Metabolic Effect of Fat Emulsion

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DURING the past few years a great deal of effort has been expended in an attempt to develop and evaluate means of providing an adequate caloric source for parenteral feeding. One approach to this problem has been the development of fat emulsions suitable for intravenous administration to patients. The technical aspects of manufacturing oil-in-water emulsions sufficiently stable to allow prolonged storage and introduction into the blood stream have been solved to a large extent. As with other intravenous infusions, such emulsions occasionally give pyrogenic reactions. Sometimes toxic effects are noted, and there have been a few reports of what appears to be a chronic toxic effect from long, continued administration of substantial quantities of emulsion.[1–3]

The most troublesome acute reactions are chills, fever, and a peculiar type of back pain usually observed after only a few milliliters of emulsion have been given. Modification of the emulsifying agents has reduced the incidence of these acute reactions to a very low level. The emulsion manufactured by the Upjohn Company (Lipomul I.V.) has the lowest incidence of acute reactions of any currently available.

The purpose of this study was to evaluate in patients a parenteral feeding program which included protein hydrolysate, dextrose, and fat in quantities considered to be practical from the standpoint of quantity of fluid and concentration of the materials being administered. For a more adequate evaluation of the full parenteral feeding program, which included fat, protein, and carbohydrate, the effects of other regimens not including fat were tested. Also in two patients a comparison between oral and intravenous feeding programs was made.

MATERIALS

The fat emulsions used in these experiments were prepared in the Department of Nutrition, Harvard School of Public Health.[4] They contained 10 or 15 per cent cottonseed oil, 1.2 per cent soya bean phosphatide, 0.2 per cent Pluronic F68, and 4.6 per cent dextrose by weight. This emulsion is similar, but not identical, to the emulsion currently being manufactured by the Upjohn Company. A 10 per cent Amigen‡ solution was diluted with an equal volume of 10 per cent dextrose immediately before use. The exact amount of fluid that was administered to the patient was determined by weighing the containers before and after each infusion. In addition to proteins, carbohydrate, fat, and minerals shown in Table I, each of these patients received generous supplements of vitamin B complex, vitamins C, and D.

METHODS OF ANALYSIS

These studies were carried out on the hospital metabolic ward. Urine samples were collected in 24-hour periods and then pooled in 2-day lots prior to analysis. Stools, which were infrequent, were pooled and analyzed once for each 6-day period. The outputs by stool were then divided over the 6-day period in which

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‡ The Amigen was supplied by Dr. Warren Cox, Mead Johnson Company.

TABLE I

Summary of Daily Intravenous* Intake and Urinary and Stool Output—Four Subjects

Subject / Case No.	Period	No. days	Av. cal/day	Av. protein intake/day (g)	Av. carbo-hydrate intake/day (g)	Av. fat intake/day (g)	Nitrogen (g)		Potassium (meq)		Sodium (meq)		Chloride (meq)	
							Av. intake	Av. excretion/day	Av. intake/day	Av. excretion/day	Av. intake/day	Av. excretion/day	Av. intake/day	Av. excretion/day
W. W.	I	12	742	81	100	0	13.0	12.4	73	58	60	53.2	81	76.9
Case 1	II	10	2,137	81	100	150	13.0	11.3	76	53.3	60	36.8	81	44.9
	III*	10	2,348	87.5*	146.2*	149.3	14.0	12.7	33.2	56.9	96.4	107.6	95.1	105.8
	IV	10	701	121	50	0	19.3	20.1	89.5	80	90	81.5	103	109
D. D.	I	8	907	81	140	0	13.0	13.0	73	54	60	73	162	97.4
Case 2	II	6	1,873	81	149	100	13.0	11.7	76	41	60	30	162	47
	III*	7	1,945	98*	153*	98.4	15.7	14.7	65	61	56.5	67	55	70
A. G.	I	6	2,067	85	192	100	13.6	15.7	78.5	70.0	63.9	56.5	85.0	96.0
Case 3	II	12	1,153	89	192	0	14.2	13.2	76.7	74.1	66.6	59.7	86.8	96.7
	III	12	1,304	177	141	0	28.3	26.9	112.5	104.3	132.0	112	132.0	108.0
M. M. / Case 4	I	8	1,978	81	174.7	100	13.0	12.7	73.9	62.1	81.7	64.9	98.8	90.8

* In period III in cases 1 and 2, feeding was oral.

