number of Determinations*)....	0 (*10*)	1 (*5*)	2 (*15*)	3 (*15*)	4 (*11*)
Pulse pressure	49 (±9.9)	39 (±8.4)	36 (±11.5)	35 (±12.3)	31 (±8.3)
Systolic	122 (±17)	117 (±23)	110 (±23)	103 (±26)	94 (±18)
Diastolic	73 (±14)	78 (±22)	75 (±18)	68 (±21)	63 (±15)
Mean	87 (±14)	90 (±22)	87 (±19)	78 (±22)	72 (±16)
Change in mean	—	+3.5%	0.0%	−10%	−17%

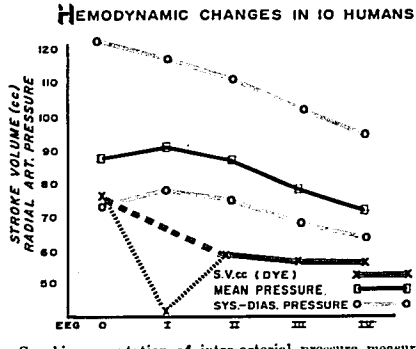

FIG. 4. Graphic presentation of intra-arterial pressure measurements.

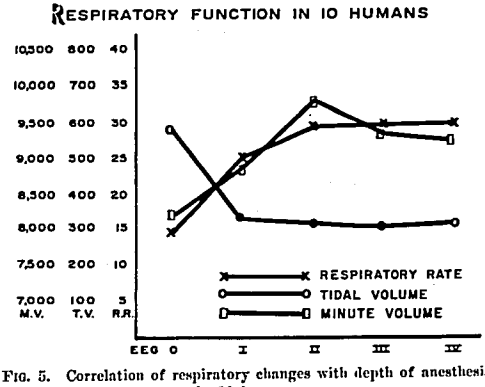

FIG. 5. Correlation of respiratory changes with depth of anesthesia in 10 humans.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

TABLE 3

RESPIRATORY FUNCTION STUDIES

Electroencephalographic Stage (*Number of Determinations*)....	0 (9)	1 (4)	2 (10)	3 (10)	4 (9)
Respiratory rate	15 (±2.0)	26 (—)	33 (±4.2)	30 (±4.4)	30 (±5.0)
Tidal volume (cc.)	573 (±97)	338 (—)	320 (±44)	315 (±52)	320 (±76)
Minute volume (l./minute)	8.2 (±1.3)	8.9 (—)	9.6 (±2.1)	9.4 (±2.7)	9.3 (±2.4)
Change in minute volume	—	+8.5%	+20%	+16%	+13%

There is an over-all increase in respiratory rate of approximately 100 per cent noted consistently in all stages of narcosis from 1 to 4. There is a concomitant reduction in tidal volume resulting in an increase in minute volumes from 8.5 to 20 per cent. These results are recorded in table 3 and illustrated graphically in figure 5.

No significant changes were noted in arterial oxygen content or saturation. The average maximum differences from the preanesthetic levels being 1.3 volumes per cent reduction in arterial oxygen content at electroencephalographic stage 2. Discounting the electroencephalographic stage 1 observations, because of insufficient number of determinations, there was a maximum average increase in venous oxygen content of only 1.1 volumes per cent. Average increases in both arterial and venous carbon dioxide of 3.5 and 2.9 volumes per cent were noted. This parallels the reduction in respiratory tidal volumes. Although the minute volumes of respiration are increased there is a less effective respiratory exchange. Arterial *p*H determinations were performed on the Beckman *p*H meter and an average difference from preanesthetic levels of only 0.02 was noted. The results of the blood gas determinations are shown in table 4.

