Acta Medica Okayama

Volume 39, *Issue* 3 1985 *Article* 3

JUNE 1985

Evaluation of Talbot's Safety Zone of Infusion Volume and Osmolality in Infusion Therapy for Decompensated Liver Cirrhosis

Shiro Yuasa* Tatsuya Itoshima†
Ryosaku Ono‡ Hideo Nagashima**

*Okayama University,
†Okayama University,
‡Okayama University,
**Okayama University,

Evaluation of Talbot's Safety Zone of Infusion Volume and Osmolality in Infusion Therapy for Decompensated Liver Cirrhosis*

Shiro Yuasa, Tatsuya Itoshima, Ryosaku Ono, and Hideo Nagashima

Abstract

Problems with infusion therapy for correcting fluid and sodium imbalance in decompensated liver cirrhosis (DLC) were investigated by establishing the safety zone of Talbot et al. for parenteral fluid therapy in 4 DLC patients infused with over 900 ml of fluid each day for at least 9 days. The safety zone was different in each case. The safe infusion volume decreased and the safe electrolyte concentration shifted to a lower osmolality when there was ascites with renal failure than ascites without renal failure. Infusion therapy was performed without deterioration of the water and sodium balance in those patients whose infusion volume and fluid osmolality were in the safety zone. In contrast, ascites retention increased and peripheral edema appeared in patients whose infusion volume and osmolality were out of the safety zone. Therefore, the safety zone should be determined repeatedly during infusion therapy.

KEYWORDS: decompensated liver cirrhosis, infusion therapy, ascites, hepatorenal syndrome

*PMID: 4024992 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **39**, (3), 179-190 (1985)

EVALUATION OF TALBOT'S SAFETY ZONE OF INFUSION VOLUME AND OSMOLALITY IN INFUSION THERAPY FOR DECOMPENSATED LIVER CIRRHOSIS

Shiro YUASA*, Tatsuya ITOSHIMA, Ryosaku ONO and Hideo NAGASHIMA

First Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan
(Director: Prof. H. Nagashima)

Received October 15, 1984

Abstract. Problems with infusion therapy for correcting fluid and sodium imbalance in decompensated liver cirrhosis (DLC) were investigated by establishing the safety zone of Talbot *et al.* for parenteral fluid therapy in 4 DLC patients infused with over 900 ml of fluid each day for at least 9 days. The safety zone was different in each case. The safe infusion volume decreased and the safe electrolyte concentration shifted to a lower osmolality when there was ascites with renal failure than ascites without renal failure. Infusion therapy was performed without deterioration of the water and sodium balance in those patients whose infusion volume and fluid osmolality were in the safety zone. In contrast, ascites retention increased and peripheral edema appeared in patients whose infusion volume and osmolality were out of the safety zone. Therefore, the safety zone should be determined repeatedly during infusion therapy.

Key words : decompensated liver cirrhosis, infusion therapy, ascites, hepatorenal syndrome.

Greater understanding of nutrition and metabolism in decompensated liver cirrhosis (DLC) has led to the use of specific amino acid preparations to improve hepatic encephalopathy and central venous hyperalimentation or feeding of an elemental diet to better the general condition (1-3). However, the quantity and composition of the infused solution are difficult to adjust in DLC patients due to ascites retention, peripheral edema, hypoalbuminemia, hyponatremia and other electrolyte abnormalities, as well as gastrointestinal hemorrhage and hepatic encephalopathy (4). Therefore, infusion requires continuous modification in DLC patients. However, the regulation of infusion has scarcely been studied (5). In this study, the infusion therapy applied was compared with the clinical course to see whether or not the safety zone of water and sodium infusion, determined by a modification of the infusion theory of Talbot *et al.*, can be applied to DLC patients.

SUBJECTS

The subjects consisted of a patient (Case 1) with DLC and 3 patients (Cases 2-4) with DLC

*Present address: Department of Internal Medicine, Himeji Red Cross Hospital, Hyogo 670, Japan.

