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Case Report Open Access

Prospective Longitudinal Examination of Hyperammonemia during L-Asparaginase Treatment within 24 Hours after Administration in Childhood Lymphoblastic Malignancies

Marios Paulides[1#], Ronny Jung[2#],Martin Chada[3], Berthold Lausen[4], Markus Metzler[3] and Thorsten Langer[5]

[1]*Drug Commission of the German Medical Association, Berlin, Germany*
[2]*Pediatrician, practioner, Roth, Germany*
[3]*University Hospital for Children and Adolescents, Erlangen, Germany*
[4]*Professor of Statistics, Department of Mathematical Sciences at University of Essex, UK*
[5]*University Hospital for Children and Adolescents, Lübeck, Germany*
[#]*These authors contributed equally to the study*

Abstract

L-asparaginase is used in virtually every protocol against acute lymphoblastic malignancies in induction and intensification. In rare cases, patients may develop hyperammonemia encephalopathy as a side-effect, resulting in severe neurologic deterioration and even death.

After an index case at our hospital, we conducted prospective longitudinal examination of blood ammonia level kinetics in further six consecutively enrolled patients treated with E.coli L-asparaginase without neurological signs of encephalopathy within 24 hours after administration.

All patients developed transient hyperammonemia above the potentially neurotoxic threshold of 60 µmol/l, with peak concentrations being reached 2 hours after L-asparaginase infusion at 144 µmol/l (range 62 -277 µmol/l). A decline to baseline values was observed after 24 hours.

We conclude that transient hyperammonemia is frequent in children treated on protocols containing L-asparaginase. A further precipitating event may lead to hyperammonemia encephalopathy with neurologic symptoms. Therefore, all patients with neurologic symptoms during treatment with L-asparaginase should receive metabolic surveillance and blood ammonia examinations in addition to monitoring for infectious or cerebrovascular complications.

Keywords: Hyperammonemia; L-Asparaginase; Encephalopathy; Children; Acute Lymphoblastic leukaemia

Introduction

Since L-asparaginase (L-Asp) was discovered as an important antilymphoblastic agent more than 40 years ago [1], it has been included in nearly all paediatric treatment protocols for acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphomas (NHL) [2,3]. Several studies and controlled clinical trials have demonstrated the efficacy of L-Asp in induction and intensification therapy of acute lymphoblastic diseases [4]. L-Asp causes depletion of the non-essential aminoacids asparagine and glutamine by hydrolysing the respective serum aminoacids to aspartic and glutamic acid and ammonia [1].

L-Asp has been reported to induce toxicity with central nervous system (CNS) symptoms such as agitation, depression, hallucination, somnolence and seizures, which may progress to coma and death [5-7]. Often, these symptoms are a result of cerebrovascular complications [1,7,8]. However, it has been known since at least 1986, that L-Asp can also result in hyperammonemia encephalopathy, lacking a cerebrovascular component [8].

This side-effect has been also observed during treatment with other cytotoxic compounds and a multifactorial genesis is under discussion [5,7,9,10]. However, L-Asp has the potential of being the direct causative agent, as its action actively produces ammonia as a metabolite [1,10]. Previous studies by Steiner et al. and Jorck et al. [11,12] were performed describing elevated ammonia levels, but information are lacking about ammonia levels within the first 24 hours after administration. After an index patient at our hospital, we conducted prospective longitudinal examination of blood ammonia level kinetics in further six patients without neurological signs of encephalopathy to explore the frequency and significance of ammonia levels under E. coli L-Asp treatment.

Case Report

We observed a case of acute severe encephalopathy during therapy with E. coli L-Asp in a 16-year-old male patient with T-non-Hodgkin lymphoma (T-NHL). During induction treatment, he received polychemotherapy including corticosteroids, vincristine, daunorubicine and a total of eight L-Asp administrations (Medac® Asparaginase 10,000 IU/m^2 every three days). Our patient developed emesis, headache, hallucinations and somnolence progressing to coma 6 hours after administration of the last L-Asp dose. Serum ammonia was 644 µmol/l (normal range 15-55 µmol/l) and analysis of the plasma amino acids showed a pathological pattern with massively increased

***Corresponding author:** Dr. Thorsten Langer, University Hospital for Children and Adolescents Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany, Tel: +49-9131-85-33733; Fax: +49-9131-85-36286; E-mail: ki-less@uk-erlangen.de