Observations of the electroencephalographic levels of narcosis corresponded to those described by Bickford (10) for thiopental and are in agreement with those described for hydroxydione by Belleville and Howland (11). Stage 1 levels are very transient and the patient may be awake on recovery and still show level 1 to 2 depression on the

TABLE 4

BLOOD GASES

Electroencephalographic Stage (*Number of Determinations*)....	0 (4)	1 (2)	2 (6)	3 (6)	4 (4)
Arterial O_2 volume per cent	16.2 (—)	16.0	14.9	15.9	15.5
Arterial O_2 saturation per cent	91.	94.	92.	95.	91.
Venous O_2 volume per cent	11.4	13.0	11.4	12.4	12.5
Arterial CO_2 volume per cent	44.8	45.7	48.3	49.1	48.9
Venous CO_2 volume per cent	47.3	49.6	51.3	49.8	50.0

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024

electroencephalogram. The oropharyngeal reflexes are not obtunded until late level 3 narcosis is reached. In the induction period all subjects, except those who reached level 4 narcosis immediately following the administration of the induction dose, showed generalized muscular twitchings.

Summary and Conclusions

The cardiorespiratory effects of hydroxydione were studied in 10 normal subjects under conditions of controlled dosage using electroencephalographic guidance as to depth of narcosis. Only moderate changes in hemodynamics were noted which were characterized by tachycardia with a slight decrease in the stroke volume. However, the cardiac index remained essentially unchanged. A pronounced tachypnea was observed consistently through all stages of narcosis accompanied by a reduction in tidal volume resulting in an increase in minute volume. As with other anesthetic agents, there was no true dose response observed. A lag period of three to eleven minutes before onset of action was noted and generalized muscular twitching occurred during induction.

The authors wish to thank Miss Beverly Robinson and Mrs. Lorraine Malek for organization and operation of the laboratory facilities which made this study possible. This study was supported in part by a grant-in-aid from Pfizer Laboratories, Inc. The trade name for Hydroxydione is Viadril (Pfizer Laboratories).

This study was presented on the "Work in Progress" program at the annual meeting of the American Society of Anesthesiologists, Los Angeles, California, October 17, 1957, and an abstract was published in Anesthesiology 19: 108, 1958.

References

1. Seyle, H.: Studies Concerning Anesthetic Action of Steroid Hormones, J. Pharm. & Exper. Therap. 73: 127 (Oct.) 1941.
2. Selye, H.: Correlation Between Chemical Structure and Pharmacologic Action of Steroids, Endocrinology 30: 437 (Mar.) 1942.
3. Laubach, G. D., P'an, S. Y., and Rudel, H. W.: Steroid Anesthetic Agent, Science 122: 3158 (July) 1955.
4. P'an, S. Y., Gerdocki, J. F., Hutcheon, D. E., Rudel, H., Kodet, M. J., and Laubach, G. D.: General Anesthetic and Other Pharmacological Properties of Soluble Steroid, 21-Hydroxypregnane Dione Sodium Succinate, J. Pharm. & Exper. Therap. 115: 4 (Dec.) 1955.
5. Robinson, C. V., Li, T. H., and Etsten, B. E.: Improved Injection Pipette for Determination of Cardiac Output by Dye Method, J. Lab. & Clin. Med. 42: 773 (Nov.) 1953.
6. Gibson, J. G., and Evelyn, K. A.: Clinical Studies of Blood Volume. Adaptation of Method to Photoelectric Microcolorimeter, J. Clin. Investigation 17: 153 (March) 1938.
7. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. 61: 523, 1924.
8. Van Slyke, D. D., and Sendroy, J., Jr.: Manometric Analysis of Gas Mixtures, J. Biol. Chem. 95: 509, 1932.
9. Donald, K. W., and Christie, R. V.: New Method of Clinical Spirometry, Clin. Sc. 8: 210 (July) 1949.
10. Kiersey, D. K., Bickford, R. G., and Faulconer, A., Jr.: Electroencephalographic Patterns Produced by Thiopental Sodium During Surgical Operations; Description and Classification, Brit. J. Anaesth. 23: 141 (July) 1951.
11. Bellville, J. W., Howland, W. S., and Boyan, C. P.: Comparison of Electroencephalographic Patterns During Steroid and Barbiturate Narcosis, Brit. J. Anaesth. 28: 50 (Feb.) 1956.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/19/4/450/610075/0000542-195807000-00002.pdf by guest on 16 April 2024