ARTERIAL AMMONIA LEVELS IN THE MANAGEMENT OF FULMINANT LIVER FAILURE

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Abstract

Previous studies have suggested that an arterial ammonia level greater than 150 μmol/L is highly sensitive for predicting subsequent development of cerebral edema in patients with fulminant liver failure. We performed a prospective cohort study to confirm this relationship. We enrolled 22 consecutive patients who presented to our transplant hepatology service with grade 3-4 encephalopathy associated with fulminant liver failure. All patients underwent placement of an intraparenchymal ICP monitor, and every 12 hourly arterial ammonia levels. The prevalence of intracranial hypertension (IHTN) in our population was 95% (21/22 patients), with 82 discrete episodes recorded. The sensitivity of arterial ammonia levels to predict the onset of IHTN was 62% (95% CI: 40.8 to 79.3) at a cut point of 150 μmol/L. Arterial ammonia levels preceding the first intracranial hypertension event were less than 150 μmol/L in 8 of 21 patients (39%). Fifty nine of 82 episodes of IHTN (73%) occurred when arterial ammonia levels were less than 150 μmol/L. We conclude that the arterial ammonia level is not useful in making decisions regarding management related to cerebral edema in patients with fulminant liver failure. In fact, since almost all our study patients with grade III or IV encephalopathy secondary to fulminant liver failure went on to develop intracranial hypertension, our study supports the contention that all such patients might benefit from ICP monitoring regardless of arterial ammonia levels.

Background

Cerebral edema is the most common cause of death in fulminant liver failure (FLF) (1,2), occurring in 80% of patients with advanced encephalopathy (3). Cerebral edema causes brain injury by compromising cerebral perfusion pressure and/or by causing cerebral herniation. Intracranial hypertension (IHTN) is the most reliable sign of cerebral edema, and is defined as an intracranial pressure (ICP) greater than 20 mmHg (4-6). Many authors have recommended ICP monitoring in FLF to guide management of cerebral edema (7,8) although this procedure entails significant hemorrhagic risk (9,10).

The pathogenesis of cerebral edema in FLF is likely multifactorial, but substantial evidence supports a causal role for hyperammonemia. Elevated ammonia levels alter neurotransmitter synthesis, and interfere with mitochondrial function causing

oxidative stress and neuronal apoptosis (4,5,6,11-16). Increased delivery of ammonia to astrocytes provides substrate for the accumulation of intracellular glutamine (17-18). The resulting osmotic effect causes astrocyte swelling and cerebral edema (6,7,19). Clinical studies have repeatedly shown that arterial ammonia levels around 150 μmol/L have a statistically significant association with the development of IHTN and cerebral edema in humans (8,20-22). Clemmensen and colleagues (8) measured arterial ammonia levels at the onset of grade III encephalopathy in 44 patients with FLF. Fourteen of those patients subsequently developed cerebral herniation. The patients who developed cerebral herniation had significantly higher mean arterial ammonia levels (230 vs. 118 μmol/L P<0.001), and *all* had ammonia levels > 146 μmol/L. At this cut point, arterial ammonia had a sensitivity of 100%, a specificity of 73% and a PPV of 64% for the subsequent development of cerebral herniation (8).

The results of this study raised the possibility that arterial ammonia levels could be used to select FLF patients likely to benefit from ICP monitoring. If arterial ammonia levels above 146 μmol/L were highly sensitive for predicting the development of IHTN, patients with arterial ammonia levels below this threshold would not likely benefit from ICP monitoring, therefore the significant hemorrhagic risk of monitor placement could be avoided (20,23).

The primary aim of our study was to confirm this premise by reassessing the sensitivity of the arterial ammonia concentration for predicting the onset of intracranial hypertension (IHTN). We chose IHTN as our dependent variable since cerebral herniation is uncommonly seen in patients managed with our neuroprotective treatment protocol (24), and because intracranial hypertension can cause brain injury by compromising cerebral perfusion in the absence of herniation. The secondary aim of our study was to determine whether following serial arterial ammonia levels are valuable in predicting the timing of recurrent IHTN episodes before and after liver transplantation.

Methods

A prospective case series was approved by the Institutional Review Board at Banner Good Samaritan Regional Medical Center, a 650 bed community teaching hospital in Phoenix Arizona. The Transplant Hepatology service identified consecutive patients admitted with FLF, as defined by standard criteria (20) between May 2004 and September 2006. All patients underwent serial neurological examinations by an intensivist, and those who developed grade 3-4 encephalopathy were evaluated for study participation. Eligible patients' families were asked to provide informed consent.

