Histidine and Iron Supplementation in Dialysis and Pre-dialysis Patients

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Summary

Chronic renal failure (CRF) patients treated with histidine alone did not show any effect with respect to anaemia or protein metabolism, despite a rise in serum histidine levels. Beneficial effect of iron with regards to anaemia and protein metabolism was seen in CRF patients treated with iron alone or in combination with histidine. Patients with combination therapy showed accelerated improvement of anaemia in comparison with patients treated with iron alone. In RDT patients, who underwent basic treatment with parenteral iron, histidine failed to show any effect with regards to anaemia, despite significantly lowered serum histidine levels. But under histidine treatment a significant rise of transferrin levels occurred in RDT patients, so that histidine must be considered as a limiting factor in protein metabolism in these cases. Histidine requirements of RDT patients are more than 1–2 g/day, and are higher than the requirements of patients conservatively treated.

Introduction

In the maintenance nutrition of the healthy adult, histidine is considered to be a non-essential amino acid. This fact is surprising in view of the absolute necessity of histidine for other mammals, such as the rat and the dog. In uraemia, however, histidine needs increase, as demonstrated by the following:

(1) Low serum levels of histidine are found in uraemic subjects (Giordano et al, 1968).

(2) Bergström et al, (1972) reported significant enhancement of nitrogen balance in uraemic subjects by the addition of histidine to an infusion-solution of eight essential amino acids.

(3) Josephson et al, (1972) reported a lack of ^{15}N-labelled histidine in uraemic subjects after intake of ^{15}N-labelled urea.

Additionally Giordano et al, (1973) reported amelioration of anaemia in RDT patients after histidine supplementation, but that study could not answer the question – was amelioration of anaemia due to a direct effect of histidine on globin synthesis, or to an enhancement of iron absorption ? To resolve this, and to evaluate iron and histidine requirements in conservatively treated CRF patients, the following controlled studies were performed.

PATIENTS AND METHODS

Forty-four out-patients with plasma creatinine above 6 mg% (mean 8.7 mg%) entered the study. All patients were treated with selective low-protein potato-egg diet (PED) with a protein content of 20–25 g/day (Kluthe and Quirin 1967). The patients were divided into four groups. Group A were controls, and patients in Group B were supplemented with 1.5 g oral L-histidine daily. Patients in Group C took 300 mg iron daily in the form of iron sulphate. Patients in Group D were treated with a combination of histidine and iron in the same dosage as above. Eight patients were eliminated from the study, two because of gastro-intestinal bleeding, two because of the start of haemodialysis, two withdrew and two died during observation.

Twenty-six dialysis patients were included in a second study. They were dialysed at the centre twice weekly with Lundia or RP5 disposable dialysers, 9–11 hr per dialysis. All patients received intravenous iron, in a dosage of 32 mg at the end of each dialysis. Patients in the histidine group received 1.5 g L-histidine daily. Six patients were excluded from the study – two were transplanted, two developed a neoplasm, one had acute hepatitis and one developed acute gastro-intestinal bleeding.

The following data were evaluated: haemoglobin or packed cell volume (PCV) as a parameter for anaemia, serum transferrin as a parameter for protein nutritional status, and serum iron and histidine levels. Furthermore protein intake and histidine intake of dialysis patients were evaluated by retrospective and prospective diet analysis. Statistical analyses have been performed using Student's 't'-test for paired data.

RESULTS AND DISCUSSION

In the control group A of conservatively treated patients, no significant changes in haemoglobin (Hb), transferrin iron or histidine occurred during six weeks of observation. Likewise, no changes in haemoglobin, transferrin and iron could be detected in group B, the group with 1.5 g histidine supplementation, although

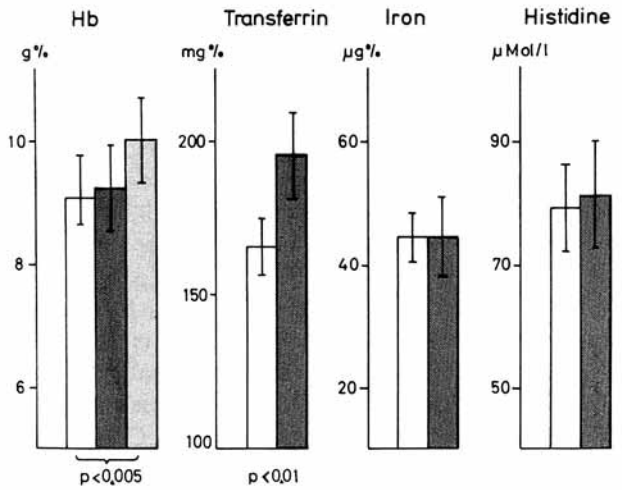

Figure 1. CRF patients (group C) treated with oral iron. White bar = before treatment, grey bar = after six weeks treatment, light grey bar = after three months treatment.

