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Carnitine in Parenteral Nutrition

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Several new functions or metabolic uses of carnitine and improvements in assessment of carnitine status impact carnitine dosing recommendations. Carnitine dosing will likely be customized for patients at different stages of the life cycle and for patients with dysfunction of different organs. Nutrition supplementation of carnitine should be 2–5 mg · kg^{-1} · day^{-1} and be administrated via the route used for administration of macronutrients. Pharmacologic supplementation of carnitine should be 50–100 mg · kg^{-1} · day^{-1} and be reserved for the removal of toxic compounds from the body.

Carnitine was discovered more than 100 years ago, and its role in fatty acid metabolism was elucidated more than 50 years ago. After the initial case report of carnitine deficiency in 1973,[1] there was an increasing interest in the clinical use of carnitine, including the use of carnitine in parenteral nutrition. In the 1980s, it was assumed that a carnitine deficiency was either a primary deficiency with low carnitine concentrations throughout the body due to a problem with carnitine transport into tissues or a secondary deficiency with a decrease in muscle carnitine concentrations due to an unusually high excretion of acylcarnitine to eliminate a toxic compound from the body. It was also assumed that carnitine deficiency would result in symptoms related to fatty acid metabolism, that free carnitine supplementation would improve the symptoms, and that the dose of carnitine should be increased if the initial supplementation did not show a benefit. Figure 1 shows the result of a PubMed search conducted on November 14, 2008, using the terms "carnitine" and "parenteral nutrition." It is clear that the publication activity of the 1980s has not been sustained in the following 3 decades. This fact should not be interpreted that the clinical importance of carnitine was overestimated in the 1980s, but rather that our understanding of carnitine metabolism was rather rudimentary and our assessment techniques were inadequate. This situation has limited advances in the clinical use of carnitine in parenteral nutrition during the past 3 decades.

Function/Use of Carnitine

Long-chain fatty acids in all tissues and medium-chain fatty acids in most tissues (an important exception is the liver) are esterified to coenzyme A in the cytosol and cannot enter the mitochondrial matrix to undergo beta oxidation without the action of carnitine and 3 proteins (carnitine palmitoyltransferase 1, carnitine acylcarnitine translocase, and carnitine palmitoyltransferase 2). Several investigations have shown the formation of acylcarnitine to be a highly regulated step and is most likely the rate-limiting step of fatty acid oxidation.[2] This first recognized function of carnitine is an example of acylcarnitines transporting an activated carboxylic acid across membranes to a location where metabolism can continue. Another example is the transport of activated very-long-chain fatty acids that have been shortened in the peroxisomes to the mitochondrial matrix, where their oxidation will be completed.

In addition to long-chain fatty acids, other activated carboxylic acids important in many different metabolic pathways form esters with carnitine, resulting in a large array of acylcarnitines comprising a patient's acylcarnitine profile. The acylcarnitine may also be formed to make a toxic carboxylic acid metabolite transportable and thus enable the cell to transport it to the blood and the kidney to remove it from the body in the urine. The best-studied examples are metabolites of drugs such as valproic acid[3] and normal metabolites that accumulate to toxic concentrations due to organ dysfunction or inborn errors of metabolism, such as propionic aciduria.

Esterification of an activated carboxylic acid to carnitine not only makes the carboxylic acid compound transportable but also maintains the high metabolic energy of the compound. This sparing of adenosine triphosphate may be important in the critically ill. A cell may also store the high-energy acylcarnitine to have it readily available for use, as has been shown for the storage of arachidonyl carnitine to repair erythrocyte membrane.

In addition to a variety of functions in the body, acylcarnitines have an expanding use in the clinical setting as a set of parameters to monitor metabolism for early detection of altered metabolism. The best-known example is the use of several acylcarnitines in expanded newborn screening that is now performed routinely in many states.[4,5] A similar approach can also be used for early detection of altered metabolism stemming from many etiologies.

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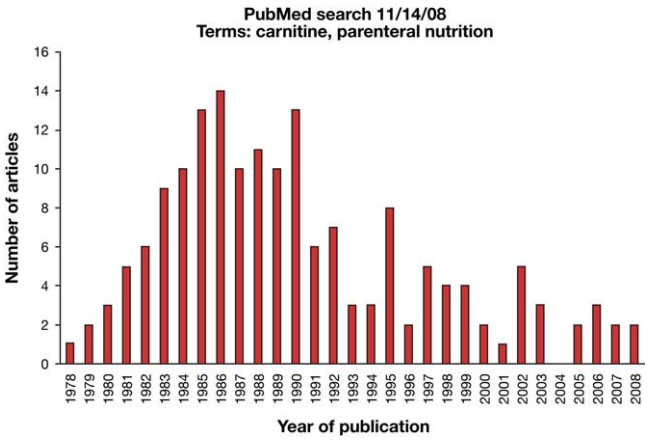

Figure 1. Results of a PubMed search conducted on November 14, 2008, with the search terms "carnitine" and "parenteral nutrition."

