Some Hematologic Changes in Patients Receiving Multiple Intravenous Infusions of Fat Emulsion

JACK S. KALEY, M.D.,* H. C. MENG, M.D., PH.D.† AND CATHERINE BINGHAM, B.S.‡

THE OCCURRENCE of anemia in laboratory animals[1–6] and in human beings[7–9] receiving long term intravenous infusions of fat emulsions has been reported. However, little is known concerning its cause.

The present work was undertaken as the first phase of a study to determine the etiology of this anemia. A group of schizophrenic patients, apparently physically well, were given daily infusions of 500 ml. of Lipomul®§ for a period of twenty to twenty-nine days. The change in the hematogram was determined at weekly intervals. The anemia which developed was of the hypochromic or hypochromic-microcytic type.

MATERIALS AND METHODS

Lipomul, a 15 per cent cottonseed oil emulsion containing 4 per cent glucose, 1.2 per cent purified soybean phosphatides and 0.3 per cent Pluronic F68, was used throughout.

The subjects were six male and one female schizophrenic patients who had been institutionalized for periods of from ten months to ten years and eight months. Their ages ranged from twenty-eight to forty-five years and body weights were from 43.2 to 71.8 kg. All patients were ambulatory and without any apparent physical disease. They were on a regular hospital diet with approximately 73 to 86 gm. protein, 82 to 112 gm. fat, 252 to 331 gm. carbohydrate and 2,161 to 2,485 calories offered daily. The amounts of vitamins A and C, thiamine, riboflavin, niacin and minerals, including iron, were equal to or higher than the recommended dietary allowances.¶ Most of the patients were receiving tranquilizers. Each patient was given 500 ml. of Lipomul daily on consecutive days except in one case (patient E. H.) where there was an interval of two days between infusions. Six of the patients received a total of thirty-one to thirty-three infusions while the other was given twenty-four (Table I).

Precautions were taken to start the infusions at a slow rate of approximately 1 to 2 ml. per minute for the first thirty minutes, after which the rate was increased so as to finish a bottle of 500 ml. in a total of three to three and a half hours. The first infusion of the series was only 300 to 400 ml. and the volumes of the final four infusions were progressively reduced to 150, 100, 50 and 50 ml.

Blood samples were drawn at weekly intervals about twenty hours after the preceding infusion. Blood hemoglobin was determined

From the Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tennessee.

* Present address: Kennestone Hospital, Marietta, Georgia. † Associate Professor of Physiology; ‡ Research Assistant, Department of Physiology, Vanderbilt University School of Medicine.

This study was supported by the Medical Research Branch, Medical Research and Development Command, Office of the Surgeon General, Department of the Army, Contract DA-49-007-MD-252.

§ Lipomul, I.V. (Lot Nos. 11-612-72, 11-612-74, KG508 and KG509), was kindly supplied by the Upjohn Co., Kalamazoo, Michigan.

¶ The intakes of nutrients are calculated from the menus. The authors wish to express their appreciation to Misses Bernice Hopkins and Emily Stanley of the Dietetic Department, Vanderbilt University Hospital, Nashville, Tennessee, for these calculations.

TABLE I
Condition of Patients* and Amounts of Lipomul Given

Patient, Sex and Age (yr.)	Initial Weight (kg.)	Height (in.)	Medication (mg./day)	Length of Hospitalization (yr.)	Total Lipomul Infused	
					No. of Infusions†	Total Volume (ml.)
N. K., M, 39	50.0	70	None	3¾	31	13,850
W. W., M, 33	55.0	68	Stelazine (10–20)	9⅔	31	13,850
R. R., M, 28	54.1	67	Compazine® (30)	4⅙	24	10,350
R. J., M, 43	43.2	66	Stelazine (10–20)	⅙	32	14,350
G. D., M, 40	55.5	67	Dartal® (20)	10⅔	33	14,850
M. D., F, 45	50.0	66	Thorazinex (75)	6¼	28	14,000
E. H., M, 29	71.8	74	Vesprin® (25–50)	1½	32	13,350

* All patients are schizophrenics.
† Number of infusions include four "tapering off" infusions in all patients except M. D.

by the method of Evelyn and Malloy.[10] Red and white blood cells and reticulocytes were counted by the standard procedures and the hematocrit was obtained by centrifuging the oxalated blood in a Wintrobe tube for half an hour at 2,500 revolutions per minute.

