Amino Acid Solutions for Intravenous Use

THE REDUCED INCIDENCE OF SYSTEMIC REACTIONS WHEN USING A LOW GLUTAMIC ACID MIXTURE

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WHETHER or not parenteral amino acids are manufactured from bovine plasma, casein, blood fibrin, or other sources rarely concerns the physician who uses them in his clinical practice. He is primarily concerned only if the patient obtains a reaction from its administration.

Despite their value in parenteral nutrition, amino acid solutions have been slowly accepted, a contributory factor being, no doubt, the reactions[1,2,5,6,8] which occur after administration. Individual intolerances to amino acids may exist, but on the whole our observations have indicated that a rapid rate of administration will produce undesirable symptoms in almost every individual. These undesirable symptoms will also disappear quickly when the rate of administration is diminished.

We have previously observed[4] that nausea was the usual first manifestation of intolerance, occurring between rates of 0.1 to 0.49 g of amino acids per kg/hr. When the rate of administration exceeded 0.49 g of amino acids per kg/hr, multiple manifestations of intolerance were universally present, i.e., vomiting, itching, tingling, abdominal cramps, flushing, and headache. This rate appeared to be the threshold beyond which troublesome symptoms regularly appeared and was fairly constant for several commercially available brands of amino acid solutions.

The work of Levey, Smyth, and coworkers[3,5,6,7] has shown that glutamic acid and possibly aspartic acid are important factors in the causation of nausea associated with the intravenous administration of amino acid solutions. This present study confirms the findings of these authors by demonstrating that an amino acid solution, in which a low glutamic acid concentration has become a commercial and economic feasibility, can be administered at substantially higher rates than those with the usual glutamic acid concentration.

METHOD OF STUDY

The subjects of this study were patients from the surgical wards of St. Barnabas Hospital, Minneapolis, either being prepared for or recovering from major surgical procedures.

Solution A is a commercially available amino acid product with the amino acid content as illustrated in Table I. Solution B has essentially the same amino acid content (Table I) except for its glutamic acid. These two solutions have been prepared in the same laboratory.‡

TABLE I

Amino Acid	5% Amino acid solution Grams per liter	
	Solution A	Solution B
Glutamic Acid	5.20	0.78–1.38
Arginine	1.70	1.62
Histidine	1.14	0.93
Lysine	3.70	3.52
Isoleucine	2.48	2.62
Leucine	4.16	4.41
Methionine	2.09	1.98
Phenylalanine	1.80	1.75
Threonine	1.78	1.73
Tryptophan	0.32	0.38
Tyrosine	0.46	0.60
Valine	3.10	3.10

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The rate of administration was controlled and calculated on the basis of the grams of amino acids per kg/hr. It was found that when a reaction of nausea occurred, it developed within a few minutes and could be eliminated, likewise, in a few minutes by decreasing the rate of administration. If a reaction of nausea did not occur, an established rate of administration was continued for 20 minutes. Thereafter a faster rate was again established, and this procedure was continued until nausea developed, or until the liter of solution was given.

Vomiting was usually the next most common manifestation of intolerance. Abdominal distress, abdominal cramps, flushing, tingling, prickling, headache, and drowsiness were occasional but inconstant observations. These latter clinical manifestations were observed in this study, but they have not been recorded here.

FINDINGS

Nausea was observed less often (23 per cent) when the rate of administration of amino acid Solution A was less than 0.35 g per kg/hr; it was a common occurrence when the rate of administration exceeded 0.35 g/kg/hr (Table II), and it became progressively greater as the rate of administration increased.

Amino acid Solution B, in which the glutamic acid content was minimal, rarely caused nausea until the rate of administration exceeded 0.50 g/kg/hr (Table II).

