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Review of the literature on fat emulsions in parenteral nutrition

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A REVIEW OF THE LITERATURE ON FAT EMULSIONS IN PARENTERAL NUTRITION

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INTRODUCTION

Although it has long been possible to provide carbohydrate as solutions of dextrose and of protein as protein hydrolysates, these methods alone have not been an adequate nor practical approach to the problem of maintenance of nutrition on a parenteral basis. For this reason, patients who are unable to absorb adequate food from the gastro-intestinal tract are often observed to slip towards or into nutritional depletion in spite of vigorous administration of solutions of sugar and amino acids.

A healthy person tolerates temporary inadequate caloric intake well. Even the acutely ill patient may withstand a poor nutritional status without serious set back to recovery if his stores of glycogen, fat, and protein were adequate at onset. In the prolonged or chronic illness, however, the circumstances are quite different especially when the patient's intestinal absorption is partially or completely interfered with by the nature of his illness. In such cases, glycogen stores are readily depleted. Fat stores supply the bulk of energy requirements, but this can not meet total body needs even with infusion of sugar and protein.

Body protein is utilized for energy even before fat deposits reach depletion, just at the time when protein is needed for antobody formation and tissue repair. Febrile states increase the demand for energy.

In recent years, it has been adequately demonstrated that the intravenous administration of fat emulsions when added to parenteral nutritional therapy can meet nutritional demands even in many serious illnesses over several week's time. This has been proven by actual clinical use. The value of fat emulsions for intravenous administration is clearly indicated and the ability of man to tolerate the infusions is an established fact. There is no need to discuss its feasibility. The problems which delay a wide use are mainly two fold; the production of emulsions which will retain their stability through handling, storage, and environmental changes, and the preparation of emulsions which are consistently non-toxic. When these problems are solved, a new concept in parenteral feeding should find its place in medicine.

The purpose of this paper is to present an informative and critical review of reports on clinical experience in the use of fat emulsions in parenteral

nutritional therapy.

HISTORY

Probably the first suggestion for the use of fats in parenteral nutrition was made by Leube in Germany in 1895. He made the suggestion from observations with the use of camphor oil injected in patients with heart failure. In the next few years several investigators attempted to determine if fats injected subcutaneously were utilized. They met with little success because of poor absorption.

Finally in 1915, Murlin and Riche prepared and infushed a fat emulsion into the veins of experimental animals.[20] This was repeated by Momura in 1929 and Baba in 1931. Their studies indicated it could be successfully accomplished and might have nutritional value.

Yamakawa in Japan in 1920 was the first to report the intravenous administration of fat emulsions into humans. Holt, Tidwell, and Scott in this country, administered fat emusion to children.[13] Further, early trials in humans were reported by Gordon and Levine in 1935; Myers, 1936; Naral, 1938; and Knainrsh in 1940.

More recent and extensive animal research has been

conducted by Stare and associates at Harvard Medical School and Meng and associates at Northwestern University College of Medicine.[4]

The major clincial studies in this country have been reported by Jordon from the University of California Medical Center and Wadsworth General Hospital, Los Angeles; Waddell, Stare and their associates from studies at Massachusetts General Hospital, Boston; and Shafiroff and his associates at New York University College of Medicine. Recently, the United States Military Hospital Service has begun studies with fat emulsions for parenteral nutrition.

ADVANTAGES AND USES

Fat emulsions find use in parenteral nutriton because of their ability to provide large quantities of calories in relatively small volumes of fluid. Fat emulsions are the only fluids yet used which are capable of meeting total body requirements for energy on a parenteral basis. Their value in medical and surgical problems complicated by inadequate intestinal absorption or in illnesses in which oral feeding is not feasible should be obvious.

Fat emulsions have a number of advantages over solutions of sugar, protein and alcohol. Fats provide a higher concentration per gram; they do not appear to be irritating to venous walls; fat is not excreted in the urine or feces thus all infused material is available for utilization; they can maintain body weight and spare the excessive catabolism of protein.

Fats provide approximately nine calories per gram compared to four calories for sugar and protein and seven for alcohol. Thus simply on a unit for unit basis, fat provides more energy.

The concentration of sugar and protein solutions

are limited due to hypertonicity. Solutions of more than 5% glucose are hypertonic. Although sugar solutions as high as 25% concentration are occasionally used intravenously, 10% solutions are the highest concentrations of practical use for repeated injections. A 10% solution of dextrose provides 400 calories per liter. Thus in order to provide appreciable calories large volumes must be used. If there were no loss by excretion and renal and cardiac status is unimpaired, about three liters may be given to an adult in a twenty -four hour period. This will provide about 1200 calories, an insufficient amount to meet total energy requirements in most patients or spare the utilization of protein stores.[4] Practically, however, a variable amount of infused sugar is excreted through the kidney unused, depending largely on the rate of administration. In illnesses complicated by renal or cardiac insufficiency, such large volumes of fluid are poorly tolerated.

Protein hydrolysates are of value in providing needed amino acids, but are poor agents for maintaining energy requirements. Given with glucose solutions or alone, they are of value in sparing and maintaining body protein, but if caloric needs are not met, they

will be utilized for energy rapidly thus diminishing their real value, They may be given in concentration of 2.5-6% alone or with dextrose. Even in low concentration repeated injections frequently results in venous irritation leading to aseptic phlebitis and venous thrombosis.

