

HEPATORENAL SYNDROME FOLLOWING ADMINISTRATION OF VINETHENE. A CASE REPORT * †

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In a report on vinethene, Goldschmidt, Ravdin et al (1) stated that, "the duration of the divinyl ether anesthesia was thus found to be a definite factor in the production of liver necrosis in the dog. The critical period in this animal was found to lie between two and three hours." The article included, as a footnote, necropsy evidence of central lobular necrosis of the liver in 2 patients from Doctor Dean Lewis' service at the Johns Hopkins Hospital who died subsequent to the administration of vinethene for two hours and forty minutes, and one hour and thirty-nine minutes, respectively. More recently, Orth et al (2) found that one hour administrations of vinethene to dogs, repeated three to seven times at weekly intervals, produced central zonal necrosis of the liver. They also found that in 2 of 4 dogs, there was a rise in the urea clearance level after a single administration of vinethene, and a progressive decrease following repeated administrations in each of 4 dogs, eventuating in death after three to seven administrations. In view of these findings, the occurrence of a toxic hepatorenal syndrome during the course of a clinical investigation of vinethene ‡ warrants a detailed report. In addition to the usual laboratory tests, the following procedures were employed in this study.

The plasma prothrombin was determined by a modification of Quick's method (3). The cephalin-cholesterol flocculation test was done exactly as outlined by Hanger (4). Emulsions prepared from mixtures of sheep brain cephalin and cholesterol are flocculated by serum from patients with disturbances of the liver parenchyma. This reaction, which may depend upon the capacity of an altered serum globulin to become affixed to the colloidal elements of the emulsion, has proved to be a very sensitive index of hepatic disease (4; 5). The post-prandial maximal plasma urea clearance tests were performed in the manner described by van Slyke et al (6). The control urea clearance values found are below the average normals as established by van Slyke (7). Repeated checks have offered no explanation. Without exception, the patients studied were free of any evidence of renal disease as

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‡ Divinyl ether, 96.5 per cent, ethyl alcohol, 3.5 per cent, phenyl-alpha-naphthylamine 0.01 per cent.

demonstrated by a negative history, physical examination and normal urinalysis.

CASE REPORT

A 33 year old woman entered the Wisconsin General Hospital in October, 1939, complaining of severe menorrhagia and pain in the right lower quadrant. An appendectomy had been performed in 1930. There had been seven pregnancies in nine years, the last occurring two years before this admission, and the fourth and sixth terminating in miscarriage at the second and third months, respectively. No renal disturbances had been recognized as accompanying the above pregnancies. The past medical history was otherwise negative. She was moderately obese, 5 feet 7 inches in height, and weighed 228 pounds. Systolic blood pressure was 158 mm. of mercury and the diastolic was 94. After examination, diagnoses of cystocele and rectocele, a small uterine fibroid, a right ovarian cyst and possible incomplete abortion were made. There was a slight anemia (11.8 Gm. of hemoglobin per 100 cc. of blood), negative blood Wassermann test, and the urea clearance was 19.6 cc. per square meter of body surface per minute. In November, 1939, under vinethene anesthesia, a dilatation of the cervix and curettage of the uterine cavity was performed. The curettements were those of an incomplete abortion. Vinethene was administered by the to and fro carbon dioxide absorption technic during forty minutes of light surgical anesthesia. There was adequate oxygen tension in the anesthetic atmosphere throughout and no respiratory obstruction was noted. The operative procedure and the anesthesia were uncomplicated. The patient's reflexes were present on leaving the operating room. Clinically, the recovery was uneventful. The patient was discharged on the sixth day after operation. The highest recorded temperature postoperatively was 100°. The urea clearances on the third and fourth days after operation were 29.5 cc. and 52.8 cc./M²/minute, respectively. The anemia was slightly more pronounced (10.5 Gm. hemoglobin) at the time of the patient's discharge.

