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Clinical study

Risk of transient hyperammonemic encephalopathy in cancer patients who received continuous infusion of 5-fluorouracil with the complication of dehydration and infection

Chuang-Chi Liaw, Hung-Ming Wang, Cheng-Hsu Wang, Tsai-Shen Yang, Jen-Shi Chen, Hsien-Khun Chang, Yung-Chang Lin, Shiumn-Jen Liaw and Chau-Ting Yeh[1]
Division of Hemato-Oncology and [1]Liver Research Unit, Department of Internal Medicine, Chang-Gung Memorial Hospital and Chang-Gung University, 10591 Taipei, Taiwan.

From 1986 to 1998, 29 cancer patients who had 32 episodes of transient hyperammonemic encephalopathy related to continuous infusion of 5-fluorouracil (5-FU) were identified. None of the patients had decompensated liver disease. Onset of hyperammonemic encephalopathy varied from 0.5 to 5 days (mean: 2.6 ± 1.3 days) after the initiation of chemotherapy. Plasma ammonium level ranged from 248 to 2387 μg% (mean: 626 ± 431 μg%). Among the 32 episodes, 26 (81%) had various degrees of azotemia, 18 (56%) occurred during bacterial infections and 14 (44%) without infection occurred during periods of dehydration. Higher plasma ammonium levels and more rapid onset of hyperammonemia were seen in 18 patients with bacterial infections (p=0.003 and 0.0006, respectively) and in nine patients receiving high daily doses (2600 or 1800 mg/m^2) of 5-FU (p=0.0001 and < 0.0001, respectively). In 25 out of 32 episodes (78%), plasma ammonium levels and mental status returned to normal within 2 days after adequate management. In conclusion, hyperammonemic encephalopathy can occur in patients receiving continuous infusion of 5-FU. Azotemia, body fluid insufficiency and bacterial infections were frequently found in these patients. It is therefore important to recognize this condition in patients receiving continuous infusion of 5-FU. [© 1999 Lippincott Williams & Wilkins.]

Key words: Azotemia, dehydration, encephalopathy, 5-fluorouracil, hyperammonemia, infection.

Introduction

Hyperammonemic encephalopathy usually occurs in patients with serious liver dysfunctions.[1–3] However, the syndrome can develop in several clinical situations without obvious liver diseases. These include inherited deficiencies of urea cycle enzymes,[1] Reyes syndrome,[1,4] administration of valproic acid,[5] ureterosigmoidostomy,[6,7] infection in a neurogenic bladder[8] and administration of chemotherapeutic agents.[9,14] The latter is frequently encountered in patients with hematologic malignancies following intensive cytoreductive therapy.[9,12]

Hyperammonemia caused by 5-fluorouracil (5-FU) was reported in recent years.[13–15] The incidence was 5.7% (16 of 280) in cancer patients treated with 24 h infusion of high-dose 5-FU (2.6 g/m^2/per week) and leucovorin.[14,15] In 1993, we reported seven cases of transient hyperammonemic encephalopathy resulting from 5-FU continuous infusion.[13] In this report, we present our experience in 29 cancer patients who developed 5-FU-related hyperammonemic encephalopathy. Additionally, some precipitating factors such as bacterial infection and dehydration are discussed.

Materials and methods

Patients

From January 1986 to September 1998, 29 cancer patients who had 32 episodes of transient hyperammonemic encephalopathy related to continuous infusion of 5-FU were found at Chang Gung Memorial Hospital. None of these patients had decompensated liver disease. The episodes were characterized by abrupt onset of altered mental status with markedly elevated plasma ammonium levels. Patients clinical characteristics and chemotherapeutic regimens are

