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CLINICOPATHOLOGIC STUDIES ASSOCIATED WITH XENON ANESTHESIA * †

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The efficacy of xenon as an anesthetic agent for human beings was established and reported by Cullen and Gross (1, 2) one year ago. The potency of the gas was stated to be at least equivalent to that of ethylene.

Studies of the clinicopathologic changes associated with the commonly used anesthetic agents have been made by numerous investigators; a composite picture of the findings has been presented by Adriani (3), whose book contains an extensive bibliography relevant to such research.

The purpose of this study was to determine the clinicopathologic changes associated with xenon anesthesia in human beings. The rareness and cost of the gas necessarily limited the study to a series of 5 cases.‡ All 5 patients had been admitted to the hospital for elective inguinal hernioplasties and were in good physical condition except for the existing hernias.

Procedure

Table 1 contains information regarding the patients, their premedications and anesthetic procedures.

The oral intake of food and fluids was restricted from midnight prior to operation. On the morning of surgery a Foley catheter was inserted, the bladder drained completely, and the urine specimen sent to the laboratory for analysis. A two-hour urine specimen was then collected for urea clearance determination before anesthesia. The bladder was again emptied immediately before anesthesia began, and the catheter was clamped for the collection of the urea clearance specimen during xenon anesthesia.

Blood samples were drawn for analysis, and bleeding and clotting times were determined about one hour before anesthesia; comparative samples were drawn and the determinations repeated after the patient

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had breathed a xenon-oxygen gas mixture for thirty minutes. The comparative specimens submitted to the laboratories for analysis by experienced technicians were as follows: (a) 4.5 cc. of blood was mixed with 0.5 cc. of 3.8 per cent sodium citrate solution and the resulting specimen used for the determinations of the hematocrit value, sedimentation rate, hemoglobin content, and for the counts of the formed elements except platelets; (b) 5 cc. of blood was mixed with solid sodium oxalate for the determination of the nonprotein nitrogen; (c) 20 cc. of blood was likewise oxalated for blood sugar, blood urea-nitrogen and creatinine determinations; (d) 20 cc. of blood was defibrinated immediately after being drawn and the specimen used for calcium, phosphorus, potassium and sodium determinations; (e) blood was drawn to

TABLE 1

DATA PERTAINING TO SURGICAL PROCEDURES DURING XENON ANESTHESIA

Patient	1	2	3	4	5
Age	45	28	34	41	40
Sex	F	M	M	M	F
Weight (pounds)	106	150	167	166	155
Premedication	Atropine 0.3 mg. I.V. @ 1110	Scopolamine 0.3 mg. I.M. @ 1145	Scopolamine 0.4 mg. H. @ 0730	Scopolamine 0.4 mg. H. @ 1230	Scopolamine 0.3 mg. I.M. @ 0850
Denitrogenation	1117–1145	1239–1300	0940–0945	1515–1521	0930–1000
Xenon anesthesia	1145–1330	1300–1407	0945–1045	1521–1742	1000–1152
Surgery	1158–1330	1322–1508	0957–1149	1640–1845	1008–1146
Supplementary basal narcotics	None	Demerol 175 mg., I.V. 1326–1333	Demerol 50 mg., I.V. @ 0955	Demerol 50 mg., I.V. @ 1637	None
Other anesthetics	None	Cyclopropane 1407–1507	Cyclopropane 1045–1149	Cyclopropane 1742–1840	None
Duration of xenon anesthesia	1 hr., 45 min.	1 hr., 7 min.	1 hr.	2 hr., 21 min.	1 hr., 52 min.
Total anesthetic period	1 hr., 45 min.	2 hr., 7 min.	2 hr., 4 min.	3 hr., 19 min.	1 hr., 52 min.

the 0.5 mark in a red cell pipet, diluted 1:200 with 2 per cent sodium oxalate solution, shaken, and the platelets counted directly in a counting chamber within five to ten minutes of drawing the sample.

Urinalyses and the nonchemical blood determinations except the bleeding and clotting times were done by the Central Laboratory of the State University of Iowa Hospitals, employing routine methods of analysis on the specimens submitted. Urea clearance tests and all blood chemistry determinations except those for nonprotein nitrogen were done by the Laboratory of Pathologic Chemistry of the hospitals. The nonprotein nitrogen determinations were done by the Pediatrics Laboratory.§

§ The authors gratefully acknowledge their indebtedness to these laboratories for their contributions to this study.

