PRELIMINARY COMMUNICATIONS

Histidine for Treatment of Uraemic Anaemia

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Summary

A group of 28 uraemic patients on dialysis treatment were given daily supplements of histidine by mouth. Plasma amino-acid concentration, plasma iron, serum transferrin, packed cell volume, and reticulocyte count were all measured before and after two months of histidine supplementation. The treatment raised the plasma histidine concentration and at the same time there was a rise in transferrin and iron levels and packed cell volume. Reticulocyte counts fell after two months of histidine supplementation.

Introduction

The role of histidine in cases of uraemia was investigated after the finding of low plasma levels of this amino-acid in patients with uraemia (Giordano *et al.*, 1967) and the small extent of incorporation of ¹⁵N into histidine in isotopic experiments (Giordano *et al.*, 1967, 1968a). In earlier work it was shown that adding a small dose of histidine to the diet could result in im-

proved nitrogen balance but generally resulted in increased globin synthesis (Giordano *et al.*, 1968 b, 1970, 1972). In fact, it was shown in vitro that reticulocytes of uraemic patients incorporated radioactive leucine at a faster rate when they came from patients who had been given histidine supplements. It seemed then that histidine, though considered a non-essential amino-acid for man, was acting in uraemia as a limiting amino-acid; and we suggested that it may be indispensable in patients with uraemia.

Anaemia is one of the more important clinical symptoms of uraemia, but relatively little has been achieved therapeutically either in dialysed or in non-dialysed patients. We have studied further the effect of histidine on the anaemia of uraemic patients, and our results indicate that histidine supplementation represents a new and promising approach to the problem.

Methods

A group of dialysed patients (one child and 27 adults) ranging from 8 to 57 years of age were studied at our centre. All were allowed a free diet after the usual instructions on electrolyte and water restrictions. The patients had been dialysed with coil kidneys for periods of from six months to six years. Clinical diagnosis and weekly hours of dialysis are given in table I. The study was first designed to include 36 patients but those who had ruptures of coils during dialysis were later excluded. The 28 patients who completed this study had no blood transfusions either before or during the study period. Supplements of iron and folic acid consisted of polyvitamin capsules containing 10 mg iron as sulphate, 1 mg copper as oxide, and 1 mg folic acid. Supplementation had been started at the beginning of dialysis treatment. Each patient was also given 3 mg folic acid intramuscularly at the end of each dialysis period. The histidine supplementation consisted of 1 g histidine monohydrochloride a day for two months, given by mouth and split between two meals. The child received 300 mg histidine monohydrochloride a day, again divided into two doses.

Plasma histidine was measured by an amino-acid analyser (Beckman Mod. 120 C). Plasma transferrin was regularly estimated as an index of the nutritional status using the technique of Mancini *et al.* (1965). Plasma iron concentration and

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TABLE I—Clinical Diagnosis and Weekly Hours of Dialysis of 28 Patients

Case No.	Age and Sex	Start of Renal Dialysis Treatment	Weekly Hours of Haemodialysis	Underlying Renal Disease
1	52 M.	12/1972	2 × 6 hours	Chronic glomerulonephritis
2	35 F.	3/1968	3 × 6 "	Chronic pyelonephritis
3	15 F.	2/1972	3 × 6 "	Chronic glomerulonephritis
4	57 M.	9/1972	3 × 6 "	Chronic pyelonephritis
5	57 M.	8/1971	3 × 6 "	Chronic glomerulonephritis
6	44 M.	6/1972	3 × 6 "	" "
7	27 F.	3/1969	3 × 6 "	" "
8	30 F.	6/1970	3 × 6 "	Chronic pyelonephritis
9	50 M.	7/1970	3 × 6 "	" "
10	52 M.	6/1970	3 × 6 "	Chronic glomerulonephritis
11	27 M.	1/1973	2 × 6 "	" "
12	58 M.	10/1971	3 × 6 "	" "
13	32 F.	3/1969	2 × 6 "	Chronic pyelonephritis
14	35 F.	3/1971	3 × 5 "	" "
15	22 F.	8/1969	3 × 5 "	" "
16	37 M.	4/1971	3 × 5 "	" "
17	42 F.	2/1973	2 × 6 "	Chronic glomerulonephritis
18	47 M.	1/1973	2 × 6 "	" "
19	8 M.	9/1971	3 × 5 "	Congenital hypoplasia
20	47 M.	8/1972	3 × 5 "	Primary hypertension
21	32 F.	9/1967	2 × 6 "	" "
22	27 F.	8/1972	3 × 5 "	Chronic glomerulonephritis
23	18 M.	9/1970	3 × 5 "	" "
24	26 M.	10/1971	3 × 5 "	" "
25	51 M.	11/1968	3 × 5 "	" "
26	53 M.	10/1970	3 × 6 "	" "
27	29 F.	10/1967	3 × 6 "	" "
28	36 M.	8/1972	3 × 6 "	" "

