Design of an Intravenous Diet of Amino-acids and Fat Suitable for Intensive Patient-care

M. J. T. PEASTON,* M.B., M.R.C.P. GLASG.

Brit. med. J., 1966, 2, 388-390

In serious illnesses complicated by dysphagia, vomiting, gastrointestinal obstruction, or ileus it is not possible to maintain nutrition by means of an adequate diet given by mouth or naso-gastric tube. The metabolic needs must therefore be supplied intravenously. Water and electrolytes are readily given, but it has been difficult to satisfy the calorie and nitrogen requirements. Failure to provide these may not adversely influence the course of an illness of moderate severity or short duration, but during severe or prolonged illnesses, especially those associated with trauma or sepsis, the demands for calories and nitrogen are increased. Unless these demands are satisfied the patient will show muscle-wasting, delayed tissue repair, and a negative nitrogen balance; the latter precedes the clinical signs. Nitrogen may be given intravenously as amino-acids, and commercial preparations have been available in this country since 1958. A high intake of calories in a relatively small volume can be provided conveniently only by a fat-emulsion (Moore, 1959). Until recently the emulsions available have produced serious toxic effects, but one prepared from soya-bean oil and egg-yolk phosphatides (Intralipid) has been extensively tested and has caused few serious reactions (Wretling, 1964).

The aim of the present study was to design an intravenous diet of amino-acids, fat, and electrolytes which was safe, was suited to everyday clinical practice, and which would preserve a metabolic balance during severe illness, and to compare it with the balance obtained with an intragastric diet of milk powder and sugar (Jones and Sechiari, 1963). A state of balance was accepted when the difference between the intake and urinary excretion lay within the range of predicted losses from the gut, skin, and lungs.

Materials and Methods

Ten male and two female patients were investigated, six of whom had severe chronic malnutrition and had become bed-fast and neglected; one of them had overt scurvy. Two patients had chronic oesophageal obstruction with resultant serious malnutrition, and two had undergone radical surgery and immediate reconstruction for extensive cancer of the head and neck. A further patient had inoperable gastric carcinoma. The patients were aged 52 to 82 years, except for a man aged 35 with schizophrenia and barbiturate poisoning. The clinical state of all the patients warranted immediate intravenous feeding, but the patients selected could also be fed intragastrically, thus permitting subsequent comparison between intravenous and naso-gastric feeding.

The amino-acid preparations used were Aminosol and Aminosol-fructose-ethanol. To each bottle of the latter 2 g. of potassium chloride (26 mEq of K) was added. The fat used was 20% w/v Intralipid, and 5,000 units of heparin were added to each 500 ml. of the emulsion. Vitamins were provided by a daily injection of Parentrovite. The half-litre bottles of amino-acids and fat were infused in pairs through a Y-shaped connector over eight-hour periods.

The intragastric diet consisted of Complan 100 g., glucose 100 g., and 3 g. of Celevec, made up to 1 litre with water. This diet was given through a naso-gastric tube in aliquots of 105 ml. each hour. The composition of the materials is given in Table I.

TABLE I.—Composition of Aminosol, Aminosol-fructose-ethanol, Intralipid, and Complan-glucose

	Calories per litre	Sodium	Potassium	Chloride	Nitrogen (g./litre)
		mEq/litre			
Aminosol 10%	320	160	—	130	12.8
Aminosol-fructose-ethanol	875	54	—	46	4.3
Intralipid 20%	2,000	—	—	—	—
Complan-glucose	860	22	28	20	4.8

Urine was collected in polyethylene bottles, measured, and aliquots were analysed for total nitrogen, urea, ammonia, amino-acids, sodium, potassium, and chloride.

Results

Design of an Intravenous Diet

The first step in the investigation was to design an intravenous diet which would maintain nitrogen balance during severe illness. The diet used by Wadström and Wiklund (1964) provided 2,500 calories and 7 g. of nitrogen for a 70-kg. subject, but resulted in a negative balance of 1.2 g. per day. It was anticipated that by giving additional calories and nitrogen a balance would be achieved. Diet A (Table II) provided 3,130 calories and 8.5 g. of nitrogen, but resulted in a negative balance. In diet B the calories and nitrogen were increased without a balance resulting. A balance was achieved in six patients by diet C, which gave 3,472 calories and 12.8 g. of