Alcohol is a potent sclerosing agent and has undesirable effects on the central nervous system. It may be given with other fluids in very low concentration, but it is not a practical source of energy in parenteral nutrition.

Emulsions of fat largely overcome the limitations and disadvantages mentioned. Fat emulsions in concentrations of 5 to 20% are being used successfully. The aqueous medium is usually 5% glucose. This is of value in four ways: the glucose does not adversely effect emulsion stability; it renders the emulsion isotonic with blood; provides an additional 200 calories per liter; and happily, provides the amount in one liter thought to be required for complete metabolism of fat, about 40 to 50 grams.[26] Thus a liter of 15% fat emulsified in 5% glucose provides approximately 1550 calories almost all of which is available for energy.

With less than two liters per day, it is possible not only to completely meet the caloric requirements of most patients, but significantly spare the catabolism of body protein.[15, 17, 18] Patients and experimental animals have gained weight while being maintained totally on fat emulsion administered intravenously.[8, 15] As a matter of fact, protein material may be used with fat emulsions. Protein as casein hydrolysate has been used in concentrations up to 6% in combined emulsions.[15] With caloric requirements met by fat, this leaves the amino acids, available in the hydrolysate, for the synthesis of protein.

Actually it is possible to infuse fat emulsion in excess of caloric needs. The important fact, however, is that fat emulsion provide a means of meeting caloric requirements on a parenteral basis and with relatively low volumes of fluid.

The ability of fat emulsion to correct nitrogen and potassium imbalance has been demonstrated in both animals and man.[4, 7, 8] As an example, Goren reported the use of fat emulsion in a patient in which nitrogen and potassium studies were made.[8] The patiant's average daily oral intake of protein and potassium were

45 grams and 1.6 grams respectfully. His caloric intake was below his need and the patient was in strong negative balances. With the infusion of 800 ml of 15% fat emulsion per day, he promptly gained positive balances. During a period when fat emulsion was not available, the patient again went into negative balance. This was promptly corrected a second time when the fat emulsion became available. The content of nitrogen of potassium in the emulsion was negligible.

An incidental though noteworthy use of fat emulsions not previously mentioned is in the parenteral administration of vitamins. These preparations offer a ready and easy medium for the administration of fat soluble vitamins.[2]

To attempt to list and discuss the many possible clinical situations in which intravenous fat emulsions are of theraputic value is somewhat beside the point and should be inferred from their caloric value. Perhaps the following account will illustrate the point. This is a report of a patient treated at the Massachusetts General Hospital in Boston in 1952.

> "D. M. was a 46 year old mechanic who was brought to the emergency ward in a condition of shock and dehydration. Three days previously

he had experienced a sudden sharp pain in the right abdomen. As the pain subsided, it was replaced by nausea, vomiting, and diarrhea. The following day he began to experience severe pain in both shoulders. The symptoms persisted; he grew increasingly weak and finally sought admission to the hospital.

"At the time of entry the patient was in profound shock and showed signs of generalized peritonitis. A diagnosis of perforated viscus was made. He responded to supportive therapy and over the course of the next few weeks the peritoneal infection localized, forming pelvic, subhepatic, and right lower quadrant abcesses. These were drained, but the condition of the patient remained critical, owing largely to persistent complete intestinal obstruction which prevented any oral intake whatever. Constant intubation was necessary, and throughout this period the patient was fed entirely by vein.

"Alcohol, dextrose, and protein hydrolysates were administered in liberal amounts; nevertheless, the patient became increasingly cachectic. After 31 days fat emulsions for intravenous use became available as an additional source of calories. For 36 days thereafter he was continued on fat intravenous feeding, but in addition to the conventional nutrients, he was given 36 infusions of fat emulsion, which provided a total of 42,214 calories. During the period of supplementation with fat the caloric intake from other sources totaled 39, 598 calories, an average of 1,100 calories per day. Fat emulsions provided an average of 1,173 calories per day.

After 67 days of complete parenteral nutrition, the patient began to retain small amounts of food. Parenteral feeding was discontinued, and his intake by mouth soon reached adequate levels. Ten days later the patient was convalescing satisfactorily."

The authors felt that this patient could not have survived had he not received the nutritional support given him by fat emulsion.

PREPARATION AND ADMINISTRATION

Fats

A wide variety of fats have been successfully administered in emulsion form. These include naturally occurring animal and plant oils and synthetically prepared neutral fat. All are triglycerides, esters of fatty acids with glycerol. All provide approximately the same caloric value. In general the more saturated fatty acids produce more stable emulsions and are the least likely to become rancid on preparation and storage. This is probably due to the greater solubility[26] and the greater resistance to hydrolysis and oxidation of the saturated fatty acids.[19]

Coconut, olive, cottonseed and corn oil have been most widely used while butter, peanut and linseed oils have been used to a lesser extent. The natural occurring oils (fats) have the advantages of being readily available and relatively inexpensive even in the purified form used for intravenous administration.

Synthetic triolein an ester of glycerol with oleic acid has proven an excellent lipid for parenteral use.[18] Tripalmiten and trilauric acids have also been successfully

administered. Synthetic fats have an advantage in that the fatty acids may be selected as desired where as the natural occurring oils are usually mixtures of various fatty acids. However, synthetic fats are more expensive and not as readily available at the present time.