TABLE II—Body Weight, Blood Pressure, Blood Urea Nitrogen, and Plasma Creatinine before and after Histidine Administration

Case No.	Before Histidine Supplementation				After Histidine Supplementation			
	Body Weight (kg)	Blood Pressure (mm Hg)	Blood Urea Nitrogen (mg/100 ml)	Plasma Creatinine (mg/100 ml)	Body Weight (kg)	Blood Pressure (mm Hg)	Blood Urea Nitrogen (mg/100 ml)	Plasma Creatinine (mg/100 ml)
1	67.1	160/80	105	9.88	66.9	155/90	100	10.60
2	42.0	105/60	85	10.40	42.1	100/65	90	10.88
3	64.3	150/80	82	9.12	64.0	140/80	86	9.12
4	55.3	165/80	80	10.88	55.3	155/80	78	9.88
5	56.0	150/100	80	10.40	56.2	140/95	82	11.00
6	55.9	135/90	107	10.40	56.1	140/90	105	10.88
7	72.0	150/70	83	10.88	72.4	130/70	89	11.06
8	62.0	160/100	75	8.16	62.1	155/100	70	8.06
9	62.6	130/70	94	12.88	62.8	130/70	90	12.10
10	52.6	115/60	82	9.12	52.4	115/65	85	9.40
11	60.0	130/80	101	10.80	60.2	135/90	110	10.20
12	60.5	140/90	110	12.16	60.0	140/90	100	12.30
13	48.8	170/110	106	11.20	49.3	160/100	102	10.88
14	62.3	160/105	84	10.40	62.7	160/100	86	10.00
15	48.0	130/80	84	11.70	47.7	130/85	80	12.00
16	57.0	180/115	102	11.20	57.3	175/125	110	11.90
17	66.3	130/70	80	10.88	66.2	140/65	76	9.80
18	70.0	160/90	86	10.40	69.8	165/90	78	10.40
19	23.0	100/60	100	9.12	22.9	95/60	88	8.40
20	71.0	150/90	102	13.02	71.3	145/80	104	11.40
21	62.0	140/85	94	10.40	61.9	140/80	96	10.05
22	55.0	160/100	86	9.12	55.4	130/80	92	9.80
23	70.0	140/95	75	8.16	69.9	130/80	70	7.85
24	48.0	135/80	82	9.12	48.5	135/70	72	8.16
25	75.0	155/95	102	10.88	75.2	160/105	110	11.40
26	63.0	160/90	88	9.40	63.1	150/100	105	11.20
27	52.0	135.75	75	8.40	52.3	140/80	70	8.10
28	66.0	145/80	100	10.88	66.2	150/90	110	11.05
Mean	58.8	145/85	90.3	10.33	58.9	141/85	90.5	10.28

packed cell volume (P.C.V.) were estimated by standard techniques. To avoid any interference from an increase in plasma volume during the interdialysis period all determinations were carried out before starting the first dialysis of the week.

Results

The concentration of histidine in the serum, serum transferrin, plasma iron, reticulocyte count, and P.C.V. were all studied before and after the two months of histidine supplementation (table II). The mean serum histidine concentration ($\pm$ S.E.) rose from 0.792 ± 0.022 mg/100 ml to 1.491 ± 0.039 mg/100 ml after histidine supplementation ($P < 0.001$; fig. 1). Transferrin also significantly increased from 198.1 ± 8.81 mg/100 ml to 268.3 ± 10.17 mg/100 ml ($P < 0.001$; fig. 2). Plasma iron increased from 56.2 ± 2.27 μ g/100 ml to 85.0 ± 2.40 μ g/100 ml after histidine supplementation (fig. 3). This difference was again statistically significant ($P < 0.001$). The P.C.V. rose from 21.09 ± 1.09 to 25.75 ± 1.13 after histidine ($P < 0.001$; fig. 4). Analysis of the reticulocyte count before and after two months

FIG. 1—Serum histidine concentrations before and after histidine supplementation.

FIG. 2—Serum transferrin levels before and after histidine supplementation.

FIG. 3—Plasma iron changes before and after histidine supplementation.

of histidine supplementation showed a fall in the proportion of reticulocytes after supplementation (from $1.73 \pm 0.12\%$ to $1.38 \pm 0.08\%$; $P < 0.001$) (fig. 5).

