Response of glutamine metabolism to glutamine-supplemented parenteral nutrition1–3

Bernadette AC van Acker, Karel WE Hulsewé, Anton JM Wagenmakers, Maarten F von Meyenfeldt, and Peter B Soeters

ABSTRACT

Background: Increasing evidence suggests that glutamine is important for the function of many organ systems and supports the use of glutamine-enriched total parenteral nutrition (TPN) during severe illness. However, the effect of prolonged glutamine supplementation on glutamine kinetics has not been studied.

Objective: We investigated the effect of 8–10 d of TPN enriched with glutamine dipeptides on glutamine kinetics.

Design: Twenty-three preoperative patients were randomly allocated to receive either TPN enriched with glutamine dipeptides (60 μmol glutamine·kg body wt−1·h−1) or isonitrogenous, isoenergetic, glutamine-free TPN. A primed, continuous, 6-h intravenous infusion of L-[5-15N]glutamine and L-[1-13C]leucine was given before (baseline) and 8–10 d after the TPN solutions were administered. Baseline measurements were performed after a 40-h administration of a standard solution of glucose and amino acids (no glutamine).

Results: Glutamine-enriched TPN increased the total appearance rate of glutamine (P < 0.05) but did not inhibit or increase the endogenous appearance rate. The standard TPN solution also increased the glutamine appearance rate (P < 0.05), but the change was much smaller than in the glutamine-supplemented group (P < 0.01). The plasma glutamine concentration did not rise significantly during either treatment, suggesting increased tissue glutamine utilization, especially in the glutamine-supplemented group.

Conclusion: In view of the enhanced glutamine requirements in response to trauma and disease by tissues such as those of the gut, the immune system, and the liver, increased glutamine availability during glutamine-enriched TPN may be beneficial preoperatively in patients with gastrointestinal disease. Am J Clin Nutr 2000;72:790–5.

KEY WORDS Glutamine metabolism, total parenteral nutrition, glutamine supplementation, glutamine dipeptides, stable isotopes, protein degradation, preoperative patients

INTRODUCTION

Glutamine is an important nonessential amino acid and its intracellular concentration is much higher than that of other amino acids. Glutamine is released in large quantities from skeletal muscle and serves as an important carrier and donor of nitrogen (1). Increasing evidence underscores the importance of glutamine for the function of many organ systems, including the intestine (2) and the immune system (3), and for maintaining the acid-base balance (4).

The rationale for the inclusion of glutamine in dietary regimens stems from the hypothesis that glutamine becomes an essential nutrient during illness. Conventional amino acid solutions used for parenteral nutrition do not contain glutamine because glutamine is unstable in solution and is not soluble at high concentrations. The manufacture of synthetic dipeptides such as L-alanyl-L-glutamine and glycyl-L-glutamine, which are stable in solution and are rapidly hydrolyzed in plasma after intravenous infusion, has made it possible to administer total parenteral nutrition (TPN) solutions that contain glutamine. Clinical trials with glutamine-enriched TPN in different patient populations showed improved survival, a diminished incidence of clinical infections, improved nitrogen economy, and maintenance of intestinal integrity (2, 5–9).

Information regarding the response of glutamine kinetics to prolonged administration of glutamine-enriched TPN is not available. Therefore, it is not clear to what extent glutamine supplementation increases the amount of glutamine available to tissues and cells and to what extent it down-regulates endogenous glutamine production. The latter is observed after acute oral glutamine administration to healthy subjects (10) and to muscular dystrophy patients (11) and has been attributed to a decrease in estimates of both glutamine de novo synthesis and glutamine release from protein breakdown.