the samples were passed. When oral diets were used, the patients ate equal portions of the same foods each day. These diets were adjusted to correspond to the preceding intravenous intake as closely as possible by calculation. During the feeding period representative portions of the diet were homogenized and analyzed for nitrogen, potassium, sodium, and chloride. As indicated in Table I and Figures 1 and 2, the analyses gave slightly higher values than calculated, thus accounting for the variations shown. The feces and diet samples were ashed, extracted, and made up to volume with hydrochloric acid. Chloride and nitrogen were determined on the homogenized samples before ashing. Sodium and potassium were determined on a flame photometer. A micro-Kjeldahl method was used for nitrogen. All samples were run in duplicate. In a few instances when the duplicate analyses were significantly different, four additional determinations were made to arrive at the correct figure.

METHODS OF ADMINISTRATION

A standardized method of administration of fluid was employed throughout. During periods when fat, protein hydrolysate, and dextrose were given, the fat emulsion was started first, followed by the mixture of dextrose and Amigen. Except for patient M. M., all fluids were given at the rate of 5 ml per minute and started between 9:00 and 10:00 A.M. Patient M. M. had a polyethylene catheter in the inferior vena cava and the solutions were administered slowly over a 24-hour period.

PLAN OF EXPERIMENT

The principal objective of this study was to evaluate the efficacy of a parenteral feeding regimen using dextrose, protein hydrolysate, emulsified fat, minerals, and vitamins. The volumes of fluid are within the limits tolerated by most patients. In order to evaluate properly the full intravenous feeding program it was necessary to compare the results with other regimens, which included (a) periods when three of the patients received 2 liters of 5 per cent dextrose and 5 per cent Amigen; (b) periods during which two patients ate three

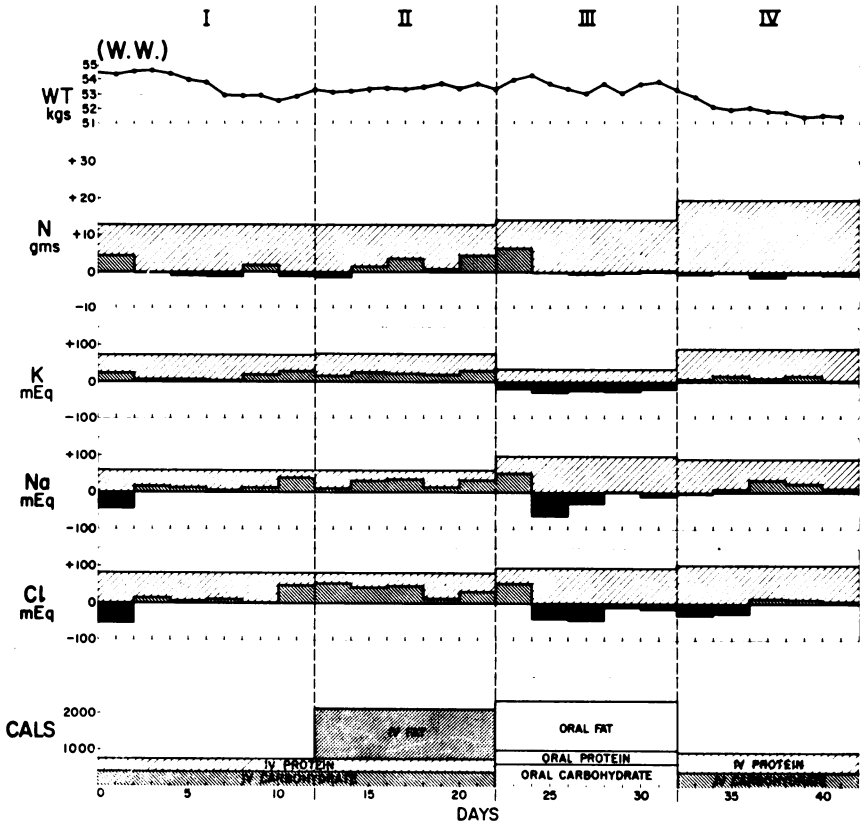

Fig. 1. Case 1, W. W. *I* and *II*. Increased nitrogen, potassium, sodium, and chloride retention during intravenous fat infusion. *III*. Oral intake. *IV*. Increased protein intake. Nitrogen, potassium, sodium, and chloride intakes are charted upward from the O line and outputs are charted downward from the top of the intake column. An excess of output over intake is shown as a solid area below the O line. A positive balance is indicated by a shaded area above the O line.

meals a day, the quantity of which was adjusted to give approximately the same amount of protein, fat, and carbohydrate as during the full intravenous feeding regimen; (c) two periods during which two patients had the protein intake increased by 50 per cent and 100 per cent. Each different regimen lasted 6 to 12 days.

