

Review

Energy sources for intravenous nutrition

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SUMMARY

Controversy exists concerning the appropriate use of carbohydrate solutions and fat emulsions as energy sources in intravenous nutritional regimens. Current evidence suggests that glucose is the carbohydrate energy source of choice and that when infused with appropriate quantities of protein it provides cheap and effective nutritional support in the majority of patients and clinical circumstances. During glucose infusion, blood glucose and acid-base balance should be closely monitored and, when indicated, exogenous insulin should be added to the regimen to combat hyperglycaemia and improve protein anabolism. Fat emulsions, although expensive, may justifiably be used in patients with moderate or severe stress to provide up to 50% of non-protein energy, especially in circumstances where attempts to satisfy energy requirements exclusively with glucose would impose an additional metabolic stress.

INTRODUCTION

Intravenous nutrition is regarded as one of the most significant advances in medical and surgical management during the past 20 years. Several studies have documented a high incidence of clinical and sub-clinical malnutrition in hospitalised patients,^{1,2} which is associated with increased morbidity and mortality. These complications of medical and surgical disease may be reduced by the appropriate provision of nutritional support by oral, enteral, or parenteral route. The therapeutic nutritional regimen should provide adequate protein and energy substrates to replete and maintain adequate nutrition and to match the increased metabolic demands of illness and infection.³ The formulation of an intravenous regimen is based on the use of solutions containing essential and non-essential crystalline amino acids to provide protein requirements, the use of carbohydrate solutions or fat emulsions or a combination of both to provide energy, and the addition of minerals, vitamins, and trace elements to satisfy daily requirements. Although a standardised regimen containing about equal proportions of crystalline amino acids and dextrose with appropriate additives will satisfy the nutritional requirements of many patients, adjustments may be needed to meet the increased demand for all nutrients during infection, or to cope with special problems such as renal failure, hepatic dysfunction, protein intolerance and the paediatric patient.³ Controversy exists concerning both the composition of amino acid solutions, and the most appropriate energy source for optimal utilisation in various diseases. This review discusses the use of hypertonic glucose solutions, glucose substitutes, and fat emulsions as energy sources in intravenous

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regimens for the management of hospitalised patients. These regimens are used in a spectrum of clinical conditions and the metabolism of these nutritional supplements under normal conditions, in starvation, and in various degrees of stress will be discussed.

ENERGY REQUIREMENTS

The relative energy requirements in health and disease differ. The basal energy expenditure of a normal 70kg man at rest is about 2,000 Kcal per day. Decreased food intake is accompanied by weight loss and a decrease in basal energy expenditure. Following elective surgical procedures, in the absence of significant complications, the post-operative energy expenditure will not ordinarily differ by more than 10% from pre-operative values. Previously well-nourished patients with multiple fractures may have an increase in basal energy expenditure of 10 – 25 %, and in major infection, such as intra-abdominal abscess or peritonitis, there may be an increase of up to 50 – 75 % above predicted normal levels. Sustained higher levels of basal energy expenditure (125 %) may occur with major thermal burns.

The metabolic response to injury is classically described as being separated into two distinct phases – an acute phase in which there is mobilisation of endogenous substrates to provide energy, and an adaptive phase in which metabolism is dependent on the availability of nutrient substrates. These phases correspond to the 'ebb' and 'flow' phases of the metabolic response to trauma originally described by Cuthbertson in 1942.⁴ The metabolic response to starvation differs from that of injury and infection, and it is important to realise that, in individual patients, varying degrees of starvation, injury, and infection may contribute to the overall changes in hormonal and substrate homoeostasis.

