Comparison of Temperature Responses to Intravenous Infusions of Dextrose and Fat Emulsions

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A FEBRILE response to intravenous fat emulsion is the most frequent untoward side effect following short-term infusions. Though this side effect is probably not now common or severe enough to limit the clinical usefulness of intravenous fat emulsion, an understanding of its mechanism is important. One hypothesis offered is that the fever is a result of rapid metabolism of the infused fat with the resultant production of large amounts of heat, rather than being the result of some specific property of the fat in the emulsion. This hypothesis suggests that any infusion containing the same caloric equivalent as a standard infusion of fat, administered and metabolized at the same rate (or faster) would result in a similar number of febrile responses. The purpose of this study was to compare the temperature responses of a group of healthy subjects to isocaloric intravenous infusions of fat emulsion and dextrose.

Intravenous fat emulsion is commonly administered at the rate of 900 calories in four-hour intervals. If a normal adult receives intravenous dextrose at the maximum rate at which there is little urinary spillage, his rate of caloric intake will approach that afforded by a standard fat emulsion infusion. At an infusion rate of 0.8 g of dextrose per kg body weight per hour, one may expect up to 5 per cent urinary loss. Therefore, we administered 250 g of dextrose at this rate to insure a total retention of about 225 g (900 cal). A dextrose infusion supplying calories at approximately the same rate as a standard fat infusion was thereby achieved. In view of the known diurnal variation in temperature and the differences in temperature among healthy subjects, control days on which temperatures were taken but no infusions given were included in the study.

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METHODS AND MATERIALS

Subjects

The subjects for the study were volunteer convalescent patients selected from the surgical wards of Walter Reed Army Hospital. Their injuries were limited to those of an orthopedic or neurosurgical nature; all were ambulatory, nonfebrile, and otherwise in good health. One had suffered from asthma as a child; another was allergic to penicillin. The majority of the subjects were in their twenties or early thirties. All subjects were measured for height at the beginning of the study and were weighed at the beginning and end of each week.

Location

The study was carried out on an enclosed porch of one ward at Walter Reed Army Hospital. No other patients were bedded on this porch. The average daily ward temperature was 77° F, and the range of the daily average temperature was 75° to 79° F; the highest hourly temperature was 81° F and the lowest 74° F.

Daily Program

Subjects reported to the ward at 8 A. M. and infusions were started soon afterwards so as to be completed just prior to lunchtime. The sub-

jects were permitted coffee during the morning, and lunch was sent in from the mess hall. In the afternoon, subjects were permitted normal activity including appointments for physical therapy, the changing of casts and so forth; the only condition being that they be available hourly for temperature readings. There was no attempt to control the quantity of food that the subjects ate either at or between meals. The study began on March 4, 1957 with a control day. On the following four days, dextrose infusions were given. The eighth day was also a control day and was followed by three days during which fat emulsion infusions were administered.

Infusions

All infusions were administered in the morning and usually lasted about four hours. The exact duration of each infusion was recorded.

(A) *Dextrose:* One 50 ml ampul of 50 per cent dextrose was mixed aseptically with a 500 ml bottle of 20 per cent dextrose to give 550 ml of a 22.7 per cent dextrose solution. On the days of dextrose infusion, each subject received in succession two bottles of a 22.7 per cent dextrose solution, a total of 1,100 ml. This amount contains 250 g of dextrose, hence, is equivalent to 1,000 calories. The 50 ml ampul of 50 per cent dextrose was Army stock issue and was prepared by Philadelphia Ampoule Laboratories. The 20 per cent dextrose was Baxter Travenol®, lot B94297, supplied by Baxter Laboratories, Morton Grove, Illinois, and Cleveland, Mississippi. The dextrose infusions were administered by means of Plexitron Intravenous Injection Sets, disposable type, made by Baxter Laboratories. This set delivers dextrose solution in drops of a size such that 15 drops make 1 ml.