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Bleeding and clotting times were determined at the bedside and in the operating room by the authors, the capillary tube method being used for the latter determination.

Electrodes were attached to the four extremities of the patient on the operating table for the purposes of continuous cathode-ray oscillographic study and periodic electrocardiographic recording. The vital signs were observed closely and the blood pressure, pulse and respiratory rates recorded about every ten minutes.

The following anesthetic procedure was used. The patient was subjected to a denitrogenation process by allowing him to breathe pure oxygen delivered at a high flow rate (5 to 10 liters per minute) in a semiclosed absorption system. Just before the xenon was turned on, the rebreathing bag was collapsed to a volume of 500 to 800 cc. A change was made to a closed to-and-fro absorption system and the oxygen flow reduced to about 250 to 300 cc. per minute. The xenon was delivered to the system from an anesthesia machine and metered on a nitrous oxide rotameter gauge. About 900 cc. of xenon was delivered per minute when the indicated rate of flow was 1 liter per minute; this rate of flow was used for adding increments of the gas to the system from time to time. After about ten minutes the oxygen content of the rebreathing bag had been reduced to approximately 20 per cent where it was maintained as closely as possible throughout the xenon anesthesia. Such maintenance was accomplished by frequent sampling of the gaseous mixture through a urethral catheter clamped in the tail of the rebreathing bag. The other end of the catheter was attached to the inlet tube of a Beckman oxygen analyzer into which the gaseous mixture was drawn by means of a vacuum bulb attached to the outlet tube of the instrument. Additions of xenon were made or the flow rate of oxygen was changed according to the indications of the oxygen analyzer.

Consciousness was lost when the concentration of xenon reached about 50 per cent, usually within several minutes after starting the flow of xenon. The surgical procedure was delayed until the oxygen content of the rebreathing bag had been reduced to about 20 per cent, at which time the xenon content was estimated to be about 75 per cent and the water vapor plus unabsorbed carbon dioxide about 5 per cent. Excitement during the induction was absent or very mild except in the third patient in whom there was a moderate amount.

Demerol was administered intravenously when operating conditions under xenon anesthesia alone were unsatisfactory.

A minimal period of one hour of xenon anesthesia was required to perform tests comparable to the preoperative tests. To conserve the xenon, cyclopropane was substituted in 3 cases after the tests were completed. Approximately 20 liters of xenon was used for each of 4 of the cases, and about twice that amount for one case. Solubility of the gas within the body plus losses due to frequent samplings, leakage and par-

tial flushings of the rebreathing bag for adjustments of the composition of the gaseous mixture accounted for the volumes of xenon used.

RESULTS

The data obtained in the comparative tests made before and during xenon anesthesia are shown in tables 2 to 7. The values in the "B"

TABLE 2

COMPARISON OF BLOOD COUNTS AND HEMODYNAMIC DATA BEFORE AND DURING XENON ANESTHESIA

Patient	1		2		3		4		5	
	B	D	B	D	B	D	B	D	B	D
Hemoglobin (gm.)	10.9	12.1	13.8	13.9	14.8	14.4	14.2	—	13.9	13.2
Red Cells (millions)	3.66	4.10	4.48	4.78	4.90	4.68	4.72	—	4.77	4.48
White Cells (thousands)	8.95	9.60	8.25	11.4	17.8	17.0	8.10	—	8.00	8.20
Hematocrit, per cent	36	40	44	45	48	49	46	—	45	46
Sedimentation rate (mm./hr.)	19	18	6	4	12	13	15	—	13	18
Bleeding time (seconds)	120	135	105	135	75	135	90	120	165	120
Clotting time (seconds)	90	120	165	180	210	300	330	180	180	180
Platelets (thousands)	*206*	*190*	*206*	*124*	*230*	*192*	*101*	*50*	*236*	*133*

B—Before anesthesia.
D—During xenon anesthesia.

