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Elimination kinetics of L-alanyl-L-glutamine in ICU patients

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Summary. A randomised, double blind, placebo-controlled study was performed giving $0.5\,g \cdot kg^{-1} \cdot day^{-1}$ of undiluted alanyl-glutamine (20%) or saline in a peripheral vein during 4 hours in ICU patients (n = 20). During the infusion period a steady state in plasma concentration was reached for alanyl-glutamine, but not for alanine, glutamine or glutamate. On the other hand there was no accumulation of any of the amino acids, as the pre-infusion concentrations were reached within 8 hours after the end of infusion. The half-life of the dipeptide was 0.26 hours (range, 0.15–0.63 h). The distribution volume of alanyl-glutamine was larger than the extracellular water volume, indicating a rapid hydrolysis of the dipeptide. There was no detectable alanyl-glutamine in the urine of any of the patients. All patients had excretion of small amounts of amino acids in urine, but the renal clearance of alanine, glutamine and glutamate were not different between the two groups.

Keywords: Vascular tolerance – Glutamine – Parenteral nutrition – Urine – Glutamate – Humans

Introduction

Glutamine is the most abundant free amino acid in the human body. It is used for protein synthesis, as an oxidative fuel and it has several key functions in intermediary metabolism. Glutamine is constantly produced in skeletal muscle and exported to the splanchnic area to be utilised mainly in enterocytes and immune competent cells (Souba et al., 1983). It has been questioned if the endogenous glutamine production is sufficient during the increased demands in severely stressed patients. Low plasma concentration of glutamine in critically ill patients is correlated to an unfavourable outcome (Oudemans van Straaten et al., 2001). Intravenous supplementation of glutamine to intensive care unit (ICU) patients decreases morbidity and mortality (Novak et al., 2002). Furthermore, intravenous glutamine supplementation to postoperative patients is associated with lower morbidity and shorter hospital stay (Mertes et al., 2000).

Conventional formulas for intravenous nutrition do not contain glutamine, because glutamine is not stable in aqueous solution (Hammarqvist et al., 1989). Earlier studies were done using *ex tempore* solutions of crystalline glutamine of limited durability. Recently this problem has been overcome by the use of glutamine containing dipeptides, which have a high solubility and stability in aqueous solution (Fürst et al., 1997). A concentrated glutamine containing dipeptide solution can be administered safely via a central or a peripheral vein (Berg et al., 2002). Also in patients fed by the enteral route, additional intravenous glutamine may be advantageous, as the efficacy of enteral administrated glutamine is not sufficiently documented (Novak et al., 2002). The daily infusion period for glutamine supplementation is not well characterised from a metabolic point of view. A short infusion period into a peripheral vein may be advantageous from the vascular tolerance point of view. On the other side a continuous infusion over 24 hours may be preferred, when a steady state plasma glutamine concentration is desired. A short infusion period may be preferred in outpatient practice within oncology or nephrology.

In this investigation the metabolic and vascular tolerance of alanyl-glutamine was studied for a 4-hour infusion period. The primary objective was to evaluate the plasma and the urine concentrations and elimination kinetics of alanyl-glutamine, the constituent amino acids alanine and glutamine, and the immediate metabolite to glutamine, glutamate. In parallel to the pharmacokinetic parameters local vascular tolerance was evaluated.

Material and methods

Patients

The study was designed as a prospective randomised, double-blinded, placebo-controlled trial to explore the metabolic and local vascular tolerance following a 4 hours infusion Twenty critically ill patients admitted to the ICU were blindly randomised into two groups. The inclusions criteria were: 1) age between 18–80 years, and 2) admitted to the unit with an expected stay in the unit of more than 24 hours. The exclusion criteria were: 1) present history of thrombophlebitis, 2) renal insufficiency as defined by a plasma creatinine concentrations $>300\,\mu$mol/L, 3) hepatic insufficiency as defined by plasma aspartate aminotransferease (ASAT) or alanine aminotransferase (ALAT) values equal or higher than threefold the upper normal values of the local hospital laboratory (male, ASAT $>2.40\,\mu$Kat/L, ALAT $>2.40\,\mu$Kat/L, female, ASAT $>1.80\,\mu$Kat/L, ALAT $>1.80\,\mu$Kat/L), and 4) pregnant or nursing women.