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glutamate (735 µmol/l), low glutamine (76 µmol/l) and a depletion of aspartic acid. Screening for metabolic disorders was normal. Cranial computer tomography (CCT) showed no pathology. The patient was transferred to the intensive care unit. Amino acids were withdrawn from his nutrition, he received a hypercaloric infusion therapy and, besides a specific therapy with sodium benzoate and arginine, hemofiltration was initiated. The patient's serum ammonia levels fell rapidly as a result of these measures (Figure 1). The drugs hemofiltration was concluded after 16 hours and the drugs were tapered within three days. Laboratory parameters describing liver function were nearly normal (alanine aminotransferase (ALT) 58 U/l, normal range 10-50 U/l). The patient tolerated subsequent chemotherapy without further episodes of hyperammonemia and is currently in complete remission five years after end of treatment without central nervous residues. As a late effect he suffer from osteonecrosis in both hip joints resulting in hip joint endoprothesis.

Kinetics Study

As ammonia represents a metabolite of the biochemical reaction catalyzed by L-Asp, ammonia production is directly linked to the L-Asp enzyme activity and the serum ammonia level is elevated during induction therapy with L-Asp [1].

To further analyze this, we prospectively investigated the kinetic of ammonia levels during L-Asp containing therapy in six consecutively enrolled children with newly diagnosed ALL after administration of L-Asp (male: n = 3, female: n=3i, common ALL: n=4, pre-B ALL: n=2). All patients received treatment according to the ALL-BFM 2000 trial after obtaining written informed consent for treatment and additional research studies from the patient's parents or proxies. Median age at diagnosis was 5 years (range 3-15 years) (Table 1). All patients received 5-week induction polychemotherapy according to the ALL-BFM 2000 protocol. The E. coli L-Asp preparation was delivered by the Medac® Company (Hamburg, Germany, originally purchased from Kyowa Hakko Kogyo, Tokyo, Japan). Blood samples for ammonia concentrations were collected before and 2, 4, 8, and 24 hours after L-Asp administration. The blood samples were drawn from central catheters and immediately placed on ice and analyzed according to the study protocol. The ammonia levels were assayed according to established, standardized enzymatic-photometric test (COBAS Integra800 according to manufacture guidelines) [13].

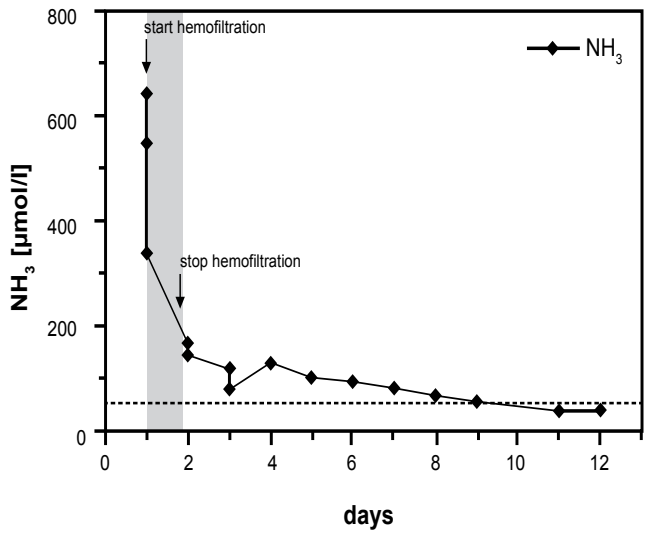

Figure 1: Ammonia levels during specific therapy and hemofiltration. The ammonia levels fell rapidly during hemofiltration therapy (grey box). The specific therapy with natrium benzoate and arginine hydrochloride was maintained until day three. Normal ammonia levels (range 15-55 µmol/l) were observed 11 days after initiation of detoxifying therapy.

Patient number	Sex	Age at diagnosis [years]	Diagnosis	Risk	Peak NH_3 [µmol/l] Normal range 15-55	Mean NH3 [µmol/l]
1	Female	4	c -ALL	MR	200	114
2	Female	13	pre B-ALL	SR	175	102
3	Female	3	c -ALL	SR	241	139
4	Male	15	c -ALL	SR	187	99
5	Male	6	pre B-ALL	HR	277	125
6	Male	3	c -ALL	HR	200	129

Table 1: Median age at diagnosis.