Assessment of Carnitine Status

The most readily accessible biological samples for carnitine assessment are blood and urine. Assessment of urinary acylcarnitine profile is very helpful in physiologic situations in which carnitine is being used to remove a toxic metabolite. It appears that plasma and red blood cells are different carnitine compartments. Because their proportionality varies significantly among patients and at different times in the same patient, the 2 compartments should be assessed separately. The relationship of the acylcarnitine profile in plasma or red blood cells (if any) to different tissue acylcarnitine profiles is still being elucidated. Thus, an abnormal value clearly indicates that something is wrong, but a normal value does not assure that tissue acylcarnitine profiles are normal. Advances in this area will be very helpful in allowing use of plasma or red blood cells as a clinical parameter to monitor a patient's metabolism.

Because different types of assays are being used and the results they give are not the same, it must be determined which assay to order. Unesterified or free carnitine can be measured by a spectrophotometric assay, a radioenzymatic assay, or a mass spectrometric assay, and all are being used to measure clinical samples at different places around the world. The first 2 assays use an enzyme to convert acetyl-CoA to acetylcarnitine. The spectrophotometric assay was the first developed and uses a free sulfhydryl reagent to react with the released coenzyme A, forming a yellow color. The problem is that there are a lot of free sulfhydryl groups in biological samples, so the blank is very high. Measurement of a small increase in yellow color with a very large blank results in many technical difficulties, including reduced sensitivity. The radioenzymatic assay uses a radiolabeled acetyl moiety of the acetyl-CoA substrate and monitors the appearance of radiolabeled product, which eliminates the issue of a high blank. Both the spectrophotometric and radioenzymatic assays only measure unesterified carnitine and are most accurate for the measurement of "total carnitine" after alkaline hydrolysis of all the esterified groups. If one assays a sample before hydrolysis and terms the result "free carnitine" and assays the same sample after hydrolysis to obtain "total carnitine," the "free carnitine" can be subtracted from the "total carnitine" to give a result often termed "acylcarnitine." The background noise for both the "free carnitine" and the "acylcarnitine" is quite high, and none of the results provides identification or quantitation of individual acylcarnitines. This information is required to address many patient care questions as well as many research questions.

The mass spectrometric assay can identify and quantify individual acylcarnitines. This is the good news and also the bad news because one has to be concerned that the acylcarnitine profile does not change during sample handling. The clinical assay was developed for newborn screening, where the alteration in metabolism is large. The most commonly used mass spectrometric assay uses a derivatization step during sample preparation that actually hydrolyzes some of the acetylcarnitine and other short-chain acylcarnitines, resulting in an artifactual decrease in their concentration and an artifactual increase in the concentration of unesterified carnitine. For most newborn screening, these artifacts are small compared with the change caused by the inborn error of metabolism and so the assays are still useful. However, for many of the smaller alterations in metabolism that need to be detected in nutritional care of patients, sample preparation must be carefully controlled both at the site of sample collection and at the site of assay. Biological samples contain enzymes that interconvert esterified and unesterified carnitines. These enzyme activities should be reduced by placing the sample on ice quickly and freezing it as soon as possible. In addition, a mass spectrometric assay that does not require a derivatization step should be ordered.

Carnitine Dosing

Only the L-isomer of carnitine should be used for supplementation. For the patient on parenteral nutrition, carnitine can be admixed with the other parenteral constituents. Carnitine can be administered to patients as a nutritional supplement to maintain physiologic concentrations. Carnitine can be administered to patients as a pharmacologic agent and is used most often to treat patients who are using carnitine to remove a toxic metabolite. It is important not to confuse nutritional supplementation of carnitine and pharmacologic supplementation of carnitine.