TABLE 1. CLINICAL FEATURES BEFORE INFUSION THERAPY, REASON FOR INFUSION THERAPY AND PROGNOSIS IN EACH CASE

	Case 1	Case 2	Case 3	Case 4
Age	48	56	67	52
Sex	male	male	male	male
Diagnoses*	LC	HCC, LC	HCC, LC	HCC, LC
Diet before infusion therapy				
Calorie (kcal/day)	1,800	2,000	1,800	1,200
NaCl (g/day)	6	6	6	3
Physical findings before infusion therapy				
Ascites	+	+	+	+
Hepatic encephalopathy	+	−	+	−
Hematemesis	−	+	−	−
Peripheral edema	−	−	−	−
Biochemical results before infusion therapy				
Total bilirubin (mg/dl)	20.7	21.3	4.2	18.3
Cholesterol (mg/dl)	51	110	148	82
Choline esterase (△pH)	0.19	0.29	0.17	0.25
Prothrombin time (sec.)	19			
Serum Na (mEq/1)	130	127	136	121
Serum K (mEq/1)	4.2	5.3	4.3	4.8
Serum creatinine (mg/dl)	0.7	1.3	1.5	1.3
Purposes for infusion therapy	HE* NS	Hematemesis NS	HE NS	NS*
Outcome and cause of death	died Coma RF	died Hematemesis	died RF*	died Hematemesis

*LC: Liver cirrhosis HCC: Hepatocellular carcinoma HE: Hepatic encephalopathy
NS: Nutritional support RF: Renal failure

and hepatocellular carcinoma. Their clinical data are presented in Table 1. They were infused with more than 900 ml/day of fluid continuously for 9-21 days by inserting a catheter into the vena cava superior from the cubital or right subclavian vein. Reasons for infusion were hepatic encephalopathy and nutritional support (Cases 1 and 3), fasting due to hematemesis (Case 2) and severe appetite loss (Case 4). Oral water intake was 50-200 ml/day in Case 1 and almost 0 ml/day in Cases 2, 3 and 4.

Ascites was found in all cases, but peripheral edema was not found in any case. Severe liver cell dysfunction was evident in all cases, but they had no renal failure at the start of infusion therapy. Serum sodium showed hyponatremia in the range of 121-136 mEq/l. No patient had severe diabetes mellitus or primary renal disease. Diagnosis was confirmed by autopsy in all cases.

METHODS

The safety zone of infusion volume (V, ml/day) and osmolality (E, mOsm/l) for parenteral

fluid therapy was determined in all 4 cases when renal failure (RF; serum creatinine over 2.0 mg/dl) was absent and in 2 cases (Cases 1 and 2) when RF was present. The following 2 equations presented by Talbot *et al.* (6) were used: $V = [L + N \times \alpha - (C + T)] / (1 - E \times \alpha)$ (Equation 1) and $V = S/E$ (Equation 2), where α = urinary volume accompanying solute excretion (ml), S = solute excretion capacity of the kidneys (mOsm/day), N = nitrogenous product (mOsm/day), L = insensible loss (ml/day), C = metabolic water (ml/day) and T = tissue water (ml/day). N, L, C and T were set at 300 mOsm/day, 900 ml/day, 300 ml/day and 100 ml/day, respectively (7), and Equation 1 was changed to $V = (300 \times \alpha + 500) / (1 - E \times \alpha)$ (Equation 3).

The safety zone was shown by 2 variables (V and E) and restricted by the maximum and minimum value of 2 factors (α and S) (Figs. 2-6). The factor α was obtained from the urinary specific gravity as the inverse of the urinary osmotic pressure, and was not measured directly (8). As the patients were seriously ill, true maximum and minimum values of α and S were hard to obtain. Therefore, the maximum and minimum α (αmax, αmin) were obtained from the lowest and the highest value among 6-9 determinations of urinary specific gravity in each case. The maximum and minimum S (Smax, Smin) were obtained in each case by doubling the highest and the lowest value among 2-7 determinations of urinary sodium excretion (6).

The actual infused volume and osmolality were calculated from the quantity and composition of the infused solution only, because oral water intake was small in each case (Table 2).

The individual safety zone was compared with the actual infused volume and osmolality in order to evaluate the effects on physical findings, water and sodium balance, and liver function tests.