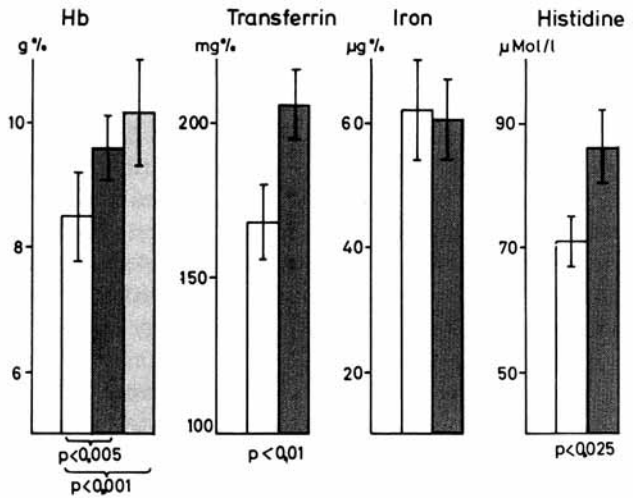

Figure 2. CRF patients (group D) treated with combination therapy (histidine + iron). White bar = before treatment, grey bar = after six weeks treatment, light grey bar = after three months treatment.

the histidine level had arisen from 82 ± 4 µmol/l to 98 ± 5 µmol/l ($p < 0.005$).

In group C, with 300 mg iron supplement, a significant rise in serum transferrin occurred from 166 ± 11 mg% to 195 ± 13 mg% ($p < 0.001$), but the anaemia did

not improve. Only after a three-month period of treatment, was there a significant rise of haemoglobin (Figure 1) from 9.1 ± 0.7 g% to 10.0 ± 0.6 g% ($p < 0.001$). In group D with (histidine + iron) combination therapy, the haemoglobin increase from 8.5 ± 0.7 g% to 9.6 ± 0.5 g% ($p < 0.005$) was significant after six weeks of treatment (Figure 2, middle bar) an even greater increase to 10.2 ± 0.8 g% ($p < 0.001$) being seen after three months. As in group B, histidine levels rose from subnormal to normal values, and as in group C, there was a significant rise of transferrin levels from 168 ± 13 mg% to 206 ± 11 mg% ($p < 0.01$).

The most important result of this study appears to be the amelioration of anaemia in conservatively treated patients with chronic renal failure. Despite the fact that these patients do not lose iron in the same quantity as dialysis patients, they are obviously iron deficient. Iron-deficiency of these patients may be due to an impaired iron-reabsorption, as found in non-dialysed CRF patients (Fam et al, 1970) combined with occult gastro-intestinal blood losses in pre-uraemic patients, furthermore the iron content of PED is reduced. Therefore renal anaemia in these cases is complicated by iron-deficiency and can be improved by iron supplements. Combined therapy of histidine and iron is better than iron therapy alone, probably because histidine enhances iron reabsorption, as demonstrated in animal experiments (Van Campen et al, 1970). Histidine alone did not improve anaemia in our cases.

A very interesting point seems to be improvement of transferrin levels in both groups receiving iron, either alone or in combination with histidine, whereas histidine alone failed to show any effect in CRF patients. Transferrin is well known as a sensitive parameter of protein nutrition in renal diseases (Kluthe et al, 1971; Quirin et al, 1973; Jontofsohn et al, 1974). From previous studies in RDT patients we had expected a fall in serum transferrin levels after iron substitution because there exists a feed-back mechanism between the iron pool and serum transferrin (Jontofsohn et al, 1974). All of our patients had low transferrin levels because of dietary protein restriction. We hypothesise that the energy usage of these patients was not optimized because of iron deficiency. It is well known that iron plays a major role as a co-enzyme in the oxidative cycle (Malmström, 1970). Iron supplements may therefore increase energy usage by activating the oxidative cycle, and in this way enhance protein metabolism. Further studies are needed to clear up this point.