Serial arterial ammonia levels were obtained in study patients. An arterial catheter was placed and 5 cc of arterial blood was drawn into a sodium heparin-containing tube every 12 hours. These samples were transported to the chemistry laboratory on ice within 30 minutes. Quantitative plasma ammonia concentrations were performed using an enzymatic kinetic assay (Roche Diagnostics, Mannheim Germany). This assay has a reportable range of 5.87-587 μmol/L and a coefficient of variability of 2%.

An intraparenchymal ICP monitor (Codman MicroSensor® - Codman/Johnson & Johnson Professional, Inc., Randolph, MA) was placed in the non-dominant frontal lobe under local anesthesia by a neurosurgeon. The ICP was monitored continuously thereafter. Hemostatic therapy and ICP management used in the study have been previously described (24). ICP monitors were removed post-transplantation when the patient could tolerate lowering of their head to zero degrees without precipitating IHTN. In patients who did not undergo transplantation, ICP monitors were removed upon clinical recovery or death.
Our main independent variable was the arterial plasma ammonia level. Our main dependent variable was intracranial hypertension, defined as an ICP > 20 mmHg for > 20 mins. We performed 3 separate sets of analyses to examine the relationship between arterial ammonia levels and IHTN: 1) we analyzed the arterial ammonia level that most closely preceded the onset of the first episode of IHTN in each patient; 2) we analyzed all arterial ammonia levels in relation to all episodes of IHTN; and 3) we analyzed all arterial ammonia levels in relation to all episodes of IHTN occurring post liver transplantation. The second and third analyses involved data values that were not independent of each other, therefore standard statistical techniques were not appropriate and time series analysis was performed. Statistical analyses were performed using SPSS 13.0 (SPSS Inc. Chicago IL.) Operating characteristics of arterial ammonia levels were calculated at a cut point of 150 μmol/L.

Results

Twenty two patients were entered – their clinical characteristics at study entry are listed in Table 1.

Table 1: Patient Characteristics:	
Mean age:	32.7 years (S.D. 10.3 yrs, range 15-56)
Gender:	17/22 (77%) female
Etiology:	acetaminophen toxicity (12 patients) hepatitis A (3) hepatitis B (1) anticonvulsant hypersensitivity syndrome (1) sulfa hypersensitivity syndrome (1) Wilson's disease (1) Cryptogenic (3)
Encephalopathy grade:	8 patients (36%) Grade III 14 patients (64%) Grade IV

Our 22 patients cumulatively underwent 3252 hours of ICP monitoring. Mean monitor duration was 147.8 +/- 143.3 hours. Monitors were left after liver transplantation in nine patients for 85.6 +/- 60.6 hours.
The prevalence of IHTN in our population was 95% (21/22 patients). Eighty-two discrete episodes of intracranial hypertension occurred. 62 occurred prior to, 4 during, and 16 after liver transplantation. The peak ICP during IHTN events was 33 +/- 13 mmHg (mean +/- S.D.) and the median duration was 60 minutes.
Relationship between arterial ammonia levels and the first episode of IHTN

The mean arterial ammonia level preceding the first intracranial hypertension event in each patient was 185 +/- 67 μmol/L (range: 96 – 337 μmol/L). The sensitivity of arterial ammonia levels to predict the onset of IHTN was 62% (95% CI: 40.8 to 79.3) at a cut point of 150 μmol/L. Arterial ammonia levels preceding the first intracranial hypertension event were less than 150 μmol/L in 8 of 21 patients (39%). We could not accurately calculate specificity or area under the receiver operator curve (AUROC) since only one patient did not develop IHTN.

Relationship between arterial ammonia levels and all episodes of IHTN

The mean arterial ammonia levels just prior to each of the individual 82 episodes of IHTN were 122 +/- 80 μmol/L (range: 15 – 270 μmol/L). Fifty nine of 82 episodes of IHTN (73%) occurred when arterial ammonia levels were less than 150 μmol/L.

Relationship between arterial ammonia levels and all episodes of IHTN occurring post liver transplantation

Nine patients underwent liver transplantation. Seventy-nine ammonia levels were obtained post-liver transplantation in these patients. Four transplant recipients experienced 16 post-operative IHTN events. The mean arterial ammonia just prior to each of these events was 70 +/- 48 μmol/L (range: 15 – 161 μmol/L). The sensitivity of the arterial ammonia level preceding each IHTN event was 13% and the specificity was 100% at a cut point of 150 μmol/L. Arterial ammonia levels were statistically lower in post-transplant IHTN episodes than in pre-transplant episodes (P<0.001).

