Original Article

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A novel highly concentrated enteral nutrition formula, EN-P05, shows nutritional effectiveness comparable to the approved OSN-001 in gastrostomized rats

Eiji Kasumi*, Yoshie Kuzumaki, Megumi Sadakata, Hiroyuki Kuzuoka, Norifumi Sato

EN Otsuka Pharmaceutical Co., Ltd., R&D Laboratories, Iwate, Japan.

Summary **Enteral nutrition is beneficial support administered as oral supplements or *via* tube feeding for patients with long-term inability to meet nutritional requirements orally. However, because of the high volumes administered, vomiting and gastroesophageal reflux are often encountered in patients receiving enteral nutrition. EN-P05 is a novel, highly concentrated enteral nutrition formula that was developed to reduce dosing volume and that satisfies the Japanese recommended daily allowance for most vitamins and trace elements, even in patients who require low-calorie control, such as home-care patients. However, whether EN-P05 can provide nutritional management equivalent to that provided by approved formulas has remained unknown. To investigate the nutritional effectiveness of EN-P05, we evaluated body weight gain, serum chemistry parameters, nitrogen balance, and fat absorption in 7-week-old gastrostomized rats that received either EN-P05 or OSN-001 for 2 weeks. No difference in organ or carcass weight was found between the groups. No significant between-group differences were observed in serum albumin, total protein, triglycerides, or total cholesterol, nor in nitrogen retention or fat absorption rate. No adverse effects associated with administration of EN-P05 were found. These results suggest that EN-P05 can provide the same nutritional management as approved formulas, even when administered in smaller volume.**

Keywords: Nutritional management, nitrogen balance, dietary fiber, trace element, carnitine

1. Introduction

Enteral nutrients are widely used for nutritional supplementation in patients after surgery and in patients who have long-term difficulty with oral ingestion, due to factors such as sequelae of stroke, neurological intractable diseases, and severe motor and intellectual disabilities (*1-5*). Approved enteral nutrition formulas are designed to satisfy the daily vitamin and mineral requirements of adults consuming approximately 1,600 kcal/day in Japan. Therefore, patients who require long-term nutrient administration and who have low activity, with maintenance energy requirements of approximately 1,000 kcal/day, need to adjust their intake volume to meet the recommended daily caloric intake. However, such adjustment may result in deficiency of some vitamins or trace elements (*6-8*). It has also been reported that deficiency may result from administration of enteral nutrition formulas that do not contain trace elements (iodine, selenium, chromium, and molybdenum) newly categorized as essential in "Dietary Reference Intakes for Japanese (2000)" (*9-13*).

In addition to these nutritional management issues, the following goals must be met in clinical practice: reduction of volume to lower the risk of aspiration, securing time for rehabilitation by shortening administration time, and use of oral nutritional supplements for nutritional treatment (*14-18*). Therefore, a high-concentration enteral nutrition formula that allows efficient ingestion of energy and nutrients in smaller volumes is required.

Created to address these problems and the needs of medical personnel, patients, and caretakers, EN-P05 is a novel, high-concentration enteral nutrition formula with

**Address correspondence to:*
Dr. Eiji Kasumi, EN Otsuka Pharmaceutical Co., Ltd., R&D Laboratories, 4-3-5 Nimaibashi, Hanamaki, Iwate 025-0312, Japan.
E-mail: eiji.kasumi@enotsuka.co.jp

a caloric density of 1.6 kcal/mL developed to satisfy the recommended daily allowance of most vitamins and trace elements in accordance with "Dietary Reference Intakes for Japanese (2015)" at a dosage of 900 kcal/day. Moreover, EN-P05 also includes carnitine, which is reported to be deficient in patients with severe physical and mental disabilities and neuromuscular diseases who require long-term tube feeding (*19,20*).

In this study, EN-P05 and OSN-001 (an approved enteral nutrition formula) were administered to gastrostomized rats for 2 weeks, and their effects on nutritional status were compared to evaluate the nutritional effectiveness of EN-P05.