The rate of dextrose infusions was set by the weight of the subject according to the formula of 0.8 g of dextrose per kg body weight per hour. The delivery rates were checked every half to three-quarters of an hour.

(B). *Fat:* The intravenous fat emulsion preparation, lipomul I.V., consisted of 1.2 per cent soybean phosphatide, 0.3 per cent pluronic F68, 15 per cent w/v vegetable oil and 4 per cent w/v dextrose, in 600 ml bottles. This preparation was provided by The Upjohn Company, Kalamazoo, Mich., under their lot number 11,612-30. Each bottle contained the equivalent of 810 cal as fat and 96 cal as dextrose, thus 906 cal in all. The caloric contribution from phosphatide in the emulsion has been disregarded. The lipomul was administered by a Fenwal HB 122 Recipient Set with PRJ 706 bottle vent. This type of set delivered the emulsion at 24 drops per ml.

A fat emulsion infusion was always preceded by a small infusion (10 to 50 ml) of 5 per cent dextrose (Army stock issue, prepared by Cutter Laboratories, Berkeley, California, and Chattanooga, Tennessee) given at a very slow rate. The fat emulsion infusion set was then inserted into the rubber adapter on the dextrose set. A slow rate of delivery of about 10 drops per min was maintained for the first 20 min of the fat emulsion infusions. It was then increased to between 60 and 70 drops per min. This resulted in a delivery time of about four hours for the entire 600 ml bottle. The rate of delivery was regulated by Hoffman clamps and was checked every half hour.

Temperatures, Pulses and Blood Pressures

Rectal temperatures and pulses were taken as near to hourly intervals as was possible. The schedule resulted in an average of 11 readings for the 12-hour period from 8 a.m. to 8 p.m. Blood pressure readings were made whenever convenient; usually three to five determinations a day.

Urine Determinations

Every urine sample voided by each subject during the 12-hour period was collected. The amount of the sample was recorded and simple tests for sugar and acetone bodies were made with Clinitest® and Acetest® tablets.

Blood Determinations

Blood samples were taken by venipuncture on the first control day and on the first and last days of fat infusions. White blood counts, differential counts, and hemoglobin and hematocrit determinations were made.

Calculations and Charting

For each infusion we wanted to determine the total number of available calories which the subject retained and the rate at which these were delivered. For dextrose, all urinary losses for the 12-hour period were subtracted from the total amount delivered on the basis of 4 cal/g of dextrose. The caloric content of the fat emulsion infusions was computed by adding the contribution of the fat, at 9 cal/g, to that of the dextrose, at 4 cal/g.

The temperature data were analyzed in several ways. A temperature profile was drawn for each subject on each day. In this way the control, dextrose, and fat reactions could be easily compared, especially in regard to the time of the highest temperatures and the extent of temperature rise. The frequency of febrile responses was determined by the criterion of at least a two degree rise above the control temperature on the day of the infusion.

RESULTS AND DISCUSSION

There were two control days, with 12 subjects participating on the first and nine on the second; an additional control day was obtained with the tenth patient on a day when he was not given a dextrose infusion, so that there were a total of 22 control records. Forty-six daily infusions of 22.7 per cent dextrose were given in a four-day period to 12 healthy men. The following week, nine of these subjects each received three daily infusions of a 15 per cent fat emulsion. The dextrose and fat emulsion infusions were approximately equal in caloric content and caloric rate of infusion. There were no febrile responses. The temperature patterns of the control days, dextrose days, and fat days were substantially the same.

The average total number of calories given in the dextrose infusions was 980 as opposed to 906 for the fat emulsion infusions, but since the dextrose infusions lasted on the average a bit longer than the fat, 4.2 hours as compared to 3.9 hours, there is an excellent correspondence between the over-all average rates of theoretic caloric infusions of 234 cal/hr for dextrose and 232 cal/hr for fat emulsion.