The patient characteristics are presented in Table 1. The patients were critically ill as documented by their APACHE II score at admission, and the majority eventually developed multiple organ failure. In terms of liver and kidney insufficiency the exclusion criteria allowed only a moderate degree of organ failure. Patients were studied on day 4 (1–47; median and range) of ICU stay. When patients were studied late during the ICU stay, the reason was that exclusion criteria 2 or 3 were above the exclusion limits earlier during the course of ICU stay. As the values decreased the patients could be included. At the time of the study 8/10 patients in treatment group and 3/10 control patients required mechanical ventilations, in addition 4/10 and 2/10 patients respectively received inotropic support. All patients were fed in accordance with the routines of the unit favouring enteral nutrition, having a defined caloric goal, usually met by a combination of enteral and parenteral nutrition. As routine parenteral nutrition included a glutamine containing amino acid solution this was changed to an amino acids solutions not containing glutamine (Vamin18®, Fresenius Kabi) during the day before the study day. Enteral nutrition was given as a standard formula (Nutrison®, Nutricia) containing 4 g glutamine/L. Patients were given 15–25 $\mathrm{kcal \cdot kg^{-1} \cdot 24\,h^{-1}}$ continuously before and during the study. On the study day, 2/10 and 2/10 patients had parenteral nutrition, only, 6/10 and 3/10 patients had a combination of enteral and parenteral nutrition, 0/10 and 2/10 patients had enteral nutrition only, and 2/10 and 2/10 patients were given 5% dextrose only in the treatment and control groups respectively.

The nature and purpose of the study and the risk involved were explained to the subjects or the next of kin orally and in writing before obtaining, informed consent. The study protocol was approved by the Ethics Committee of Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden and carried out in accordance with the Declaration of Helsinki (2000).

Study solutions

The solutions infused were L-alanyl-L-glutamine (200 mg/ml, Dipeptiven®, Fresenius-Kabi) or placebo, NaCl 9 mg/ml (Sodium Chloride, Fresenius-Kabi). The osmolarity of the alanyl-glutamine solution was 921 mOsm/L and the pH value 5.4–6.0. The osmolarity of NaCl was 290 mOsm/L and the pH value was approximately 6. The solutions were delivered blinded by the local hospital pharmacy.

Table 1. Patients characteristics

Pat no.	Diagnosis treatment group	Gender (F/M)	Age (years)	APACHE II at admission	Days in ICU at start of study	Total days in the ICU
1	Ceacal perforation	F	63	25	19	24
2	Osteitis, mediastinitis	F	66	24	3	46
3	Colon perforation, bleeding shock, septic shock	M	66	29	14	44
4	Malignant lymphoma, septic shock	M	59	31	5	12
5	Postop esophagectomy	F	57	19	3	6
6	Vertebral fractures, pneumonia	M	49	19	1	4
7	Pneumonia, acute myocardial infarction, cardiac failure	M	57	26	4	14
8	Peritonsillitis	F	67	24	7	23
9	Subarachnoidal hemorrhage, Hodgkin lymphoma	M	59	13	7	9
10	Ruptured aortic aneurysm	M	67	36	1	1
	Control group					
11	Ileus, peritonitis	M	55	15	4	7
12	Acute myeloid leukemia, Pneumonia	F	40	25	3	4
13	Meningitis	M	35	19	1	9
14	Postop liver transplantation	M	46	19	47	52
15	Pancreatitis, pneumonia	M	55	18	5	9
16	Pneumonia	M	76	33	5	16
17	Pancreatitis	M	46	23	4	7
18	Gastrointestinal bleeding, acute myocardial infarction	M	48	15	1	2
19	Ruptured aortic aneurysm	M	65	15	1	2
20	Pneumonia	M	76	36	1	5