Correspondence to C-C Liaw, Division of Hemato-Oncology, Department of Internal Medicine, Chang-Gung Memorial Hospital, 199 Tung Hwa North Road, 10591 Taipei, Taiwan.
Tel: (+886) 3328 1200; Fax: (+886) 3328 6697

presented in Table 1. The chemotherapeutic regimens (Table 2) for all the patients included continuous infusion of 5-FU. The absence of obvious liver diseases was determined by liver function tests, liver ultrasonography or computed tomography. Liver function tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP) and total bilirubin. Renal function tests included serum blood urine nitrogen (BUN) and serum creatinine (Cr). Both liver and renal function tests and total carbon dioxide (TCO_2) were determined using Hitachi 736-40 Autolyzer (Tokyo, Japan). Plasma ammonium levels were measured using the Kodak Ektachen DT 60 Analyzer (Rochester, NY). The normal range of plasma ammonium levels at Chang Gung Memorial Hospital is less than 170 μg%.

Table 1. Patient characteristics

	No. of patients/ no. of episodes
Total no.	29/32
Sex	
male	20/22
female	9/10
Age (years)	
≤ 60	17/19
>60	12/13
median (range)	58 (33–78)
Primary site	
stomach	6/7
oral cavity	6/6
colorectal	4/4
esophagus	4/4
nasopharynx	2/4
lung	2/2
hypopharynx	1/1
pancreas	1/1
cervix	1/1
bladder	1/1
unknown	1/1
Previous 5-FU chemotherapy	
yes	15/17
no	14/15
Presence of liver metastasis	
presence	2/2
absence	27/30

The recorded time of onset of hyperammonemic encephalopathy was defined as from the start of chemotherapy to the time of consciousness altertion. Therapeutic regimens for treating hyperammonemic encephalopathy included neomycin enema, neomycin via a nasogastric tube, lactulose and i.v. fluid. Antibiotics were added if patients had evidence of infection.

Statistical analysis

Plasma ammonium levels were checked daily during periods of hyperammonemia. The duration of hyperammonemia was defined as the time of first recognition of consciousness alteration to the time of the plasma ammonium level returning to normal. Student's *t*-test was used to detect the significance of differences between the subgroups. Survival time was defined as the time from hyperammonemia diagnosis until the patient's death.

Table 2. Chemotherapeutic regimens and 5-FU dosages

Dose of 5-FU (mg/m^2/day)	Chemotherapeutic regimens and dose (mg/m^2/day)	No. of patients/no. of episodes
2600		8/8
	F 2600 d1/LV 100 d1	8/8
1800		1/1
	F 1800 d1–3	1/1
1000		18/21
	F 1000 d1–5/P 100 d1	2/2
	F 1000 d1–4/P 100 d1	3/5
	F 1000 d1–4/P 75 d1	1/1
	F 1000 d1–3/M 6/P 50 d1	6/7
	F 1000 d1–3/B 10 d2, 3/P 50 d1	3/3
	F 1000 d1–3/B 10 d2, 3/Ca 300 d1	1/1
	F 1000 d1–3/I 1200 d2–4/P 50 d1	1/1
	F 1000 d1–3/Ca 100 dl	1/1
500		2/2
	F 500 d1–5/LV 35 d1–5	1/1
	F 500 d1–3/LV 35 d1–3/P 50 d1	1/1

F: 5-fluorouracil; LV: leucovorin: P; cisplatin; M: mitomycin; B: bleomycin; Ca: carboplatin; I: ifosfamide; d: day.

Definitions of potential precipitating factors

The potential precipitating factors studied included infection, dehydration, constipation and azotemia. Fever, chills, leucocytosis and positive bacterial cultures were evidence of infection. Dehydration was recognized as the presence of obvious emesis during the course of chemotherapy and/or poor fluid intake due to intestinal obstruction or other causes. Constipation was defined as no stool passage for more than 3 days due to severe obstipation or intestinal obstruction. Azotemia with a serum Cr level greater than 2.0 mg% before giving chemotherapy was also defined as an aggravating factor.