METABOLIC RESPONSE TO STARVATION

The sequence of events leading to death in starvation is usually decreased food intake, protein wasting, weakness of respiratory muscles, atelectasis, pneumonia, and death. The metabolic response to starvation has an initial and a late phase: the initial phase is directed toward maintaining glucose production to meet the needs of the brain, nervous tissue, and red blood cells (gluconeogenic phase), and the late phase toward minimising the rate of protein breakdown (protein-conservation phase). Fat derived from adipose tissue stores is the main endogenous fuel in all but the postprandial state and satisfies 85 % of daily energy needs in prolonged fasting. During starvation, in the absence of an exogenous carbohydrate supply, there is an increase in glucose production and a reduction in extracerebral glucose utilisation. Blood glucose concentration declines and results in decreased circulating insulin and glucagon which stimulates lipolysis (providing non-esterified fatty acids for energy requirements of muscle and liver) and hepatic ketogenesis. Liver and muscle glycogen stores rapidly become depleted, and glucose production subsequently depends on gluconeogenesis from lactate and amino acids, principally alanine and glutamine from muscle protein. During the initial 72 hours of starvation, alanine output increases and hepatic glucose output is able to keep pace with the rapid rates of glucose utilisation in the brain. Pyruvate, lactate, and the glycerol skeleton of triglyceride are also used as gluconeogenic substrates. If fasting extends beyond one week, nitrogen loss progressively declines and there is a reduction of hepatic gluconeogenesis. Blood glucose levels remain unchanged and there is a reduction

in glucose utilisation. These changes are accompanied by an increase in circulating ketone bodies, which are formed from fatty acids in the liver. There is a reduced need for gluconeogenesis which is reflected in a decreased output of alanine from muscle.

METABOLIC RESPONSE TO INJURY AND INFECTION

Following the stress of injury or infection, the pattern of endogenous fuel substrate utilisation differs from that observed in uncomplicated starvation. The most obvious differences are protein wastage, hyperglycaemia, and anaerobic glycolysis with lactate production. Injury induces a wide range of integrated changes in haemodynamics, neuroendocrine secretions (in particular, insulin, glucagon, corticosteroids, and catecholamines), and tissue metabolism. Provided that the injury is not fatal, the immediate phase of depressed local metabolism is followed by a period of increased general metabolism due to the increased cellular activity of the repair process, elimination of damaged and devitalised tissue, and increased catabolism of protein. There is also increased oxygen consumption and heat production, and the increased nitrogen excretion closely parallels the increased energy expenditure.

The changes in energy metabolism are most important for survival and repair. There is increased sympathetic activity for 48–72 hours which ensures an adequate mobilisation of carbohydrate and fat stores, resulting in hyperglycaemia and increased plasma non-esterified fatty acids, but the rates of oxidation of both substrates are unaltered. Following the acute reaction to injury, which may last up to 72 hours, there is an increase in heat production and rise in body temperature associated with an increase in urinary excretion of nitrogen, inorganic sulphate, phosphate, potassium, and creatinine. The excess nitrogen is derived from catabolism of muscle protein and the oxidation of non-nitrogenous residues accounts for some of the extra heat production. This obligatory protein loss cannot be completely abolished in the immediate post-traumatic period, even with large intake of protein and calories. Protein catabolism is accelerated to a greater extent than protein anabolism and the prolonged proteolysis of muscle protein leads to excessive hepatic gluconeogenesis, depletion of muscle protein, weakness, reduction of protein synthesis, diminished enzyme function, and loss of immunocompetence.

Hyperglycaemia and a diabetic glucose-tolerance curve are characteristic of the response to injury and infection, despite a normal insulin response to hyperglycaemia. Glucose uptake by the tissues is unaltered, suggesting insulin resistance in the tissues. Adipose tissue still responds to hyperinsulinaemia by suppression of lipolysis. Alanine, lactate, and glycerol all provide an increasing flow of gluconeogenic substrate to the liver which releases more glucose under the influence of alanine-induced hyperglucagonaemia. There may be impairment of uptake of other metabolic fuels (non-esterified fatty acids, ketone bodies) leading to the oxidation of branched-chain amino acids derived from muscle protein to satisfy the local energy requirements of muscle. Thus, hyperglycaemia reflects an augmentation of the glucose pool to maintain glucose oxidation rates rather than a need for overall energy provision from proteolysis. Although the nitrogen excretion following injury parallels the increased resting metabolic expenditure and weight loss, the energy contribution of protein is only about 20 % of daily expenditure, the residual energy requirement being met by mobilisation of fat stores.