Blood volume was estimated at intervals during the infusion period by the method of radioactive I^{131}-labeled serum albumin;[11] the radioactivity of whole blood was determined. The plasma volume and red blood cell mass were calculated from the blood volume and hematocrit.

RESULTS

General Condition of the Patients: The condition of the patients receiving infusions of Lipomul will be published in detail elsewhere.[12] It can be noted here that the fat emulsion did not cause immediate thermogenic or other reactions in any patient. A gain in body weight of 0.5 to 3.7 kg. was observed in all patients but one, who showed no change. In two patients delayed reactions of moderate (M. D.) or mild (R. J.) severity occurred. Hemorrhagic episodes were not observed.

Development of Anemia: Table II shows the changes in hemoglobin, hematocrit, erythrocyte and reticulocyte counts and erythrocyte indices of all patients. A progressive reduction in hemoglobin occurred in all patients except subject E. H. who showed no significant change after four weeks of daily infusions of Lipomul. The decrease in hemoglobin was over 20 per cent of the control values in two patients (N. K. and R. J.), greater than 15 per cent in three (W. W., R. R. and G. D.), while only 6.8 per cent in one (M. D.).

The decrease in hematocrit after three to four weeks of Lipomul infusions was approximately equivalent to that of hemoglobin in three patients (N. K., W. W. and R. R.), but was less in two (R. J. and G. D.) and more in one (M. D.). The decrease ranged from 10.1 to 24.3 per cent of the preinfusion levels. There was no significant change in the hematocrit of patient E. H.

The erythrocyte counts of all patients except E. H. also were reduced. However, the reduction was 10 per cent or less of the preinfusion levels in four of the six subjects (N. K., W. W., R. R. and G. D.), while the decrease was 13.1 and 16.0 per cent in patients M. D. and R. J., respectively.

Hemoglobin, hematocrit and erythrocyte count were further reduced in patient M. D. when a delayed reaction characterized by chill, fever and anorexia was encountered.

A decrease in mean corpuscular hemoglobin (MCH) was found in five patients (N. K., W. W., R. R., R. J. and G. D.). Of these, three showed an approximately equivalent reduction of mean corpuscular volume (MCV), but no change in mean corpuscular hemoglobin concentration (MCHC) (N. K., W. W. and R. R.); in the other two patients, the