This woman was readmitted in 1940, having had two menstrual periods in the interval, both characterized by excessive flow. The physical findings had not changed. The systolic blood pressure was 122 mm. and the diastolic was 65. The blood contained 12.4 Gm. of hemoglobin per 100 cc. and 4 million red cells per cu. mm. The urea clearance was 29.6 cc./M²/minute. A dilatation, curettage and complete perineal repair were performed under vinethene anesthesia ten weeks after the first administration. The duration of anesthesia was one hundred four minutes. The degree of narcosis and the technic of administration were similar to those employed for the previous operation. Her condition was good throughout the operation and the reflexes were present when the patient returned to bed. Persistent nausea and emesis characterized the first ten days of the postoperative period. On the fifth day after operation, the patient was lethargic, slightly jaundiced, and there was hemorrhage from the nose, mouth and vagina. Later on this day, 500 cc. of citrated fresh whole blood was given by transfusion without reaction. It was the opinion of medical consultants that the transfusion was not responsible for the persistence of the above physical signs. This patient was extremely ill and her recovery was doubtful until about the end of the seventh week after the second operation. The marked fall in the urea clearance value, indicating kidney damage, and the clear cut evidence of impaired liver function as shown by the changes in the icteric index, the plasma prothrombin time and

TABLE 2
VINETHENE

Number of Patients with One Administration Each	Operation	Duration (Minutes)	Variation of * Urea Clearance from Pre-operative Control		Impairment of † Liver Function from Pre-operative Control	
			1st Test	2nd Test	1st Test	2nd Test
1	Perineoplasty	90	111% ↑	21% ↑	No Data	
1	Perineoplasty	128	22% ↑	7.6% ↑	No Data	
1	Perineoplasty	130	1.9% ↑	20% ↑	No Data	
1	Perineoplasty	96	9.5% ↑	2.3% ↑	None	None
1	Perineoplasty	100	25% ↑	8.9% ↓	None	None
1	Hysterectomy	74	15% ↑	41% ↓	No Data	

ETHER

1	Hysterectomy	90	3.3% ↓	6.6% ↑	3+	1+
1	Hysterectomy	125	12% ↑	22% ↑	2+	None
1	Ovarian suspension	65	4.3% ↓	86% ↑	None	None
1	Perineoplasty	100	77% ↑	24% ↑	None	None
1	Perineoplasty	130	16% ↑	36% ↑	None	None
2 administrations with 9 week interval	Perineoplasty	125	0.2% ↓	4.0% ↑	None	None
	Hysterectomy and herniorrhaphy	145	33% ↓	13% ↑	None	None

CYCLOPROPANE

1	Uterine suspension	70	3.4% ↓	3.0% ↑	No Data	
1	Hysterectomy	125	82% ↑	39% ↑	No Data	
1	Perineoplasty	145	94% ↑	29% ↓	None	None
1	Perineoplasty	125	28% ↓	42.5% ↓	None	None
1	Perineoplasty	130	17% ↓	15% ↓	None	None

CHLOROFORM

1	Saphenous ligation	60	7.4% ↓	17% ↑	1+	4+
1	Breast biopsy	50	15% ↑	13% ↑	None	None

Laboratory data of kidney and liver function following the administration of several anesthetic agents. This does not include the case report.

* The postoperative urea clearance and liver function tests were done on either the third or fourth and fifth days. Changes of 25 per cent or less from the control urea clearance value have been considered of no clinical significance. The significance of a rise of the urea clearance value is as yet not clearly understood. ↑ Rise, ↓ Fall.

† Based on changes of the cephalin-cholesterol reaction and expressed as such. Usually there were more than two determinations of each liver function test. In no instance was there clinical evidence of renal or hepatic damage.

cephalin-cholesterol reaction, point to a toxic hepatorenal syndrome. See Table 1 for complete laboratory and clinical data.

FURTHER STUDIES

A small number of patients was studied in a similar manner before and after the administration of vinethene, diethyl ether, cyclopropane and chloroform. Table 2 shows the results. The series is too small to justify any conclusions, but indicates that variations in liver and kidney function can occur, following operation and anesthesia, with various agents.

SUMMARY

Ravdin (8, 9) has suggested that vinethene should be used for short administrations only. The experience with the patient whose clinical course is herein reported in detail would support Ravdin's view. Orth (2) found that administrations of vinethene to dogs, repeated at weekly intervals, produced central zonal necrosis of the liver and a progressive decrease of the urea clearance values. There were two administrations of vinethene to the above mentioned patient of forty and one hundred four minutes, respectively, ten weeks apart. The last administration was followed by intense jaundice, hemorrhage and decreased urine output. In addition, there was evidence of impaired liver function as demonstrated by the changes in the cephalin-cholesterol reaction, the prothrombin time and the icteric index. Kidney function was damaged as shown by a fall of the urea clearance value. Since wide experience has shown that prolonged administrations of other agents, repeated at varying intervals, have not been followed by a clinical course comparable to that presented by this patient, it seems justifiable to infer that the above findings were due to vinethene. We would therefore question the advisability of either prolonged or repeated administrations of this agent.

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