ENERGY PROVISION

The substrate and hormone changes that characterise the responses to starvation, injury and infection are designed initially to ensure survival and subsequently to initiate repair processes at the expense of endogenous tissue stores, which further compromises host metabolism. It is against this complex biochemical background that nutritional support of the hospitalised patient is usually undertaken. Intravenous nutritional regimens are designed to replenish existing deficiencies, to minimise further tissue consumption, and to provide sufficient energy and protein substrates to stimulate and maintain anabolism and repair. An important limiting factor of intravenous nutrition is the ability of tissues to metabolise the infused nutrients: on the one hand, there is the requirement for large quantities of exogenous nutrient substrates to satisfy nutrient requirements while, on the other hand, local and general metabolic responses to starvation, injury and infection may reduce the efficient utilisation of those substrates. This may lead to unnecessary complications of therapy such as the over-enthusiastic infusion of hypertonic glucose solutions to the septic patient leading to worsening of pre-existing hyperglycaemia, excessive glycosuria, osmotic diuresis, increased fluid and electrolyte losses, dehydration, and non-ketotic coma. The most important determinant of outcome in a patient receiving nutrition exclusively by vein is the ability to supply and metabolise sufficient protein to compensate for the catabolism of endogenous protein, to synthesise acute phase proteins, to maintain immunocompetence, and to preserve the integrity of major organ systems. Protein economy and the utilisation of exogenous crystalline amino acids improves as non-protein energy provision increases and thus the success or failure of a nutritional regimen is dependent on the appropriate choice of a non-protein energy source.

There are essentially three practical methods of delivering non-protein energy in intravenous regimens — glucose, glucose substitutes, or lipids. Glucose is available in concentrations from 5% to 70% and may be used exclusively as the energy source provided minimal amounts of fat are given to avoid essential fatty acid deficiency. Glucose substitutes — fructose, sorbitol, xylitol — also are available in a range of concentrations, but they appear to have no particular advantage over glucose. Fat emulsions (10% or 20%) have a high energy value, but the daily dosage should not exceed 2.5 g/kg body weight and should not make up more than 60% of the total energy intake. Each regimen has its advocates, but rational choice of an energy source has to take into consideration the type of patient, disease process, therapeutic goal, expense, substrate utilisation, method of delivery, and potential complications.

GLUCOSE

The average oral diet contains about 45% carbohydrate and 40% fat, and together these two energy-yielding substrates supply approximately 90% of daily energy requirements. Glucose infusions are used extensively in surgical practice, both to maintain hydration together with electrolyte solutions and as a source of energy. Glucose can be metabolised by all the tissues of the body and it is a pre-requisite for protein anabolism. A normal person can assimilate up to 800 g of glucose per day, but glucose is taken up by muscle and adipose tissue only in the presence of insulin. Many studies have documented improvement in cardiac, respiratory, and hepatic function as well as improvement in cellular function as a result of glucose infusion both with and without exogenous insulin. (Table I).