Dietary carnitine is found in animal products. Milk is the main source of carnitine for infants. The concentration of carnitine increases as the proportion of type I fibers increases. Thus, as the redness of the meat increases, the carnitine concentration increases. The typical carnitine intake of omnivore humans is 2–5 $mg \cdot kg^{-1} \cdot day^{-1}$,

which averages to about 250 mg/day for the mythical 70-kg human. Nutritional supplementation of carnitine should be dosed in this order of magnitude. Pharmacologic supplementation of carnitine is usually dosed at one order of magnitude higher (50–100 $mg \cdot kg^{-1} \cdot day^{-1}$), with an adult often receiving 3 g/day of carnitine. Clearly the dose should be titrated to the needs of the patient and will vary for different patients and for the same patient at different times.

There is less experience with supplementation of acylcarnitines, such as acetylcarnitine. However, as our understanding of the function of each acylcarnitine grows and our ability to assess the status of each acylcarnitine advances, the use of these compounds for supplementation will undoubtedly increase. When we supplement with unesterified carnitine or a specific acylcarnitine, we should not consider more to be better. Supplementation of carnitine in the setting of a low concentration of carnitine can bring improvement. If a very large amount of carnitine is supplemented, the need to eliminate the excess carnitine and the need to bring the acylcarnitine profile back into a physiologic pattern may be the source of metabolic stress that leads to adverse effects. Indeed, parenterally fed preterm neonates supplemented with 48 $mg \cdot kg^{-1} \cdot day^{-1}$ of carnitine on days 4–7 of life had increased time to regain birth weight compared with nonsupplemented neonates.[6]

Carnitine in Enteral Nutrition

The distinction of nutritional supplementation of carnitine and the pharmacologic supplementation of carnitine is also important for enterally administered carnitine. Pharmacokinetic studies of carnitine suggest that carnitine should be administered 3 or 4 times a day. In many cases, commercially available carnitine capsules or tablets contain more than the 250 mg needed for an adult during an entire day for nutritional supplementation, so current packaging is not very convenient. Purity is another problem with some commercially available products. When several commercial products have been analyzed for carnitine content, there has been wide variation in the content of carnitine actually found in the products.[7]

Carnitine is absorbed in the small intestine via more than one transporter, and the type of transport varies with the dose of the carnitine being supplemented. Surgical resection and gastrointestinal pathology can certainly have an impact on carnitine absorption, but there are still questions that need to be addressed concerning recommendations for the individual patient with short-bowel syndrome. The effects of the presence of food and interactions with coadministered medications are not well understood.

Carnitine at Different Stages of the Life Cycle

Carnitine accretion occurs during the last trimester of gestation.[8] Thus, a preterm neonate arrives with reduced stores. Breast milk is a rich source of highly bioavailable carnitine, providing 2–5 $mg \cdot kg^{-1} \cdot day^{-1}$ of carnitine. Thus, the neonate receiving carnitine-free parenteral nutrition has a greatly reduced exogenous source of carnitine when compared with the breast-fed neonate.[9] Pregnancy and lactation bring additional importance for adequate carnitine. The healthy adult receiving no exogenous carnitine appears to be able to synthesize adequate endogenous carnitine, but this is less clear for infants and children and for the elderly.[5]

Carnitine in Patients With Dysfunction of Different Organs

Declining renal function leads to an accumulation of toxic compounds and an accompanying increase in acylcarnitine formation and excretion, which can lead to increased excretion of carnitine. Membranes of the kidney selectively resorb free carnitine and excrete acylcarnitines, but hemodialysis membranes lack this selectivity. Patients receiving hemodialysis treatment often have altered acylcarnitine concentrations.[10,11]

Cardiac and skeletal muscle dysfunction and carnitine metabolism dysfunction are often associated.[12] Even in cases in which it is unclear which dysfunction came first, assessment of carnitine status is still important. The liver is the major site of carnitine metabolism; thus, it is not surprising that hepatic function and carnitine metabolism are interrelated. The importance of carnitine in brain metabolism is less intuitive, but recent studies suggest that it may be important in brain development, several brain diseases, and dementia.[13]

Clinical Care Priorities

Translational science activities in the field of carnitine are ongoing. Although it is true for all nutritional areas, it is extremely important in the field of carnitine not only that the research findings in the basic sciences be readily translated to the care of patients but that the issues facing patient care be readily translated to basic science hypotheses that can be tested.

In the clinical setting, some of the important patient care questions are as follows:

1. Which symptoms may respond to carnitine supplementations?
2. What sample should be assayed, and what assay should be requested for assessment of carnitine status?
3. What commercially available products should be used, at what dose, and at what frequency?