Study protocol

During 12 hours before start of the study, the use of intravenous glutamine-containing solutions was not allowed. The study solution was given separately in a peripheral vein of the arm in a standardized manner. The cannulae were inserted just before infusion and removed immediately after infusion as described in detail elsewhere (Berg et al., 2002). The solution was infused during 4 hours with an infusion rate of $0.625\,ml \cdot kg^{-1} \cdot h^{-1}$ (corresponding to $0.125\,g$ dipeptide $\cdot kg^{-1} \cdot h^{-1}$ or $0.085\,g$ glutamine $\cdot kg^{-1} \cdot h^{-1}$). At the end of infusion and at 24 hours, 48 hours, 72 hours and 7 days followings treatment the local vascular tolerance was assessed by visual inspection and palpation according to a modified Maddox score, focusing upon erythema, swelling, pain and palpable venous cord (Berg et al., 2002).

Sampling procedure

Blood samples were taken from an arterial cannulae at −30 min and −15 min, immediately before start of the infusion, at 1, 2, 3, and 4 h, during the infusion, and at 4 h 3 min, 4 h 6 min, 4 h 9 min, 4 h 12 min, 4 h 15 min 4 h 30 min and 5 h, 6 h, 7 h, and 8 h following the infusion. Urine was collected during the infusion period (0–4 h) and in the period following the infusion (4–8 h). For amino acid and dipeptide analyses blood samples were immediately put on ice and centrifuged (4°C, $2.800 \times g$ for 10 min) within 30 minutes. For deproteinization, 1 ml plasma was mixed with 100 μL sulphosalisylic acid (30%) in which 1 mM norvaline as an internal standard was included. The samples were immediately mixed with vortex vibrator, kept at 4°C for 1 hour, and centrifuged (4°C, $2.800 \times g$ for 15 min). The protein-free supernatant was transferred to an Eppendorf tube and kept at −80°C until analyses. The total urine volume per time interval was collected in a container containing 10 ml 2N H_2SO_4 and thoroughly mixed. Subsequently an aliquot (10 ml) was stored at −80°C until analysis. All tubes containing plasma and urine were shipped frozen to the Institute for Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Germany, for analysis.

Analysis

Plasma and urine concentrations of amino acids and of alanyl-glutamine were determined by HPLC-analysis system with fluorescence detection after on column derivatisation as described elsewhere (Fürst et al., 1990b; Graser et al., 1985).

Pharmacokinetic calculations

The pharmacokinetic parameters were estimated using non-compartmental analysis (Gabrielsson and Weiner, 2000). The terminal plasma half-life $t_{1/2Z}$ was calculated from the slope of the elimination curve in a lin-log presentation. The clearance Cl was calculated from the dose of dipeptide administered and the area under the time concentration curve during infusion time and elimination time. This area under the time concentration curve is also the background information when the mean resisdence time MRT_{inf} is calculated. MRT_{inf} illustrates the average time an individual dipeptide molecule stays in plasma following the administration. The terminal and steady state distribution volumes Vz and Vss were calculated from the clearance and slope of elimination curve, and the clearance and MRT_{inf} respectively.

Statistics

Data of all patients, including outliers, are presented as medians (25, 75 percentiles). Comparison between groups were done using Student's t-test, and $p < 0.05$ was considered statistical significant. All calculations except descriptive statistics of pharmacokinetic variables were performed using SAS 8.01 software package. Descriptive statistics for pharmacokinetic variables were performed at Pharm Assist AB (Uppsala, Sweden) using Statistica 6.0 (StatSoft, Tulsa, OK, USA) software package, except urinary data, were Microsoft Excel 97 was used.

Results

Patients

The severity of critical illness of the patients was unevenly distributed between the two groups as reflected by the median APACHE II scores at admission, 25 (range 13–36) as compared to 19 (range 15–36) in the treatment and control groups respectively (Table 1). Patient no. 10 (in the treatment group) died within 36 h following an abdominal aortic aneurysm repair, when anastomosis leakage ensured and re-operation was considered futile. The clinical course of all other patients included was uneventful in terms of routine blood tests, circulatory or ventilatory stability during and immediately after the study period. Data presented below represent all patients randomised including the outliers, which are also presented separately.