TABLE I
Relative merits of intravenous glucose

Advantages

- Readily available in a wide range of concentrations 5 – 70%
- Easily stored
- Cheap
- Stimulates endogenous insulin production
- Reduces proteolysis and gluconeogenesis

Disadvantages

- Hypertonic solutions require central infusion
 - Glucose intolerance may require exogenous insulin
 - Osmotic diuresis
 - Lack of fat and essential fatty acids
 - Hepatotoxicity
 - Stimulates fat synthesis
 - Increased CO₂ production
 - Central venous thrombosis
 - Septicaemia and bacterial infection
 - Metabolic complications (acidosis, hypophosphataemia)
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Glucose solutions are readily available in a wide range of concentrations from 5% to 70%. They are cheap and are easily stored. Five and 10% solutions may be infused via peripheral lines but higher concentrations require the use of a central vein with the inherent risks of mechanical complications and infection. Because of the range of concentrations available, each regimen may be tailored to the energy requirements of individual patients. Glucose infusion stimulates insulin production from the pancreas which enhances protein anabolism and reduces proteolysis and gluconeogenesis. In many patients, glucose may be used as the sole energy source.

The disadvantages of glucose as an intravenous energy source are usually related to two factors – firstly, the supply of glucose in excess of the energy requirements, and, secondly, changes in body metabolism as a result of injury and infection which interfere with the cellular metabolism of glucose. These conditions may produce hyperglycaemia and osmotic diuresis leading to fluid, electrolyte, and acid-base imbalance and requiring the use of exogenous insulin to maintain normoglycaemia. Excessive intravenous glucose may also lead to impairment of biochemical liver function tests, increased fat synthesis and deposition, hypophosphataemia, and increased CO₂ production. Due to the hypertonicity of the solutions, central venous thrombosis may occur and bacterial contamination with septicaemia is common unless a strict protocol is followed for the management of central venous lines. Infusion regimens that contain no fat will lead to essential fatty acid deficiency after several weeks. Concentrated glucose infusions should always be given with an adequate protein intake to avoid the development of 'iatrogenic kwashiorkor'.

The energy requirements in starvation and nutritional depletion without stress are relatively easily supplied by glucose infusion alone. However, there is an upper

limit to the rate of glucose oxidation, and endogenous fat continues to be used for a portion of the total energy requirements.⁵ Excess glucose is converted to fat which is inefficient as lipogenesis consumes energy that is not recovered during subsequent lipolysis. In mild and moderate stress, there is usually hyperglycaemia due to increased gluconeogenesis rather than reduced glucose oxidation.⁶ Glucose infusion will not completely abolish gluconeogenesis and fat oxidation and mobilisation of endogenous fat continues even when glucose is supplied in quantities that satisfy energy requirements. Large glucose loads may also decrease free fatty acid oxidation and cause additional stress by increasing oxygen consumption and carbon dioxide production and norepinephrine excretion in the urine.⁷ Intolerance to glucose may be even more pronounced in the severely stressed critically ill patient and large quantities of exogenous insulin may be required.

Intravenous regimens containing crystalline amino acids and glucose as the non-protein energy source have been shown to improve nitrogen balance in a number of disease states and clinical situations.^{8, 9, 10} The weight of evidence from clinical studies shows that, with adequate protein intake, nitrogen retention and utilisation improves as energy intake increases, until energy requirements are satisfied.^{10, 11} Energy supply in excess of requirements produces no additional nitrogen sparing and may give rise to significant biochemical, hepatic, and respiratory complications.^{8, 12, 13}

GLUCOSE SUBSTITUTES

Fructose, sorbitol, and xylitol have been suggested as alternative intravenous sources of carbohydrate when hyperglycaemia and significant losses of glucose in the urine are features of the metabolic response to injury and infection. This recommendation is based on their rapid metabolism compared with that of glucose, their 'insulin independence' and their similar protein and antiketogenic effects. However, studies of their comparative metabolism show that the term 'insulin independence' is misleading, as these substrates are rapidly converted to glucose in the liver, and further metabolism by extrahepatic tissues requires the presence of insulin.¹⁴ The theoretical advantages of these solutions would therefore appear to be unfounded and are outweighed by their disadvantages. At high rates of infusion, significant metabolic acidosis, hypophosphataemia, and hyperuricaemia may occur, particularly in patients who are nutritionally depleted or who already have elevated plasma lactate levels as a result of their disease process.¹⁵ If these solutions are used, they should be used cautiously and their infusion rates should not exceed 0.5 g/kg body weight/hour or they should be used in combination with glucose to minimise the risk of complications.^{16, 17} However, the ease of monitoring blood glucose, glycosuria, and acid-base balance, and the use of appropriate exogenous insulin therapy when indicated suggests that glucose is the carbohydrate energy source of choice in intravenous regimens. The therapeutic success of glucose and insulin therapy in patients who are critically ill and severely stressed leaves few indications for the clinical use of glucose substitutes.¹⁸