In this article we report the effect of the administration of glutamine dipeptide–enriched TPN for 8–10 d on the appearance rate of glutamine (Ra,glu) in plasma, on glutamine release from protein breakdown, and on de novo synthesis of glutamine in patients with gastrointestinal disease who were scheduled to receive TPN preoperatively.
Subjects and Methods

Subjects

Twenty-three patients admitted for gastrointestinal surgery and scheduled to receive TPN preoperatively were randomly allocated to receive either glutamine dipeptide–enriched TPN (GTPN) or standard (no glutamine) TPN (STPN). Patients were eligible for the study if they were nutritionally depleted. Nutritional depletion was defined as a body weight < 95% of ideal according to the Metropolitan Life Insurance Company (12) or a loss in body weight of > 10% of the original weight within the previous 6 mo. The patients were stratified according to neoplastic and nonneoplastic disease and were studied before surgery was performed. If there were any clinical signs of high metabolic stress, such as fever (> 38.5 °C), hypothermia (< 36 °C), or evidence of sepsis or intraabdominal abscesses, the patients were excluded. Other exclusion criteria were renal or hepatic insufficiency, pregnancy, type 1 diabetes, ileus, heart failure, ascites, or receipt of parenteral nutrition within 14 d before the study.

Patient characteristics are summarized in Table 1. Patients with Crohn disease were hospitalized because of chronic stenosis (n = 4) and exacerbation (n = 1). One patient with chronic pancreatitis had pseudocysts; the 2 other patients had an exacerbation of chronic pancreatitis. Stenosis of the colon was due to previous diverticulitis in all 4 subjects. Of the patients with gastric or colorectal cancer, none had signs of disseminated disease at surgery. The study was approved by the ethics committee and review board of the University Hospital Maastricht and the procedures followed were in accordance with the Helsinki Declaration of 1964, as revised in 1989. Written, informed consent was obtained from all patients before commencement of the investigation. All investigators except the pharmacist were blinded to the randomization.

Feeding regimen

TPN was administered via a central venous catheter. On the first 2 d, all patients received a commercially available standard solution of glucose and amino acids (Nutriflex; NPBI International BV, Emmer-Compascuum, Netherlands) in an amount of 50% of the planned study mixture volume. This baseline infusion period was intended to create a more standardized condition at baseline, to improve comparability of the patients at the onset of the study. After the 2-d baseline infusion, patients received the required amount of study GTPN or STPN for an additional 8–10 d (± 1 d). Fat, glucose, and amino acids were given in an “all-in-one” solution, formulated according to the measured body weight and the calculated total energy expenditure of the patient. The TPN solutions were prepared freshly each day under sterile conditions by the Department of Clinical Pharmacy (University Hospital Maastricht). The GTPN and STPN formulas were isonitrogenous (0.24 ± 0.01 g N·kg⁻¹·d⁻¹) and isocaloric (159 ± 5 kJ·kg⁻¹·d⁻¹) and had equal volumes. The GTPN group received TPN supplemented with the dipeptides glycyll-L-tyrosine and glycyll-L-glutamine. Patients received a total amount of 0.21 ± 0.01 g glutamine·kg⁻¹·d⁻¹. The GTPN solution had fewer total essential amino acids than did the STPN solution (Table 2). Nonprotein energy accounted for 134 ± 4 kJ·kg⁻¹·d⁻¹. Glucose and fat (Intralipid 20%; Pharmacia-Upjohn, Erlangen, Germany) each contributed 50% to the nonprotein energy content. Standard electrolytes, trace elements, and vitamins were added to the TPN solutions according to individual requirements and hospital routine. The daily doses of electrolytes and micronutrients are shown in Table 3. During the study period, a maximum of 500 mL water or tea per day was allowed orally.

Study design

On the morning of day 2, ie, 1.5 d after administration of the standard glucose and amino acid solution began, 2 catheters were placed in the subjects: 1 in an antecubital vein for isotope infusion and 1 in the radial artery for blood sampling. The arterial catheter was kept patent by a slow saline infusion. At 0830, a

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient characteristics at study entry¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glutamine-supplemented TPN (n = 6 M, 4 F)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60 ± 6²</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 4</td>
</tr>
<tr>
<td>Percentage ideal body weight (%)</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>49 ± 4</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Plasma glutamine (μmol/L)</td>
<td>578 ± 38</td>
</tr>
</tbody>
</table>