Recommendations for clinical care based on current knowledge are as follows:

1. Nutritional supplementation of carnitine should be 2–5 $mg \cdot kg^{-1} \cdot day^{-1}$ and be administrated via the route used for administration of macronutrients. (For example, if 50% of the protein is administered parenterally, 50% of the carnitine should be administrated parenterally. It probably would be more practical to administer it all via the parenteral route, but as we learn more about the role of carnitine in the intestinal tract, we may find advantages for the enteral route.)
2. Pharmacologic supplementation of carnitine should be 50–100 $mg \cdot kg^{-1} \cdot day^{-1}$ and be reserved for the removal of toxic compounds from the body, such as treatment of inborn errors of metabolism.

Research Priorities

As stated earlier, advances in carnitine research have been slowed during the past 2 decades due to our rather rudimentary understanding of carnitine metabolism and inadequate assessment techniques. Because of recent improvements in the carnitine assay, we can now identify and quantify individual acylcarnitines. The research community can now ask questions about carnitine metabolism and assessment of carnitine status that could not be addressed before this technological advancement.

In the research setting, some of the important questions are as follows:

1. What are the functions of individual acylcarnitines in different tissues under different physiologic conditions?
2. How should acylcarnitine profile analyses be interpreted?

Question and Answer Session

DR BUCHMAN: When you talk about using pharmacologic doses of carnitine to remove toxins, is this the Hollywood kind of toxins like a carnitine enema kind of thing? What kind of toxins are we talking about?

DR BORUM: No, it is very legitimate medicine, but it is not nutritional supplementation. In inborn errors of metabolism we have, I think, saved lives and changed the quality of life for many children by giving them carnitine, so it is not just the crazy stuff. In the past, we had to severely limit their protein intake to limit their carboxylic acid levels. This led to poor growth. Now we can use pharmacologic doses of carnitine to remove these toxic carboxylic acids. I do think it is important that we do not mix nutritional supplementation with pharmacologic administration. When giving higher pharmacologic doses, there is a different effect than when dietary replacement doses are administered. In fact, some of the beneficial nutrient effects of carnitine may be lost at higher doses.

DR SHIKE: Are you saying that this issue of removal of toxic metabolites applies only to those with inborn errors of metabolism?

DR BORUM: Not necessarily. I am suggesting that we may create situations in parenteral nutrition where an organic acid accumulates to a higher concentration than what is needed by the cell and that one way for the body to get rid of that is to use carnitine, so that may be one reason for nutritional supplementation.

DR SHIKE: Why is it specific to parenteral nutrition and different from oral nutrition? For example, why would someone on a high-fat diet like the Atkins diet not fall into that group? Why are we singling out parenteral nutrition?

DR BORUM: If you consume a high-fat diet and don't consume excess calories in the process, then the amount of carnitine that would be consumed in that diet would be fine because most high-fat diets have a lot of carnitine. If in parenteral nutrition everything is not just exactly perfect and there is a modest elevation in the level of an organic acid, then that might be a situation where a low level of carnitine in the body would result in abnormalities. I'm not suggesting you need 100 mg carnitine per kilogram of body weight to get rid of it, but it is a situation in which carnitine nutritional supplementation may be very important.

DR MOUKARZEL: Carnitine can be synthesized by the body from its components lysine and methionine, so as you said, it is not an essential nutrient; you told us it is conditionally essential. We conducted a study 20 years ago and showed that patients on parenteral nutrition, children mainly, had 50% of the normal plasma carnitine concentration without any symptom or sign of deficiency. When we remeasured the carnitine concentration 2 years later in the same patients, we showed that the total and acyl carnitines were still stable at 50% of normal. Does that mean there was carnitine deficiency despite the absence of any symptom, sign, or biochemical abnormality? I don't know what your answer will be, but this might mean carnitine is essential in some conditions such as inborn errors of metabolism or immature metabolism, as may be the case in premature babies, but perhaps carnitine may not be essential for other patients who are not under any physiologic stress. What do you think?

DR BORUM: We found that in adult surgical patients, plasma carnitine is not well correlated with either muscle or liver carnitine. In piglets, a model for children, plasma, red blood cells, liver, muscle, renal, and brain carnitine are all separate metabolic compartments; one can be low while another is normal. I am not sure that a normal plasma carnitine level signifies normal carnitine status. Carnitine might not be essential under certain physiologic circumstances but become essential under other physiologic circumstances. For example, valproic acid leads to increased carnitine excretion, and patients who receive this medication should receive a carnitine supplement. We have had patients on long-term valproic acid therapy with elevated venous ammonia concentrations that have decreased following carnitine supplemen-

tation, and I would recommend 2–5 mg · kg^{-1} · day^{-1} in these circumstances.