FAT

Fat emulsions have been used extensively in intravenous regimens in Britain and Europe for many years, but it is only in recent years that extensive experience of the use of fat as an intravenous energy source has been obtained in the United

TABLE II
Relative merits of intravenous fats

Advantages

- Available in 10% or 20% emulsion
- Isotonic and may be infused peripherally
- Source of essential fatty acids
- High energy density
- No metabolic complications

Disadvantages

- Expensive
 - Not recommended as sole energy source
 - Not 'protein-sparing' when used alone
 - Hyperlipaemia
 - May inhibit white blood cell functions
 - Hepatotoxicity
 - Impaired pulmonary diffusion capacity
 - Fungal infections
 - Alterations in coagulation and thrombocytopenia
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States. Emulsions of 10% or 20% soy-bean or cotton-seed oil are available, which are isotonic, have a high energy density, and may be infused via a peripheral vein. It is recommended that the infusion rate should not exceed 2.5g/kg body weight/day and that fat should provide no more than 60% of the non-protein energy. Fat emulsions provide a source of essential fatty acids and deficiency can be prevented by supplying approximately 5% of energy requirements as polyunsaturated fat by the intravenous or enteric route. Apart from hyperlipaemia, there are few metabolic complications, although hepatotoxicity, inhibition of white cell function, coagulation defects, and thrombocytopenia may all occur. A further limiting factor is their expense in comparison with hypertonic glucose. (Table II).

When used alone, fat is not protein-sparing, the minimal improvement in nitrogen sparing being accounted for by the free glycerol present in the fat emulsion.^{19, 20} In starved and nutritionally depleted patients, similar nitrogen balances have been observed in groups of patients receiving the same total energy and nitrogen intake when 83% of their non-protein energy was either lipid or hypertonic glucose.²¹ In stressed hypermetabolic patients, there is a progressive decrease in nitrogen retention as the percentage of total energy provided by glucose decreases and by fat emulsion increases.⁸ Other studies have shown similar nitrogen-sparing effects of the lipid and glucose systems in moderately injured, infected, and malnourished patients and it has been suggested that the choice between the regimens should be based on factors other than ability to improve nitrogen balance.²² In the critically ill patient, at least two-thirds of the measured or predicted metabolic requirements should be supplied as glucose, and fat emulsions should be used as a source of essential fat and to stabilise body fat mass and increase body weight. In starvation, lipid clearance from the blood stream and its use as an energy source is very similar to the chylomicron and

appears to be enhanced by the simultaneous administration of glucose. In moderate stress, there is more complete oxidation of exogenous lipid and no additional stress associated with increased oxygen consumption, CO₂ production, and norepinephrine excretion or fatty liver seen in patients receiving glucose infusion for prolonged periods. In severe stress, the ability to clear fat emulsions is markedly impaired and fat oxidation is reduced.