2. Materials and Methods

2.1. *Enteral nutrition formulas*

EN-P05 and OSN-001 (RACOL®-NF) were prepared at EN Otsuka Pharmaceutical Co., Ltd. (Hanamaki, Japan). The composition of each enteral nutrition formula is shown in Table 1.

Table 1. Nutritional composition of EN-P05 and OSN-001

Items	EN-P05 (/100 mL)	OSN-001 (/100 mL)
Protein (g)	6.40	4.38
Fat (g)	5.15	2.23
Carbohydrate (g)	21.22	15.62
Fiber (inulin[a]) (g)	1.6	-
Minerals		
Sodium (mg)	144.0	73.8
Potassium (mg)	294	138
Calcium (mg)	142.2	44.0
Magnesium (mg)	65.8	19.3
Phosphorus (mg)	177.8	44.0
Chloride (mg)	222	117
Iron (μg)	1,955	625
Zinc (μg)	2,133	640
Manganese (μg)	710	133
Copper (μg)	160	125
Iodine (μg)	23.0	-
Selenium (μg)	9.0	-
Chromium (μg)	7.0	-
Molybdenum (μg)	5.3	-
Vitamins		
Vitamin A (μg RE)	151.0	62.1
Vitamin D (μg)	2.67	0.34
Vitamin E (mg)	2.67	0.44
Vitamin K (μg)	13.33	6.25
Vitamin B1 (μg)	249	380
Vitamin B2 (μg)	285	245
Vitamin B6 (μg)	250	375
Vitamin B12 (μg)	0.80	0.32
Vitamin C (mg)	35.6	28.1
Nicotinamide (mg)	2.67	2.50
Pantothenic acid (μg)	1,067	958
Folic acid (μg)	42.7	37.5
Biotin (μg)	8.90	3.86
Carnitine (mg)	26.7	-
Choline (mg)	97.8	-
Energy (kcal)	160	100

[a]: artificially synthesized inulin-type fructans with a polymerization degree of approximately 6 to 30 fructose molecules. RE, retinol equivalents.

2.2. *Animals*

Six-week-old male Sprague-Dawley rats (Charles River Laboratories Japan, Inc., Yokohama, Japan) were housed in stainless metabolism cages (CT10-S; CLEA Japan, Inc., Tokyo, Japan) under controlled temperature (23 ± 3°C) and humidity (50 ± 20%), with a 12-hour light-dark cycle. The rats were fed commercial laboratory chow (CRF-1; Oriental Yeast Co., Ltd., Tokyo, Japan) and were allowed drinking water *ad libitum* for about 1 week before the experiments began. All animal experiments conformed to the guidelines for the care and use of laboratory animals established by the Animal Use and Care Committee of EN Otsuka Pharmaceutical Co., Ltd.

2.3. *Surgical procedure for gastrostomy*

The gastrostomy surgical procedure followed the method of Murakami *et al*. (*21*). After an overnight fast, the rats were anesthetized with isoflurane (Pfizer Inc., New York, NY, USA). Laparotomy was performed through a midline incision. An 8-Fr catheter (Terumo Corporation, Tokyo, Japan) was then inserted into the stomach. The distal end of the catheter was tunneled subcutaneously through the left lateral abdominal wall, and exited at the interscapular region. The proximal end of the catheter was attached to a swivel spring, which allowed the rats freedom of movement in their individual cages. Penicillin G potassium (2,000 U; Meiji Seika Pharma Co., Ltd., Tokyo, Japan) was intraperitoneally administered after laparotomy.