Aqueous medium

Although emulsions of fat in pure water may be prepared 5% dextrose water is ordinarily used. The glucose may be used as stock solution or dissolved at the time of emulsification. Either way the water used is double or preferably triple distilled. The glucose renders the emulsion isotonic and does not reduce the stability of the emulsions. Isotonic saline solutions can be used, but with emulsions to be stored more than a few days the addition of electrolyte adversely effects emulsion stability. For emulsions in which the pH does not nearly approach that of blood (fat emulsion tends to be slightly acid) calculated amounts of a weak base must be added. This is usually disodium hypophosphate. When needed this salt is added to emulsion just prior to administration.[6, 24]

Emulsifying agents

Neutral fats may be made to form emulsions with water alone, but in general the products are not stable enough to with stand autoclaving and readily separate on standing. Therefore it is desirable to add an emulsifying agent or agents to the mixture. What ever the agent it should have the following properties; preserve stability and resist destruction through homogenization, autoclaving, and storage; be relatively free of toxic effects itself and produce an emulsion which is non toxic, and be capable of either being metabolized or eliminated from the body. The search for such an agent is a major challenge. Agents now in use appear to maintain stabilization well, but none are entirely free of toxic effects. The ideal stabilizer is yet to be found.

Perhaps the best stabilizing agents are soaps, but they are uniformly potent hemolytic agents and can not be used.

Two groups of stabilizing agents have been tried. These are the hydrophilec colloidal materials and the surface-active agents. The former is thought to bring about stabilization by forming a protective film over

the finely divided fat particles. This prevents coalescence and preserves Brownian movement. The latter group are thought to act by orientation at the oil-water interphase where a repellent charge is imparted to the particle.[2, 19, 27]

Hydrophilic Agents: Among the first agents tested were the gelatins, water soluble proteins derived from collogens by heating in dilute acid or alkaline solutions. Although gelatins may be injected into the blood stream alone without undue adversity, McKibbin found in studies with dogs that when used as emulsifying agent for fats, there resulted an emulsion which produced pulmonary emboli.[2] Furthermore they were effective as stabilizing only in relatively high concentration. Despite these adverse indications, gelatins in very low concentrations have been successfully used as co-stabilizers. Their use in humans, however, has been quite limited.[7]

Ferry added cholesterol to emulsions given to dogs in concentrations up to 0.42%. This appeared to aid in stabilization but resulted in cholesterolemia and impairment of liver function.[3] This was apparently due to an inability of the animals to secrete the

sterol. Although the hepatic changes were shown to be reversible in the absence of previous liver damage the use of cholesterol was discouraged.

The most widely used emulsifying agents are lecithins. These are phosphatides made up of glycerol to which is attached two fatty acid chains and a phosphoric acid in combination with choline. Both egg and soybean lecithins have been tried, but the latter being considerably less expensive is now used almost exclusively. Soybean phosphatides in purified form have proven to be good stabilizing agents in low concentration. They are effective alone, or with other co-stabilizers. It does have a slight hemolytic effect in some patients, but this has been insignificant with concentrations up to 1% without ill effect. Emulsions with lecithin as the sole stabilizer have been used successfully after five and one half months storage.[13, 2, 10, 15, 11]

Hydrolysis of lecithin removes fatty acid groups from the molecule. The remaining product, lysolecithin is hemolytic. This may explain in part the hemolytic action.

Cerebrosides are compounds found in supporting

yields one molecule each of a hexose sugar, sphingosine and a fatty acid. Cerebrosides appear to be effective stabilizing agents, possible equal to or better than lecithins. Johnson infused 79 patients with 10% olive oil emulsion.[11] Thirty nine received the emulsion stabilized solely with 1% cerebrosides; forty received the emulsion stabilized with the same concentration of lecithin. The former group had a smaller percentage of untoward reactions. The number of infusions was too small to be conclusive, but this may indicate an advantage to the use of cerebrosides. However, the availability of these compounds at present is not sufficient to allow wide use.

Johnson stored samples of his emulsions, both lecithin and cerebroside stabilized, for one and one half years at refrigerator and room temperatures. Except for a few droplets at the surface of the emulsions stored at room temperature neither showed any change in fat particle size.

Surface Active Agents: In general the surface active agents are highly hemolytic and are difficult to utilize for intravenous administration. As previously stated soaps are of no value for this reason. However,

sodium cholate, Tweens, Spans and Demal have been tried. With exception of sodium cholate these agents have met with some success. The major problem with surface active agents is to find a type which is effective in low enough concentration to be free of toxic effects and still produce a stable emulsion.

Sodium cholate is the salt of cholic acid; the most abundant acid in bile. It is a strong emulsifying agent. Meng and Freeman reported that up to 31.5 mg/kg could be given to dogs without significant hemolytic results. For an average adult receiving a liter of emulsion this would allow a concentration of about 0.2% of the salt. This amount, 2 grams per liter, is inadequate to maintain stability alone. Where tried it has been used in combination with other stabilizing agents. Unfortunately it appears to have an additive and perhaps a potentiating effect in the production of anemia when used with other stabilizers. Johnson discarded sodium cholate after preliminary tests in man.