TABLE II

The Incidence of Nausea in Relation to Grams of Amino Acid per Kilogram per Hour

Rate of administration g/kg/hr	Using Solution A		Using Solution B (low glutamic acid)	
	Incidence of nausea	Total tests made	Incidence of nausea	Total tests made
0 to 0.3499	42 (23%)	181	1	63
0.35 to 0.4999	13 (37%)	35	0 (1.5%)	11
0.50 to 0.9999	10 (43%)	23	11 (19%)	57

As the rate of administration increased beyond that, other and multiple manifestations of intolerance became evident with both Solutions A and B; and in all instances in which an effort was made to increase the rate, a point of intolerance could be reached even in the low glutamic acid group.

COMMENTS AND CONCLUSIONS

While our previous report[4] was concerned mainly with the occurrence of untoward reactions more severe than nausea, our present data deal more particularly with the minor reaction of nausea. Our findings indicate that an amino acid solution, of a composition commonly available commercially, shows a nausea rate of 23 per cent when rates of administration below 0.35 g/kg/hr are studied. The lowering of glutamic acid content of such a solution considerably increases the tolerable administration rate.

The administration of intravenous amino acid should preferably be given at a considerably slower rate than that used with most intravenous solutions. A rapid rate is undesirable because at more rapid rates of administration the amino acid is utilized by the body with less efficiency. Nevertheless, the hospitalized patient is often interrupted by numerous diagnostic and other therapeutic procedures and it is at such time that the administration rate of the intravenous fluid is apt to fluctuate. As a result of these interruptions the rate of administration of amino acids may exceed a rate of 0.35 g/kg/hr with remittent nausea. If, therefore, a solution could be given at a more rapid rate, during such unavoidable episodes, a very practical advantage would be obtained for the patient.

Our data have shown that a mixture of amino acids for parenteral use with a low glutamic acid content causes much less nausea and fewer undesirable clinical symptoms than have been observed with a solution essentially identical except for a high glutamic acid content.

REFERENCES

1. Cannon, P. R., Frazier, L. E., and Hughes, R. H.: Protein hydrolysates. Food for the sick. *Research Review*, Office of Naval Research, November 1950, p. 13.
2. Frost, D. V., Hansen, J., and Olsen, R. T.: Intravenous use of high levels of fibrin and casein hydrolysates in hyperproteinemic dogs. *Arch. Biochem.* 10: 215, 1946.

3. LEVEY, S., HARROUN, J. E., and SMYTH, C. J.: Serum glutamic acid levels and the occurrence of nausea and vominting after the intravenous administration of amino acids solution. *J. Lab. & Clin. Med.* 34: 1238, 1949.
4. RICE, C. O., and STRICKLER, J. H.: Parenteral nutrition in surgery. *South Dakota J. Med. & Pharm.* 9: 1, 1956.
5. SMYTH, C. J., LASICHAK, A. G., and LEVEY, S.: The effects of orally and intravenously administered amino acids mixtures on voluntary food consumption in normal men. *J. Clin. Investigation* 26: 439, 1947.
6. SMYTH, C. J., LASICHAK, A. G., and LEVEY, S.: The effect of rate of administration of amino acids preparations on the urinary wastage of amino acid nitrogen in man. *J. Clin. Investigation* 27: 412, 1948.
7. SMYTH, C. J., LEVEY, S., and LASICHAK, A. G.: The relationship of glutamic and aspartic acids to the production of nausea and vomiting in man. *Am. J. M. Sc.* 214: 281, 1948.
8. WERNER, S. C.: The use of mixtures of pure amino acids in surgical nutrition, *Ann. Surg.* 126: 169, 1947.

After Malthus

"...A clergyman-economist named Malthus forecast in 1803 that man's reproductive capacity would some day outrun his capacity to produce food. The events since then have proven that while Malthus was quite ignorant of many of the factors, favorable and unfavorable, which would affect the date of its fulfillment, his dire prophecy was sound. Malthus could not foresee how enormously agricultural productivity would be later increased by the use of mechanical power, fertilizers, plant and animal breeding, etc. On the other hand he was also unaware how modern preventive medicine would prolong life and enormously accelerate the yearly gain in population. The present human race numbers three times as many as that of Malthus' day and the twentieth century far surpasses any previous one in the rate of accumulation."

—R. R. Williams. *Am. Scientist* 44: 318, 1956.