2.4. *Experimental design*

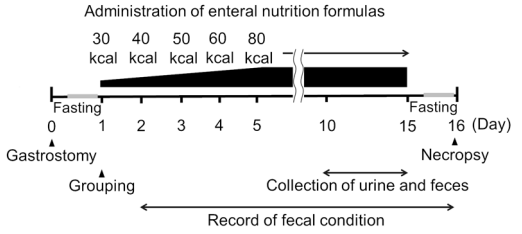

Figure 1. Experimental design. After gastrostomy, the rats received enteral nutrition in the amounts of 30, 40, 50, 60, and 80 kcal on Days 1, 2, 3, 4, and 5 to 14, respectively. After completion of administration of enteral nutrient, the animals were fasted overnight and necropsied the next day.

The experimental design is schematically outlined in Figure 1. The day after gastrostomy surgery, the rats were randomized into two groups, pair-matched according to body weight on Day 1: the EN-P05 group (n = 10) and the OSN-001 group (n = 10). The rats were administered EN-P05 or OSN-001 for 14 days *via* an infusion pump (SP-115; JMS Co., Ltd., Tokyo, Japan)

over approximately 16.5 h per day, beginning at 17:00. Taking the effects of their postoperative condition into account, the administered volume of enteral nutrition formulas was gradually increased over time. The fecal condition of each rat was recorded on Days 2 to 16, according to the following descriptions: no feces, normal feces, loose feces, watery feces. Urine and feces were collected on Days 10 to 15 (total of 5 days); the feces were lyophilized and weighed.

2.5. *Blood collection and measurement of organ weight*

On Day 16, blood samples were obtained with a vacuum blood collection tube (Terumo Corporation) from the vena cava of all rats under isoflurane anesthesia. After euthanasia, all rats were necropsied and organs were removed and weighed.

2.6. *Clinical chemistry analysis*

All blood samples for clinical chemistry analyses were centrifuged at 1,500× g for 15 minutes at 4°C, after which the serum was collected. Serum albumin, total protein, triglycerides, and total cholesterol were quantified with a clinical chemistry analyzer (Fuji DRI-CHEM 3500V; Fujifilm Medical Co., Ltd., Tokyo, Japan), in accordance with the manufacturer's instructions.

2.7. *Nitrogen balance*

The amount of nitrogen in urine and feces collected over a 5-day period and in the two enteral nutrition formulas was measured with the general Kjeldahl method. Using the obtained values, nitrogen retention, biological value, nitrogen retention rate, and apparent nitrogen absorption rate were calculated using the following formulas:

Nitrogen retention (mg/5 days) = Nitrogen intake – Urinary nitrogen excretion – Fecal nitrogen excretion

Biological value (%) = 100 × Nitrogen retention/(Nitrogen intake – Fecal nitrogen excretion)

Nitrogen retention rate (%) = 100 × Nitrogen retention/Nitrogen intake

Apparent nitrogen absorption rate (%) = 100 × (Nitrogen intake – Fecal nitrogen excretion)/Nitrogen Intake

2.8. *Fat absorption*

The amount of fat in feces collected over a 5-day period and in the two enteral nutrition formulas was measured using an acid decomposition method. Briefly, the samples were digested with hydrochloric acid (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and fat was extracted in an organic solvent containing diethyl ether, petroleum ether, and ethanol (Wako Pure Chemical Industries, Ltd.) at a ratio of 5:5:2. After centrifugation at 76× g, the supernatant was obtained and evaporated by heating; the residue was weighed as fat. Using the obtained values, the amount of apparent fat absorption and apparent fat absorption rate were calculated using the following formulas:

Apparent fat absorption (mg/5 days) = Fat intake – Fecal fat excretion

Apparent fat absorption rate (%) = 100 × (Fat intake – Fecal fat excretion)/Fat intake

2.9. *Statistical analysis*

The results are expressed as means ± SD. Statistical analysis was performed using one-way ANOVA. The frequency of recorded fecal conditions in each group was calculated and a chi-square test was conducted. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. *Changes in body weight and organ weight in gastrostomized rats administered each enteral nutrition formula*