In the trial with dialysis patients no changes in PCV and transferrin occurred during three months of observation in the control group. Histidine dosage of 1.5 g/day did not improve anaemia (Figure 3). Since all our RDT patients were treated with parenteral iron, this may be evidence that histidine does not have a direct influence on anaemia, and that the improvement of anaemia observed by Giordano (1973) in his patients treated with oral iron could be due to enhancement of iron reabsorption. On the other hand, a significant rise in serum transferrin levels from 181 ± 16 mg% to 202 ± 17 mg% ($p < 0.01$) after histidine treatment was observed, in the same way as reported by Giordano et al (1973) and recently

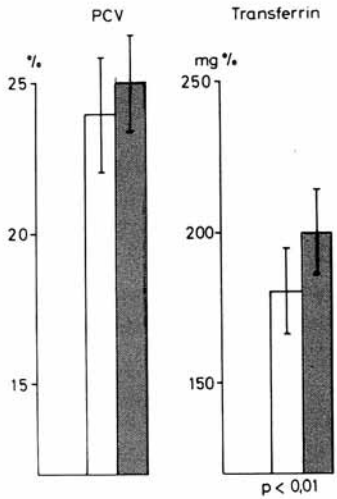

Figure 3. RDT patients treated with 1.5 g/day oral histidine. White bar = before treatment, grey bar = after three months treatment.

by Kult et al (1974). In our patients with a dietary protein intake of about 1 g/kg daily serum transferrin levels were lowered. These signs of protein deficiency may be explained by amino-acid losses during haemodialysis and by uraemic disorders of amino-acid metabolism. The beneficial effect of histidine with respect to transferrin underlines the importance of histidine in uraemia. In spite of a histidine intake of 1–2 g/day, RDT patients showed more definite signs of histidine deficiency than CRF patients with only 0.4 g/day histidine intake. So serum histidine was significantly lower in RDT patients with 64 ± 4 μmol/l than in CRF patients with 80 ± 3 μmol/l ($p < 0.005$). The following explanations may be relevant – RDT patients lose about 0.3 g histidine at each dialysis, but this is too small to be the only explanation, and the more severe impairment of histidine metabolism in RDT patients than in conservatively treated CRF patients must be taken into consideration.

CONCLUSIONS

(1) Oral-iron supplementation in conservatively treated CRF patients has beneficial effects with regard to anaemia and protein metabolism.

(2) There is no direct effect of histidine on anaemia in CRF. Histidine, however, is able to optimize iron supplementation by enhancing its reabsorption.

(3) Histidine seems to be a limiting factor of protein metabolism in RDT patients. Therefore, histidine supplementation in these patients is followed by a

rise in serum transferrin.

(4) The histidine requirements of RDT patients are higher than are those for conservatively treated patients.

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Open Discussion

KOPPLE (Los Angeles) We have done studies in both normal and chronic uraemic patients receiving iron supplements with histidine-deficient diets. They developed anaemia due to failure of normal erythropoiesis which was relieved by histidine alone. However our own studies confirm that histidine does not relieve uraemic anaemia.

V CAMBI (Italy) You showed that there was a difference between haemoglobin in histidine-treated patients and (histidine + iron) treated patients. Was this difference significant and was the diet comparable in both groups? What statistical analysis did you make to show that this was not a chance difference?

JONTOFSOHN The statistical analysis was made using Student 't'-tests from paired data.

K S MIRAHMADE (Los Angeles) We have used 2 g of histidine in five anaemic dialysis patients and have seen no change in haematocrit or serum albumin. We think that if the patient is on an adequate protein diet (80 g) histidine

supplementation will not increase haematocrit.

A M TANNENBERG (New York) Did these patients receive both oral and intravenous iron?

JONTOFSOHN No, they received only intravenous iron.

TANNENBERG Did you analyse the bone marrow in these patients for adequacy of iron stores?

JONTOFSOHN Yes. In the dialysis patients there was stored iron, but in the conservatively treated patients, we found signs of iron deficiency.