DR MOUKARZEL: How did you determine this dose recommendation?

DR BORUM: The amount of 2 to 5 mg · kg^{-1} · day^{-1} came from fairly extensive work looking at the oral intake of carnitine in both children (including neonates) and adults. I don't see a reason to increase it 10-fold, particularly when we know that in some cases when infants received up to 100 mg · kg^{-1} · day^{-1}, a reduction in growth was observed.

DR BUCHMAN: To put the plasma concentration in perspective, if we take a child with a so-called primary or congenital carnitine deficiency who has a cardiomyopathy, typically the total plasma carnitine concentration would be 5%–10% of normal. If in patients on parenteral nutrition it is 50% of normal; does that mean we need to get to 5% or 10% of normal to have a deficiency?

DR BORUM: No, I don't think it means that.

DR BUCHMAN: But why is the total plasma carnitine concentration much lower in patients with obvious carnitine deficiency than it is in patients on parenteral nutrition?

DR BORUM: The situation that you are talking about with the cardiomyopathic patient is often where there is an inborn error in the transport protein and there are problems getting carnitine into the heart but also problems maintaining carnitine in the plasma. If there is a situation in which you are administering some kind of toxin or a toxin is accumulating, increased urinary carnitine excretion occurs. This results in decreased plasma carnitine concentration. In the patient on parenteral nutrition, the same thing can happen. If in addition to parenteral nutrition the patient is given valproic acid, for example, plasma carnitine will become quite depleted. We have to be careful, however, not to assume plasma carnitine is the gold standard that indicates body carnitine status.

MS SABINO (Hartford, CT): What would be other examples besides valproic acid that would result in the accumulation of organic toxins, how would one know the problem existed, and would large doses of supplemental carnitine be an appropriate therapy? How long would you treat?

DR BORUM: The type of toxins include antiretroviral therapy, nucleotide reverse trancriptase inhibitors, such as zidovudine, and some pesticides. These can cause a myopathy, and if muscle biopsy specimens are obtained, there are often ragged red fibers evident, which are frequently seen in "secondary carnitine deficiency." There is histologic improvement, and improvement in the myopathy occurs with carnitine supplementation. The list of potential toxins, though, is incomplete.

MS SABINO: I am aware of 2 adult case studies with patients who had elevated direct bilirubin concentrations, and following carnitine supplementation (1 g, I think) there was a decrease in the degree of cholestasis. Can you please comment on these case studies?

DR BORUM: I am aware of those case studies. I don't know the mechanism of action that occurred in those particular patients. I don't think there are data that demonstrate carnitine should be a treatment for hyperbilirubinemia in adults or babies. We know that carnitine is in the bile. We know that carnitine is important in the peroxisome for the metabolism of various substances that impact the serum bilirubin concentration, but I don't think we know the answer to what happened in those patients and whether carnitine was indeed therapeutic.

DR MELISSA MASELLI (Southern Surgical, Slidell, LA): We see a lot of bariatric surgical patients who have high serum triglyceride concentrations and end up on parenteral nutrition. Should they receive carnitine supplementation?

DR BORUM: I am pretty conservative about the use of carnitine. Hypertriglyceridemia may occur for a variety of reasons that have nothing to do with carnitine.

DR DESAI (Duke University, Durham, NC): Are there any data on the use and benefit of carnitine in patients who are being treated with corticosteroids and concomitantly on parenteral nutrition? Is there a cutoff weight you use for carnitine administration in neonates?

DR BORUM: I don't know about the corticosteroids. In terms of neonates, different people in this room will have different opinions based on the available data. I think as long as carnitine supplementation is between 2 and 5 mg · kg^{-1} · day^{-1}, it should be safe and routinely provided to preterm or low-birth-weight neonates who require parenteral nutrition, although the beneficial effects of carnitine have not been proven.

DR DAN GRIFFTH (Emory University, Atlanta, GA): Could you explain the mechanism of how carnitine gets rid of ammonia in valproic acid toxicity?

DR BORUM: To get rid of ammonia, urea has to be synthesized in the liver. The first step in this process is the synthesis of carbamyl phosphate. That requires *N*-acetylglutamate as a coactivator of the enzyme involved (carbamyl phosphate synthase). It is believed that *N*-acetylglutamate gets its acetate group from acetylcarnitine. Therefore, an adequate amount of acetylcarnitine is needed to quickly synthesize sufficient carbamyl phosphate, which then enters the urea cycle and ammonia is then disposed.

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Reprint requests

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Conflicts of interest

The author discloses no conflicts.