First, to investigate the effect of EN-P05 on the growth of rats, body weight was measured during the period of enteral-nutrient administration and the weight gain from Day 1 to Day 15 was calculated. Body weight change of the EN-P05 group remained slightly higher compared to the OSN-001 group (Figure 2). Body weight and weight gain were significantly higher in the EN-P05 group than in the OSN-001 group on Day 15, the end date of enteral-nutrient administration. However, there was no significant difference between groups in body weight on Day 16, the day of necropsy after an overnight fast. Moreover, there were no differences between groups in the weight of the carcass, liver, kidney, spleen, or fat tissues on the day of necropsy (Table 2). Notably, the cecum with its contents was approximately twice as heavy in the EN-P05 group as in the OSN-001 group. These results indicated that the body weight gain in the

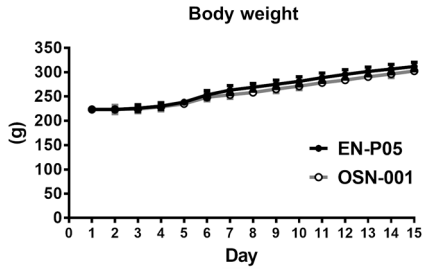

Figure 2. Body weight change of gastrostomized rats throughout the experiment (Days 1 to 15). Individual rats were weighed daily. The results shown are expressed as means ± SD (*n* = 10/group). Body weight was recorded as the weight of the rat with a gastrostomy catheter left *in situ*.

EN-P05 group was caused by an increase in the weight of the cecum and its contents.

3.2. *Nutritional markers in serum*

Next, a clinical chemistry analyzer was used to check nutritional markers in serum to investigate the effect of enteral nutrition formulas on nutritional status. There was no difference in serum albumin, and no significant difference in total protein concentration, serum triglycerides, or total cholesterol between groups (Table 3).

Table 2. Nutritional parameters in gastrostomized rats

Items	EN-P05 group	OSN-001 group
Body weight (g)		
Day 1	223.30 ± 6.38	223.31 ± 6.36
Day 15	311.93 ± 8.90**	302.70 ± 7.04
Day 16	289.25 ± 8.67	282.49 ± 5.63
Weight gain, Days 1-15	88.63 ± 6.67**	79.39 ± 5.85
Organ weight (g)		
Liver	8.25 ± 0.28	8.42 ± 0.38
Kidney	2.13 ± 0.12	2.07 ± 0.12
Spleen	0.64 ± 0.08	0.62 ± 0.10
Epididymal adipose tissue	2.97 ± 0.36	3.13 ± 0.44
Perinephric adipose tissue	3.67 ± 0.36	3.59 ± 0.64
Cecum	6.57 ± 1.40**	3.57 ± 1.53
Carcass (g)	215.99 ± 8.05	214.03 ± 8.51

Results shown are mean ± SD (n = 10/group). Carcass weight was determined as weight of rat body with all organs removed except the head; the cecum was weighed with its contents. Statistical significance was determined using one-way ANOVA (**$p < 0.01$).

Table 3. Serum biochemistry in gastrostomized rats

Items	EN-P05 group	OSN-001 group
Albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.4
Total protein (g/dL)	5.3 ± 0.3	5.2 ± 0.3
Triglycerides (mg/dL)	83 ± 20	98 ± 24
Total cholesterol (mg/dL)	59 ± 9	59 ± 8

Results shown are mean ± SD (n = 10/group). Statistical significance was determined using one-way ANOVA.

Table 4. Nitrogen balance in gastrostomized rats

Items	EN-P05 group	OSN-001 group
Nitrogen intake (mg/5 days)	2,550.48	2,782.76
Fecal nitrogen excretion (mg/5 days)	227.36 ± 49.24**	179.46 ± 32.78
Urinary nitrogen excretion (mg/5 days)	1,336.50 ± 116.07**	1,708.00 ± 120.07
Nitrogen retention (mg/5 days)	986.62 ± 100.50	895.30 ± 130.54
Biological value (%)	42.49 ± 4.43**	34.37 ± 4.82
Nitrogen retention rate (%)	38.68 ± 3.94**	32.17 ± 4.69
Apparent nitrogen absorption rate (%)	91.09 ± 1.93**	93.55 ± 1.18

Results except nitrogen intake are shown as the mean ± SD (n = 10/group). Statistical significance was determined using one-way ANOVA (**$p < 0.01$).