FIG. 4—Packed cell volumes before and after histidine supplementation.

FIG. 5—Proportion of reticulocytes present before and after histidine supplementation.

Discussion

Our earlier studies on the effects of histidine supplements in uraemia suggested that globin synthesis might be stimulated, but such a conclusion could not be fully justified on the basis of experiments in vitro (Giordano *et al.*, 1968 b, 1970, 1972). The data obtained in the present study add further evidence, for they show that serum transferrin, plasma iron, and P.C.V. all rise

after the plasma histidine level is raised by relatively small dietary supplements.

Anaemia may ameliorate spontaneously during the course of regular dialysis (Eschbach *et al.* 1967), particularly in the second and subsequent years, and this has been our experience with many patients. On the other hand we have been unable to relate P.C.V. to better control of uraemia (see table II).

The increase in serum transferrin may be an effect of a better nutritional status rather than a consequence of increased iron. In fact, when iron levels rise transferrin levels do not directly follow the change of serum iron (Masson, 1971). A strict correlation between the nutritional status of patients and levels of transferrin has, however, been established (Antia *et al.*, 1968; McFarlane *et al.*, 1969). In addition to its nutritional effect the importance of histidine for synthesis of haemoglobin is multifactorial: it is needed for linking the haem group to the globin molecule which, in fact, contains a high proportion of histidine.

Recently, moreover, it has been suggested that histidine regulates gastrointestinal absorption of iron (Van Campen and Gross, 1970), and this could explain the increase in plasma iron observed in our patients. It is not clear whether adding histidine to the diet enhances haemoglobin synthesis by a direct stimulatory effect on the reticulocytes or by its availability for incorporation into the haemoglobin molecule. The fact that reticulocyte counts were not increased after histidine supplementation may favour the second hypothesis.

Our results indicate that histidine has a beneficial effect on anaemia in uraemia. Since histidine is an innocuous and relatively inexpensive compound we suggest that it be used in an extensive controlled trial as a regular dietary supplement in dialysed patients.

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References

- Antia, A. V., McFarlane, H., and Soothill, J. J. (1968). *Archives of Disease in Childhood*, **43**, 459.
- Bergstrom, J., Fusts, P., Josephson, B., and Norre, L. O. (1970). *Life Sciences*, **7**, 787.
- De Santo, N. G., De Pascale, C., Esposito, R., Balestrieri, C., and Giordano, C. (1968). *Biochimica Applicata*, **15**, 556.
- Eschbach, J. W., Funk, D., Kuhn, I., Schribner, B. H., and Finch, C. A. (1967). *New England Journal of Medicine*, **276**, 653.
- Giordano, C., Esposito, R., De Pascale, C., and De Santo, N. G. (1967). In *Proceedings of 3rd International Congress of Nephrology, Washington, 1966*, ed. G. E. Schreiner, vol. 3, p. 214. Basle, Karger.
- Giordano, C., De Pascale, C., De Cristofaro, D., Capodicasa, G., Balestrieri, C., and Baczyk, K. (1968 a). *Proceedings of the Conference on Nutrition in Renal Disease, Manchester 1967*, ed. G. M. Berlyne, p. 23. Edinburgh, Livingstone.
- Giordano, C., De Pascale, C., Balestrieri, C., Cittadini, D., and Crescenzi, A. (1968 b). *American Journal of Clinical Nutrition*, **21**, 394.
- Giordano, C., De Pascale, C., De Santo, N. G., Esposito, R., Cirillo, D., and Stangherlin, P. (1970). In *Proceedings of the 4th International Congress of Nephrology, Stockholm 1969*. Ed. N. Alwall and F. Berglund, vol. 2, p. 196. Basle, Karger.
- Giordano, C., De Santo, N. G., Rinaldi, S., De Pascale, C., and Pluvio, M. (1972). In *Uremia, An International Conference on Pathogenesis, Diagnosis and Therapy, Freiburg*, p. 138. Stuttgart, George Thieme.
- McFarlane, H., Adcock, K. J., Ogbeide, M. J., Adeshina, H., Taylor, G. O., Reddy, S., Gurney, I. M., and Mordia, J. A. (1969). *Lancet*, **1**, 392.
- Mancini, G., Carbonara, A. O., Heremans, J. F. (1965). *International Journal of Immunochemistry*, **2**, 235.
- Masson, P. (1971). *La Ricerca Clinica Laboratoria*, **1**, 1.
- Van Campen, D., and Gross, E. (1969). *Journal of Nutrition*, **99**, 68.