TABLE II—Changes in Hemogram and Blood Volume

No. of Infusions	Date (1958)	Red Blood Cell Count (millions)	Hemoglobin (gm.)	Hematocrit (%)	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Mean Corpuscular Hemoglobin Concentration	Reticulocytes (%)	Blood Volume (ml.)	Plasma Volume (ml.)	Red Cell Mass (ml.)	White Blood Cell Count (millions)
Patient N. K.												
0	11/20	3.98	13.5	29.5	99.2	33.9	34.2	0.6	—	—	—	7,500
7	11/26	4.17	12.5	39.5	94.7	30.0	31.6	0.6	4,043	2,446	1,597	6,300
14	12/4	4.18	—	35.9	85.9	—	—	0.9	—	—	—	7,000
21	12/11	3.93	11.8	36.0	91.6	30.0	32.8	0.7	4,020	2,573	1,448	5,500
28	12/19	3.75	10.4	29.9	79.7	27.7	34.8	0.6	4,316	3,026	1,290	5,150
% Δ after 28 infusions		− 5.8	−23.0	−24.3	−19.6	−18.3	1.8	...	6.8	23.7	−19.2	−31.3
Patient W. W.												
0	10/10	4.07	13.5	41.9	102.9	33.2	32.2	0.9	—	—	—	9,350
7	10/16	-	12.5	40.0	- -	—	31.2	0.8	4,563	2,738	1,825	
14	10/23	4.10	12.3	39.0	95.1	30.0	31.5	0.8	-	-	-	5,350
21	10/30	4.01	11.1	35.6	88.8	27.7	31.2	0.9	4,607	2,967	1,640	4,650
27	11/6	3.70	11.1	35.0	94.6	30.0	31.7	- -	—	—	—	4,250
% Δ after 27 infusions		− 9.1	−17.8	−16.5	− 8.1	− 9.6	−1.6	...	1.0	8.4	−10.1	−54.5
	1/16/59	4.38	11.4	33.0	75.3	34.5	34.5	...	...	...	...	7,500
Patient R. R.												
0	10/17	5.45	16.3	49.0	89.9	29.9	33.3	0.9	4,376	2,232	2,144	8,900
7	10/23	5.62	14.9	45.0	80.1	26.5	33.1	0.9	...	...	...	5,700
14	10/30	4.87	13.5	40.5	83.2	27.7	33.3	0.9	4,670	2,779	1,891	5,450
21	11/6	5.06	13.8	41.8	82.6	27.3	33.0	...	...	...	...	5,050
% Δ after 20 infusions		− 7.2	−15.3	−14.7	− 8.1	− 8.7	−0.9	...	6.7	24.5	−11.8	−43.2
Patient R. J.												
0	9/17	4.80	14.7	42.8	89.2	30.6	34.3	1.4	...	...	...	14,950
7	9/25	4.30	13.4	40.9	95.0	31.2	32.8	1.0	4,230	2,500	1,730	8,725
14	10/2	4.56	13.5	40.0	87.7	29.6	33.8	0.9	...	...	...	7,550
21	10/9	4.03	11.4	36.0	89.3	28.3	31.7	1.0	3,682	2,356	1,326	6,850
% Δ after 21 infusions		−16.0	−22.4	−15.9	0.1	− 7.5	−7.6	...	−13.0	− 5.8	−23.4	−54.4
28	10/16	...	...	34.2	...	...	...	1.0	...	...	...	...
	10/30*	4.24	10.8	33.8	79.8	25.5	32.0	...	...	...	...	4,950
	1/16/59	4.87	13.9	42.0	86.2	28.5	30.5	...	...	...	...	10,450
Patient G. D.												
0	9/10	4.64	12.1	37.5	80.8	26.1	32.3	0.9	...	...	...	11,825
7	9/17	4.34	11.8	36.7	84.6	27.2	32.2	0.7	...	...	...	13,775
14	9/25	4.10	11.4	35.0	85.4	27.8	32.6	0.8	4,577	2,975	1,602	6,625
21	10/2	3.88	11.4	34.8	89.7	29.4	32.8	0.9	...	...	...	10,900
29	10/9	4.17	10.0	33.7	80.8	24.0	29.7	0.8	4,008	2,657	1,351	8,800
% Δ after 29 infusions		−10.1	−17.4	−10.1	0.0	− 8.0	−8.0	...	−12.4	−10.7	−15.7	−25.6
	1/16/59	4.44	13.4	39.2	88.3	30.2	34.0	...	...	...	...	9,200
Patient M. D.												
0	7/9	4.05	10.3	34.2	84.4	25.4	30.1	...	...	...	...	9,250
7	7/16	5.03	11.3	35.8	71.2	22.5	31.6	...	...	...	...	7,050
14	7/24	4.51	10.0	33.0	73.2	22.2	30.3	...	...	...	...	9,700
21	7/30	3.40	10.1	31.0	91.2	29.7	32.6	...	...	...	...	8,100
28	8/6	3.52	9.6	30.0	85.2	27.3	32.0	...	...	...	...	9,250
% Δ after 28 infusions		−13.1	− 6.8	−12.3	0.9	7.5	6.3	...	...	...	...	0
	8/11†	3.06	8.5	27.3	89.2	27.8	31.1	...	...	...	...	4,325
Patient E. H.												
0	11/20	4.37	11.8	40.0	91.5	27.0	29.5	0.6	...	...	...	5,600
7	11/26	4.48	13.2	42.5	94.9	29.5	31.0	0.8	5,294	3,044	2,250	7,000
14	12/4	3.94	12.4	39.5	100.2	31.5	31.5	0.7	...	...	...	7,250
21	12/11	3.98	12.2	39.2	98.5	30.6	31.1	0.7	5,880	3,575	2,305	5,800
28	12/19	4.38	12.1	39.2	89.5	27.6	30.9	0.8	5,321	3,235	2,086	6,350
% Δ after 28 infusions		0.2	2.5	− 2.0	− 2.2	2.2	4.7	...	0.5	6.3	−7.3	13.4

