Histidine Supplements in the Treatment of Uraemic Anaemia

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INTRODUCTION

In the last few years there have been many approaches to the treatment of uraemic anaemia, such as spleen removal (Bischel et al, 1972), iron supplementation and the limitation of blood loss during dialysis.

We would like to report on the use of histidine which represents a new approach in the management of the anaemia of chronically uraemic patients.

It was reported by us that plasma histidine levels are low in uraemic patients maintained both on low protein diet and on regular dialysis therapy (RDT) (Giordano et al, 1967). It was also reported from our laboratory that the role of histidine was extremely important in view of the fact that histidine supplementation in uraemic patients increases the rate of globin synthesis. This effect was more important than the role of histidine in improving nitrogen balance (Giordano et al, 1968, 1969). The influence of histidine on nitrogen balance and its improvement in uraemic patients has also been stressed by others (Bergström et al, 1970). A more recent report confirms the role of histidine supplementation on globin synthesis (Giordano et al, 1971).

The purpose of the present work was to study the effect of histidine supplementation on the anaemia of uraemic patients.

MATERIAL AND METHODS

Twenty patients, 8 females and 12 males, aged from 8 to 51 years, were studied. They had all been dialysed using coil kidneys from 2 months to 6 years. Four patients were on 2 x 6 hours dialysis a week; 4 patients were on 3 x 5 hours dialysis a week and 12 patients were on 3 x 6 hours dialysis a week. No blood transfusions or extra iron supplementation were given. All the patients were given 1g of histidine (mono-HCl) by mouth each day for 9 weeks, except for the child who was given 0.3g a day.

Plasma histidine concentration was estimated by an aminoacid analyser. As an index of the nutritional status transferrin levels were assayed using
immunological methods. Plasma iron concentration and haematocrit were determined by standard techniques. Because of the habitual increase in plasma volume of patients between dialyses all blood specimens were obtained before starting the first dialysis of the week.

RESULTS

The effects of histidine supplementation were studied in relation to the following parameters: plasma histidine concentration, plasma transferrin concentrations, plasma iron levels and haematocrit.

Figure 1 gives the data on plasma histidine concentrations. The aminoacid level rose from $0.799 \pm 0.03 \text{mg/100ml plasma}$ up to $1.459 \pm 0.05$. The difference was statistically significant ($P = <0.001$).

Figure 2 indicates that plasma transferrin increased from $204 \text{mg/100ml}$ to $265 \text{mg/100ml}$. This increase was also statistically significant ($P = <0.001$).

Plasma iron concentration was found to be increased after histidine supplementation. The increase was from $58.4 \pm 3.03 \mu\text{g/ml}$ ($P = <0.005$) (Figure 3).

The haematocrit rose from 20.8 to 25.0 as shown in Figure 4. This last change was also statistically significant ($P = <0.001$).
Figure 2

Figure 3
DISCUSSION

Previous data have indicated that circulating reticulocytes incorporate labelled leucine at a faster rate when the blood specimen is taken from patients fed supplementary amounts of histidine (Giordano et al, 1968, 1969, 1971). This effect was interpreted to indicate that histidine was a limiting aminoacid for globin synthesis and therefore for haemoglobin formation.

The present study was initiated to test clinically the significance of this result and to ascertain whether or not supplementation of histidine to patients on RDT might ameliorate the anaemia through better haemoglobin synthesis. The results indicate that through a repletion of plasma histidine it was possible to normalise transferrin levels and to obtain an almost normal serum iron concentration. The first data might indicate that transferrin is higher because better nutrition was resumed as a consequence of histidine supplementation. A strict relationship between nutritional status and transferrin levels has been stressed (Antia et al, 1968; McFarlane, 1969).

The plasma iron concentration is also increased concomitant with histidine supplementation. This is very interesting data and in the light of experimental work might indicate that histidine supplementation also regulates better iron absorption through the intestinal mucosa. Finally, the fact that the haematocrit was significantly increased is in favour of the hypothesis that histidine administration is of benefit in the treatment of uraemic anaemia.
SUMMARY

Twenty uraemic patients on RDT from 2 months to 6 years were given daily histidine supplementation for 9 weeks in order to study the effect of this amino-acid on their plasma iron, haematocrit and nutritional status. At the end of the study the haematocrit, plasma iron, plasma transferrin and plasma histidine levels rose significantly. These results suggest that histidine supplementation is of benefit for the anaemia of uraemic patients.

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REFERENCES

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OPEN DISCUSSION

J BERGSTROM (Stockholm): I would like to congratulate you on your results with regard to anaemia. I would like to ask you one question — were these patients on a protein restricted diet, and if they were, by how much? I ask because if the patient is on a free diet, do you think that he would still need extra histidine?

GIORDANO: I think that some of the data should answer the question themselves, because the plasma histidine levels were reduced in all patients, despite the fact that the patients were actually on a free diet.

T J BUSSEMIEER (Minneapolis): The question I'd like to ask you is did you
follow the phosphorus levels and the pHs of your patients? We found of course that phosphorus affects the level of the haematocrit and perhaps the pH does too.

GIORDANO: We have followed the phosphorus levels and pH routinely, but not purposefully. So we do have this data, but we don't know what to do with them. Would you suggest to us what could come out from this data exactly?

BUSELMEIER: I'm not sure, but what has been previously suggested was that higher phosphate levels supplement red blood cell enzymes and the monophosphate shunt etc. This prevents haemolysis and perhaps more important allows a more efficient release of oxygen to the tissues, so that in uraemia, patients who have low haemocrits and haemoglobins could get by as normal with these lower haemocrits. More recently our investigations indicate that a low pH would allow us such advantages as well.

L. MIGONE (Chairman): There was a discussion at the last Freiburg Conference between you and Dr Bergstrom on the action of histidine. Is the action on haematocrit related to a positive nitrogen balance? If you give more protein containing histidine you may get a similar effect, or do you think histidine has a more specific pharmacological action, comparable, for example, to the role of methionine in the production of guanidino succinic acid?

GIORDANO: Actually, nitrogen balance is an algebraic expression of all protein syntheses which take place in the body. But what we are trying to indicate is that if you select one protein synthesis, say globin synthesis, you invariably find that histidine plays a major role. We focused down to only one kind of protein synthesis. So actually both concepts are not in disagreement: one is larger, the other one is a detailed one.

MIGONE: Did you give two, three, four grams of histidine?

GIORDANO: We have just tried to give the minimum amount of histidine.