RESULTS

Maximum and minimum urinary volume accompanying solute excretion (αmax, αmin) and solute excretion capacity of the kidneys (Smax, Smin). Urinary volume, specific gravity

TABLE 2. COMPOSITION OF INFUSION SOLUSION IN EACH CASE

	Case 1	Case 2	Case 3	Case 4
Water (ml/day)	1,520±390	2,220±500	1,550±380	1,440±200
Range	900−2,000	1,200−2,700	1,000−2,000	1,300−2,000
Na (mEq/day)	70±30	90±50	70±50	30±10
Range	30−110	10−170	5−150	20−50
Cl (mEq/day)	50±30	90±40	100±50	70±10
K (mEq/day)	0−3	0−3	0−4	0−1
	(17 days)	(8 days)	(7 days)	
	60±9	30±22	22	
	(4 days)	(4 days)	(1 day)	
Glucose (g/day)	250±90	360±110	230±50	300±20
Protein (g/day)	16±5	14±6	0	8±4
Amino acids (g/day)	14±6	28±6	25±9	40±5
Lipids (g/day)	0	0	0	25 (1 day)
Calorie (kcal/day)	1,120±340	1,600±500	1,000±220	1,350±80
Non-protein calorie/N (kcal)	220±90	240±60	260±130	180±20
Calorie/ml (kcal)	0.7±0.1	0.7±0.2	0.7±0.2	1.0±0.2

TABLE 3. URINARY VOLUME (UV), URINARY SPECIFIC GRAVITY (USG) AND URINARY SODIUM EXCRETION (UNaV) DURING ASCITES RETENTION AND RENAL FAILURE IN EACH CASE

1. During ascites retention

	Case 1	Case 2	Case 3	Case 4	Total
UV (ml/day)	n = 14	n = 8	n = 10	n = 12	n = 44
M±SD	1,290±340	1,880±770	720±220	1,170±350	1,230±570
Range	600−1,900	980−3,500	300−1,000	500−1,760	300−3,500
USG	n = 9	n = 7	n = 8	n = 7	n = 31
M±SD	1,016±2	1,013±2	1,015±4	1,015±3	1,015±3
Range	1,012−1,020	1,009−1,016	1,010−1,021	1,011−1,019	1,009−1,021
UNaV (mEq/day)	n = 5	n = 3	n = 4	n = 7	n = 19
Mean	65	78	6	10	21
M−SD — M+SD	49−88	58−105	3−16	6−18	6−69
Range	43−99	62−109	2−18	4−23	2−109

2. During renal failure

	Case 1	Case 2	Case 3	Case 4	Total
UV (ml/day)	n = 10	n = 7			n = 17
M±SD	1,120±950	750±390			970±770
Range	30−3,100	280−1,400			30−3,100
USG	n = 6	n = 6			n = 12
M±SD	1,015±3	1,014±2			1,015±3
Range	1,009−1,018	1,012−1,017			1,009−1,018
UNaV (mEq/day)	n = 2	n = 6			n = 8
Mean	12, 29	20			19
M−SD — M+SD		7−59			7−50
Range		4−67			4−67

TABLE 4. MAXIMUM AND MINIMUM URINARY VOLUME ACCOMPANYING SOLUTE EXCRETION (αMAX, αMIN) AND SOLUTE EXCRETION CAPACITY OF THE KIDNEYS (SMAX, SMIN) DURING ASCITES RETENTION (AR) AND RENAL FAILURE (RF) IN EACH CASE

		αmax (ml)	αmin (ml)	Smax (mOsm)	Smin (mOsm)
Case 1	AR	2.8	1.7	198	86
	RF	3.7	1.9	58	24
Case 2	AR	3.7	2.1	218	124
	RF	2.8	2.0	134	8
Case 3	AR	3.3	1.6	36	4
Case 4	AR	3.0	1.8	46	8
Normal[7]		10.0	1.0	500	50