Various esters of fatty acids with sorbital, Tweens and Spans, have been tried as co-stabilizers.[4, 11] Their use has been associated with an increased incidence of anemia and elevation in blood pressure. The reason

for the latter is not known. If used in concentrations not exceeding 0.5%, they may still prove of value.

Better success has been achieved with a polyglycerol ester known as Demal 14. Toxic effects with this agent appear to be minimal. It has been used successfully in concentrations up to 1%. The substance has a good stabilizing effect. When used as a co-stabilizer it allows a reduction in the concentration of phosphatides to about half that needed along.

Homogenization and Sterilization

Homogenization and sterilization of fat emulsions intended for intravenous administration are highly important factors. Although various techniques have been tried there is no great variation in the general principles now in use. Commercialization will no doubt bring improvements in various details, but the general method will probably prevail.

The following is a description of the pertinent steps. The fat, with emulsifying agents, is mixed with glucose and water by hand driven or power driven mixers to produce a crude emulsion. This mixture is then run through an ordinary dairy homogenizer several times, usually about 15 times. The resultant emulsion, now

hot, is filtered, preferably while still hot and collected in sterile bottles. While still hot it is autoclaved for 15 minutes at 15 pounds pressure per square inch. To keep oxidation and hydrolysis of the fat to a minimum this process is best carried out under an atmosphere of nitrogen. Positive nitrogen pressure can be used to speed up filtration.[19, 11, 24]

The emulsion produced by this method is made up of fat particles with mean diameters of about 0.5 microns with a range of from 0.2 to 2.0 microns.

As previously stated, emulsions prepared in this manner have been stored up to one and one half years without change in particle size.

Rate of administration

The rate at which fat emulsion should be infused depends not only on the volume but upon the concentration of fat and individual patient tolerance. Kinsell reported rates of administration greater than 20 grams of fat per hour for six hours exceeds the tolerance of the average patient. Jordon, however, reported the infusion of a large number of patients at rates up to 40 grams per hour for five hours with no significant adverse effects. His average rate of administration was

23.5 grams per hour. He felt, however, that in general the slower the rate the better the tolerance.[17, 18]

For the average patient, then, a 15% emulsion infused at a rate of 2 ml per minute (about 20 drops) will deliver approximately 18 grams per hour and should be well tolerated. Exceptions to this should be noted in certain diseases. These include the nephrotic syndrome and glomerulonephritis associated with hyperlemia in which the rate of clearance from the blood stream is retarded; hepatic cirrhosis in which the rate of utilization is slower; severe cardiac disease in which rapid increases in circulating blood volume may be detrimental; regional enteritis and ulcerative colitis in which fat emulsions are poorly tolerated and tend to produce nausea and vomiting. In each of these, a slower rate is probably indicated. It has also been observed that the incidence of pyrogenic and other systemic reactions tend to be higher in the post operative patient; it is advisable to start with smaller amounts and infuse at slower rates than usual until the patient tolerance is improved.[9, 15, 16]

SIDE EFFECTS

A number of different methods of classification of side effects due to the intravenous administration of fat emulsions appear in the literature. Probably neither is completely satisfactory. Each has merit in as much as it aids in the understanding of the various effects. Some are purely for convenience. The methods used include classification according to: symptoms, organ systems involved, time of onset, etiology and incidence.

Since neither classification is fixed or unalterable, they are discussed below as best for convenience, comprehension, and ease of discussion. In general, however, the various effects are presented in order of greatest incidence or severity.

Pyrogenic reactions

This is actually a generalized systemic reaction but is discussed separately because it has consistently been the most commonly observed side effect. The reported incidence varies from 5 to 70% in humans. This would seem to suggest considerable differences in either the production or administration of emulsions. On

closer study and comparison of the reports, however, there is remarkable agreement. The differences exist largely in criteria for pyrogenicity as will be seen.

Despite extensive research and numerous theories, no adequate explanation has as yet been advanced to explain elevations in body temperature during the intravenous administration of fat emulsions. It is perhaps significant that most patients react not at all while others become febrile during one infusion, but fail to react to subsequent infusions even with the same emulsions. Furthermore, there appears to be little correlation between the type or severity of illnesses and the incidence of febrile response to infusions.

The largest group of patients so far studied and reported was by Waddell and associates at the Harvard Medical School.[17] They gave 1466 infusions to 426 patients at Massachusetts General Hospital over a four year period. The infusions consisted of 10 and 15% emulsions of coconut oil, cottonseed oil, and olive oil, mixture of coconut and olive oils, peanut oil and synthetic triolien stabilized with soybean phosphatides. About 18% or 1 in 6 infusions were accompanied by some elevation in temperature. Elevations of 2° F

were considered tolerable and in only 5% or 1 in 20 was there an elevation of more than two degrees. Infusions in patients showing more than a 2% elevation were discontinued so that it is difficult to suppose what would have happened in these. All cases of temperature elevation returned to initial levels within 1 to 2 hours following the completion of the infusion or discontinuance. because of elevations greater than 2°. A few instances of post-infusions temperature elevations were observed, but whether these were due to the emulsion or the patient's illness was difficult to determine. Otherwise all pyrogenic reactions occurred during the infusions. No serious results due to temperature elevation were observed.

