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Transient hyperammonemia related to chemotherapy with continuous infusion of high-dose 5-fluorouracil

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Hyperammonemic encephalopathy has been reported in patients receiving chemotherapy (CT). It is characterized by abrupt alteration in mental status with markedly elevated plasma ammonium levels in the absence of obvious liver disease. This paper reports seven patients who developed transient hyperammonemia during chemotherapy. The regimens all included continuous infusion of high-dose 5-fluorouracil (5-FU). The onset of hyperammonemic encephalopathy was 1.5–4 days after the start of CT. Five cases had infection and six had prerenal azotemia at the time of hyperammonemia. After management, plasma ammonium levels all returned to the normal range within 2 days. Except for one persistent coma, status of consciousness cleared completely. The true mechanism of transient hyperammonemia is unclear. The excess production of ammonium due to metabolites of 5-FU added to precipitating factors such as infection, hypovolemia or constipation may be the explanation for transient hyperammonemia in our study.

Key words: Chemotherapy, 5-fluorouracil, transient hyperammonemia.

Introduction

Hepatic encephalopathy ordinarily occurs in patients with serious liver dysfunction.[1–3] However, certain disorders without obvious liver disease might be associated with hyperammonemia.[1] Transient hyperammonemia related to chemotherapy is rarely reported.[4–7] It is characterized by the abrupt alteration of consciousness with markedly elevated plasma ammonium levels in the absence of obvious liver disease. The actual mechanism of the hyperammonemia is not known. In this paper, we report seven cases who developed transient hyperammonemia during chemotherapy (CT), in which the regimens all included continuous infusion of high-dose 5-fluorouracil (5-FU).

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Materials and methods

From January 1986 to December 1992, seven patients with solid tumors, without obvious liver disease, were proven to have developed hyperammonemic encephalopathy during CT. The chemotherapeutic regimens all included continuous infusion of high-dose 5-FU (Table 1). The absence of obvious liver disease was determined by liver functional tests, liver ultrasonography or computed tomography. Liver functional tests [including serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphate (ALP) and total bilirubin], renal functional tests [including serum blood urea nitrogen (BUN) and creatinine (Cr)] and total carbon dioxide (TCO_2) were analyzed using a Hitachi 736-40 Autoanalyzer (Tokyo, Japan). Plasma ammonium levels were measured by a Kodak Ektachen DT 60 Analyzer (Kodak, Rochester, NY).

Modes of therapy for treating hyperammonemic encephalopathy included neomycin enema, neomycin via nasogastric tube, lactulose and intravenous fluid. Antibiotics were added if the patients had any infection. Plasma ammonium levels were checked daily during the period of hyperammonemia.

The time of the diagnosis of hyperammonemic encephalopathy was calculated from the start of CT to the time of consciousness alteration. The period of hyperammonemia was measured from the time of hyperammonemia diagnosis to the time that the plasma ammonium level returned to normal. The survival was measured from the time of hyperammonemia diagnosis to the patient's death.

Results

The characteristics of chemotherapeutic regimens of the seven patients are summarized in Table 1. There were four men and three women, with ages

Table 1. Clinical characteristics and chemotherapeutic regimens of patients with transient hyperammonemia

Patient no.	Age/sex	Primary site	Chemotherapeutic regimen	Previous treatment[a]	Liver metastasis
1	68/F	lung	5-FU 1.0 g/m^2 D1–3 mitomycin C 6 mg/m^{2}D1 cisplatin 50 mg/m^2 D1	RT	(−)
2	62/M	hypopharynx	5-FU 1.0 g/m^2 D1–3 bleomycin 10 mg/m^2 D2,3 cisplatin 50 mg/m^2 D1	RT	(−)
3	46/M	nasopharyngeal carcinoma	5-FU 1.0 gm/m^2 D1–3 bleomycin 10 mg/m^2 D2,3 cisplatin 50 mg/m^2 D1	RT, CT	(−)
4	53/M	esophagus	5-FU 1.0 g/m^2 D1–5 cisplatin 100 mg/m^2 D1	no	(−)
5	44/F	rectum	5-FU 1.8 g/m^2 D1–3	no	(+)
6	49/M	pancreas	5-FU 1.0 g/m^2 D1–3 mitomycin C 6 mg/m^2 D1 cisplatin 50 mg/m^2 D1	CT	(−)
7	65/F	esophagus	5-FU 1.0 g/m^2 D1–3 mitomycin C 6 mg/m^2 D1 cisplatin 50 mg/m^2 D1	CT	(+)