Case 1. W. W.(MGH #481814) was a 26-year-old man who suffered from Friedrich's ataxia. This disease had progressed slowly since childhood so that at the time of admission there was evidence of pyramidal and spinocerebellar tract degeneration and also some cerebellar involvement. He was unable to walk and spent most of each day in a wheelchair and occupied his time with handicraft work. His admission to the hospital was for the purpose of investigating a complaint of dyspnea on exertion. He was found to have no significant heart disease, although myocarditis was considered. He volunteered to be a subject for a parenteral feeding experiment which lasted seven weeks. During five of these weeks he was fed only intravenously (Fig. 1). He suffered no ill effects of this rather strenuous program. He was very hungry during the first three days of each intravenous feeding period. This hunger was accentuated approximately three hours following the infusion of dextrose-Amigen solution presumably because of fluctuation of blood sugar concentration.

Case 2. D. D.(MGH #873507) was a 48-year-old man who entered the hospital for a hip arthroplasty necessitated by degeneration of the hip joint secondary to trauma. In November, 1954, this operation was carried out. While on the rehabilitation ward five months later he developed acute cholecystitis and underwent a cholecystectomy. Convalescence from this operation was uneventful. One month later he was transferred to the metabolic ward as a volunteer subject for a parenteral feeding experiment. He was fed intravenously for 14 days (Fig. 2; Table I), and this was followed by a seven-day period of oral intake providing approximately

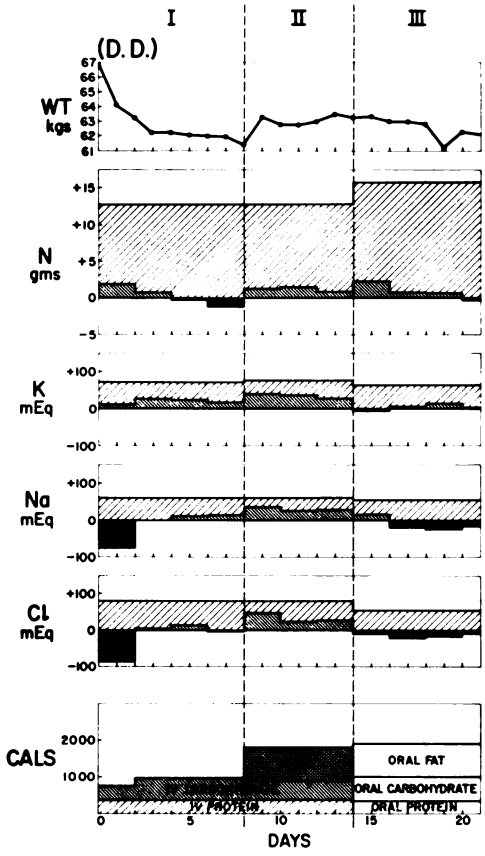

Fig. 2. Case 2, D. D. *I.* Increasing nitrogen excretion on calorie-deficient regimen. *II.* Restoration of positive balance on addition of fat and retention of sodium and chloride. *III.* Oral intake for comparison with intravenous period. Excretion of sodium and chloride from period II.

the same amount of protein, carbohydrate, and fat. Throughout the whole experiment he was in bed except for brief periods of sitting in a wheelchair and gait training in a walker each day. He remained well throughout the experiment and rarely complained of hunger during the two weeks of intravenous feeding.

Case 3. A. G.(MGH #743224) was a 63-year-old man who was admitted to the hospital for treatment of carcinoma of the esophagus. Two years previously he had had electrocoagulation of a carcinoma of the floor of the mouth followed by a radical neck dissection. The esophageal lesion had caused dysphagia to the extent that he could not eat solid foods, but he took liberal quantities of high-caloric liquids including 1 pint of whiskey each day. He had lost 15 pounds of body weight in the two years prior to admission, but was well nourished, with normal body fat. The lesion was considered inoperable, and a course of x-ray therapy was begun. He was a chronic alcoholic, but the only flocculation test. He remained in the hospital only on the condition that he be supplied with whiskey "for his nerves." Four days after beginning x-ray treatment he was started on parenteral feeding. The feeding program and the results are shown in Table I and Figure 3. The calories shown as alcohol were supplied by mouth as a 90-proof, commercial brand of whiskey. Throughout the period of observation he ran a low-grade fever (100 to 101° F.) and felt poorly. The fever started the day x-ray treatment was begun.