In Los Angeles, Jordon and associates recently reported a study of 633 infusions with 209 patients. A single type of emulsion was used throughout; 10% sesame oil stabilized with soybean phosphatides. About 70% of all the infusions were accompanied by some elevation of body temperature. However, using Waddell's criteria for tolerability, a rise in temperature not over 2° F, this incidence falls to 10%. This figure approaches that of the Harvard group. Furthermore it

includes 32 infusions in patients whose temperatures were over 100° at onset. Including the infusions with febrile patients, only 3% had elevations above 102°. Like Waddell's patients all elevated temperatures returned to initial levels promptly following the infusions and no serious results were noted.

Similar results to those above were reported by Shafiroff in 22 patients[7] and Johnson with 79 patients.[11] Material from these reports are included in the following.

The nature of temperature responses with intravenous fat emulsions is similar to pyrogenic reactions in general; a rather sharp rise in temperature, often associated with a chill, to a maximum. With the infusions of fat emulsion the temperature once elevated tends to remain so throughout the infusion. Secondary elevations following the infusion are rare. Following the infusion the temperature returns to initial levels within a few hours; usually within two hours. Eight hours is the longest reported.

Emulsions intended for human use are carefully prepared to insure sterility and cultures are taken to ascertain this. Furthermore it is common practice to test new preparations for pyrogenicity and other

reactions in laboratory animals before administering them to humans. Emulsions showing significant untoward reactions in animals are discarded. Despite these cautions pyrogenic responses are still observed in man.

Various explanations proposed to explain this include bacterial contamination, hydrolytic products of fat, emulsifying agents, 'colloidal phenomena', increased rates of oxidation in the body and intravascular hemolysis. Neither has been conclusively incriminated. One investigator suggests that this and other systemic reactions may be due to "the interaction of the emulsion with the patient's body in a particular physio-chemical state which may vary from day to day" and not primarily to the structure or composition of the fat emulsion.[18] The nature of this "physio-chemical state", however, is unsolved at this time.

Some investigators feel that pyrogenic reactions in general are due to the presence of extremely soluble polysaccharides produced by bacterial metabolism and released on disintegration of the organisms. With this in mind Johnson and associates at Northwestern University Medical School compared the administration of freshly prepared and stored emulsions in animals. They reported

that the fresh preparations "may not give pyrogenic reactions", but the same emulsions after several weeks storage caused reactions even though the stability of the emulsion remained unchanged. They were unable to demonstrate bacterial contamination, however.

The apparent development of pyrogenicity with stored emulsions was also suggested by Mann[6]. He observed the occurrence of pyrogenic reactions in six patients receiving multiple infusion, but this occurred only in emulsions stored for four or more weeks. Since the emulsions were sterile, he concluded that the pyrogenic effect was not bacterial in origin.

In contrast to this Jordon in his large series did not observe an increased incidence of reactions with storage.[18] His emulsions were stored at room temperature and used up to five and one half months storage.

Morton recalled that in diseases associated with intravascular hemolysis (malaria, for example) there is a characteristic febrile response. He suggests a possible correlation. In support of this view, he described one case in which a patient receiving fat emulsion showed significant hemolysis (plasma hemoglobin above 10 mg%. This patient also developed a fever.

The incidence of hemolytic effects in humans receiving intravenous fat emulsion, however, has been low. The two reactions correlate poorly. More will be said about hemolysis later.

The production of unphysiological products of partial hydrolysis is suggested by the development in some emulsions of pyrogenicity on standing. To avoid unnecessary hydrolysis and oxidation, it has recently become the practice to homogenize and autoclave under an atmosphere of nitrogen. This does not eliminate slower processes which might take place on standing. Therefore it would seem advisable to bottle the emulsions in air tight vacuum type bottles. Comparative reports in the literature on these aspects are as yet few. Therefore conclusions at this time would be premature.

It is known that unsaturated fatty acids are more susceptible to hydrolysis and oxidation than are saturated acids.[19, 29] However, in the large series reported by Waddell, synthetic triolein, a fat composed of three unsaturated acid groups, (oleic acid), ranked second to best, as regards freedom from pyrogenicity among six fats used. It was felt that this ruled out oleic acid, at least, as contributing to pyrogenicity.[17] Most

of the emulsions were used within 2 months thus limiting to some degree effects of storage. This single report is inconclusive.

In 1949 Shafiroff infused twenty-two surgical patients with a combined emulsion made up of 10% coconut oil, 5% glucose and 5% protein hydrolysate.[7] He noted that the most commonly observed side effect was elevation in body temperature. These were characterized by prompt elevation during the infusion and a gradual decline following the infusion. From these observations he suggested that the pyrogenic effect might be due to an increased rate of oxidative processes within the body resulting in excessive heat production. This in turn should be related to rapid rates of infusion.

Two years later Neptune administered 15% coconut oil emulsions to nine patients, one of whom received twenty one infusions.[10] This was one of the first uses inmman on a large scale of emulsions of greater than 10% fat. The rate of administration averaged 8 ml per minute, about twice the rate ordinarily used. Despite the higher concentration of fat and rapid rate of infusion no significant alterations in body temperature were observed. In addition Neptune pointed out that

the "body's mechanisms for heat regulation should handle increased heat production due to metabolism." Cited as an example is the low incidence of fever even in severe thyrotoxicosis, a disease characterized by "super catabolism".