TABLE II.—Composition of the Intravenous Diets

	Diet		
	A	B	C
Materials:			
Aminosol-fructose-ethanol (l.) ..	2.0	1.0	1.5
Aminosol 10% (l.)	—	0.5	0.5
Fructose 20% (l.)	0.5	—	—
Intralipid 20% (l.)	0.5	1.5	1.0
Potassium chloride (g.)	6	6	6
Composition:			
Calories	3,130	4,035	3,472
Water (l.)	3.0	3.0	3.0
Nitrogen (g.)	8.5	10.5	12.8
Carbohydrate (g.)	400	150	225
Fat (g.)	100	300	200
Sodium (mEq)	108	134	161
Potassium (mEq)	78	78	78
Chloride (mEq)	167	186	209

TABLE III.—Nitrogen Balance During Intravenous Feeding

Intra- venous Diet	No. of Patients	Mean Duration of Balance (days)	Daily Nitrogen (g.)		Daily Nitrogen Balance (g.)	
			Intake	Urinary Output $\pm$ S.D.	Uncor- rected	Cor- rected
A	3	5.3	8.5	12.1 (3.74)	-3.6	-5.2
B	4	5.5	10.6	12.0 (2.63)	-1.4	-3.0
C	6	5.0	12.8	11.1 (2.11)	1.7	0.1

* Lecturer in Clinical Pharmacology, University of Liverpool, and the Intensive Care Unit, Whiston Hospital, Prescot, Lancashire.

nitrogen. About half a litre (mean 0.4 l.) of water was allowed by mouth for purposes of oral hygiene. The comparison of nitrogen balances obtained on these diets is shown in Table III.

The urinary outputs of water, nitrogen, and electrolytes during the administration of diet C to six patients are given in Table IV, together with the corrections for losses from the gut, skin, and lungs. It will be seen that a state of balance existed for nitrogen, sodium, and potassium, but that water and chloride balance was positive.

TABLE IV.—Balance Results on Intravenous and Intragastric Diets

Variable	Intake ± S.D.	Output ± S.D.	Balance	Correc- tion	Interpre- tation
<i>Intravenous diet C</i>					
Calories	3,472				
Water (l.)	3.4 ± 0.19	1.82 ± 0.45	1.58	1.0	Positive balance
Nitrogen (g.)	12.8	11.1 ± 2.1	1.7	1.6	Balance
Sodium (mEq)	161	132 ± 65.3	29	5-30	Balance
Potassium (mEq)	78	64 ± 19.7	14	5-20	Balance
Chloride (mEq)	209	164 ± 62	45	5-30	Positive balance
<i>Intragastric diet</i>					
Calories	2,580				
Water (l.)	2.5 ± 0.35	1.59 ± 0.55	0.91	1.0	Balance
Nitrogen (g.)	11.9 ± 1.4	9.4 ± 2.65	2.5	1.6	Positive balance
Sodium (mEq)	82 ± 43.9	50 ± 34.9	32	5-30	Balance
Potassium (mEq)	69 ± 7.9	39 ± 12.3	30	5-20	Positive balance
Chloride (mEq)	77 ± 43.9	78 ± 42.0	-1	5-30	Negative balance

During intravenous feeding there was rapid clinical improvement and no sweating or diarrhoea was noted. Thrombophlebitis was the only side-effect of the intravenous diet, and was seen in 10 of the 12 patients.

Comparison of Intravenous and Intragastric Diets

The intravenous diet C was given to six patients for a five-day period, followed by intragastric feeding for an equal time. The intakes of nitrogen and potassium were similar on the two diets, but the intravenous diet provided more water, calories, sodium, and chloride. These differences are shown in Table IV, together with the balance results obtained. During intragastric feeding there was a state of balance for water and sodium, and a more positive balance for nitrogen and potassium, with a small deficit of chloride.

The results shown in Table IV were next compared statistically. It was shown that time produced no cumulative effect during each diet. The further tests are best illustrated by reference to a single component of the diets—for example, sodium. For each patient the difference in intake of sodium during each diet was obtained (DI_{Na}). Similarly, for each patient the sodium balance for each diet was calculated and the mean difference (DNI_{Na}) and 95% confidence limits were obtained (Table V). The relationship of DI to DNI was tested by regression analysis. No significant relationship was found, and zero lay within the 95% confidence limits. A similar result was obtained for nitrogen, and the result for potassium was of doubtful significance. For water and chloride zero was outside the confidence limits and the balance between these diets therefore differed. This analysis confirmed the conclusions made from inspection of the balance results given in Table IV—

TABLE V.—Statistical Comparison of Balance Results on Intravenous and Intragastric Diets

Variable	Mean Difference in Net Intakes	95% Confidence Limits	
		Lower	Upper
Water	0.69	0.22	1.16
Nitrogen	-0.91	-3.9	2.08
Sodium	-3.88	-52.75	44.99
Potassium	-16.25	-34.48	1.98
Chloride	43.45	19.11	67.79

namely, that there was a positive balance for water on the intravenous diet and a negative balance for chloride on the intragastric diet.