Plasma concentrations

Plasma concentrations of alanyl-glutamine, glutamine, alanine and glutamate are given in Figs. 1–4. All concentrations increased during the alanyl-glutamine infusion in comparison with the control group and with the baseline concentrations. For the dipeptide a steady state was reached after 2 hours as illustrated by the constant median value over time, but for the constituent amino acids such a steady state was not obtained in all patients. After stopping the infusion there was a rapid elimination of

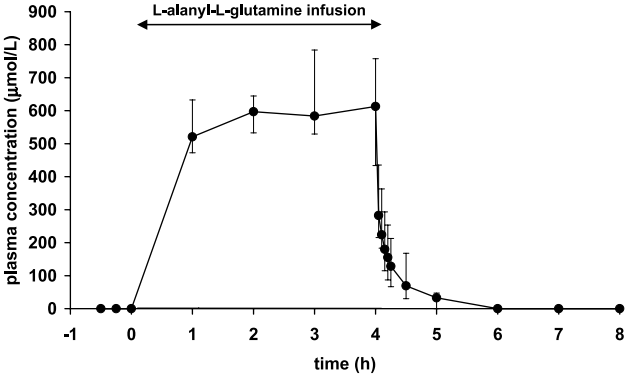


Fig. 1. The plasma concentration of L-alanyl-L-glutamine before, during and after a 4 hours infusion of L-alanyl-L-glutamine $0.125\,g \cdot kg^{-1} \cdot h^{-1}$ (filled symbols) or placebo (open symbols), in ICU patients ($n = 10 + 10$). No alanyl-glutamine was detected in the patient receiving placebo. Values are given as medians and (25,75) percentiles

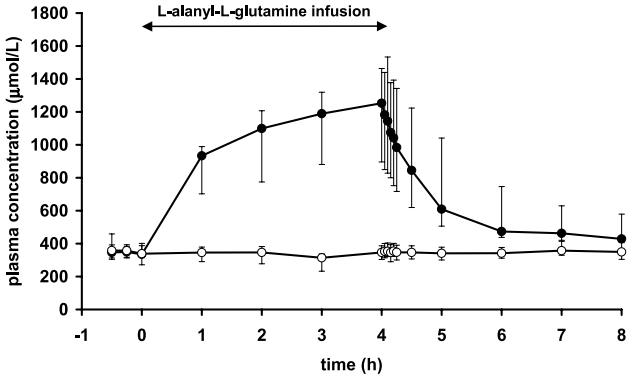


Fig. 2. The plasma concentration of glutamine before, during and after a 4 hours infusion of L-alanyl-L-glutamine $0.125\,g \cdot kg^{-1} \cdot h^{-1}$ (filled symbols) or placebo (open symbols), in ICU patients (n = 10 + 10). Values are given as medians and (25,75) percentiles

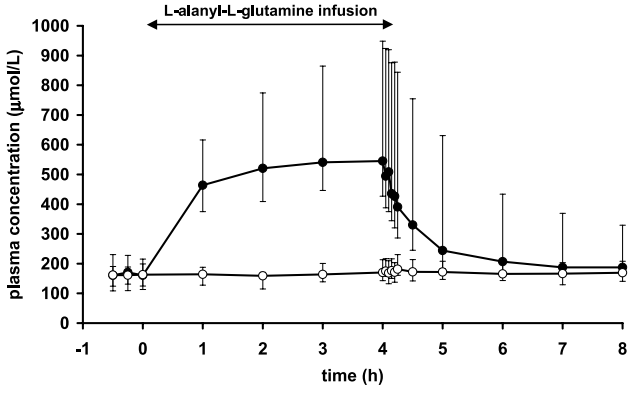


Fig. 3. The plasma concentration of alanine before, during and after a 4 hours infusion of L-alanyl-L-glutamine $0.125\,g \cdot kg^{-1} \cdot h^{-1}$ (filled symbols) or placebo (open symbols), in ICU patients (n = 10 + 10). Values are given as medians and (25,75) percentiles