Case 4. M. M.(MGH #768575) was a 56-year-old woman with chronic heart disease. An embolus of the superior mesenteric artery necessitated the resection of her entire small bowel distal to the second portion of the duodenum and right half of her colon. A duodenocolostomy was performed. Her immediate convalescence proceeded uneventfully, but she was never able to retain food or liquid in her stomach. Vomiting and watery diarrhea continued steadily even when nothing was taken by mouth. She lost weight rapidly. Approximately four weeks after operation a daily intravenous feeding program of 1,000 ml of 10 per cent dextrose and water, 1,000 ml of 10 per cent fat emulsion, 1,000 ml of 10 per cent Amigen, and 500 ml of 5 per cent dextrose and saline was begun. In addition she received 40 meq of potassium chloride and generous vitamin supplements in each daily ration. After one week of this daily feeding program the balance study summarized in Figure 4 was carried out. This was continued for eight days, and terminated when the patient had an aortic embolus. An embolectomy was performed, but the patient died a week later of infection originating from a localized right gutter abscess which had been present since her original operation. The results of the eight-day balance study are shown in Table I and Figure 4.

DISCUSSION

The balance studies carried out in these four patients supplement those previously reported from this department by VanItallie, Moore, Geyer, and Stare[5] and allow further examination of some of the many aspects of the problem of parenteral feeding. Three of these subjects were well nourished at the start of the experiment. In patients W. W. (Case 1) and D. D. (Case 2) initial periods of moderate caloric restriction lasting 12 and 8 days, respectively, undoubtedly had some influence upon the result obtained when a caloric supplementation by intravenous fat was given. It seems reasonably clear that emulsified fat supplied under these circumstances will promote nitrogen retention. Note should be made of the fact that the caloric intake was about 30 calories per kg per day and nitrogen intake was 13 g per day.

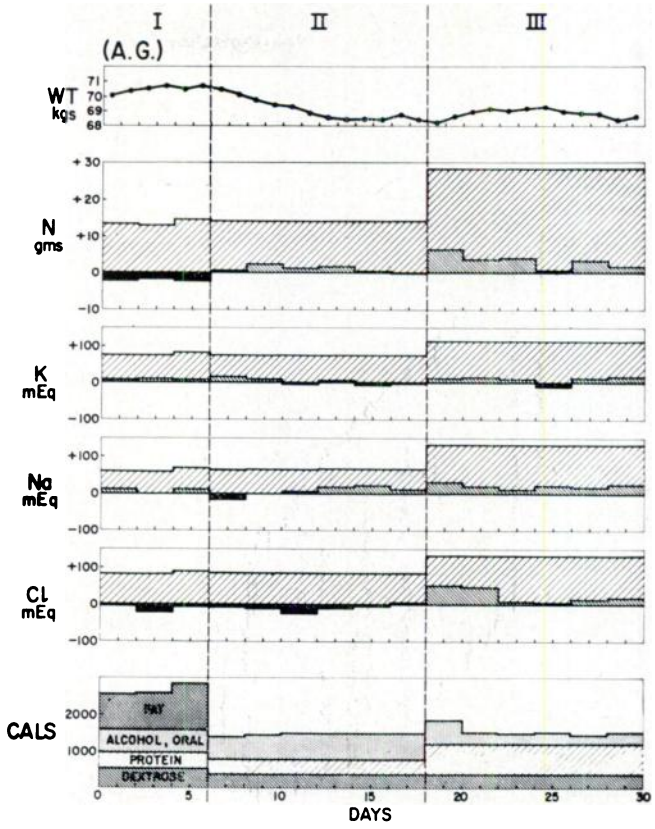

Fig. 3. Case 3, A. G. *I.* Negative nitrogen balance while receiving intravenous fat. *II.* Approximate equilibrium on calorie-deficient regimen. *III.* Positive balance gradually returning to equilibrium on high-protein intake.