¹There were no significant differences between treatment groups (Fisher’s exact test). TPN, total parenteral nutrition.
²x ± SEM.
³Within the past 6 mo.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Compositions of the total-parenteral-nutrition (TPN) solutions²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glutamine-supplemented TPN</td>
</tr>
<tr>
<td>Fat</td>
<td>48</td>
</tr>
<tr>
<td>Glucose</td>
<td>120</td>
</tr>
<tr>
<td>Total amino acids</td>
<td>40.3</td>
</tr>
<tr>
<td>Ile</td>
<td>1.6</td>
</tr>
<tr>
<td>Leu</td>
<td>2.3</td>
</tr>
<tr>
<td>Lys</td>
<td>2.6</td>
</tr>
<tr>
<td>Met</td>
<td>1.6</td>
</tr>
<tr>
<td>Phe</td>
<td>1.7</td>
</tr>
<tr>
<td>Tyr</td>
<td>0.7</td>
</tr>
<tr>
<td>Thr</td>
<td>1.6</td>
</tr>
<tr>
<td>Trp</td>
<td>0.5</td>
</tr>
<tr>
<td>Val</td>
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<tr>
<td>Ala</td>
<td>4.7</td>
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<tr>
<td>Arg</td>
<td>3.3</td>
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<tr>
<td>Asp</td>
<td>1.0</td>
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<tr>
<td>Glu</td>
<td>1.6</td>
</tr>
<tr>
<td>His</td>
<td>2.0</td>
</tr>
<tr>
<td>Pro</td>
<td>2.0</td>
</tr>
<tr>
<td>Ser</td>
<td>1.3</td>
</tr>
<tr>
<td>Gly</td>
<td>3.3</td>
</tr>
<tr>
<td>Gln</td>
<td>5.8</td>
</tr>
</tbody>
</table>

²The volume of TPN administered each day averaged 2.2 ± 0.3 L (± SD).
primed, constant intravenous infusion of L-[5-15N]glutamine (0.68 μmol·kg⁻¹·h⁻¹; prime 0.68 μmol/kg) and L-[1-13C]leucine (7.63 μmol·kg⁻¹·h⁻¹; prime 7.63 μmol/kg) began and continued for 6 h. The tracers were purchased from Cambridge Isotope Laboratories (Woburn, MA). Sterile and pyrogen-free stock solutions of the tracers had been prepared by the Department of Clinical Pharmacy and were kept at room temperature (L-[1-13C]leucine) or −80°C (L-[5-15N]glutamine). The stock solutions were diluted with normal saline before the start of each tracer infusion. At the end of the tracer infusion, a sample of the infusate was taken for measurement of the concentration and enrichment of leucine and glutamine.

Blood samples were drawn into chilled heparin-containing tubes before the start of the tracer infusion for measurement of background enrichment and 2, 3, 4, and 5, and 6 h after onset of the infusion. Plasma was obtained by centrifugation of whole blood at 2200 × g at 4°C for 5 min. For the measurement of plasma glutamine concentration, plasma was deproteinized with sulfosalicylic acid, vortex mixed, frozen in liquid nitrogen, and stored at −80°C. For tracer enrichment measurements, plasma was frozen and stored at −80°C until analyzed. Tracer infusion and blood sampling were repeated on the last day of GTPN and STPN treatment to investigate the effect of these TPN solutions on protein metabolism. So that conditions were standard, the tracers were infused from 0830 to 1430 on both days while the patients were in a semirecumbent position in bed, and the catheters were inserted in the same position.

Analytic methods

Plasma enrichment of glutamine [mole percent excess (MPE)] was measured by using a tert-butyldimethylsilyl derivative and gas chromatography–combustion isotope ratio mass spectrometry (MAT 252; Finnigan, Bremen, Germany), as described previously (13). Plasma enrichment of α-ketoisocaproate ($E_{p,KIC}$; in MPE) was measured by using a quinoxalinoltrimethylsilyl derivative and gas chromatography–mass spectrometry (Finnigan Incos XL; San Jose, CA) in a manner similar to that described previously (14). Final values for KIC determinations were corrected by using calibration curves. The concentration of glutamine in plasma and in the tracer infusate was determined by fully automated HPLC (15).

Calculations

The $R_{a,glu}$ in plasma (in μmol·kg⁻¹·h⁻¹) was calculated as

$$R_{a,glu} = i_{[15N]glu} \times [(E_{glu}/E_{p,glu}) - 1]$$

(1)

where $i_{[15N]glu}$ is the tracer infusion rate (in μmol·kg⁻¹·h⁻¹) and $E_{p,glu}$ is the enrichment of glutamine (in MPE) in the tracer infusate, and $E_{glu}$ is the mean plasma glutamine enrichment between 2 and 6 h of tracer infusion. As shown previously, when $R_{a,glu}$ is obtained in this way it is overestimated by ≥20% because of slow equilibration of the glutamine tracer in the large muscle glutamine pool (13).