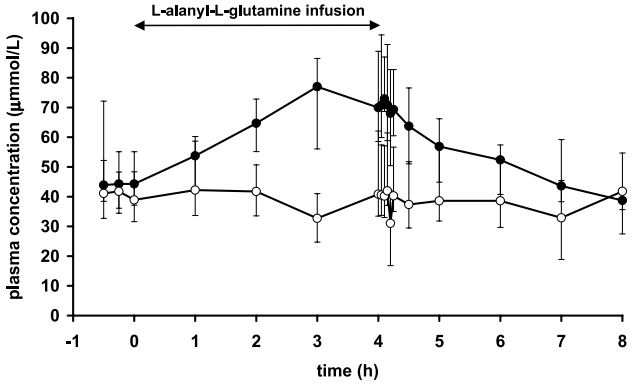


Fig. 4. The plasma concentration of glutamate before, during and after a 4 hours infusion of L-alanyl-L-glutamine $0.125\,g \cdot kg^{-1} \cdot h^{-1}$ (filled symbols) or placebo (open symbols), in ICU patients (n = 10 + 10). Values are given as medians and (25,75) percentiles

Table 2. Peak concentrations and half-lives of alanyl-glutamine and related amino acids in plasma of ICU-patients (n = 10) receiving a 4 hour alanyl-glutamine infusion

		Ala-Gln	Gln*	Ala*	Glu*
C_{max}	median	652	860	415	29
(μmol/l)	25%	536	525	307	24
	75%	875	1652	1060	86
$t_{1/2Z}$ (h)	median	0.26	0.93	0.83	0.55
	25%	0.15	1.12	0.41	0.38
	75%	0.63	1.39	1.36	1.20

C_{max} peak concentration, $t_{1/2Z}$ plasma half-life in terminal part of the elimination slope
* Base-line adjusted values

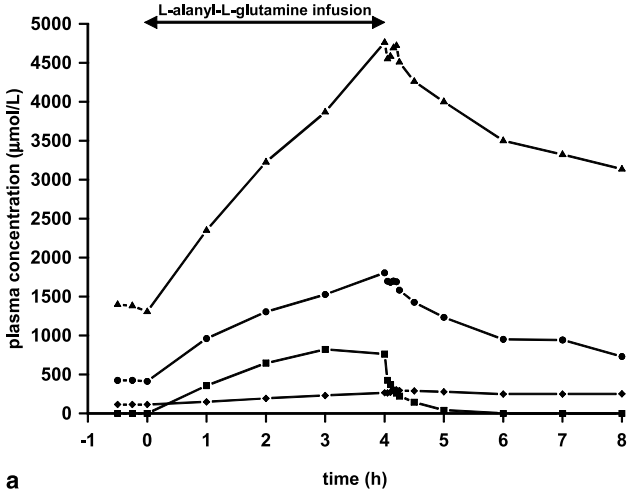
alanyl-glutamine and the elimination period could be divided into a rapid alpha-phase and a slower betaphase. The peak concentration values (C_{max}) for the absolute values of alanyl-glutamine, alanine, glutamine and glutamate as well as the baseline adjusted values of alanine, glutamine and glutamate are given in Table 2, together with the terminal half-lives of the elimination slope. For alanyl-glutamine the volume of distribution based on the terminal phase (V_z), as well as the estimated volume of distribution at steady state (V_{ss}), the whole body clearance (Cl), and the mean residual time extrapolated to infinity (MRT_{inf}), are given in Table 3.

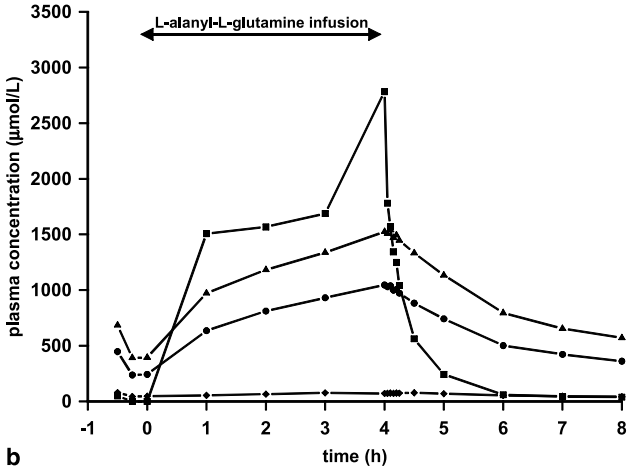
In terms of the plasma concentrations of alanyl-glutamine, glutamine, alanine and glutamate, 3 patients (no. 2, 7 and 10), could be considered as outliers. Individual curves of these three patients are given in Fig. 5a–c.