ENERGY SOURCES — GLUCOSE VERSUS FAT

The non-protein energy requirements of an intravenous diet may be supplied by hypertonic glucose solutions or fat emulsions. In all situations, glucose is the carbohydrate energy source of choice as it is inexpensive, associated metabolic acidosis is unusual, and hyperglycaemia is easily treated with exogenous insulin.¹⁵ In normal and starved patients, equal energy fat and carbohydrate regimens with amino acids produce similar nitrogen balances.^{21, 23} In hypermetabolic patients with burns or infection, carbohydrate appears to have a greater impact on nitrogen retention than does fat. Nitrogen retention improves as carbohydrate intake increases, provided that total energy intake matches total metabolic expenditure.⁸ The nitrogen-sparing effect of carbohydrate appears to be mediated through insulin, and additional nitrogen retention may be achieved with exogenous insulin.²⁴ The explanation of this apparent difference between fat and carbohydrate as energy sources in hypermetabolic patients is related to the muscle fuel deficit that exists secondary to a failure of keto-adaptive mechanisms and suppression of hepatic ketone body output by glucose. In addition, inflammatory tissues are glycolytic and have a major capacity for anaerobic metabolism. Endogenous fat is the primary fuel for skeletal muscle and hepatic gluconeogenesis, while glucose and lactate provide energy for the injured tissues.²⁵ Thus, fat emulsions will stabilise body fat and serve as an exogenous fuel, but will not affect nitrogen balance, whereas exogenous glucose stimulates insulin which reduces muscle proteolysis and nitrogen excretion.

Although fat emulsions appear to have limitations as energy sources in hypercatabolic, injured, or septic adults, it is important that some fat be given in depleted states to ensure that essential fatty acid deficiency does not occur. Skin rashes, thrombocytopenia, increased haemolysis, and impaired wound healing may appear after a period of several weeks of fat-free intravenous nutrition. The clinical abnormalities are accentuated by growth in children and the hypermetabolism of infection and are associated with low serum levels of essential polyunsaturated fats and a compensatory increase of saturated fatty acids. The ratio of the trienoic and tetraenoic fatty acids rises in deficiency states and may be used as a guide to the adequacy of replacement therapy with intravenous fat emulsions. Deficiency may be prevented by supplying approximately 4% of total energy requirements as polyunsaturated fat. In infected patients receiving intravenous nutrition with no oral intake, 500 ml of fat emulsion (Intralipid 10%) may be given on alternate days to satisfy this requirement and the triene/tetraene ratio is measured at intervals. Small amounts of polyunsaturated fat (safflower oil) may be given by tube if the enteric route is available.

Fat and carbohydrate may also have differing effects on body composition measurements. Although intravenous hyperalimentation is often associated with weight gain and positive nitrogen balance, it is only recently that direct measurement of changes in body composition has contributed to our knowledge of the tissue changes involved. A study of the relative merits of glucose and fat as

energy sources showed that in two groups of patients with gastrointestinal disease requiring intravenous nutrition, marked differences in body composition were noted after a two-week infusion period with the substrates.¹⁷ The group receiving dextrose as its sole energy source gained weight due to gains in body fat and body water, but in the group which received 60% of its non-protein energy as fat, there was a significant gain of protein but not water and fat. The authors suggested that the differences in water retention might be particularly significant to the critically ill patient and indicated that more studies were necessary to define the respective roles of fat and carbohydrate as energy sources in several clinical situations. The ability to preserve muscle and visceral protein mass and stimulate anabolism is critical to the successful outcome of hypermetabolic illness, and it appears that this goal may be achieved with an adequate protein intake, and a modest energy excess utilising a range of nutrient mixtures.^{27, 28}

The septic and injured patient seems to utilise endogenous fat preferentially as an energy source even when dextrose is administered in quantities above energy expenditure. Administration of a large dextrose load to hypermetabolic patients does not suppress net fat oxidation as it does in the depleted patient, but there is an increase in oxygen consumption, continued oxidation of fat, and an increase in the conversion of glucose to glycogen.⁷ This is associated with an increase in CO₂ production which is not seen when fat emulsions are used. The excess CO₂ has to be excreted by the lungs, and in patients with infection and compromised pulmonary function, respiratory distress may be precipitated. In this situation, a large dextrose intake may represent an additional physiological stress. Fat emulsions must be used with caution in a patient with respiratory distress or 'shocked lung', as fat emboli may occur, further compromising respiratory performance.

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