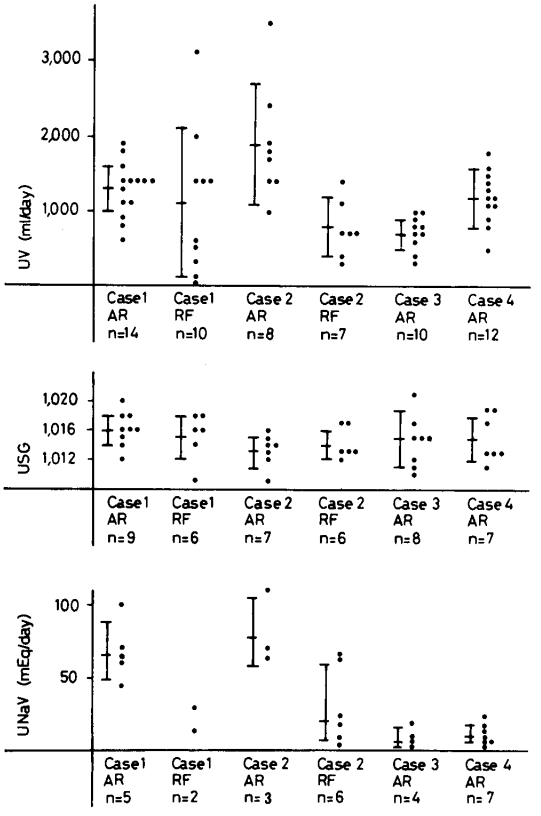

Fig. 1. Urinary volume (UV), urinary specific gravity (USG) and urinary sodium excretion (UNaV) during ascites retention (AR) and renal failure (RF).

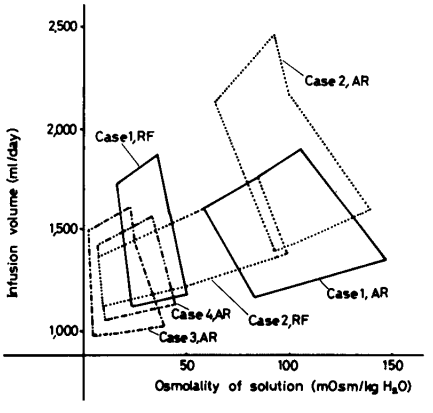

Fig. 2. Safety zone of infusion volume and osmolality during ascites retention (AR) and renal failure (RF).

and sodium excretion did not show any differences between the ascites retention (AR) group and the RF group (Table 3), but sodium excretion decreased during the RF stage in the same patients (Fig. 1). There were no differences in αmin and αmax between the AR and RF groups (Table 4), whereas the ranges of Smin

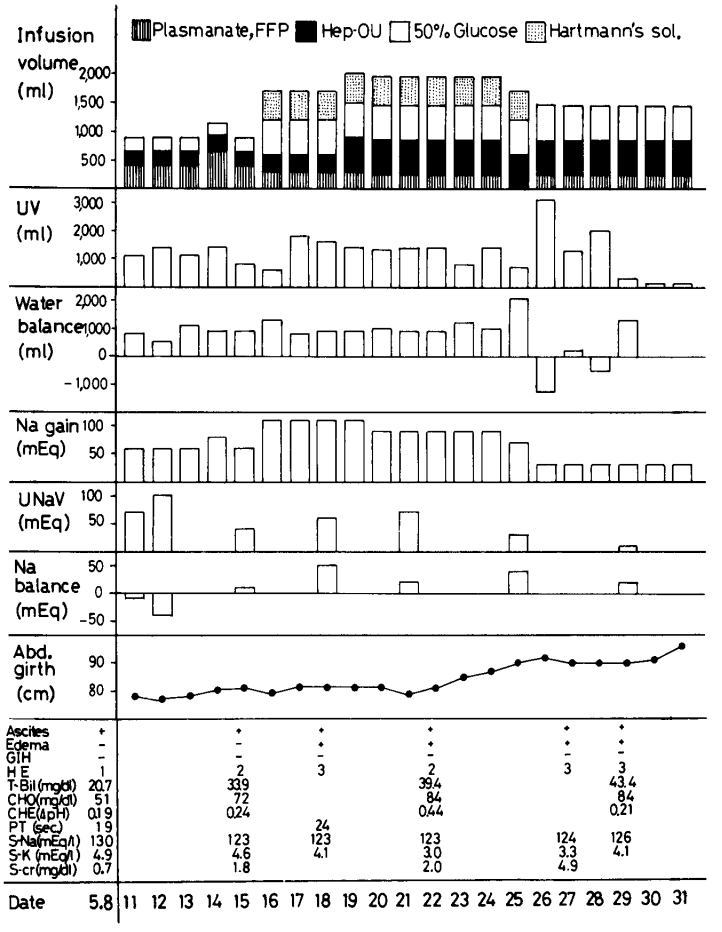

Fig. 3-1. Clinical course and water and sodium balance of Case 1. Water balance = (infusion volume + oral water intake) − urinary volume. Explanation of abbreviations in figures; UV: urinary volume, UNaV: urinary sodium excretion, GIH: gastrointestinal hemorrhage, HE: hepatic encephalopathy, T: tarry stool, H: hematemesis, CHO: cholesterol, CHE: choline esterase, S-cr: serum creatinine, PT: prothrombin time.