Control subjects

The plasma ammonium levels of the control subjects were studied in 1996 and 1997. There were five control groups. Group A included cancer patients without liver metastasis (36 patients) before 5-FU continuous infusions and Group B consisted of Group A patients at 48 h after beginning 5-FU continuous infusions. Group C included cancer patients with consciousness disturbance due to infection (34 patients). Group D included cancer patients with consciousness disturbance due to liver metastasis with hepatic failure and/or combined with infection (36 patients). Group E consisted of patients with consciousness disturbance due to decompensated liver disease with hepatic failure (32 patients). Mean plasma ammonium levels in Groups A, B, C, D and E were 79 ± 27, 87 ± 33, 103 ± 52, 247 ± 97 and 283 ± 113 μg%, respectively.

Results

Patient characteristics

The clinical characteristics of the 29 patients with 32 episodes of hyperammonemic encephalopathy are summarized in Table 1. There were 20 male and nine female whose ages ranged from 33 to 78 years (median: 58 years). Cancers most frequently originated from the gastrointestinal tract, and head and neck. All patients had locally advanced and/or metastatic diseases. All chemotherapeutic regimens (Table 2) included continuous infusion of 5-FU. Other drugs given concurrently included cisplatin (20 episodes), leucovorin (10), mitomycin (7), bleomycin (4), carboplatin (2) and ifosfamide (1). Liver metastases were detected in two patients before giving chemotherapy. Seventeen patients had received the same 5-FU-containing chemotherapeutic regimens before this course without development of hyperammonemic encephalopathy.

The biochemical data of the 32 episodes were recorded before giving chemotherapy. Mean AST was 22 ± 7 U/l (6-36 U/l, n=32), ALT was 14 ± 10 U/l (2-25 U/l, n=21), ALP was 95 ± 61 U/l (42-307 U/l, n=32), bilirubin was 0.6 ± 0.3 mg% (0.2-1.1 mg%, n=22), BUN was 20 ± 12 mg% (7-58 mg%, n=21) and Cr was 1.6 ± 1.1 mg% (0.5-6.0 mg%, n=32). Before giving chemotherapy, all patients were demonstrated with normal AST and ALT.

Potential precipitating factors

The potential precipitating factors of hyperammonemia are listed in Table 3. There were 11 cases of renal function impairment (serum Cr > 1.4 mg%). Four of these patients, including colorectal cancer (2 patients), cervical cancer (1) and bladder cancer (1), suffered from obstructive uropathy. After percutaneous nephrostomy tube drainage, the serum Cr for these four patients became 6.0, 3.2, 2.4 and 2.4 mg%, respectively.

At the time of hyperammonemia discovery, all 29 patients exhibited mental status changes that including lethargy and confusion. Eighteen cases had infections with fever and leucocytosis, and three of these patients had obvious emesis during chemotherapy. Among these 18 patients, seven became progressively comatose.

The remaining 11 patients who had 14 episodes of hyperammonemia without evidence of infections were dehydrated. In 13 episodes, patients had complications of obvious nausea and vomiting during chemotherapy. Two cases also had severe constipation or intestinal obstruction due to cancerous peritonitis. Two patients (one with nasopharngeal

Table 3. Potential precipitating factors

Precipitating factors	No. of patients/ no. of episodes
Infection only	14/14
Infection+dehydration	3/3
Infection+azotemia	1/1
Dehydration only	7/10
Dehydration+azotemia	1/1
Dehydration+constipation	1/1
Dehydration+azotemia+constipation	2/2

cancer and another with gastric cancer) who had severe emesis during chemotherapy experienced three and two episodes of hyperammonemia, respectively. One patient, who developed hyperammonemia without emesis, was dehydrated because of poor intake. He was also concurrently severely constipated and had hyperglycemia due to diabetes mellitus.

AST was monitored in 11 patients during hyperammonemic episodes and mild AST elevation was found in six patients. All six patients had infection. Severe liver impairment with AST levels reaching 2068 U/l was found in only one patient. Mean AST in the rest of the episodes was 45 ± 26 U/l (15–89 U/l). Most patients (26 of 32, 81%) had varying degrees of azotemias at the time of hyperammonemia. Mean BUN was 40 ± 21 mg% (9–87 mg%, n =26) and serum Cr was 2.3 ± 1.6 mg% (0.7–9.0 mg%, n=31). TCO_2 was checked in 17 episodes; in 12 it was found to be decreased. Mean TCO_2 was 18.3 ± 5.1 meq/l (12.7–27.3 meq/l).