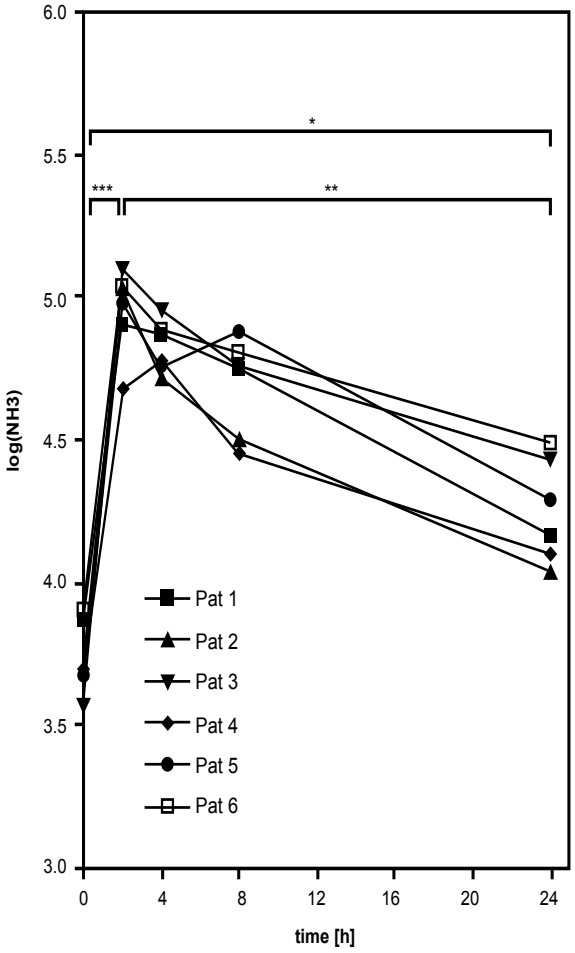

Figure 2: Kinetics of NH_3 levels after administration of L-Asparaginase. Peak ammonia levels were observed 2 hours after administration of L-Asp. The increase was statistically significant (*** p=0.0002). Ammonia levels decreased within 24 hours after L-Asp treatment but remained statistically elevated after 24 hours (** p=0.007; * p=0.01).

The baseline ammonia levels taken before L-Asp administration showed a median plasma level of 43 µmol/l (range 21-47 µmol/l). We observed a significant and steep increase of ammonia concentration

with a peak 2 hours after administration of L-Asp and a decrease 4 hours after administration of L-Asp (Figure 2). Median peak ammonia concentrations 2 hours after L-Asp administration were 144 µmol/l (range 62-277 µmol/l). The median ammonia plasma levels 24 hours after L-Asp administration were 68 µmol/l (range 30-134 µmol/l). There was no significant difference between the plasma ammonia levels of individual patients at different time points of the analysis (data not shown). Moreover, we did not observe any neurological abnormalities or hypersensitivity reactions among the patients.

Discussion

A probable cause for the hyperammonemia during L-Asp administration could be the insufficient ca pacity of th e he patic ur ea cycle for metabolizing the accrued amount of ammonia through L-Asp activity [1,14]. Although our index patient showed a maximum ammonia level of 644 µmol/l and neurological symptoms we could not observe any abnormalities of the urea cycle. Retrospective anamnesis yielded an alimentary protein excess the day before L-Asp administration in this case. Hyperphenylalaninemia, e. g. after concomitant odansetron treatment, has been implicated to be the precipitating agent aiding in manifestation of toxicity from the hyperammonemia in some patients [1]. Also, our index patient received a higher dose of E. coli L-Asp (10,000 IU/m2 vs. 5,000 IU/m2 in our study population). None of our investigated patients showed acute neurological symptoms, similar to the case report by Sudour et al. [1] and the prospective studies by Steiner et al. and Jorck et al. [11,12]. In addition to the previously published data, now data are presented about ammonia levels within the first 24 hours after administration. The time period of the first 24 hours after administration of L-Asp is the most important, regarding evelated ammonia levels. Furthermore, we could not observe any EEG abnormalities after 8 administrations of L-Asp, except one patient who had a verified toxoplasmosis of the CNS. All of our patients showed elevated, neurotoxic ammonia levels (> 60 µmol/l) for more than 24 hrs after administration of L-Asp without developing neurological symptoms. This has been also described previously [11,12].

Conclusion

We propose the analysis of plasma ammonia level in any case of neurological symptoms during induction therapy of lymphoblastic malignancies with L-asparaginase. Furthermore plasma ammonia levels measured within the first 24 hours after the administration are important. The maximum plasma ammonia level is expected 2 hours after administration of L-asparaginase. The role of elevated ammonia levels for neurological effects remains to be defined and requires further investigation in a larger number of patients.

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