3.3. *Nitrogen balance*

To explore the details of protein nutritional status, the nitrogen balance was assessed over a 5-day period, from Day 10 to Day 15. Nitrogen intake over the 5 days was about 200 mg higher in the OSN-001 group than in the EN-P05 group, and fecal nitrogen excretion was significantly higher in the EN-P05 group than in the OSN-001 group (Table 4). Thus, the apparent nitrogen absorption rate was lower in the EN-P05 group than in the OSN-001 group. However, because urinary nitrogen excretion was significantly higher in the OSN-001 group than in the EN-P05 group, the biological value and nitrogen retention rate were significantly lower in the OSN-001 group than in the EN-P05 group.

3.4. *Fat absorption*

Next, fat absorption was examined to investigate the state of lipid nutrition in detail. Fat intake over a 5-day period was about 4 g higher in the EN-P05 group than in the OSN-001 group, and fecal dry weight was significantly higher in the EN-P05 group than in the OSN-001 group (Table 5). Apparent fat absorption over a 5-day period was higher in the EN-P05 group than in the OSN-001 group, whereas the apparent fat absorption rate was very similar between the groups. These data suggest that the difference in apparent fat absorption directly reflected the difference in fat intake.

3.5. *Fecal condition in gastrostomized rats administered each enteral nutrition formula*

As EN-P05 is a highly concentrated enteral nutrition formula, whether it would adversely affect the fecal condition of rats with gastrostomy was investigated. No rats in either group had watery feces during the study period; however, the frequencies of loose feces and fecal condition patterns were significantly different between groups (Table 6). Focusing on temporal changes in fecal condition, no difference between groups was found in the fecal condition pattern during the period from Days 2 to 5, in which the administered

Table 5. Fat absorption in gastrostomized rats

Items	EN-P05 group	OSN-001 group
Fat intake (g/5 days)	12.73	8.80
Fecal fat excretion (g/5 days)	0.41 ± 0.12*	0.29 ± 0.06
Fecal dry weight (g/5 days)	3.34 ± 0.80**	2.00 ± 0.38
Apparent fat absorption (g/5 days)	12.32 ± 0.12**	8.51 ± 0.06
Apparent fat absorption rate (%)	96.79 ± 0.93	96.68 ± 0.66

Results except fat intake are shown as the mean ± SD (n = 10/group). Statistical significance was determined using one-way ANOVA (*$p < 0.05$, **$p < 0.01$).

Table 6. Fecal conditions in each period in gastrostomized rats

Items	Frequency		*p* value
	EN-P05 group	OSN-001 group	
Days 2 to 16:			< 0.01
No feces	5 (3.3)	10 (6.7)	
Normal feces	32 (21.3)	5 (3.3)	
Loose feces	113 (75.3)	135 (90.0)	
Watery feces	0 (0.0)	0 (0.0)	
Days 2 to 5:			0.57
No feces	4 (10.0)	6 (15.0)	
Normal feces	5 (12.5)	5 (12.5)	
Loose feces	31 (77.5)	29 (72.5)	
Watery feces	0 (0.0)	0 (0.0)	
Days 6 to 16:			< 0.01
No feces	1 (0.9)	4 (3.6)	
Normal feces	27 (24.5)	0 (0.0)	
Loose feces	82 (74.5)	106 (96.4)	
Watery feces	0 (0.0)	0 (0.0)	

Data are shown as number of observations (percentage). Statistical significance was determined with the chi-square test for only three items (No feces, Normal feces, and Loose feces) between the groups, because the frequency of Watery feces in each period was 0.

dose of enteral nutrition formula was gradually increased. After the maximum dose of enteral nutrients was achieved on Day 6, normal feces were observed in the EN-P05 group at a frequency of approximately 25%, whereas no normal feces were observed in the OSN-001 group.