Plasma ammonium levels and onset of hyperammonemic encephalopathy

The plasma ammonium level ranged from 248 to 2387 μg% at the first day of consciousness change. The mean level (626 ± 431 μg%) in patients with 5-FU-related hyperammonemia was significantly higher than those in patients with consciousness disturbance due to infection, liver metastasis and liver disease ($p < 0.0001$). The time from administering the chemotherapy to development of hyperammonemic encephalopathy varied from 0.5 to 5 days (mean: 2.6 ± 1.3 days).

Correlation of clinical factors with plasma ammonium levels is listed in Table 4. In the 18 patients who had infections, the plasma ammonium levels ranged from 272 to 2387 μg% (mean: 808 ± 495 μg%). In the remaining 11 patients who had 14 episodes of hyperammonemia without evidence of infection, the plasma ammonium levels ranged from 248 to 707 μg% (mean: 392 ± 133 μg%, p=0.003). The onset of hyperammonemic encephalopathy after the initiation of chemotherapy was also more rapid in the patients with infections (mean: 2.0 versus 3.5 days, p=0.0006).

In the nine patients with daily doses of 2600 or 1800 mg/m^2 of 5-FU, the plasma ammonium levels ranged from 707 to 2387 μg% (mean: 1076 ± 530 μg%). In the remaining 20 patients with 23 episodes of hyperammonemia, who received a daily dose 1000 or 500 mg/m^2 of 5-FU, the plasma ammonium levels ranged from 248 to 1164 μg% (mean: 450 ± 211 μg%, p=0.0001). The onset of hyperammonemic encephalopathy after chemotherapy was also more rapid in the patients given high

Table 4. Correlation of clinical factors with plasma ammonium levels

	No. of episodes	Plasma NH_3 level (μg%) [mean ± SD (range)]	p	CT to Dx (day)[a] [mean ± SD (range)]	p
Sex					
male	22	557 ± 297 (248–1317)	0.07	2.6 ± 1.3 (0.5–5.0)	0.44
female	10	779 ± 629 (285–2387)		2.6 ± 1.4 (1.0–5.0)	
Age (years)					
≤60	19	629 ± 489 (250–2387)	0.32	2.7 ± 1.4 (1.0–5.0)	0.35
>60	13	622 ± 349 (248–1317)		2.0 ± 1.2 (0.5–3.5)	
Primary site					
GI	16	795 ± 536 (248–2387)	0.02	2.2 ± 1.3 (0.5–5.0)	0.06
others	16	457 ± 190 (250–882)		3.0 ± 1.2 (1.0–5.0)	
Previous 5-FU CT					
yes	17	655 ± 330 (250–1317)	0.43	2.5 ± 1.3 (1.0–5.0)	0.44
no	15	600 ± 513 (248–2387)		2.7 ± 1.3 (0.5–5.0)	
Presence of infection					
absence	14	392 ± 133 (248–707)	0.003	3.5 ± 1.2 (1.0–5.0)	0.0006
presence	18	808 ± 495 (255-2387)		2.0 ± 1.0 (1.0–4.0)	
Daily dosage of 5-FU (mg/m^2/day)					
1000, 750	23	450 ± 211 (248–1164)	0.0001	3.2 ± 1.1 (1.5–5.0)	<0.0001
2600, 1800	9	1076 ± 530 (707–2387)		1.1 ± 0.4 (1.0–3.5)	

CT: chemotherapy; Dx: diagnosis; NH_3: ammonium; GI: gastrointestinal.
[a]Time from start of chemotherapy to diagnosis of hyperammonic encephalopathy.

daily doses (2600 or 1800 mg/m^2) of 5-FU (mean: 1.1 versus 3.2 days, $p<0.0001$).