Table 3. Distribution volume and whole body clearance of L-alanyl-L-glutamine in ICU-patients (n = 10) receiving a 4 hour alanyl-glutamine infusion

		Ala-Gln
V_z (L/kg b.w.)	median	0.371
	25%	0.247
	75%	0.483
V_{ss} (L/kg b.w.)	median	0.493
	25%	0.298
	75%	0.600
Cl ($L \cdot h^{-1} \cdot kg^{-1}$)	median	1.01
	25%	0.77
	75%	1.37
MRT_{inf} (h)	median	0.502
	25%	0.313
	75%	0.730

V_z distribution volume based on terminal phase of elimination; V_{ss} distribution volume based at steady state; *Cl* volume body clearance; *MRT* mean residence time extrapolated to infinity





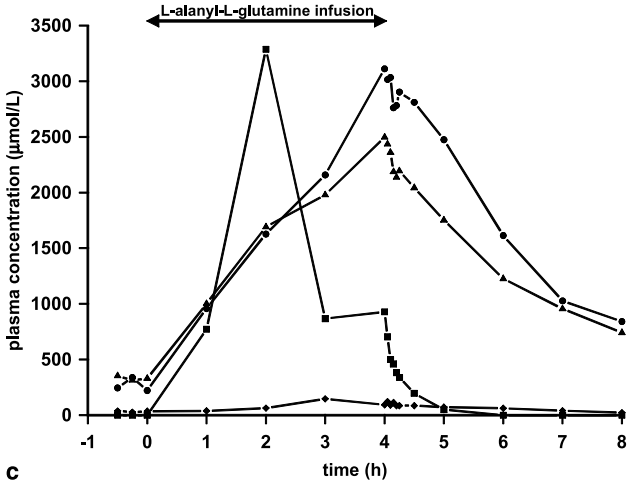


Fig. 5. The plasma concentrations of L-alanyl-L-glutamine (■), glutamine (▲), alanine (●) and glutamate (◆), before, during and after 4 hours infusion of L-alanyl-L-glutamine in the 3 outliers; **a**) patient 2, **b**) patient 7, and **c**) patient 10

Patient 2 had a prolonged stay in the ICU but nothing in her clinical course gave reason to suspect abnormal glutamine kinetics. Patient 7 had a considerable overweight (142 kg), which according to the study protocol was not an indication for exclusion or dose adjustment. Consequently a dose corresponding to the total body weight was given. Patient 10 died during the study period, 17 h after the start and 13 h after the end of the infusion, as referred to above. At inclusion and at start of the dipeptide infusion, the rapid deterioration of the clinical course was not possible to foresee.

Urine excretion

The excretion during 0–8 hours of alanine, glutamine and glutamate in the urine and the calculated urinary clearance are given in Table 4. No alanyl-glutamine was detected in the urine. Patient no. 10 in the treatment group had a very low urinary output, and was therefore excluded. All patients had an excretion of small amounts of amino acids but only 5 patients in each group had detectable amounts of glutamate. Clearances of alanine, glutamine and glutamate were not different between the two groups.

Local tolerance

No signs of tenderness, indurations, swelling, erythema or thrombophlebitis scoring according to the modified Maddox score during or after the infusion in any patients in any of the two groups.

