Glutamine metabolism in critically ill patients.

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We hypothesize that exogenous, enterally provided glutamine contributes substantially to the de novo synthesis of arginine in critically ill patients.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON26363

Bron
Nationaal Trial Register

Verkorte titel
DIPEP HUMAN ICU

Aandoening

ICU, intensive care
critically ill patients, ernstig zieke patiënten
glutamine
citrulline
arginine
alanyl-glutamine
metabolic route, metabole route
enteral nutrition, enterale voeding

Ondersteuning

Primaire sponsor: VU University medical Center
Overige ondersteuning: VU University medical Center

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The whole body rate of appearance of glutamine, citrulline and arginine, as well as the conversion of endogenous and exogenous, enterally supplied glutamine into citrulline and arginine at the whole body level.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:

Critically ill patients are likely to benefit from additional glutamine. Novak et al. demonstrated in their meta analysis that glutamine administration reduced morbidity and Oudemans-van Straaten showed that the magnitude of glutamine deficiency correlates with ICU mortality. In addition, low arginine and citrulline levels correlate with severity of inflammation in critically ill children. Although arginine administration can be beneficial for some groups of trauma and cancer surgery patients, its action as substrate for nitric oxide synthesis and subsequent hemodynamic instability and oxidative stress, may be responsible for disappointing results when supplied to severe critically ill patients. Since glutamine can generate arginine by the citrulline pathway in the kidney, supplying glutamine potentially may be a more physiologic and safe way to administer arginine in the metabolically stressed ICU patient. Hence, positive effects of glutamine could be partially due to the substrate that glutamine delivers for the synthesis of arginine. However, when the intestinal-renal axis is disturbed by renal failure, glutamine administration might not gain similar effects.

We hypothesize that exogenous, enteral provided glutamine contributes substantially to the de novo synthesis of arginine in critically ill patients, which is of clinical significance. Furthermore we hypothesize that patients suffering from acute renal failure have a lower de novo arginine synthesis.

Objective:

The objective of this clinical study is: To study whether L-glutamine given enterally as the dipeptide L-alanyl-L-glutamine enhances the de novo arginine synthesis in critically ill patients. Secondary objective is to determine the relative contribution of the splanchnic bed to this metabolic route. Tertiary objective is to study whether patients with acute renal failure metabolize amino acids (including glutamine) differently.

Outcome:

The whole body rate of appearance of glutamine, citrulline and arginine, as well as the conversion of endogenous and exogenous, enteral supplied glutamine into citrulline and arginine at the whole body level.

First pass effect of the gut will be calculated using the difference between the whole body rate of appearance of the amino acids when the tracers are given intravenously or enterally.

Renal metabolism will be calculated by comparing the tracer whole body rate of appearance of the amino acids in a group with normal kidney function and a group with ARF.

Design:

This is an randomized, clinical trial with 2 groups of 10 critically ill patients.
Patients are randomly assigned to one of the two groups:

Group 1 (control group): 10 patients receive enteral nutrition in the small intestine.

Group 2 (treatment group): 10 patients receive isonitrogenous enteral nutrition including 0.5 g/kg L-alanyl-L-glutamine/hr (=0.475 g/kg glutamine and 0,165 g/kg/day alanine) in the small intestine.

Group 3 (ARF group): 5 patients receive enteral nutrition in the small intestine.

Number of patients:

n=25 (control: n=10; treatment n=10, ARF n=5).
Description of subjects and main criteria for inclusion:

Critically ill patients, staying one week or longer on the ICU, receiving enteral nutrition by a feeding tube.

Tracers: A primed, continuous infusion of L-[2-15N]glutamine; L-[5-13C-4,4,5,5,2H4]citrulline; L-[ring-2H5] phenylalanine; L-[2H2]tyrosine; L-[ring-2H4]tyrosine; L-[guanidino-15N2]arginine (enteral or parenteral).

Route of administration, duration of protocol and tracer infusion:

Group 1 and group 3 (control group and ARF group): Patients will receive enteral tube feeding, containing 1.5 g/kg protein/day (including 0.15 g/kg/day glutamine) for at least 5 days.