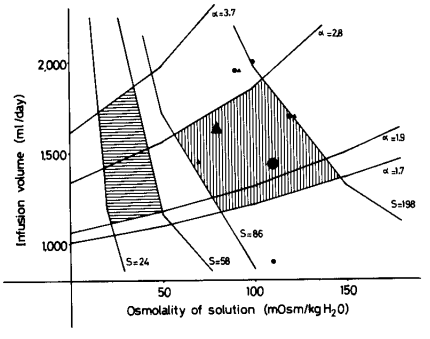

Fig. 3-2. Homeostatic safety zone of Case 1 during ascites retention ▥ and renal failure ▤. Explanation of signs in figures; •, ● (mean): Infusion volume and osmolality of solution during ascites retention. ▲, ▲(mean): Infusion volume and osmolality of solution during renal failure.

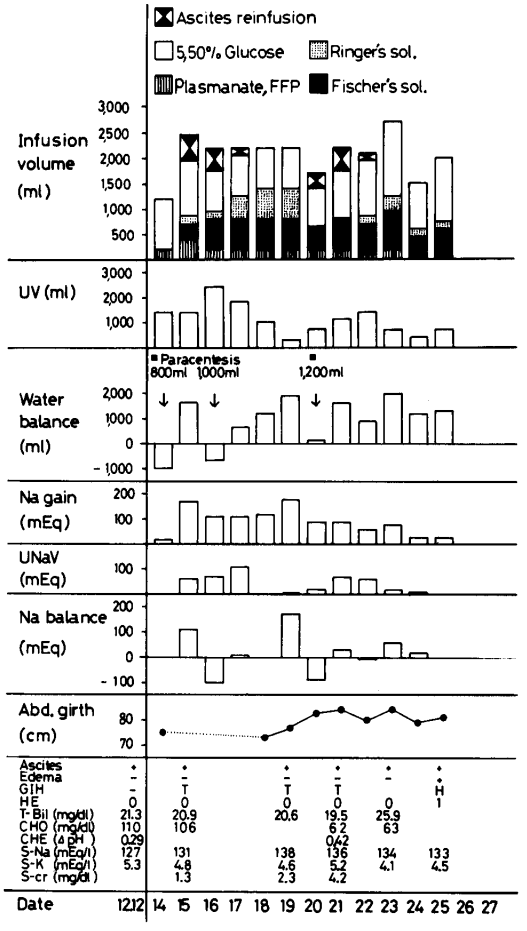

Fig. 4-1. Clinical course and water and sodium balance of Case 2. Water balance = infusion volume − (urinary volume + removed ascites volume).

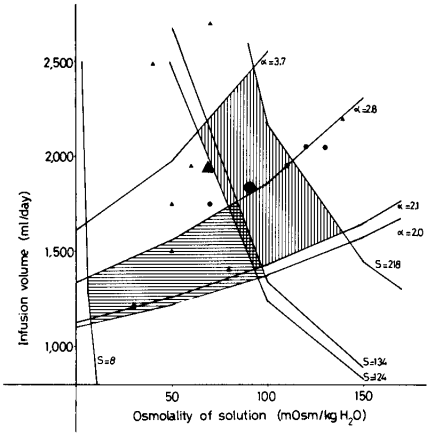

Fig. 4-2. Homeostatic safety zone of Case 2 during ascites retention ▥ and renal failure ▤.