Nitrogenous Products in the Urine on the Intravenous and Intragastric Diets

In four patients five days of intravenous diet C were followed by five days on the intragastric diet of Complan-glucose, and subsequently by two or three days on which the diet C was given via the naso-gastric tube. The total nitrogen and ammonia in the urine during the three diets was similar (Table VI). The urea nitrogen on the intravenous diet was less than that found during intragastric feeding with Complan-glucose. The urinary output of amino-acids was similar in the two diets. When the results for urea and ammonia were added (catabolic nitrogen) and expressed as a fraction of the total urinary nitrogen the values obtained during feeding with Complan-glucose were within the normal range of 80-90% (Peters and Van Slyke, 1931). When amino-acids and fat were given either intravenously or intragastrically this fraction was abnormally low.

TABLE VI.—Nitrogen Excretion (g./day) During Intravenous and Intragastric Feeding

	Nitro- gen Intake	Total Nitro- gen Output	Nitro- gen Balance	Urea Nitro- gen	Ammonia Nitrogen	$\frac{\text{Urea } N_2 + \text{Ammonia } N_2}{\text{Total } N_2} \times 100$
Diet C given intra- venously	12.8	10.9	+1.9	6.1	1.2	67
Diet C given intra- gastrically	12.8	9.9	+2.9	5.7	1.1	69
Complan- glucose diet	12.0	9.9	+2.1	7.6	1.1	88

Discussion

Severe illnesses require differing intakes of calories, water, nitrogen, and electrolyte, which cannot be provided by a single diet. The intravenous diet described led to rapid clinical improvement and was quickly prepared and easily organized. The patients probably had multiple deficits before treatment, and the diet quickly produced a state of balance. The calorie and nitrogen supplied by diet C are suitable for intravenous feeding during many severe illnesses, but the water and sodium intakes may be excessive for some conditions. It would be preferable to have an amino-acid preparation of low electrolyte content and add salts according to the likely needs, a practice already applied to the Complan-glucose diet. During prolonged feeding with diet C calcium and magnesium should be added.

Whenever possible, intragastric feeding is preferable to intravenous feeding, but the comparison made between the diets showed that the intravenous diet was a satisfactory substitute. Both diets have been used in the treatment of over 200 patients admitted to an intensive-care unit (Jones and Peaston, 1966). It is believed that the diets helped to reduce the mortality of severe illnesses and shorten convalescence. The only side-effect was thrombophlebitis, and its incidence has been reduced by changing the site of infusion each day.

The intravenous diet probably decreased the production of urea. The reduced output of urea, without alteration of ammonia excretion, suggests a decrease in protein catabolism (Folin, 1905).

Summary

When given during severe illnesses an intravenous diet of amino-acids, fat emulsion, and electrolytes resulted in a balance for nitrogen, sodium, potassium, and chloride, and a positive

balance for water. The results in six patients were compared with those obtained during intragastric feeding of the same patients. The intragastric diet of milk powder and glucose maintained metabolic balance except for a negative chloride balance. The urinary total nitrogen, ammonia, and amino-acids were similar on the two diets, but urea excretion was reduced on the intravenous diet, suggesting a decrease in protein catabolism.

The investigation was suggested by Professor A. Wilson and Dr. E. Sherwood Jones and supported by grants from the Liverpool

United Hospitals Research Committee, Regional Hospital Board, and the Cancer and Polio Research Club of Liverpool.

REFERENCES

- Folin, O. (1905). *Amer. J. Physiol.*, **13**, 117.
 Jones, E. S., and Peaston, M. J. T. (1966). *Practitioner*. In press.
 — and Sechiari, G. (1963). *Lancet*, **2**, 19.
 Moore, F. D. (1959). *Metabolic Care of the Surgical Patient*, p. 467. Saunders, Philadelphia.
 Peters, J. P., and Van Slyke, D. D. (1931). *Quantitative Clinical Chemistry*, vol. 1, p. 339. Baillière, Tindall and Cox, London.
 Wadström, L. B., and Wiklund, P. E. (1964). *Acta chir. scand.*, Suppl. No. 325, p. 50.
 Wretling, A. (1964). *Ibid.*, Suppl. No. 325, p. 31.