During GTPN administration, endogenous $R_{a,glu}$ (Endo$R_{a,glu}$) in plasma was calculated as

$$\text{Endo}R_{a,glu} = R_{a,glu} - \text{Inf}_{glu}$$

(2)

where Inf$_{glu}$ is the rate of intravenous delivery of glutamine (endogenous glutamine) from TPN. When no exogenous glutamine is delivered:

$$\text{Endo}R_{a,glu} = R_{a,glu}$$

(3)

In the absence of exogenous glutamine, 2 sources contribute to the $R_{a,glu}$ proteolysis and de novo synthesis. Theoretically, shrinkage of the intracellular free glutamine pool may also contribute to the $R_{a,glu}$ but we assumed that the amount of glutamine release from this source was negligible during the study period. Proteolysis was measured by using the endogenous whole-body appearance rate of leucine ($EndoR_{a,leu}$ in μmol·kg⁻¹·h⁻¹). $R_{a,leu}$ was calculated by using plasma KIC enrichment (16):

$$R_{a,leu} = i_{[13C]leu} \times [(E_{leu}/E_{p,KIC}) - 1]$$

(4)

Where $i_{[13C]leu}$ is the tracer infusion rate (in μmol·kg⁻¹·h⁻¹), $E_{leu}$ is the enrichment of leucine (in MPE) in the tracer infusate, and $E_{p,KIC}$ is the average enrichment of KIC in plasma between 2 and 6 h of tracer infusion. $EndoR_{a,leu}$ was calculated as

$$\text{Endo}R_{a,leu} = R_{a,leu} - \text{Inf}_{leu}$$

(5)

where Inf$_{leu}$ is the rate of TPN-derived exogenous leucine infusion from $R_{a,leu}$. Glutamine arising from protein degradation ($PD_{glu}$) was calculated as

$$PD_{glu} = R_{a,glu} \times (4.32 \times 131)/(9.18 \times 146)$$

(6)

where 4.32 and 9.18 are the assumed glutamine and leucine contents of body protein (g/100 g protein), respectively, and 146 and 131 are glutamine and leucine molecular weights (g/mol), respectively (17). Glutamine arising from de novo synthesis ($DNS_{glu}$) was calculated as

$$DNS_{glu} = EndoR_{a,glu} - PD_{glu}$$

(7)

Statistics

Data are presented as means ± SEMs, unless stated otherwise. The Mann-Whitney $U$ test was used to compare the treatment groups at baseline. Within each group, the effect of 8–10 d of TPN was tested by using the Wilcoxon signed-rank test. Fisher’s exact test was performed to determine whether the number of patients with pancreatitis and Crohn disease was different between the groups. A two-factor repeated-measures analysis of variance, with time as the within-subjects factor and treatment as the between-subjects factor, was performed to determine the main effects of time and treatment and the time-by-treatment interaction. A $P$ value < 0.05 was considered statistically significant. The analyses were performed by using SPSS (release 8.0; SPSS Inc, Chicago).

RESULTS

On admission there were no significant differences in patient characteristics, nutritional status, or underlying disease between the GTPN and STPN groups (Table 1). The number of patients with pancreatitis and Crohn disease was not significantly different between the groups. During the 10-d study period, 2 patients in the GTPN group required surgical intervention for reasons unrelated to the TPN (tumor bleeding and intraabdominal abscess drainage). 1 patient with colorectal cancer in the STPN group refused tracer infusion and blood sampling at the end of study, and 1 patient with stenosis of the colon in the STPN group discontinued TPN because of an unexplained generalized rash. One patient with chronic pancreatitis in the STPN group was suspected to have portal hypertension and was excluded because portal hypertension is likely to influence glutamine metabolism.
In the remaining 18 patients, there were no significant differences in patient characteristics or in the type of underlying disease between the treatment groups. The volume of feeding per day was similar in both groups: 2219 ± 135 and 2243 ± 78 mL/d in the GTPN and STPN groups, respectively. Addition of 0.21 ± 0.01 g glutamine · kg body wt⁻¹ · d⁻¹ for 9 ± 1 d did not induce a rise in the concentration of plasma glutamine. On day 2, when 50% of energy requirements was provided by a glucose and amino acid infusion, the plasma glutamine concentration in the STPN group was 564 ± 27 μmol/L; the concentration was 592 ± 38 μmol/L at the end of study during full feeding. In the GTPN group, plasma concentrations were 610 ± 39 μmol/L at study entry and 641 ± 42 μmol/L after 8–10 d of GTPN infusion.