Discussion

Our study showed that almost all patients with grade III or IV encephalopathy secondary to fulminant liver failure will develop intracranial hypertension – this supports the possible benefit of intracranial pressure monitoring in all such patients regardless of arterial ammonia levels. Although the high prevalence of IHTN in our study population prevented us from calculating the specificity of arterial ammonia levels, sensitivity is the key characteristic of this test in terms of our research question. Our study shows that arterial ammonia levels > 150 μmol/L are not sensitive for subsequent development of IHTN, and therefore should *not* be used to identify a subset of patients unlikely to benefit from ICP monitoring.

Our study did not confirm the clinical utility of arterial ammonia levels in predicting neurological injury in patients with FLF, as suggested by Clemmensen et al (8). This could be because the clinical event of interest in the two studies differed – Clemmensen focused on cerebral herniation, and we measured IHTN directly. Cerebral herniation occurred in 14 of Clemmensens' 44 patients, but it was not observed in our patients. Our study utilized a management protocol specifically designed to prevent cerebral herniation (24). It is unknown how many of our patients with IHTN would have gone on to herniate if IHTN had not been detected and aggressively treated.

Several other studies have examined the predictive value of arterial ammonia levels for cerebral edema and IHTN in patients with acute liver failure. Bernal and colleagues studied 165 patients with acute liver failure and grade 3-4

encephalopathy and found that arterial ammonia on admission was higher in those who later developed IHTN (121 vs 109 μmol/L $p<0.05$ (20). However, the sensitivity of an ammonia cut-point of 150 μmol/L was only 40%, and the positive predictive value (probability that a patient with ammonia > 150 μmol/L would develop IHTN) was only 16%.

Bhatia and colleagues studied 80 patients with ALF, 58 of whom had grade 3-4 encephalopathy (21). They calculated an optimal cut-point for arterial ammonia for predicting mortality was 124 μmol/L by ROC analysis. Patients with ammonia levels above this cutpoint had a higher frequency of cerebral edema (47% vs. 22% *P*=0.02). Sensitivity and positive predictive values can be calculated from data presented in their paper, and are 71% and 48% respectively.

Our results confirm those of Bernal and Bhatia in that all 3 studies showed that the operating characteristics of the arterial ammonia test are insufficient for triaging ALF patients in regards to invasive ICP monitoring. But our study has several important differences. IHTN or cerebral edema was detected in only 29% of Bernal's patients and 35% of Bhatia's. Both studies relied heavily on physical examination to diagnose these outcomes despite evidence that it lacks the sensitivity to do so (1,3,25-27). Our study utilized the gold standard (ICP monitoring) in all our patients. We found a much higher prevalence of IHTN – 95% in patients with grade 3-4 encephalopathy. This high prevalence explains the higher positive predictive value in our study, and suggests that previous studies may have suffered from significant underdetection of IHTN and cerebral edema.

Our study is also unique in that we performed repeated measures of arterial ammonia. This was important in terms of our hypothesis that patients' risk for IHTN might change over time in response to treatments such as lactulose, continuous renal replacement therapy, and liver transplantation. Unfortunately, we found that repeated measures of arterial ammonia were no more clinically useful than the single levels used in previous studies.

Our study has several important limitations. Our limited sample size produced wide confidence intervals about our estimation of sensitivity. Our study only included patients with advanced encephalopathy - it's possible that arterial ammonia levels might demonstrate improved prognostic significance earlier in the course of FLF. We did not attempt to analyze the effect of cumulative ammonia exposure over time.

Our findings, and those of previous investigators, suggest that other factors besides peak ammonia levels are important in the pathogenesis of FLF-induced cerebral edema. Two other proposed causative factors are pathological alterations in cerebral blood flow (28-32) and systemic inflammatory response (30,33-34). The interplay of all three factors may be critical to the pathogenesis of cerebral edema in FLF and this might explain why simple measurement of serum ammonia is not sufficient to predict IHTN.

Further work is needed to elucidate the pathogenesis of IHTN in FLF and identify variables that predict which patients will develop this life-threatening complication. Until then, we suggest that *all* patients with grade 3 or 4 encephalopathy secondary to FLF are at high risk. Our study shows that arterial

ammonia levels in these patients cannot be relied upon to accurately triage patients in regards to their risk for IHTN. Thus, it is not helpful in determining which patients might benefit from ICP monitoring, nor determining when ICP monitoring can safely be discontinued.

Conclusions

An arterial ammonia level of 150 μmol/L is poorly sensitive for determining which patients with ALF will develop IHTN and should not be used to determine which patients are likely to benefit from ICP monitoring. The prevalence of IHTN in FLF patients with grade 3-4 encephalopathy is so high that no other predictive test is likely to be of added value. Although arterial ammonia levels are correlated with episodes of IHTN, most individual IHTN episodes occur when arterial ammonia levels are < 150 μmol/L. After successful transplantation IHTN events can continue to occur even as ammonia levels enter the normal range.

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