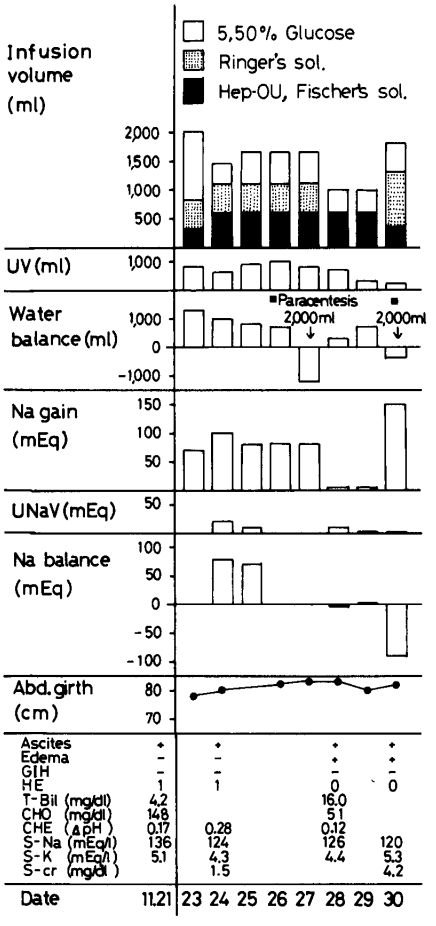

Fig. 5-1. Clinical course and water and sodium balance of Case 3. Water balance = (infusion volume + oral water intake) − (urinary volume + removed ascites volume).

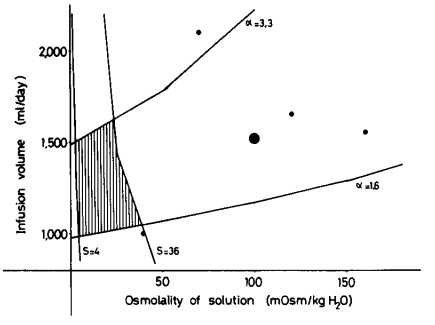

Fig. 5-2. Homeostatic safety zone of Case 3 during ascites retention.

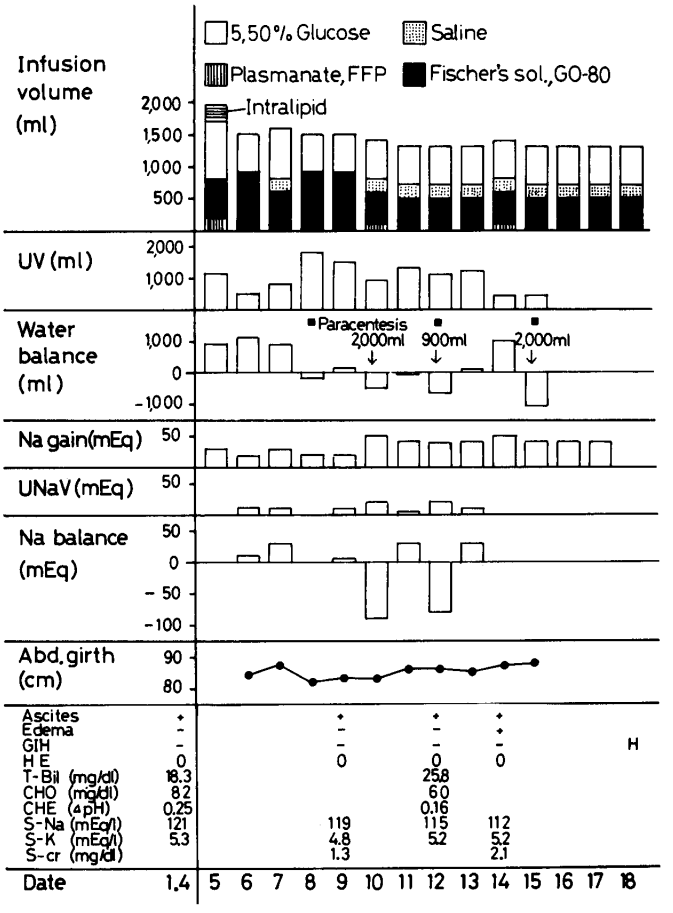

Fig. 6-1. Clinical course and water and sodium balance of Case 4. Water balance = (infusion volume + oral water intake) − (urinary volume + removed ascites volume).

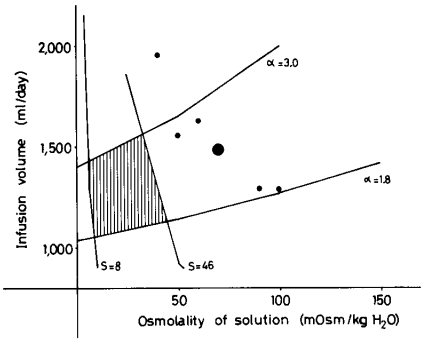

Fig. 6-2. Homeostatic safety zone of Case 4 during ascites retention.

and Smax were narrower in the RF group (8-24 mOsm, 58-134 mOsm) than in the AR group (4-124 mOsm, 36-218 mOsm) (Table 4).