The time courses of plasma [¹⁵N]glutamine and [1-¹³C]KIC enrichment are shown in Figure 1. Similar KIC enrichment values were obtained before and after treatment. Glutamine enrichment in plasma decreased in both treatment groups but to a larger extent in the GTPN group (P < 0.05). At baseline, there were no significant differences in $R_{a,gln}$, $P_{D_gln}$, DNS$_{gln}$, or $R_{a,leu}$ between the 2 groups.

Whole-body protein degradation during treatment, estimated from $EndoR_{a,leu}$, did not change significantly from baseline in either group: from 81 ± 4 to 79 ± 5 μmol·kg⁻¹·h⁻¹ in the STPN group and from 96 ± 7 to 96 ± 11 μmol·kg⁻¹·h⁻¹ in the GTPN group.

The response of glutamine kinetics to GTPN or STPN is shown in Figure 2. Although the total $R_{a,gln}$ in plasma increased significantly in both treatment groups (from 281 ± 16 to 361 ± 34 μmol·kg⁻¹·h⁻¹ in the GTPN group and from 250 ± 8 to 267 ± 14 μmol·kg⁻¹·h⁻¹ in the STPN group), the rise in $R_{a,gln}$ observed during GTPN treatment was significantly larger than that observed during STPN treatment (P < 0.01). As shown in Figure 2, the rise in $R_{a,gln}$ observed in the GTPN group, was largely attributed to parenteral glutamine administration. Whereas $EndoR_{a,gln}$ increased significantly during STPN treatment (from 250 ± 8 to 267 ± 14 μmol·kg⁻¹·h⁻¹), no significant change...
occurred in the EndoRGln of GTPN-treated patients (from 281 ± 16 to 299 ± 31 μmol·kg⁻¹·h⁻¹). Administration of GTPN did not change PDgln (from 40 ± 3 to 41 ± 5 μmol·kg⁻¹·h⁻¹) or DNSgln (from 241 ± 14 to 258 ± 27 μmol·kg⁻¹·h⁻¹) significantly. In the STPN group, PDgln did not change significantly (34 ± 2 μmol·kg⁻¹·h⁻¹ at baseline and 33 ± 2 μmol·kg⁻¹·h⁻¹ at the end of the study), whereas DNSgln increased significantly from 216 ± 8 to 234 ± 13 μmol·kg⁻¹·h⁻¹.

**DISCUSSION**

In this study, Rₐ,gln as measured from the dilution of infused l-[5-¹⁵N]glutamine in plasma, increased to a larger extent after 8–10 d of GTPN than after an equal period of STPN. EndoRₐ,gln (ie, PDgln and DNSgln) was not affected adversely by the inclusion of glutamine in the TPN solution.

To our knowledge, the present study was the first to evaluate the effect of prolonged parenterally administered glutamine on glutamine kinetics. Acute oral glutamine administration in a much larger dose than that used in our study (800 μmol·kg⁻¹·h⁻¹ for 5 h) resulted in a 20–30% decrease in EndoRₐ,gln in both healthy volunteers (10) and in children with Duchenne muscular dystrophy (11). The decrease in the estimated DNSgln accounted for 90% of the decrease in EndoRₐ,gln. PDgln also decreased significantly in the 2 studies, but to a smaller extent and not significantly so in the healthy volunteers (10). On the basis of these findings, the authors suggested that acute oral glutamine administration might have an acute protein-sparing effect by decreasing whole-body protein degradation and DNSgln therefore sparing nitrogen precursors (11).