TABLE 3

COMPARISON OF PLATELET COUNTS AND BLEEDING AND CLOTTING TIMES IN CONTROL TEST

Control	1		2		3		4	
	B	D	B	D	B	D	B	D
Platelets (thousands)	*238*	*154*	*142*	*90*	*146*	*94*	*218*	*168*
Bleeding time (seconds)	180	60	60	60	90	180	150	180
Clotting time (seconds)	240	150	180	165	120	180	105	105

TABLE 4

COMPARISON OF DIFFERENTIAL BLOOD COUNTS BEFORE AND DURING XENON ANESTHESIA

Patient	1		2		3		4		5	
	B	D	B	D	B	D	B	D	B	D
	Percentages									
Segmented	*57*	*80*	*68*	*77*	*74*	*77*	58	—	*45*	*44*
Lymphocyte	*39*	*16*	*32*	*19*	*26*	*22*	36	—	*48*	*53*
Eosinophil	4	2	0	0	0	0	1	—	1	2
Basophil	0	0	0	1	0	0	1	—	2	0
Monocyte	0	2	0	3	0	1	4	—	4	1

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TABLE 5

COMPARISON OF BLOOD CHEMISTRY DATA BEFORE AND DURING XENON ANESTHESIA

Patient	1		2		3		4		5	
	B	D	B	D	B	D	B	D	B	D
Calcium	10.5	10.0	11.0	9.2	9.2	9.2	9.5	9.6	10.6	10.6
Creatinine	1.6	1.4	1.4	1.6	—	—	—	—	1.2	1.0
Nonprotein nitrogen (NPN)	32	48	32	22	20	—	—	—	26	23
Phosphorus	3.6	3.1	3.8	4.2	3.1	3.7	3.2	4.6	3.3	3.2
Potassium	*20.8*	*17.1*	*21.5*	*18.0*	*19.2*	*18.0*	*26.6*	*24.4*	*15.8*	*18.7*
Sodium	340	345	339	346	344	328	332	332	362	345
Sugar	*86*	*71*	*95*	*74*	*77*	*86*	*90*	*80*	*95*	*86*
Blood urea nitrogen (BUN)	13	13	13	14	15	17	12	13	13	15

Values reported are milligrams per cent.

TABLE 6

COMPARISON OF URINALYSES BEFORE AND DURING XENON ANESTHESIA

Patient	1		2		3		4		5	
	B	D	B	D	B	D	B	D	B	D
Sp. gr.	—	—	—	—	1.014	1.011	1.020	—	1.016	1.007
pH	7.0	6.5	7.0	6.0	5.0	5.0	5.5	5.0	6.5	6.5
Albumin	0	0	0	0	0	0	0	Trace	0	0
Blood	0	0	0	0	0	0	0	0	0	0
Sugar	0	0	0	0	0	0	0	0	0	0
Microscopic examination under high power field; noncentrifuged sample	Neg.	Occ. white blood cell	Mucus	15–20 white blood cells	Neg.	Occ. white blood cell	Rare white blood cell	15–20 white blood cells with small clumps	Neg.	Occ. white blood cell

TABLE 7*

COMPARISON OF UREA CLEARANCE BEFORE AND DURING XENON ANESTHESIA

Patient	1		2		3		4		5	
	B	D	B	D	B	D	B	D	B	D
Volume (cc.)	79	18	90	14	90	92	106	54	185	90
Time (min.)	120	105	120	60	120	60	120	60	120	70
Vol./min. (cc.)	0.66	0.17	0.75	0.23	0.75	1.5	0.88	0.90	1.54	1.29
Blood urea nitrogen	13	13	13	14	15	17	12	13	13	15
Urine urea nitrogen	490	483	924	—	539	350	658	875	364	469
Clearance (cc. of blood/min.)	30	15	62	—	31	25	52	64	35	36
Clearance (% of normal)	56	28	115	—	58	47	95	118	65	67

columns refer to determinations made before anesthesia; those in the "D" columns refer to determinations made during xenon anesthesia.