In 1951 Shafiroff compared the effects of different concentrations of fat "under as near identical conditions as possible".[9] Each of 19 patients received infusion over a twelve hour period. Seven received 1000 cc of a 10% emulsion, six received a liter of 15% and six received a liter of 20% emulsion. Among the patients having an elevation in body temperature, the average increase was 2.8° F. Those receiving 10% fat had the fewest pyrogenic reactions and those receiving 15% and 20% the greatest number. Assuming relative increase in rate of utilization with increased concentration of fat a direct relationship with pyrogenicity is indicated. Why then are not all infusions with high potency fat emulsions accompanied by pyrogenic response?

In sharp contrast to Shafiroff's report is a similar series reported by Itallie and associates a year later.[15] The infusions consisted of combined emulsions with 5% glucose, 5% protein hydrolysate while the fat

content was varied to include 10%, 12.5% and 15%. Thirty five patients were included in the series, fifteen of whom received five to thirty six infusions. In all these infusions not one significant pyrogenic or other untoward reaction occurred. It is difficult to explain the marked difference in the two series. The latter is a much larger series and would seem to repute any conclusions thus far drawn that increased oxidation (with up to 15% fat emulsions) have any direct relationship to elevations in body temperature.

In conclusion it should be recalled that in over 2000 infusions reported the incidence of significant pyrogenic reactions is only about 10%. The temperatures return to initial levels within a few hours after completion of the infusions. Patients reacting to one infusion may not react to subsequent infusions. A febrile state itself is not a contraindication when the patient is in need of nutrition available as fat emulsions. The incidence of pyrogenic response is no higher in febrile patients. The degree of fever may be a factor, however, and in patients with a high pre-infusion fever these materials should be used with caution and careful observation. Finally an elevation in temperature

over 2^{o} F during an infusion ought to be accepted as an indication for discontinuation at least until the temperature has fallen.

Systemic reactions

This includes a group of effects which have been referred to as "Reactions due to colloids", "Generalized reactions" and "Systemic reactions". With a few exceptions they have been consistently observed by each investigator reporting a large series of infusions.[7, 9, 11, Most are purely symptomatic. A few may be objectively observed. The reactions most consistently observed include chills, dysnea, chest pain, back pain, nausea and vomiting, flushing of the skin, apprehension, blurring of vision and arthralgia. These reactions appear to be related to another and can be discussed as a group with essential differences pointed out where pertinent. Except for its higher incidence, the pyrogenic reaction also appears to be related to this group.

In the largest series reported the percentage of patients having one or more of these reactions was 2.5 or 1 patient in 50. Since a patient may react to one infusion and not to another the percentage of infusions

accompanied by reactions is less; about 1% or 1 in 150. These figures represent data from infusions with emulsions of several different types of fat. In smaller series and with single emulsions the incidence has varied from none to somewhat greater than 1%. In general the incidence of systemic reaction is low.

One common characteristic of these reactions is their abrupt onset.[11, 17, 18] Although they may occur separately or in combination certain reactions may follow one another rapidly in a characteristic pattern. This is best described by Waddell[17]; "development in rapid order of flushing and warmth of the face and neck, sensation of constriction or apprehension in the chest, cyanosis and severe pain in the back."[11] More often the reactions occur alone.

Another characteristic rather consistently observed is the relationship of certain reactions to fairly definite time of onset during the infusion. The reactions fall into three groups on this basis: first, flushing, back pain, chest pain and dyspnea usually occur after the administration of only a few milliliters of emulsion; second, chills alone or chills associated with elevations in body temperature rarely occur before the

administration of 100 ml and if not occurring before the infusion of 300 ml will then seldom develop; third, nausea and vomiting, headache, blurring of vision, dizziness, and arthralgia are late manifestations rarely occurring before the infusion of 500 ml.

Chills are second to pyrogenic reactions in evidence. This is true because of the tendency for less severe chills than those occurring alone to preceed or accompany any of the other reactions.

A striking similarity of these reactions is the prompt improvement on discontinuance of the infusion. Stopping an infusion for 15 to 20 minutes will nearly always result in either marked improvement or complete disappearance of the reaction. Once the reaction has subsided the infusion may be resumed, more often than not, without recurrence. This is especially true of reactions occurring early in the infusion.

An exception is the development of arthralgia. This reaction, usually described as an aching all over, tends to occur only with large infusions, 1000 cc or more, and comes on toward completion. Once present the condition usually persists for several hours and disappears gradually.

A common characteristic, including pyrogenicity, is that once a patient has reacted to an infusion his chances of reacting to a second are no greater than among patients in general. A patient may receive several subsequent infusions without a reaction of any kind. In a series of 569 patients, four had more than one episode.[18] This fortunate circumstance is difficult to explain. Apparently the reactions are not on an allergic basis.