Group 2 (treatment group): Patients will receive enteral tube feeding for 5 days + 0.5 g/24hr L-alanyl-L-glutamine containing 1.5 g/kg protein (including 0.475 g/kg/day glutamine).

Both groups: The tracer protocol will be performed on the 4th and 5th day after (after at least 3 days of enteral feeding). In randomized order the tracers will be given enterally or parenterally.

Within 2 of the patients (1 control; 1 intervention), the tracer protocol will additionally be conducted at a third and fourth day (day 6 and 7), in which enteral feeding will be stopped 2 hours in advance to enable postprandial measurements and comparison. Tracers will be given intravenously and enterally alternately.

For group 3, tracers will be given intravenously after a minimum of 3 days of enteral feeding. Tracers will be administered when CVVH filter change is necessary.

Doel van het onderzoek

We hypothesize that exogenous, enterally provided glutamine contributes substantially to the de novo synthesis of arginine in critically ill patients.

Onderzoeksopzet

On day 4 and 5 (group 1 and 2 only) after ICU admission, stable isotopes will be given to quantify metabolic routes.

Onderzoeksproduct en/of interventie

1. Group 1 (control group): 10 patients will receive enteral tube feeding, containing 1.5 g/kg protein/day (including 0.15 g/kg/day glutamine) for at least 5 days;

2. Group 2 (treatment group): 10 patients will receive enteral tube feeding for 5 days + 0.5 g/24hr L-alanyl-L-glutamine containing 1.5 g/kg protein (including 0.475 g/kg/day glutamine).

Each group will receive stable isotopes of glutamine, citrulline, arginine, phenylalanine and tyrosine on two consecutive days, enterally and intravenously in a randomized cross-over manner.

Within 2 patients the tracer protocol will also be performed on the 6th and 7th day. Feeding will be stopped two hours in advance.

3. Group 3 (acute renal failure (ARF)): 5 patients will receive enetral tube feeding, containing 1.5 g/kg protein/day (including 0.15 g/kg/d glutamine) for at least 5 days.

Patients will receive stable isotopes of glutamine, citrulline, arginine, phenylalanine and tyrosine intravenously.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Age: > 18;

2. BMI >18,5 and < 35;

3. Ability to tolerate enteral nutrition, provided by postpyloric tube, meeting full protein/energy requirements based on indirect calorimetric measurements;

4. Expected ICU or medium care stay of a minimum of 5 days;

5. Any ICU patient who is considered ‘stable’;

6. Hemodynamics: No new vasoactive medication during 24 hrs preceding inclusion, maximum dose of vasoactive medication < 5 ml/h;

7. Respiration: PaO2/FiO2 ratio > 200, PEEP < 15 cm H2O;

8. Having obtained his/her or his/her legal representative’s informed consent.

For group 3:

1. Requiring CVVH;

2. No endstage kidney disease (defined by need for dialysis for longer than 3 months);

3. No persistent acute renal failure (loss) (defined as need for renal replacement therapy for more than 4 weeks).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Planned admission for recovery after elective surgery;

2. Pregnancy;

3. Liver failure, defined by bilirubin levels > 100 µmol/L;

4. Hyperammonaemia;

5. Kidney failure, represented by increase in serum creatinine levels to > 150 umol/l, in the absence of primary underlying renal disease, or oliguria, defined as urine output < 0.5 ml/kg during the previous 4 hours;

6. Urea cycle defects;

7. Chronic corticosteroids use (> 7.5 mg/ day > 3 weeks);

8. Proven bowel malabsorption possibly interfering with intestinal absorptive function, e.g. celiac disease, crohn’s disease, presence of fistulas, major intestinal malabsorption disorder, or short bowel syndrome;

9. Parenteral feeding;

10. Use of medium chain triglycerides or glutamine/citrulline supplements.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Enkelblind
Controle:	Actieve controle groep

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-07-2010
Aantal proefpersonen:	25
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	13-04-2010
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2161
NTR-old	NTR2285
Ander register	MEtC VUmc : 09/083
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A