Higher plasma ammonium levels were also seen in 15 patients (16 hyperammonemia episodes) with gastrointestinal cancer patients (mean: 795 ± 536 μg%, p=0.02), of whom seven patients received high daily doses of 5-FU.

Outcomes

Three patients with infections expired within 2 days following hyperammonemia episodes. Plasma ammonium levels of the other 29 episodes returned to normal ranges (mean: 76 ± 30 μg%, 30–136 μg%) after 2 days of therapy. Twenty-three patients with 25 episodes of hyperammonemia regained consciousness when their plasma ammonium levels returned to normal. Four patients with infections remained in comatose.

Follow-up

The follow-up period after recovery from hyperammonemia ranged from 1 day to 26 months. Twenty-four patients died, three patients were lost to follow-up and only two patients were alive with the disease. Fourteen patients died within 2 months. Seven patients received another two to six courses of the same chemotherapeutic regimens after recovery from the hyperammonemia episodes without occurrence of hyperammonemic encephalopathy.

Discussion

Chemotherapy-related hyperammonemia has been reported infrequently.[9-14] It usually occurs in patients with hematologic malignancies after administration of intensive cytoreductive therapy that resulted in profound neutropenia.[9-12] The phenomenon has been seen in acute leukemia treatment with continuous infusion of high dose Ara-C or L-asparaginase. It has also been observed in hematologic malignancies following bone marrow transplantation.[9-12] The true causes of hyperammonemia from chemotherapy are unclear.

Infection or pharmacologic etiologies have been considered as causes of hyperammonemia.[9] While severe infectious diseases can cause some degree of hepatic dysfunction,[16] fulminant hepatic failure with jaundice was rarely found to be associated with it.[17]

Identification of the phamacologic etiology involved in hyperammonemia has been difficult.[9] Deamination of Ara-C in the liver, blood and peripheral tissue,[18] and hydrolysis of the amido group of L-asparaginase increase the release of ammoniunm.[11]

Hyperammonemia caused by continuous infusion of 5-FU has been mentioned recently.[13-15] Regimens including continuous infusion of 5-FU plus cisplatin were most commonly used in our patients. However, the mechanism is unclear. It was proposed that the intermediate product of 5-FU directly inhibits the ATP-producing Krebs cycle.[14] This results in lactic acidosis and the impairment of the ATP-dependent urea cycle. At least two distinct pathogenetic entities of 5-FU-related encephalopathy including dihydropyrimidine dehydrogenase (DPD) deficiency type and 5-FU calobolite type were suspected by Yeh *et al.*[15] 5-FU is not considered a hepatoxic drug.[19]

Pharmacologically, 5-FU is inactivated by dihydrouracil dehydrogenase (mainly in the liver) and degraded to 5-flurodihydrouracil (F-DHU), which is further rapidly degraded to 5-fluoro-β-alanine (F-BAL), carbon dioxide and ammonium.[20,21] However, administering 5-FU by itself without other precipitating factors is not an independent risk factor for developing hyperammonemia. Seven of our patients received the same chemotherapeutic regimens after recovery from the hyperammonemia episodes without occurrence of hyperammonemic encephalopathy.

Because the ammonium source from 5-FU metabolites alone does not usually lead to hyperammonemia, other aggravating factors ought to be recognized. Most of our patients were experiencing azotemias and were suffering from infections or body fluid loss. The clinical courses of hyperammonemic complications seem to mimic ureterosigmioid urinary diversion or infection in a neurogenic bladder. The major precipitating factors were thus proposed to be infections and dehydration (mainly from chemotherapy-induced emesis). Among the 32 episodes, 18 (56%) had bacterial infection and 14 without infection (44%) had evidence of body fluid insufficiency. Two patients who suffered from severe emesis during each cycle of chemotherapy experienced more than one episode of hyperammonemia.