The route and quantity of glutamine administration were not the only aspects in which the present study differed from the previous investigations. Hankard et al (10, 11) studied subjects postabsorptively during an intervention with glutamine supplementation compared with saline or flavored water, whereas in the current study patients were in the fed state and received either glutamine-supplemented TPN or an isonitrogenous solution of glutamine-free TPN. The 2-d baseline TPN infusion used in the present study may have influenced the results. Ingestion of protein and amino acids was shown previously to decrease protein breakdown and increase DNSgln in muscle (1, 18). The latter is attributed to increased availability of the precursors for glutamine production in muscle: glutamate, aspartate, asparagines, and the branched-chain amino acids (1, 18). Therefore, the present finding that protein degradation was not affected by 9 d of GTPN or STPN infusion may have resulted from the fact that the patients had already received TPN at entry. Compared with the baseline measurements, when 50% of energy requirements was provided by an infusion of glucose and amino acids, administration of the full amount of TPN did not further decrease protein breakdown in the present study. Additionally, replacement of part of the amino acids in the TPN solution with glutamine had no additional effect on protein degradation.

A small increase from baseline in DNSgln occurred during infusion of both GTPN and STPN, which was significant in the STPN group but not in the GTPN group. Differences in the administered amount of glutamine precursors probably underlie this gradual response in DNSgln because the sum of glutamate, aspartate, asparagines, and branched-chain amino acids was 11% higher during GTPN than at baseline and as much as 36% higher during STPN than at baseline. Therefore, the 2-d baseline TPN infusion may also explain the lack of a significant rise in DNSgln in the GTPN group.

Whereas EndoRₐ,gln did not change significantly in the GTPN group, systemic Rₐ,gln increased significantly, indicating that more glutamine was available for uptake by cells that need this amino acid. In view of the important role of glutamine in many metabolic processes [eg, a vehicle for interorgan transport of nitrogen and carbon skeletons (1, 19), a metabolic substrate for rapidly dividing cells (20, 21), a precursor for nucleotides and glutathione (22, 23), and a regulator of acid-base balance (4)], an increased amount of available glutamine is supposedly beneficial during periods of inadequate endogenous glutamine production resulting from glutamine depletion, increased glutamine requirements, or both. Such periods may occur during severe illness, when the need for glutamine is enhanced, as indicated by the increased uptake of glutamine by the liver and the spleen after trauma (24). Prolonged periods of high metabolic stress eventually lead to depletion of endogenous glutamine stores. Consequently, the body may no longer have the capacity to cope with the increased requirements.

The increase in total Rₐ,gln observed during GTPN was in proportion to the amount of glutamine in the supplemented dipeptides, suggesting rapid hydrolysis in plasma and complete bioavailability of glutamine in the synthetic dipeptide. Thus, the lack of a significant rise in plasma glutamine concentrations in the GTPN group was not due to incomplete bioavailability of the glutamine dipeptide, but rather to increased utilization of glutamine. A previous study by our group showed that parenteral glutamine administration can increase plasma glutamine concentrations in nutritionally depleted patients in whom plasma glutamine concentrations are already low before TPN therapy is started (25). Plasma glutamine concentrations at baseline were in the normal range in
the present group of patients. Apparently, the quantity of intravenously infused glutamine in this study, which amounted to 20–25% of EndoR\textsubscript{\text{gln}} is instantaneously extracted from the plasma pool. Much larger quantities of glutamine probably need to be administered to induce increased plasma concentrations in subjects with initial concentrations in the normal range (5, 10, 11).

In conclusion, we showed that administration of glutamine dipeptide–supplemented TPN to nutritionally depleted patients increases \( R_{\text{gln}} \) in plasma without inhibiting endogenous glutamine production. The lack of a significant rise in plasma glutamine concentrations with glutamine infusion suggests that tissue glutamine utilization increased. In view of the enhanced glutamine requirements in response to trauma and disease by tissues such as those of the gut, the immune system, and the liver, increased glutamine availability during glutamine-enriched TPN may be beneficial for the type of patients included in this study.

We acknowledge M Meers, AP Gijsen, and F van de Vegt for measuring glutamine and KIC enrichments; E Hardy (Department of Clinical Pharmacy) for handling the randomization procedure and for preparing the TPN solutions; and M Rouflart for practical advice and assistance in the management of the patients.

REFERENCES