Table 4. Urine excretion and renal clearance of amino acids in ICU-patients receiving a 4 hour alanyl-glutamine infusion

		Gln	Ala	Glu[1]
Urine excretion (µmol/8 h)				
Treatment	Median	363	176	71
group (n = 9)	25%	109	78	17
	75%	1084	318	254
Control	Median	239	190	23
group (n = 10)	25%	52	44	12
	75%	267	305	47
Cl_R (ml/min)				
Treatment	Median	0.70	0.90	0.65
group (n = 10)	25%	0.26	0.44	0.47
	75%	3.74	2.34	11.9
Control	Median	1.39	2.17	0.63
group (n = 10)	25%	0.32	0.64	0.39
	75%	1.79	3.14	3.0

Cl_R renal clearance
[1] (n = 5 in both groups, not all the patients did have detectable glutamate in urine)

Discussion

The metabolic and local tolerance of a 20% alanyl-glutamine solution during a 4 hour intravenous infusion was investigated in ICU patients. A dose of 0.5 g dipeptide/kg was given. Plasma kinetics and urine elimination of the dipeptide, alanine, glutamine and glutamic acid was studied and local tolerance registered. The elimination phase of the dipeptide and the constituent amino acids showed a return to pre-infusion concentrations within 8 hours after the end of the infusion. Therefore it is not likely that alanylglutamine, glutamine, alanine and glutamate will accumulate during administration of this dose of alanyl-glutamine. In all individual patients a steady state concentration was reached for the dipeptide but not for the three amino acids during the 4 hour infusion. The alanyl-glutamine was totally eliminated from plasma within the study period in all patients.

In terms of the plasma concentration of alanyl-glutamine and the constituent amino acids there were three outliers. The very high concentrations of glutamine, alanine and glutamate in patient no. 2 (Fig. 5a) cannot be explained at present. The baseline values of the patient showed to be extremely high already at inclusion. However, no further accumulation of any of the amino acids when extrapolated to 24 h after the infusion was seen. No patient with such a high plasma concentration of glutamine has been reported in literature, although singular patients with hyperglutaminemia are reported among ICU patients (Oudemans-van Straaten et al., 2001). This patient had slightly elevated values of liver enzymes (ASAT/ALAT), but below the limits of the exclusion criteria, during and after the study period. Bilirubin concentration was only slightly elevated as was the plasma lactate concentration. Taken together these blood tests give the picture of a moderate liver insufficiency often seen in long-staying ICU patients with multiple organ failure. However, other blood tests reflecting liver function, such as INR showed values indicating a more compromised liver function in terms of the synthetic capacity of clotting factors. The possibility of an inborn error of metabolism was considered, but determination of the plasma glutamine concentration of this particular patient, in an extra sample obtained one year after completion of the study, revealed completely normal plasma glutamine concentration. Patient no. 7 (Fig. 5b), with a considerable overweight, showed high plasma concentrations of alanyl-glutamine, glutamine and alanine. This can be explained by the large dose given in relation to his fat-free mass. Still the dipeptide as well as the constituent amino acids were eliminated in a normal manner after the end of the infusion. The clinical recommendation is to adjust the glutamine supplementation to the lean body mass of the patient. Patient no. 10 (Fig. 5c), who died following an aortic aneurysm repair, showed a slow elimination of alanine and glutamine. Still an extrapolation of the plasma glutamine concentration suggested a return to basal within 24 hours. In summary, also the three outliers described showed metabolic tolerance in terms of having a rapid elimination of alanyl-glutamine and no accumulation of the amino acids contained in the dipeptide. Two outliers could be explained in terms of overweight and death. Patient no. 2 was identified as an outlier exclusively on laboratory measurements. The large variability among ICU patients is a well-known fact, which calls for adjustment of treatment on the individual cases.

During the 4 hours of infusion, alanyl-glutamine concentrations reached a steady state, whereas for alanine and glutamine this was not the case. This is most likely related to the large distribution volumes for alanine and glutamine. The half-life of the alanyl-glutamine is less than 5 min after a bolus injection in healthy volunteers (Albers et al., 1988, 1989), which in theory should result in a steady state within less than an hour. The critical ill patients had a median half-life of alanyl-glutamine of 0.26 hours (16 min). Here some patients were in the range of young healthy subjects, while other patients had a longer half-life. Naturally, this explains the large scatter in plasma concentration of alanyl-glutamine after the 4 hour infusion, and it also explains why a steady state was apparently not reached in all subjects. From a clinical safety perspective, however, the results indicate that a comparatively large dose of alanyl-glutamine given during a short time period is readily eliminated in this group of critically ill patients. In addition, the lack of accumulation in the three outliers further underlines the metabolic tolerance.