[a] RT: radiotherapy.

ranging from 44 to 68 years (median: 53 years). The types of malignancy in the seven patients were varied. All had locally advanced and/or metastatic diseases. The chemotherapeutic regimens all contained continuous infusion of high-dose 5-FU. Other concurrently given drugs included cisplatin (six cases), mitomycin (four cases) and bleomycin (two cases). Three patients (Cases 3, 6 and 7) had received CT (the same regimen) previously. Liver metastases were detected in two patients before CT. Case 3 had a history of diabetes mellitus.

The biochemical data of the seven patients are summarized in Table 2. Before CT, most cases had normal liver and renal functions. Case 6 had a serum ALP level up to 307 U/l because of biliary obstruction. Case 5 had renal functional impairment because of obstructive uropathy. After percutaneous nephrostomy tube damage, the serum creatinine decreased to 3.2 mg%.

During hyperammonemia periods, mild hepatic dysfunction was noted in Cases 1, 2, 6 and 7. Case 5 had severe liver impairment with SGOT levels reaching 2068 U/l. Furthermore, prerenal azotemia and a decrease of TCO_2 were noted in six of the seven patients.

The plasma ammonium levels, probable precipitating factors, treatment outcomes and survival of the seven patients are summarized in Table 3. At

Table 2. Biochemical data of patients with transient hyperammonemia[a]

Patient no.	SGOT (U/l)		SGPT (U/l)		ALP (U/l)		Bil(T) (mg%)		BUN (mg%)		Cr (mg%)		TCO (meq^2/l)
	A	B	A	B	A	B	A	B	A	B	A	B	
1	26	41	—	—	117	103	—	—	18	24	0.7	0.7	25.1
2	17	41	10	—	84	171	1.1	1.2	20	42	1.1	1.3	14.1
3	9	15	—	—	70	72	—	0.7	—	37	1.2	1.4	14.4
4	26	—	25	—	100	—	0.4	—	21	68	1.1	3.4	13.9
5	6	2068	7	—	44	60	0.6	1.4	31	52	3.2	4.6	17.9
6	19	15	11	—	307	137	0.2	0.5	—	46	1.2	2.8	13.0
7	15	89	8	—	48	—	0.7	—	15	51	0.9	3.0	15.0
Normal range	0–34		0–36		28–94		0–1.3		6–21		0.4–1.4		23–31

[a] A = biochemical data checked before chemotherapy; B = biochemical data checked during hyperammonemic status.

Table 3. Plasma ammonium levels, probable precipitating factors, treatment outcomes and survival of patients with transient hyperammonemia[a]

Patient no.	Plasma ammonium level (μg%)			CT to Sx (day)	Probable precipitating factors	Outcome	Survival
	Dx	24 h	48 h				
1	674	65	—	1.5	I	CR	2 weeks
2	480	71	51	3.5	I	CR	3 weeks
3	346	72	—	4.0	C,D	CR	4 weeks
4	333	97	—	4.0	D	CR	14 weeks
5	2387	170	59	2.0	I	PC	2 days
6	648	66	33	1.5	I,D	CR	19 weeks
7	1164	297	68	2.0	I	CR	22 weeks

[a] Sx: symptoms of hyperammonemia; Dx: diagnosis of hyperammonemia syndromes; I: infection; D: dehydration; C: constipation; A: azotemia; CR: consciousness recovery; PC: persistent coma.

the time of diagnosis of hyperammonemia, all seven patients exhibited mental status changes, including lethargy and confusion. Cases 1, 5 and 7 became progressively comatous. The plasma ammonium levels ranged from 333 to 2387 mg% at the first day of hyperammonemia. The intervals between the development of hyperammonemic encephalopathy and the start of CT varied from 1.5 to 4 days. Five patients with infection had fever and leucocytosis at the time of diagnosis of hyperammonemia. Case 3 was dehydrated because of diabetes mellitus with hyperglycemia (serum glucose 355 mg%). He concurrently had severe constipation. Cases 4 and 6 became dehydrated because of severe vomiting during CT.