Four Cases of Bromism

G. NUKI,* M.B., M.R.C.P.; P. RICHARDSON,† M.B., B.S.; M. J. GOGGIN,‡ M.B., B.S.
 R. I. S. BAYLISS,§ M.D., F.R.C.P.

Brit. med. J., 1966, **2**, 390–391

Although bromide poisoning was described by Huette (1850), it was Wuth (1927) who drew attention to its high incidence in psychiatric hospital wards. The "bromide hazard" was well recognized in the 1930s (Diethelm, 1930; Wagner and Bunbury, 1930; Barbour *et al.*, 1936), when vast quantities of bromides were prescribed. Today, however, when their use has been largely replaced by barbiturates, phenothiazines, and other tranquillizers, it seems likely that bromide intoxication is not considered promptly enough in the differential diagnosis of obscure neuropsychiatric problems.

Case 1

A 59-year-old woman had been in poor health for many years. Her main complaints were of constipation and fatigue, which were so extreme that she seldom went out and spent much of her day resting on a sofa. At times she was confused, her speech slurred, and her memory poor. In June 1965 she slipped and fractured the neck of her femur. Her post-operative condition gave cause for alarm. She was drowsy, disorientated, and incontinent. She was emaciated; her tongue was dry and furred. She had bilateral ptosis, constricted pupils, extreme muscular weakness, and depressed tendon reflexes. There were no localizing signs in the central nervous system, and biochemical tests showed no evidence of renal, hepatic, or other metabolic disorder. It was then learned that she had for many years been taking an "innocuous sleeping mixture" prescribed originally for her husband in 1939. Each night she took at least three tablespoonfuls, containing in all 30 minims (1.5 ml.) of tincture of morphine and 60 gr. (3.9 g.) of ammonium bromide. The serum bromide level was found to be 380 mg./100 ml. Her mental and physical condition improved gradually but strikingly on withdrawal of the bromide mixture and the administration of ammonium chloride and mersalyl.

Case 2

A 76-year-old woman, admitted to hospital for terminal nursing in December 1964, had been taking mist, gelsem. et hyoscy. co. *B.N.F.* for trigeminal neuralgia since 1952. In 1958 she began to have lapses of memory. A year later a diagnosis of cerebral arteriopathy was made when she began to have paranoid delusions. Her condition gradually deteriorated, and by 1961 she was incapable

of doing housework and had made several suicidal gestures. During the month before admission she became incoherent and developed incontinence of urine, while continuing to complain of trigeminal neuralgia. Examination revealed a cachectic, dehydrated old woman who moaned and muttered unintelligibly but showed no localizing signs in the central nervous system. Simple rehydration produced such striking clinical improvement that a review of her drug therapy was suggested. As mist, gelsem. et hyoscy. co. *B.N.F.* contains 650 mg. of bromide per 15 ml. the serum bromide level was determined and found to be 285 mg./100 ml. She was treated with sodium chloride, a high fluid intake, and mercurial diuretics. Clinical improvement roughly paralleled the fall in her serum bromide, though she had some episodes of confusion. Three months after admission she was well, apart from slight lapses of memory, and her serum bromide had fallen near to zero.

Case 3

A 59-year-old man was admitted to hospital in May 1965 with a six-months history of progressive mental deterioration and a two-months history of dragging his right foot. A week before admission he became paranoid and violent before lapsing into a semicomatose state. He was found at home, in bed, dehydrated, too weak to move, and surrounded by broken furniture. He was dysarthric and his pupils were constricted. Tendon reflexes were diminished in both legs but increased in the right arm, with an equivocal right plantar response.

On admission to a general hospital medical ward, examination revealed sordes in the mouth and an acneiform rash on the chest. There was nominal dysphasia as well as dysarthria and disorientation. He had mild incoordination of the left arm and leg, but there were no pyramidal signs. Investigation showed normal serum electrolytes, urea, sugar, vitamin B₁₂, Wassermann reaction, Kahn test, and chest and skull radiographs. Lumbar puncture showed nothing abnormal except for a cerebrospinal fluid protein of 110 mg./100 ml.

The patient was transferred to a neurosurgical unit, where ultrasound suggested a shift from left to right, though a left carotid arteriogram and ventriculography were normal. An E.E.G. was not contributory, as it was performed after burr-holes had been made.

A space-occupying lesion having been excluded, he was returned to the medical ward, where over a period of days he improved to the extent of being able to hold a rational conversation. It then transpired that he had taken a bromide-and-chloral mixture for 18 years since his discharge from a mental hospital after what was described as an hysterical illness. In the week before admission he had doubled his dose, as it seemed to be losing its effectiveness in calming his symptoms of anxiety. His serum bromide level 10 days after the last dose was still 202 mg./100 ml. He was treated

* Medical Registrar, Westminster Hospital, London.

† Senior House Officer in Medicine, St. Stephen's Hospital, London.

‡ Medical Registrar, Mount Vernon Hospital, London.

§ Consultant Physician, Westminster Hospital, London.