The results of these two experiments are in conformity with the results of other experiments designed to test the relationship between caloric intake and nitrogen metabolism.[6–14] The control periods (*I*) in these same two subjects illustrate another aspect of the overall problem of parenteral nutrition and the relationship between caloric supply and nitrogen retention. On a caloric intake of less than 1,000 calories per day there was only slight negative nitrogen balance, and it is obvious from the weight records that the deficit in calories was being made up from fat stores. The temporary nature of this adjustment is shown by the increasing negativity of the nitrogen balance. It appears that caloric supplementation with intravenous fat will reverse this trend and that maintenance at this level of calorie and nitrogen intake will sustain posi-

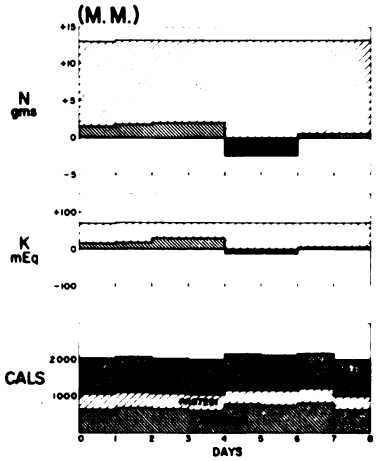

Fig. 4. Case 4, M. M. Eight-day balance study carried out on seriously ill patient five weeks after resection of entire small bowel and right colon, and one week after beginning the intravenous feeding program, which continued through the study period.

tive balance, or at least equilibrium, for 6 to 10 days (and probably longer, as discussed below).

The substitution of the oral method for intravenous feeding demonstrated no detectable difference between whole food protein per os and protein hydrolysate administered intravenously. Further, emulsified vegetable fat (cottonseed oil) introduced directly into a systemic vein appears to be equivalent to mixed animal and vegetable fat taken orally. The rather widely held clinical impression that the oral route of feeding is advantageous was not borne out by the results of these two comparisons.

The experiment carried out on patient A. G. (Case 3) was considerably different from the others. There was no initial period of caloric restriction, and a moderate dose of whiskey was taken orally throughout the experiment. The patient was a chronic alcoholic with some hepatic impairment and he was receiving radiation therapy. Despite these qualifying factors certain conclusions are obvious. First, the provision of what was thought to be adequate calories and protein did not insure nitrogen retention or even equilibrium. Second, the prompt change to positive nitrogen balance after the fat infusion was stopped indicates that, in this patient, fat infusion was a detriment as far as maintaining nitrogen equilibrium was concerned. Whether this was due to unrecognized toxic reaction to the emulsion or failure to metabolize the extra fat because of pre-existing hepatic impairment is not known. The facts that a nitrogen deficit of 2 g per day was associated with fat administration and that positive balance promptly ensued when the fat was stopped are indicative of something more than only failure to metabolize the additional fat.

For this patient the optimal intravenous feeding regimen was a high-protein, fat-free intake which resulted in nitrogen retention even at submaintenance caloric levels. Further study of the metabolic effect of emulsified fat administration to patients with hepatic impairment is needed but, pending this, some reservations must be held concerning the utilization of fat by such patients.

The eight-day balance study carried out on patient M. M. (Case 4) illustrates one additional point—that a very ill patient can be maintained in nitrogen equilibrium for prolonged periods by intravenous feeding with protein hydrolysate, dextrose, and emulsified fat. This balance study was carried out five weeks after resection of almost all of this patient's intestine. We have no explanation for the two-day period of negative balance interposed between periods of slight positive balance, but it seems reasonably certain that in general she was in equilibrium and not wasting body stores of protein.

It will be noted in Table I that patients W. W. and D. D. showed a definite retention of sodium and chloride during periods when fat was being administered intravenously. Subsequent oral feeding periods were accompanied by excretion of sodium and chloride in excess of intake. Fat administration therefore appears to have been responsible for unusual sodium retention. The significance of this finding is not clear. On the basis of present information there is little to indicate adrenal stimulation as a result of fat administration. It seems possible that the introduction of a relatively large quantity of surface-active phospholipid used as emulsifiers might affect membrane permeability throughout the body. For short periods of fat administration and when sodium intake is low, this effect does not appear to be a serious limitation to the use of emulsified fat, but it bears consideration in patients with limited cardiac reserve and during longer periods of fat administration, particularly if salt is being given concurrently. Further study of this effect of fat emulsions is obviously needed.

SUMMARY

The effect of intravenous fat emulsion on nitrogen, potassium, sodium, and chloride metabolism was studied in four subjects, using the balance technic. It is concluded that fat emulsion promotes nitrogen and potassium retention in some patients, but that in other patients administration of fat emulsion under similar circumstances may be associated with excess nitrogen losses. Comparison of oral

and intravenous feeding failed to demonstrate any difference in nitrogen metabolism, and it is concluded that the two methods are equivalent. Attention is directed to the fact that sodium and chloride retention may be associated with administration of intravenous fat.

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