Management of hyperammonemic encephalopathy in the seven patients included intravenous fluids, neomycin enema, neomycin and lactulose via nasogastric tube. Antibiotics were given to five patients for infection. Plasma ammonium levels all normalized after 2 days of therapy. All except one (Case 5) recovered consciousness when the plasma ammonium returned to normal.

Case 5 suffered from urinary tract infection with septic shock, remained comatose and eventually died. Her serum bilirubin was 1.4 mg%, SGOT 2068 U/l and ALP 60 U/l. A liver necropsy revealed no malignant cells, many acidophilic cells and bodies with cholestasis.

All patients were followed-up after recovery from hyperammonemia. The follow-up period ranged from 2 days to 22 weeks. All seven patients died within 6 months. Plasma ammonium levels were checked again in three patients (Cases 1, 4 and 6) because of consciousness changes. Case 1 became lethargic because of a lung infection 12 days after hyperammonemia. The plasma ammonium level was 59 μg% and he died soon after. Case 4 developed diffuse liver metastases and lung infection 3 months after hyperammonemia. Consciousness was altered with a plasma ammonium level at 185 μg% before death. Case 6 uneventfully received two courses of CT (the same regimens) after hyperammonemia. However, he developed a lung infection and hyperglycemia (serum glucose 697 mg%) 2 weeks after last course of CT. A change in consciousness was noted when the plasma ammonium level was 29 μg%.

Discussion

Hyperammonemic encephalopathy usually occurs in patients with serious liver dysfunction.[1–3] However, the syndrome can develop under certain conditions without obvious liver disease. These include inherited urea cycle enzyme deficiencies,[1] Reye's syndrome,[1,8] administration of valproic acid,[9] ureterosigmoidostomy,[10,11] neurogenic bladder[12] and CT.[4–7]

Hyperammonemia related to CT is reported infrequently. It usually occurs in patients with hematologic malignancies during the period of neutropenia following intensive cytoreductive therapy, such as acute leukemia treated with continuous infusion of high-dose cytosine arabinoside (Ara-C) or hematologic malignancies undergoing bone marrow transplantation.[4,5]

In this study, all seven patients developed hyperammonemia without obvious pre-existing liver disease. Unlike the previous reports, our seven cases were not of hematologic malignancies and did not have neutropenia when the hyperammonemic encephalopathy developed. Also, the CT regimens were different from those for hematologic malignancies. All seven cases had high-dose 5-FU given

as a continuous infusion, along with other concurrently given drugs including cisplatin, bleomycin and mitomycin.

The cause of this syndrome is unclear. Infectious or pharmacologic etiologies have been considered.[4] Some degree of hepatic dysfunction occurs in many infectious diseases.[13] Overwhelming infection resulting in septic shock can cause multiple organ failure.[14] Infrequently, fulminant hepatic failure with jaundice is found to be associated with severe bacterial infection.[15] The most prominent pathologic feature of septic liver is intrahepatic cholestasis.[13,14]

In our series, five patients suffered from infection while hyperammonemia occurred. Four (Cases 1, 2, 6 and 7) had mild hepatic dysfunction. Case 5 had markedly elevated SGOT with low ALP and mild elevation of total bilirubin probably due to septic shock. Fulminant hepatic failure with hyperbilirubinemia was unlikely in our patients.

Hyperammonemia due to infection had been reported in patients following ureterosigmoidostomy[10,11] or with neurogenic bladders.[12] Urea-splitting organisms were responsible for the ammonia production.[10–12] In our series, no patients received the above procedure or had neurogenic bladder.

Whether infection contributes to or causes hyperammonemia in patients receiving CT is not known. Infection is also a precipitating factor in hepatic encephalopathy.[1,2] It can increase tissue catabolism and cause dehydration or prerenal azotemia leading to an increased nitrogen load and increased ammonia production.[2] Five of our cases had infection during the period of CT while hyperammonemic syndrome occurred. Four of them had prerenal azotemia and decreased carbon dioxide.