A comparison of blood counts and hemodynamic data is shown in table 2. Except for the platelet counts, the results of all the tests in this group were essentially the same before and during anesthesia, and fell within the limits of experimental error. A definite downward trend in the platelet counts during anesthesia was apparent; the average decrease amounted to 30 per cent. Because of the fact that the number of platelets in the circulating blood is known to fluctuate under diverse stimuli (4, 5, 6), it was suspected that the observed decreases may have been the result of the system rather than of the anesthetic agent. To rule out such an effect, control tests were performed on 4 healthy medical students. They had taken nothing orally after midnight, and upon arrival in the morning were put to rest on cots for one hour. Scopolamine, 0.3 mg., was then injected intramuscularly, and one-half to one hour later platelet counts, bleeding time and clotting time were determined. As for the patients, denitrogenation with oxygen was carried out for fifteen minutes, and then the system was converted to closed absorption. After the controls breathed oxygen in the latter system for one-half hour the tests were repeated. The results of these control tests are shown in table 3. A decrease in the platelet counts occurred as in the anesthetized patients; the average decrease in the controls was 32 per cent. Bleeding and clotting times were erratic as they were for the patients.

A comparison of the differential leukocyte counts is shown in table 4. In 3 of the 4 patients on whom these determinations were made there was a relative increase in the number of segmented cells and a relative decrease in the number of lymphocytes; the fourth patient showed opposite changes but of a lesser degree. The average numbers of segmented cells before and during xenon anesthesia were 61 per cent and 69 per cent, respectively. The average lymphocyte count decreased from 36 per cent to 28 per cent during anesthesia. Changes in the eosinophil, basophil, and monocyte counts were erratic.

A comparison of blood chemistry data is shown in table 5. The changes in the concentrations of calcium, phosphorus, creatinine, nonprotein nitrogen, urea nitrogen and sodium were either erratic or of very low magnitude. Four of the 5 patients had lower potassium and blood sugar levels during xenon anesthesia. The average milligram percentages of potassium before and during anesthesia were 20.7 and 18.2, respectively; the values for blood sugar were 89 and 79 in the same order.

A comparison of urinalyses is shown in table 6. The only striking change is the increased numbers of white blood cells occurring in the urine specimens during anesthesia. These cells could be attributed to the presence of the indwelling catheters.

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A comparison of urea clearances is shown in table 7. No consistent change occurred in either the urinary output or urea clearance.

Blood pressures and respiratory rates were not appreciably altered during anesthesia with xenon. Electrocardiographic studies made on these patients and on several other patients who had received xenon anesthesia showed no evidence of predisposition toward arrhythmia; a tendency toward a relative bradycardia, however, was observed.

COMMENT

The data obtained in this study indicated changes in only a few of the entities examined. Two of these changes, the decrease in platelet count and the increase in white blood cells in the urine, are attributable to causes other than the anesthetic agent.

The trend toward a relative elevation in the segmented cells in the peripheral blood during xenon anesthesia as conducted in these experiments is consistent with the findings for ether, nitrous oxide, cyclopropane, ethylene and chloroform, as reported by Adriani (3). This study suggested the elevation to be relative rather than absolute.

The suggestive decrease in serum potassium which occurred during anesthesia in this study follows the trend of this ion during ether and cyclopropane anesthesia, as reported by Fay *et al.* (7, 8) in studies on dogs. Larson and Brewer (9) reported a drop in serum potassium in dogs owing to administration of morphine, ether or sodium pentobarbital; however, in view of the fact that the simultaneous administration of 2,4-dinitrophenol prevented the fall which occurs after sodium pentobarbital is given, these authors suggested that the lowering of serum potassium by anesthetics is a result of lowered metabolic rate. Decreased metabolic activity rather than a specific effect of xenon may account for the drop in the serum potassium level.

Adriani (3) reported a rise in plasma sugar with ether, cyclopropane, ethylene and chloroform, and no change with nitrous oxide. In contrast to these reported changes, the evidence from this study shows no rise but rather a suggestive fall with xenon anesthesia.

There was no evidence of respiratory depression from xenon in the concentrations used. The only observed effect on the circulatory system was a tendency toward a relative bradycardia. No abnormalities of rhythm attributable to xenon were noted electrocardiographically or oscillographically.

Since statistical analyses of the data were not made because of the small series, the significances of these changes are not known.

CONCLUSIONS

The evidence available from this limited study indicated a minimal disturbance of biochemic and physiologic processes by xenon in so far as these processes are reflected in the entities examined.

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THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

Dr. Francis J. Audin, Secretary of the New England Society of Anesthesiologists, has announced meetings of the Society as follows:

February 6, 1953, St. Francis Hospital, Hartford, Connecticut.
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