4. Discussion

In the present study, the effectiveness of a novel highly concentrated enteral nutrient, EN-P05, was compared to that of an approved one, OSN-001, in gastrostomized rats. There was a significant between-group difference in weight gain, which could be due to an increase in cecum weight in the EN-P05 group. Several studies have reported that dietary fiber causes hypertrophic changes in the cecum and increases fecal volume in rats, without causing toxicity (*22*). The water-soluble dietary fiber, inulin, which is present in EN-P05, may therefore have caused the increased cecum weight in the EN-P05 group. The finding of no difference between groups in the weights of other organs suggests that there was no substantial body weight difference between groups.

In regard to nitrogen balance, the biological value and nitrogen retention rate were significantly higher in the EN-P05 group than the OSN-001 group. It has been reported that differences in protein content among enteral nutrition formulas are associated with differences in urinary nitrogen excretion in rats, and that the biological value and nitrogen retention rates change in relation to these differences (*23-25*). Therefore, the differences in the biological value and nitrogen retention rates in the present study may be attributable to the use of two enteral nutrition formulas with different protein content. Moreover, the apparent nitrogen absorption rate was significantly lower in the EN-P05 group than the OSN-001 group. This result may be explained by higher nitrogen excretion into feces because of the inulin contained in EN-P05, which is a dietary fiber known to increase the excretion of exogenous and endogenous nitrogen (*26-29*). Although the three parameters described above differed between the groups, there was no such difference in the total amount of nitrogen retention, serum albumin concentration, or total protein concentration. Therefore, we consider that protein nutritional status was equivalent in the two groups.

Regarding fat absorption, there was a between-group difference in apparent fat absorption, but not in the actual weight of epididymal or perinephric adipose tissue at the time of necropsy, and not in triglycerides or total cholesterol concentration in serum. These data suggest that lipid nutritional status was equivalent in the two groups.

In this study, EN-P05-administered gastrostomized rats had better fecal condition than OSN-001-administered gastrostomized rats. Of note, normal feces were observed in the EN-P05 group at a frequency of approximately 25%, but were not observed in the OSN-001 group from Day 6. The fecal condition might be influenced by the amount of moisture present in each formula. Because OSN-001 is less concentrated than EN-P05, and the amount of water per unit of energy is larger, it is conceivable that the larger volume of fluid flowing into the intestinal tract in the OSN-001 group caused the increased frequency of loose feces. It is also possible that the observed differences in fecal status may involve dietary fiber. Fermentation of dietary fibers by gut microbiota yields short-chain fatty acids, which provide an energy source for colonic epithelial cells, enhance water absorption from colonic epithelium, and control mucosal immunity (*30*). Moreover, high concentration of short-chain fatty acids helps to maintain low pH in the colon for colonic microbiota and prevents infection by enteropathogenic organisms that can cause diarrhea (*31*). These findings suggest that inulin, a dietary fiber included in EN-P05, also promoted good fecal condition in the gastrostomized rats, *via* promotion of colonic water absorption and prevention of pathogen overgrowth resulting from production of short-chain fatty acids.

In summary, the nutritional effectiveness of EN-P05 versus OSN-001 when administered for 2 weeks to gastrostomized rats were compared. There were no differences between the EN-P05 group and OSN-001 group in body weight, organ weight, blood biochemical test values, nitrogen retention, or fat absorption rate. Additionally, there were no adverse effects associated with administration of EN-P05. These results suggest that EN-P05 is as nutritionally effective as OSN-001, and as useful for nutritional management as

conventional enteral nutrition formulas, even in a lower administration volume.

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