The safety zone of infusion volume and osmolality. The safety zone of infusion volume and osmolality was established during the AR and RF stages in each case, substituting αmin, αmax, Smin and Smax in Equations 2 and 3 (Fig. 2). The zone was different for each case during both the AR and RF stages. In Cases 1 and 2, the zone became smaller during the RF stage than during the AR stage, and shifted toward lower osmolality.

Comparison of the infused volume and osmolality with the safety zone. In Case 1 (Figs. 3-1, 3-2), the infused volume (1,430 ml/day on the average) and electrolyte concentration (110 mOsm/l) were within the safety zone for 11 days during the AR stage, but the volume (1,630 ml/day) and osmolality (80 mOsm/l) were in sodium excess for 10 days during the RF stage. In Case 2 (Figs. 4-1, 4-2), ascites reinfusion combined with regular infusion therapy increased the urinary volume and sodium excretion during the AR stage, but did not show a remarkable effect during the RF stage. Infusion volume (1,830 ml/day except reinfusion) and osmolality (90 mOsm/l) were within the safety range for 5 days during the AR stage, but the volume (1,930 ml/day) and osmolality (70 mOsm/l) were in water excess for 7 days during the RF stage. In Case 3 (Figs. 5-1, 5-2), the infusion volume (1,510 ml/day) and osmolality (100 mOsm/l) were in sodium excess for 7 days during the AR stage. In Case 4 (Figs. 6-1, 6-2), the volume (1,490 ml/day) and osmolality (70 mOsm/l) were in sodium excess for 9 days during the AR stage.

Comparison of the clinical course with the accordance of infusion therapy to the safety zone. When the infused volume and electrolyte concentration were within the safety zone during the AR stage of Cases 1 and 2, the abdominal girth did not increase and sodium balance did not become worse. On the contrary, when the infused volume was in excess (Case 2 during the RF stage) or when the electrolyte concentration was in excess (Case 1 during the RF stage, and Cases 3 and 4 during the AR stage), the abdominal girth increased and sodium balance became worse. As the present cases were in the terminal stage of liver cirrhosis and hepatocellular carcinoma, ascites retention increased, peripheral edema and renal failure appeared, and liver function deteriorated. Water and sodium balance deteriorated in all cases. Spironolactone and loop diuretics had been used from before the start of infusion, and the doses were increased during infusion. All patients died 9-22 days after the start of infusion therapy.

DISCUSSION

The safety zone of parenteral fluid therapy proposed by Talbot *et al.*, relating to the renal capacity of water and sodium excretion, was determined during the AR and RF stages in DLC patients. When the infused volume and electrolyte concentration were within the safety zone, the clinical course was good without deterioration of the water and sodium balance, but when they were out of the zone,

ascites increased, peripheral edema appeared, and the water and sodium balance became worse. These results indicate that the infusion theory of Talbot *et al.* is applicable to DLC patients. However, the safety zone for each case varied during both the AR and RF stages (Fig. 2), so it was difficult to determine a standard safety zone. Determination of a safety zone for each case from the urinary osmotic pressure and urinary sodium excretion is necessary to determine the infusion volume and osmolality during every stage of the disease.

The safety zone during the RF stage became smaller than that during the AR stage, and shifted to a lower osmolality (Fig. 2), reflecting a decrease in the ability to dilute the urine and excrete sodium in DLC (9). When infusion therapy is performed on patients with water or sodium excess during the AR and RF stage, the safety zone becomes even smaller. During RF, when oliguria below 500 ml/day was observed in spite of the use of diuretics, the infusion volume must be reduced to below 1,000 ml/day (10).

The safety zone for infusion therapy obtained from water and sodium excretion capacity is useful not only in the determination of infusion volume and composition at the beginning of or during infusion therapy, but also in selecting the proper treatment for patients with ascites and in determining the quantity and composition of an elemental diet. The safety zone is small during AR and RF, and it is evident that usual parenteral hyperalimentation (2,300 ml water, 122 mEq Na, 60 mEq K, 500 g glucose, 70 g lipid, 20 g amino acids, 2,630 kcal/day) (11) is difficult to perform in DLC patients, because both the infusion volume and the sodium dose are too much. However, the infusion volume within the safety zone cannot give a sufficient nutritional supply to DLC patients. Therefore, if an elemental diet with a low sodium and high caloric density formula can be given to the patient, it is recommended over infusion therapy (3).