Parenthetically, we may note that the delivery rates demonstrate the advantage of fat emulsions over dextrose for high caloric infusions. To get an isocaloric rate of intake, we had to give an average of 262 ml/hr of dextrose solution but administered only 154 ml/hr of fat emulsion. In addition, the dextrose had to be quite concentrated, 22.7 per cent, and thus had the liability of being locally irritating. There was some spillage of dextrose into the urine, but in all cases it was less than a 5 per cent urinary loss. At least 225 g of dextrose was retained during each intravenous dextrose infusion. Six fat emulsion infusions in three patients gave rise to urinary acetone bodies. After five of these infusions the urine showed trace amounts and after one a strongly positive reaction for acetone.

TABLE 1

	Average temperature range °F	Average rise	Mean temperature
Control days	98.2– 99.8	1.6	99.0
Dextrose infusion days	98.4–100.0	1.6	99.1
Fat emulsion infusion days	98.4–100.0	1 6	99 1

By all the indices that were assembled to assess the temperature rises, we conclude that no febrile responses occurred and that there were no differences in temperature on the control, dextrose and fat emulsion days. As may be seen in Table I, the average temperature ranges, temperature rises, and average mean temperatures are almost identical in all three circumstances. The profiles on temperature charts point to the same conclusion. In almost all cases, the control, dextrose, and fat emulsion profiles are neatly superimposable on one another.

Subsequent to this study two patients were given 1,200 ml of the same lot of intravenous fat emulsion on a single day; both had moderately severe febrile reactions. The next day following another infusion of the fat emulsion one of these had an even greater temperature rise and other untoward symptoms. Three months earlier he had suffered a severe reaction to long-term infusion of large amounts of intravenous fat emulsion.[1] When 22.7 per cent

TABLE II

	Greasy taste	Head-ache	Nausea	Feels warm	Aching arm	Dizzi-ness	Poor appetite	Good appetite
Control								
22 studies in 12 patients								
Number of reactions	0	0	0	0	0	0	1	9
Number of patients reacting	0	0	0	0	0	0	1	9
I. V. dextrose								
46 infusions in 12 patients								
Number of reactions	0	1	3	1	2	14	11	28
Number of patients reacting	0	1	2	1	2	7	5	9
I. V. fat emulsion								
27 infusions in 9 patients								
Number of reactions	11	5	2	3	4	3	2	16
Number of patients reacting	6	3	2	2	3	3	2	8

intravenous glucose was infused daily for one week to this patient, no fever developed.

The second patient had not previously received intravenous fat emulsion. After the temperature rise on the first infusion, there were no temperature rises for three weeks during which period he received 1,200 ml of lipomul daily. After three weeks of these large daily infusions this patient also suffered a severe reaction.[1] The experiences of these two patients suggest that the febrile response is due to a specific property of intravenous fat or a personal idiosyncrasy of certain subjects.

The blood data revealed few abnormalities over the period of study. Seven subjects had a high eosinophil count on a differential smear. Most of these counts were high prior to intravenous fat infusion and were not elevated further by intravenous fat.

Six out of nine patients followed for a period of two weeks had small weight gains, one remained constant, and two lost weight. Each day the patients were asked about their appetites, also, whether they suffered from headaches, dizziness and so forth. The incidence of these minor reactions is indicated in Table II. In addition to questioning subjects about their appetites, the amounts they had eaten for lunch were noted. The high incidence of good appetites and reports of definite hunger are surprising in view of the extra calories the patients had received during the morning infusions.

SUMMARY

Forty-six daily infusions of 22.7 per cent dextrose were given in a four-day period to 12 healthy men. The following week, nine of these subjects each received three daily infusions of a 15 per cent fat emulsion. The dextrose and fat emulsion infusions were approximately equal in caloric content and caloric rates of infusion. There were no febrile responses. The temperature patterns of the control days, dextrose infusion days and fat infusion days were substantially the same.

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REFERENCE

1. Levenson, S. M., Upjohn, H. L., and Sheehy, T. W.: Two severe reactions following the long term infusion of large amounts of intravenous fat emulsion. *Metabolism*, 6:807, 1957.