In healthy volunteers the distribution volume equals the volume of extracellular water (Albers et al., 1988, 1989; Stehle, 1991). Here, in the ICU-patients, the larger distribution volume cannot be explained by an increase in extracellular water only. This may indicate that the dipeptide is rapidly hydrolysed at the cell membrane and distributed as glutamine into the cell. Although the calculated $t_{1/2}$ of alanyl-glutamine showed a 4-fold variation between the 25–75% percentiles, the estimation of distribution volume, whole body clearance and residence time showed a corresponding variability, which was only 2-fold (Table 3). Probably this is also reflective of the large distribution volume in ICU patients.

All patients excreted small amounts of alanine, glutamine and glutamate in the urine. The amounts of amino acids excreted were larger in the treated group, which was expected, as the plasma concentrations were higher in the treatment group. However, excretion was only 0.2% of the amino acids taken in. There were no differences between the groups concerning the urinary clearance of the amino acids. There was no detectable leakage of alanyl-glutamine into the urine. The dipeptide was most likely completely hydrolysed by the peptidase activity in the kidney (Adibi et al., 1987; Fürst et al., 1990a). The results demonstrate that alanyl-glutamine is not excreted in the urine despite high plasma concentrations and that urinary leakage of amino acids in ICU patients is a general phenomena of critically ill patients not related to the plasma concentration of the amino acids.

In the present study 0.5 g/kg of alanyl-glutamine corresponding to 0.35 g/kg of glutamine was given as a 4 hours infusion to critically ill patients. A total dose of about 35 g alanyl-glutamine (25 g glutamine) was actually given. This design was chosen to study the metabolic tolerance of alanyl-glutamine in the worst-case scenario. The 0.5 g/kg of alanyl-glutamine was given over a very short time period to a patient group in which metabolism may be compromised. There are several reports when comparatively large doses of glutamine have been given to patients or healthy volunteers (Karner et al., 1990; Roth et al., 1992; Tjäder et al., 2004; van Zaanen et al., 1994). In these studies no information concerning elimination kinetics is available, although a stable plasma concentration of glutamate within the normal range is reported (Tjäder et al., 2004). None of these studies report of any adverse effects related to the comparatively large doses (40–60 g/24 h) of glutamine given. Here the conclusion was that 0.5 g/kg of alanyl-glutamine was well tolerated, without any excessive urinary losses of the dipeptide or any of the amino acids, when given during 4 hours to a group of metabolically severely compromised patients. Such a short infusion period may be desirable in groups of patients who receive intravenous nutrition on an outpatient's basis, where a short infusion period of a glutamine-containing dipeptide in a peripheral vein, may be the only possibility to provide glutamine. In hospitalised patients such a short infusion period will probably not be the chosen, as a steady state of the plasma glutamine concentration will not be attained (Wischmeyer et al., 2001).

The difference in elimination kinetics between the dipeptide and the constituent amino acids may be noted (Table 2). This is reflected in the half-live of the dipeptide being less than 1/3 of half-lives of the amino acids, and also by the failure of some patients to obtain a plasma steady state of the constituent amino acids during the 4 h dipeptide infusion. In addition the C_{max}, the maximal baseline adjusted concentration in plasma, for glutamine was approximately double that of alanine, although the half-lives were similar. Clearance calculated for alanine, using non-compartmental analysis, is double that of glutamine, explaining the difference in rise of plasma concentration. However, further studies designed to address this question are needed for any definite conclusion on this point.

In summary, an intravenous infusion of a 20% alanyl-glutamine solution was metabolically well tolerated, in terms of plasma kinetics and urinary elimination, in a group of ICU patients. The elevated plasma concentration of alanyl-glutamine and the constituent amino acids following the infusion returned back to basal within 8 hours after the end of infusion. There was no difference in local tolerance between the dipeptide and normal saline. The study design allows for no conclusions concerning the optimal administration time for infusion of glutamine-containing dipeptides as a part of nutritional support.

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