It is necessary to improve the sodium excretion capacity in order to enlarge the safety zone. Ascites reinfusion increased the infusion volume without causing water excess. In Case 2 (Fig. 4-1), ascites reinfusion increased the infusion volume up to 2,500 ml/day in the early stage of infusion therapy resulting in a decrease in the abdominal girth, negative balance of water and rather good sodium balance. These effects were, however, temporary, and ascites reinfusion did not increase the urinary volume or sodium excretion effectively in the later stage when there was renal failure. Moreover, ascites reinfusion sometimes induces disseminated intravascular coagulation (12) and dissemination of cancer in patients with hepatocellular carcinoma. In this case, normal fresh frozen plasma with electrolytes and glucose may replace ascites reinfusion (13).

In summary, the safety zone of infusion therapy was useful in the fluid therapy of DLC patients. However, the zone is often smaller than the volume necessary for nutritional supply.

REFERENCES

1. Watanabe, A., Higashi, T., Hayashi, S., Obata, N. and Nagashima, H.: Parenteral nutrition in patients with severe liver diseases — Normalization of deranged amino acid pattern in serum. *Acta Hep. Jpn.* **20**, 28-41, 1979 (in Japanese).
2. Fischer, J.E., Rosen, H.M., Ebeid, A.M., James, J.H., Keane, M. and Soeters, P.B.: The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery* **80**, 77-91, 1976.
3. Smith, J., Horowitz, J., Henderson, J.M. and Heymsfield, S.: Enteral hyperalimentation in undernourished patients with cirrhosis and ascites. *Am. J. Clin. Nutr.* **35**, 56-72, 1982.
4. Hecker, W.R. and Sherlock, S.: Electrolyte and circulatory changes in terminal liver failure. *Lancet* **2**, 1121-1125, 1956.
5. Host, W.R., Serlin, O. and Rush, Jr., B.F.: Hyperalimentation in cirrhotic patients. *Am. J. Surg.* **123**, 57-62, 1972.
6. Talbot, N.B., Crawford, J.D. and Butler, A.M.: Homeostatic limits to safe parenteral fluid therapy. *N. Engl. J. Med.* **218**, 1100-1108, 1953.
7. Furukawa, T., Kato, T., Inada, H., Hayashi, R., Abe, H., Kajitani, F. and Itakura, N.: Mathematical analysis on parenteral fluid therapy in body fluid disturbances — Automatic construction of homeostatic safety zone with a digital computer —. *J. Jpn. Soc. Intern. Med.* **59**, 1201-1213, 1970 (in Japanese).
8. Rose, B.D.: *Clinical Physiology of Acid-base and Electrolyte Disorders.* McGraw-Hill, New York, pp. 383, 1979.
9. Mizumura, T. and Takeuchi, J.: Renal tubular function in liver cirrhosis — Renal tubular handling of water, sodium and acid. *Saishin-Igaku* **32**, 116-122, 1977 (in Japanese).
10. Scribner, B.H.: *Teaching Syllabus for the Course on Fluid and Electrolyte Balance.* University of Washington School of Medicine, Seattle, pp. 123, 1953.
11. Kitaoka, T., Tamura, K. and Takahashi, K.: Infusion practice depending on disease state. Frequent errors. *Naika* **50**, 697-703, 1982 (in Japanese).
12. Mataseshe, J.W., Beart, Jr., R.W., Bartholomew, L.G. and Baldus, W.P.: Fatal disseminated intravascular coagulation after peritoneovenous shunt for intractable ascites. *Mayo Clin. Proc.* **53**, 526-528, 1978.
13. Yuasa, S., Kayasuga, N., Yamashita, J., Ohta, W. and Kariya, T.: A trial for refractory ascites on liver cirrhosis — combination of paracentesis and intravenous infusion of fluid composed of fresh frozen plasma, minerals and glucose. *Kotsu-Igaku* **35**, 48-54, 1981 (in Japanese).