Despite lack of evidence pointing to an allergic basis antihistamines have been used with some success although the results have often been equivocal. The reason for this is that the reactions tend to be short lived; especially if the infusion is temproarily discontinued as previously stated. So it is difficult to know whether the antihistamines helped or whether the reactions simply terminated spontaniously. Pyribenzamine, 25 mg, added directly to 600 ml bottles was given to 65 patients in a total of 185 infusions. The incidence of reactions in this group was no less than 404 patients who received no antihistamines.[17, 18]

Jordon felt that the immediate administration of 20 mg of benodryl at the onset of certain reactions was

of some help and in two types of reactions of definite benefit. Back pain and chest pain appeared to be improved by benadryl, but objective evaluation is difficult. Flushing of the skin seemed to be diminished by the intravenous injection of benadryl; this reaction, however, is usually of short duration. Dyspnea, unless, associated with a chill, "responded with remarkable improvement." Antihistamines would be expected to antagonize capillary dilitation and bronchial constriction due to the release of histamine, but in addition benadryl, at least, has a weak atropine like action not associated with histamine antagonism.[27] Which, if either, of these properties is responsible for improvement of flushing and dyspnea is not clear. In general the value of antihistamine in the responses of patients to fat emulsions apears limited.

A few electrocardiographic recordings taken during attacks of chest pain have failed to demonstrate significant changes. Though not conclusive this at least suggests a non cardiac basis for this reaction.

Nausea with vomiting is the most serious reaction encountered. It will often subside on slowing or temporarily stopping the infusion. Failure to do so,

however, is ample indication for discontinuance. Like other reactions nausea and vomiting rarely recurs on subsequent infusions.

A rare reaction, possibly not related to those described above, is the appearance of urticaria.[17] Two distinct types have been observed. Most are characterized by a generalized rash which disappears promptly on administration of benadryl or adrenalin. Two cases of maculopapular eruptions limited to the chest and upper extremities persisted several days despite the use of antihistamines. Except for mild pruritus neither type is associated with much discomfort.

Post infusion reactions

These include the occasional development of headache, anorexia and dizziness.

Headaches are almost always frontal in location, of variable intensity, but rarely severe. They are not to be associated with hypertension. Usually they are relieved by salycilates.

Anorexia, without nausea, may occur. This is usually described as a sense of abdominal fullness associated with a lack of hunger. Once present it tends

to persist through one meal or throughout the day of the infusion. Occasionally there is an associated slight headache.

Dizziness most often occurs after large infusions. It develops when the patient attempts to ambulate immediately after completion of the infusion. Though of low incidence this reaction probably warrants keeping patients in bed for a short time following the infusion.

It is interesting and perhaps significant to note the similarity in the reactions observed after the intravenous administration of other substances of a colloidal nature. Nissin, in England, reports an almost identical list of reactions to the administration of saturated iron oxide in the treatment of iron deficiency anemias.[22] Similar responses to the administration of whole blood occur, especially those seen 'early' in infusions of fat emulsion. The association with hypersensitivity with blood has been more definite, however.

In conclusion the following facts bear stressing. The incidence of so called systemic or generalized reactions is low. With the exception of nausea and vomiting, none are serious. Most are transient. The

reactions are characteristically appreciably diminished or completely abolished by slowing or temporarily stopping the infusion. There is little or no tendency for the reactions to recur even on subsequent administration of the same emulsion. There have been no deaths in humans due to these or other untoward reactions. Fear of precipitating reactions of the types described is not a contraindication to the use of intravenous fat emulsions.

Hemolysis and Anemia

Although anemic tendencies have been observed in humans receiving intravenous fat emulsions the incidence is low and with few exceptions slight. In 1949 Mann reported the appearance of a moderate normocytic anemia in each of six patients receiving repeated infusions of 15% cocnut oil stabilized with soybean phosphatides and Demal 15, a polyglycerol ester.[6] As in observations on laboratory animals the anemia improved within a few days after the infusions were discontinued. Two years later Shafiroff failed to find significant changes in red cell counts or hemoglobin in nineteen patients receiving emulsions of 10, 15, and 20% fat, but with lower concentrations of stabilizers.[7] This suggests that

the difficulty may lie in concentration of stabilizers rather than in fat.

That fats do have some adverse effect on red cell stability was demonstrated by Creditor.[12] He studied the effects in two patients. One received synthetic fat , the other olive oil; both stabilized with low concentrations of phosphatide and Demal. Each patient received three infusions of 500 ml several days apart. During each hyperlipemic state there was a definite increase in red cell fragility as measured by suspending cells in hypotonic saline solutions and there were corresponding slight increases in plasma hemoglobin. The increased fragility could be reversed in vetro by 'washing' the cells free of lipid. With only one infusion was there an increase in fecal urobilinogen. This was the only instance showing plasma hemoglobin in excess of 10 mg%; the only explanation offered was that fat particles in high concentration may adhere to the cells and in some way alter membrane stability.

It is fairly clear that emulsifying agents in common use are capable of producing hemolysis, but in concentrations used the effect is minimal. High lipid concentrations in the blood stream are also apparently

capable of contributing to hemolysis by increasing red cell fragility. Though anemic tendencies occurring with intravenously administered fats are mild, it is advisable to determine red cell levels and hemoglobin in every patient considered for infusion.