The pharmacologic basis of this syndrome remains obscure. None of our cases with hyperammonemia received drugs such as valopric acid, aspirin or L-asparaginase. Aspirin has been associated with Reye's syndrome.[1] Asparaginase had been reported to cause hyperammonemia in acute lymphoblastic leukemia by hydrolyzing the amido group of asparagine and by its glutaminase activity.[6] The etiology of hyperammonemia syndrome in patients with acute leukemia receiving continuous infusion of high-dose Ara-C or hematologic malignancies undergoing bone marrow transplantation is not known.[4,5] The use of high-dose Ara-C for acute leukemia or high-dose alkylating agents such as cyclophosphamide or busulfan before marrow transplantation may produce hepatic veno-occlusive disease (VOD).[16] Bearman *et al.* reported that grade III or IV liver toxicity occurred in 8.7% of marrow transplantation cases.[17] The development of hepatic VOD before transplantation was the common contributing factor.[17] However, Mitchell *et al.*[4] suggested otherwise because of no clinical or pathologic evidence.

From a pharmacological viewpoint, Ara-C undergoes deamination in the liver, plasma and peripheral tissues, thereby increasing ammonium production.[18,19] In our study, all seven patients received continuous infusion of high-dose 5-FU. 5-FU rarely causes hepatotoxicity.[16] Pharmacologically, 5-FU can be inactivated by dihydrouracil dehydrogenase (mainly in the liver) and degraded to 5-flurodihydrouracil (F-DHU). F-DHU is rapidly degraded further to 5-fluoro-β-alanine (F-BAL), carbon dioxide and ammonium.[18,20,21] Thus, ammonia production is increased when 5-FU is given.

Hyperammonemic encephalopathy does not develop in patients receiving CT without an aggravating factor. Cases 3, 6 and 7 had received another course of CT wherein regimens were identical to those causing hyperammonemia. None of the three patients had an altered mental status. We know that hepatic encephalopathy caused by liver disease can be precipitated by infection, hypovolemia, azotemia and constipation. Thus, a pharmacologic etiology adding to the precipitating factors may be considered in the hyperammonemic syndrome in patients receiving CT. The precipitating factor in hematologic malignancies is infection, because neutropeia in these patients might cause infection.

The probably aggravating factors in our cases included infection (five cases), hypovolemia (three) and constipation (one case). Furthermore azotemia was noted in six patients. Case 5, with rectal adenocarcinoma, received very high-dose 5-FU and suffered from septic shock with high SGOT levels and aggravating renal impairment. Her plasma ammonium level was higher than the other cases, reaching up to 2387 μg%.

After hyperammonemia, we checked the plasma ammonium levels again in Cases 1, 4 and 6 because of further episodes of consciousness change. Cases 1 and 6 had another episode of consciousness change because of infection or hyperglycemia, but their plasma ammonium levels were normal. Case 4 had another episode of consciousness change because of infection and diffuse liver metastases, but the plasma ammonium level was only mildly elevated. Thus, plasma ammonium levels were not

markedly elevated without the administration of high-dose 5-FU, even if patients had diffuse liver metastases. We therefore think that high-dose 5-FU is likely to be the main contributing factor causing hyperammonemia.

The interval between the development of hyperammonemic encephalopathy and the start of CT is variable in hematologic malignancies.[4] The intervals in our cases were brief, ranging from 1.5 to 4 days. Most patients with hematologic malignancies died during the episode of hyperammonemic encephalopathy in spite of drug therapy and hemodialysis. Management in our cases included lactulose, neomycin, enemas, hydration and antibiotics if indicated. Plasma ammonium levels all normalized within 2 days of therapy. Six of seven recovered consciousness. One remained in a coma in spite of therapy and died 2 days later.

Conclusion

The paper reports seven patients who developed transient hyperammonemia during CT. The regimens all included continuous infusion of high-dose 5-FU. The onset of hyperammonemic encephalopathy was shortly after the start of CT. Most cases had infection and prerenal azotemia. After management, the plasma ammonium levels all returned to the normal range within 2 days. Most cases had their consciousness cleared completely. The true mechanism of transient hyperammonemia is unclear. The excess production of ammonium due to 5-FU adding to precipitating factors such as infection, hypovolemia or constipation may be the explanation for this phenomena. We suggest that transient hyperammonemia be ruled out in patients receiving high-dose 5-FU continuous infusion if they have a change in consciousness.

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