* Determinations made during the recovery phase fron a very mild delayed reaction.
† Determinations made during a delayed reaction.

TABLE III
Mean Percentage Changes in Hemogram*

Data	Red Blood Cells	Hemoglobin	Hematocrit	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Mean Corpuscular Hemoglobin Concentration
After 7 infusions	3.2	− 4.2	− 2.9	−1.2	−5.7	−1.9
After 14 infusions	−1.7	− 8.6	− 8.4	−6.3	−5.8	0
After 21 infusions	−9.7	−12.6	−11.9	−1.7	−2.5	−1.0
After 28 infusions	−9.5	−16.2	−15.8	−6.7	−6.7	−0.4

* Patient E. H. was not included in the average since his hemogram did not show any significant change.

mean corpuscular hemoglobin concentration was also reduced (R. J. and G. D.). The mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration of patient M. D. were increased while those of E. H. showed no significant changes.

Reticulocytosis did not occur during the entire period of Lipomul infusion.

Follow-up studies of patients W. W., R. R., R. J. and G. D. indicated that the recovery from anemia was slow and the blood findings required three months to return to the preinfusion levels. This was especially true with regard to hemoglobin concentration and hematocrit. Thus, the hemoglobin and hematocrit were still at low levels approximately two and a half months after the termination of infusions in patients W. W. and R. R. (Table II).

The weekly mean percentage changes in the hemograms are summarized in Table III. After one week of infusions, the changes were variable among individual patients and the mean changes were not significant. After two or more weeks, however, the pattern of change became quite consistent and the means were significant.

Changes in Leukocyte Count: A progressive decrease in leukocyte counts was found after three to four weeks of daily infusions (Table II) in all patients but E. H. and M. D. The decreases ranged from 25.6 to 54.5 per cent of the preinfusion levels. In patient M. D., however, leukopenia was demonstrated at the time of her illness five days after the last infusion.

Blood Volume: Blood volume was estimated at intervals in six of the seven patients. Four patients (N. K., W. W., R. R. and E. H.) showed no significant change and the other two (G. D. and R. J.) showed a decrease of 12.4 and 13.0 per cent. The plasma volume, calculated from the blood volume and hematocrit, was increased in four patients from 6 to 25 per cent and decreased 6 to 11 per cent in 2. The red blood cell mass was decreased in all six patients from 7.3 to 23.4 per cent.

COMMENTS

The patients in the present study were apparently well physically although their initial control hemograms were somewhat lower than normal in several instances. Our results, therefore, provide further evidence that multiple intravenous infusions of fat emulsions may lead to anemia in man, as reported by other investigators.[7–9]

This anemia is of the hypochromic or hypochromic-microcytic type and it is usually apparent after two weeks of daily infusion and obvious after three weeks. The degree of anemia is such, however, that it does not constitute a contraindication to giving Lipomul for a two-week period. Furthermore, no other untoward effects were encountered within this time interval.

The results of the present study do not provide an explanation for the mechanism of this anemia. However, it is reasonable to believe that (1) the reductions in the hemoglobin, hematocrit and erythrocyte counts were not attributable to hemodilution, although this may have been a contributing factor in

some of the patients. Thus, the decrease in cell mass was much greater than the change in plasma volume in some patients; and the reduction of the hemoglobin concentration greater than that of erythrocyte count in most of the subjects. (2) External or internal hemorrhage was not observed; thus, it is not likely that the anemia was due to blood loss. (3) Our preliminary studies[13] have shown that the serum iron and total iron binding capacity of serum are progressively decreased following long term intravenous infusions of Lipomul. This suggests the presence of a block in the synthesis of hemoglobin. (4) Watkin,[7] Levenson, et al.[8] and Mueller[9] have demonstrated increases in reticulocytes in the peripheral blood accompanying anemia produced by multiple fat infusion. We could not confirm these findings.