Urea is the principal end product from nitrogen metabolism. Urea resorption is determined by water resorption.[22,23] Ammonium is the principal metabolite of 5-FU,[20,21] it then is converted to urea in the liver.[1-3,24,25] No obvious liver diseases in our 29 patients were identified that might have influenced urea metabolism. However, when patients became hypovolemic, urea originating from 5-FU was resorbed from renal tubules, resulting in elevated blood urea nitrogen.

If patients are suffering from severe infections (or sepsis), more ureagenesis occurs from both 5-FU

metabolism and from the acceleration of muscle proteolysis.[26,27] Moreover, sepsis could lead to inadequate blood flow to tissues and result in multiple organ failure.[27] In these cases, urea cannot be fully excreted by the kidneys.

Rising blood urea nitrogen leads to increased diffusion of urea into the intestinal lumen, where it is then converted to ammonium by bacterial urease.[24] Ammonium is again resorbed into circulation and hyperammonemic encephalopathy develops.[1-3,24,25] This view is further supported by the finding that higher plasma ammonium levels and more rapid development of hyperammonemic encephalopathy were seen in the patients suffering from infections, compared to those without infections.

Besides infection and hypovolemia, constipation and azotemia also contribute to the development of hyperammonemic encephalopathy.[1-3,24,25,28,29]

Peak plasma ammonium level in the 29 patients was significantly higher than in the control subjects who had developed consciousness disturbance due to infection, liver metastasis or decompensated liver disease. Higher plasma ammonium levels and more rapid development of hyperammonemic encephalopathy were also seen in the patients receiving high daily doses of 5-FU. Excess production of ammonium from 5-FU metabolites, along with the precipitating factors described above, may be the explanation for this penomena.[13] Higher plasma ammonium levels were also seen in patients with gastrointestinal cancers. This was probably due to more patients with gastrointestinal cancers receiving high daily doses of 5-FU.

Cancers from the gastrointestinal tract and head and neck were the most commonly seen primary malignancy in our cases. Poor fluid intake and the ease of developing infection due to advanced locoregional tumor invasion and obstruction may be the high risk factors. Four of our cases had pelvic malignancies, including colorectal cancer and cervical cancer, which are frequently complicated with obstructive uropathy and cancerous peritonitis, causing azotemia, intestinal obstruction or constipation. These conditions are aggravating factors in the development of hyperammonemic syndrome.

The lag time from the start of chemotherapy to the development of hyperammonemic encephalopathy in our patients was rather short, ranging from 0.5 to 5 days. The lag times were variable in the previously reported hematologic malignancy cases.[9]

We managed hyperammonemia in our patients similar to that of hepatic encephalopathy. We stopped the chemotherapy to eliminate exogenous ammonium, then gave a neomycin enema, neomycin and lactulose via a nasogastric tube to reduce intestinal sources of ammonium. Intravenous fluids were given to correct hypovolemia and to help excretion of large amounts of urea. Antibiotics were given to patients with infections.

Plasma ammonium levels and metal status in most patients (23 of 30, 77%) returned to normal within 2 days after adequate management. Seven of the patients who remained unconsciousness suffered from infections at the time of hyperammonemia. Most of our patients had locally advanced or metastatic disease and over half within 2 months of onset of hyperammonemic encephalopathy.

Conclusion

Hyperammonemic encephalopathy can occur in patients receiving continuous infusion of 5-FU. Azotemia, body fluid insufficiency and bacterial infections were frequently found in these patients. The true mechanism for development of hyperammonemia in these patients is unclear. Excess production of ammonium and impairment of urea excretion is the proposed pathogenic mechanism for hyperammonemic encephalopathy. The presence of infection and a high daily dose of 5-FU were associated with higher serum ammonium levels. The majority of patients recovered rapidly when adequate treatment was given. Our data suggest that serum ammonium levels should be monitored in patients receiving continuous infusion of 5-FU who developed altered consciousness. Management for hyperammonemic encephalopathy should be immediately initiated after recognition of this syndrome.

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