Vasomotor reactions

In early experiments with fat emulsions, Geyer reported a vasodepressor effect in the cat and in human volunteers. This was found to be due to some contaminent in crude soybean phosphatides used for emulsification. Although the substance was not isolated on fractionation, refined lecithins now in use are free of this effect.[6]

Increase in blood pressure and cardiac rate on the other hand are not uncommonly observed especially with large infusions. Elevations in blood pressure are mainly systolic with little change in diastolic. Elevations in blood pressure and cardiac rate are almost always associated. The increase in systolic pressure is rarely more than 20 ml of mercury; the rate seldom more than 20 beats per minute. The highest elevations are seen in conjunction with chills. Both characteristically return to preinfusion levels soon after completion

of the infusion. These changes appear to be physiological responses to increased blood volumes. Though neither effect is great, some caution in administering fat emulsions, as with intravenous fluids, in general, is indicated with hypertensive patients.[9, 15, 17, 18]

Tissue changes

In early experiments with laboratory animals both fat and emulsifying agents were implicated in the production of undesirable tissue changes.[1, 2, 3, 4] Animals sacrificed for histological studies often showed marked increase in fat globules in liver, spleen, kidney, lung and bone marrow. Caseating granulomotous lesions were often demonstrable especially in lung preparations. These findings could often be correlated with severe secondary anemias. Most of these effects were in animals receiving emulsions containing relatively large fat particles. With improvement in homogenization and use of selected purifide stabilizing agents, these changes were largely overcome.[4, 6]

Direct assay of tissue changes in humans is limited to incidental biopsy at surgery and occasional autopsy material. In reports from one liver biopsy[7] and

ten autopsies[6, 8, 9, 18] the greatest changes observed were slight increase in intracellular fat in hepatic tissue, but none could be called abnormal. There was no increase in fat in the kidneys, lung or liver and no demonstrable lesions attributable to fat in any tissue examined. This evidence probably rules out danger of producing pathological tissue changes with use of well prepared fat emulsions. It also indicates a high degree of utilization.

Accidental extravascular injection

With use of fluids for intravascular administration occasional extravascular injection is bound to occur. The reaction to fat emulsion is variable and seems to depend on the individual patient tolerance. Of six patients in whom this accident occurred, five developed localized inflammation. Of these one had to be drained because of pain and poor absorption.[7] The other four absorped the fat emulsion and the inflamation subsided. The sixth, a patient who received 400 ml in the axilla, rapidly absorped the material with no apparent ill effect.[18] Neither patient became seriously ill as a result of the accidant. The application

of moist heat appears to be of value in reducing the discomfort and hastening absorption. Though undesirable, there appears to be no grave danger to the infusion of fat emulsion intended for intravenous use into the subcutaneous tissues.

SUMMARY

There is a growing interest in the use of fat emulsions for parenteral nutrition. Much of the available literature has been reviewed. This review is primarily directed towards observations on clinical use.

The advantages and indications for use have been presented. Some discussion as to the types of fats used has been included and re-mentioned where pertinent.

The problem of stability and the use of various emulsifying agents has been discussed in some detail. It has been shown that emulsions of compatible and fairly uniform particle size can be produced by a method in general use; this method is briefly described.

F Fat emulsions used were not produced on a commercial basis. Nevertheless this review includes reports on its use with several hundred patients who received well over a total of 2000 infusions. Most of the infusions were with emulsions produced by the method described.

Particular emphasis has been placed in a critical discussion of reactions and side effects observed on

clinical use. Some discussion of methods of preventing and treating untoward reactions has been made where pertinent. The pyrogenic reaction is the most commonly occurring effect; nausea and vomiting the most serious. There have been no deaths or serious consequences reported as a result of administering fat emulsions to patients.

Studies of biopsy and autopsy material, although limited, have shown no abnormal tissue changes resulting from the infusion of fat emulsions intravenously.

Most infusions in adult patients have ranged from 500 to 1000 ml per day of 10 to 20% fat emulsions. Some patients have received over 2000 ml in one day. A large percentage have received two or more infusion and many have received multiple infusions. It is possible to furnish calories in excess of body requirements by intravenous infusion of fat emulsion. One instance of a life saving procedure is cited.

This paper does not include a review of the literature concerning the utilization of fats infused in this manner. The utilization of properly administered fat emulsions by vein is an established fact.

CONCLUSIONS

Several medical centers are using fat emulsions which retain their stability after storage. Emulsions successfully used after five and one half months storage indicate the problem of stabilization can be solved. For wide clinical use and general acceptance, these materials will have to be prepared in such a way as to retain their stability and remain non toxic for an indefinite period. Indications are that this will be accomplished in the near future. I believe that the answer to these problems lies largely in the selection of fats and the discovery of better suited stabilizing agents. This may require the use of synthetic fats exclusively, where by the fatty acids may be chosen as desired. This may result in a compromise between those fatty acids which best meet specifications for preparation and storage of emulsions and those best suited for intravenous administration.

Even at the present time the untoward effects of infusing fat emulsions into humans are not serious enough to contraindicate their use and by no means as adverse as popular opinion imagines. Like any other

theraputic agent entrusted to the medically trained the user must be familiar with their ingredients and informed in their use. With this doen there is no reason, save availability, why the physician or surgeon should not take advantage of their theraputic value. In the near future I believe they will do so. With further perfection and commercial production he may be obliged to use them when indicated.

To date, fat emulsions offer our best answer in the approach to parenteral nutritional therapy. Their inclusion in nutritional therapy is the only solution, yet devised, capable of meeting total nutritional requirements of the patient who must depend solely on intravenous feeding for long periods of time. To the acutely ill patient, whose nutritional status may otherwise be temporarily inadequate, their use offers a more rapid and efficient recovery.

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