SUMMARY AND CONCLUSIONS

1. Seven, apparently physically well, institutionalized schizophrenic patients were given daily intravenous infusions of 500 ml. of a fat emulsion (Lipomul I.V.) for twenty to twenty-nine consecutive days.

2. The emulsion was tolerated well by all patients during the infusion period. Mild to moderate delayed reactions were observed in two patients three to seven days after the last of the infusions was given.

3. A progressive hypochromic or hypochromic-microcytic anemia and leukopenia occurred in six of the seven patients.

ACKNOWLEDGMENTS

We are deeply indebted to Dr. O. S. Hawk, Superintendent and Dr. A. L. White, Assistant Superintendent of the Tennessee Central State Hospital for making these patients available for this study. The assistance given by Dr. Rudolph H. Kampmeier, Professor of Medicine, Vanderbilt University School of Medicine is also greatly appreciated.

We wish to acknowledge our appreciation to Mr. E. B. Bridgeforth, Department of Preventive Medicine, for assistance in the analysis of the data.

REFERENCES

1. Collins, H. S., Kraft, L. M., Kinney, T. D., Davidson, C. S., Young, J. and Stare, F. J. Parenteral nutrition. III. Studies on the tolerance of dogs to intravenous administration of fat emulsions. *J. Lab. & Clin. Med.*, 33: 143, 1948.
2. Mann, G. V., Geyer, R. P., Watkin, D. M., Smythe, R. L., Dju, D. C., Zamcheck, N. and Stare, F. J. Parenteral nutrition. VII. Metabolic studies on puppies infused with fat emulsions. *J. Lab. & Clin. Med.*, 33: 1503, 1948.
3. Meng, H. C. and Freeman, S. Experimental studies on the intravenous injection of a fat emulsion into dogs. *J. Lab. & Clin. Med.*, 33: 689, 1948.
4. Meng, H. C. and Early, F. Studies of complete parenteral alimentation on dogs. *J. Lab. & Clin. Med.*, 34: 1121, 1949.
5. Mann, G. V., Geyer, R. P., Watkin, D. M. and Stare, F. J. Parenteral nutrition. IX. Fat emulsions for intravenous nutrition in man. *J. Lab. & Clin. Med.*, 34: 699, 1949.
6. Lerner, S. R., Chaikoff, I. L. and Entenman, C. A fat emulsion for intravenous feeding. *Proc. Soc. Exper. Biol. & Med.*, 70: 388, 1949.
7. Watkin, D. M. Clinical, chemical, hematologic and anatomic changes accompanying repeated intravenous administration of fat emulsion to man. *Metabolism*, 6: 785, 1957.
8. Levenson, S. M., Upjohn, H. L. and Shecky, T. W. Two severe reactions following the long-term infusion of large amounts of intravenous fat emulsion. *Metabolism*, 6: 807, 1957.
9. Mueller, J. F. Recent advances in intravenous fat alimentation. *Am. J. Clin. Nutrition*, 6: 472, 1958.
10. Evelyn, K. A. and Malloy, H. T. Microdetermination of oxyhemoglobin. *J. Biol. Chem.*, 126: 655, 1938.
11. Crispell, K. R., Porter, B. and Nieset, R. T. Studies of plasma volume using human serum tagged with radioactive iodine 131. *J. Clin. Invest.*, 29: 513, 1950.
12. Kaley, J. S. and Meng, H. C. Clinical and physiological changes in schizophrenics receiving multiple intravenous infusions of fat emulsion. To be published.
13. Meng, H. C. and Kaley, J. S. On the possible mechanism of anemia accompanying multiple intravenous infusions of fat emulsion. To be published.