CONCISE REPORT

Hematin Administration to an Adult With Lead Intoxication

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Lead poisoning and acute intermittent porphyria (AIP) may exhibit similar neurologic manifestations, and they have in common elevated excretion of urinary aminolevulinic acid (ALA). Despite their similarities, the possible pathophysiologic connection between AIP and lead poisoning is not known. Because intravenous hematin administration has produced biochemical improvement in AIP, a hematin trial in lead intoxication was of interest with respect to some of the heme metabolism abnormalities observed in that condition. Significant diminution of urinary ALA and coproporphyrin excretion occurred in association with intravenous hematin administration.

IN RECENT YEARS the heme molecule has received increased attention with respect to its potential role in the regulation of globin synthesis,[1,2] the nature of its extracellular catabolism,[3-5] its effect on the regulation of heme biosynthesis,[6,7] and its effect on the excess urine excretion of porphyrin precursors and porphyrins in acute intermittent porphyria (AIP).[8,9] Because of our experience with the in vivo effects of heme on some parameters of heme biosynthesis in rats[7] and humans,[9] we have been interested in the potential effects of intravenous hematin in other disorders that alter heme metabolism.

The toxic effects of lead on heme biosynthesis are well known. These are manifested by increased urinary excretion of aminolevulinic acid (ALA) and coproporphyrin and an elevated red cell protoporphyrin concentration. In addition, the clinical findings in lead intoxication are often similar to those in AIP during an acute exacerbation.[10] We present our experience using intravenous hematin in an adult male with chronic lead intoxication, with particular attention to some of the heme metabolism abnormalities observed in that patient.

MATERIALS AND METHODS

Porphyrin Precursor and Porphyrin Measurements

Quantitative determinations of urinary ALA and porphobilinogen (PBG) were performed by the method of Mauzerall and Granick, as modified by Marver et al.[11] Urinary uroporphyrin and coproporphyrin were measured by the method of Schwartz et al.[12] Fecal porphyrins were measured by the method of Bauer.[13] Red cell protoporphyrin concentrations were determined by the method of Poh-Fitzpatrick et al.[14] Red cell uroporphyrinogen I synthase activity was determined by the method of Magnussen et al.[15]

Preparation and Administration of Hematin

Hematin (ferric protoporphyrin IX) was crystallized from HB_sAg-negative human blood according to the method of Fischer.[16] A solution of hematin and mannitol (1:1, by weight) in 0.25% sodium carbonate

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was passed through a 0.22-μ Millipore filter. The filtrate was lyophilized and sealed in sterile amber vials. Each batch was tested for sterility and pyrogenicity before it was released for human use. The hematin preparation was granted investigational approval by the Food and Drug Administration (IND BB-1077). The protocol and informed consent for hematin administration to individuals with lead intoxication were approved by the Clinical Research Committee, National Cancer Institute (protocol 77-C-146).

The hematin was reconstituted with sterile physiologic saline to a concentration of 2 mg/ml immediately before its injection. This hematin solution was injected daily in the largest accessible arm vein over a 10–15-min period at a dosage of 3.6 mg/kg.

CASE HISTORY

A 48-yr-old black male was referred to the Metabolism Branch with a diagnosis of chronic lead intoxication. He had been seen in several outpatient facilities and had received at least two courses of chelation treatment without symptomatic remission during 2 yr before his referral to the NIH. The exact nature of this prior treatment was not known. The patient complained of intermittent nausea, abdominal pain, diarrhea, and constant numbness in his lower extremities. Examination and laboratory studies revealed a gingival "lead line," hypoesthesia in his lower extremities, hemoglobin 11.9 g/dl, hematocrit 37.1%, reticulocyte 6.1% (uncorrected), G6PD activity normal, hemoglobin AA, direct and indirect Coombs test negative, ^{51}Cr red cell survival $T_{1/2}$ of 19 days (normal, 23–32 days), and serum lead concentration 87 μg/dl (normal, < 40). Initial porphyrin studies are listed in Table 1.

The patient's informed consent was obtained prior to beginning the study. Hematin was injected daily for 16 days at a dosage of 300 mg (3.6 mg/kg). During the first 11 days of hematin administration (Fig. 1, days 23–33) the patient noted diminution of abdominal discomfort, nausea, and lower-extremity numbness and aching. Abdominal discomfort, nausea, and vomiting recurred on the 12th day of hematin administration (Fig. 1, day 35) for an unknown reason. These symptoms remitted over 72 hr, and they were absent on the final day of hematin treatment (Fig. 1, day 38). The urinary ALA and coproporphyrin excretions diminished steadily until the 12th day of hematin, when elevations in those values occurred in association with the symptomatic exacerbation noted previously. The urinary ALA and coproporphyrin excretions during the 16 days of hematin administration were significantly below baseline values ($p < 0.002$) by the Mann-Whitney U test.

At the conclusion of this evaluation the patient was treated first with intravenous Ca-EDTA (a total of 2 g) and then with penicillamine (250 mg b.i.d.) for 5 mo. The urinary ALA and coproporphyrin became normal within the first month of therapy. Red cell protoporphyrin diminished by approximately 75% after 3 mo of treatment. It was normal when measured 4 mo later. At that time, 7 mo after chelation treatment began, the peripheral neuropathy was unchanged, and symptoms of abdominal discomfort and nausea were present occasionally.

DISCUSSION

This is the first report of hematin administration to an individual with lead intoxication. The data (Fig. 1) indicate that the elevations of urinary ALA and coproporphyrin in lead intoxication are reversed by intravenous hematin adminis-

Table 1. Initial Porphyrin Studies

	Patient	Normal
Urine		
Aminolevulinic acid	17.5 mg/24 hr	<2 mg
Porphobilinogen	1.5 mg/24 hr	<2 mg
Uroporphyrin	212 μg/24 hr	<60 μg
Coproporphyrin	1485 μg/24 hr	<300 μg
Fecal		
Coproporphyrin	100.5 μg/g dry weight	<30
Protoporphyrin	189.5 μg/g dry weight	<60
Red cell		
Protoporphyrin	479 μg/dl	<100
Uroporphyrinogen I synthase	33.4 nmoles/ml RBC/hr	>30

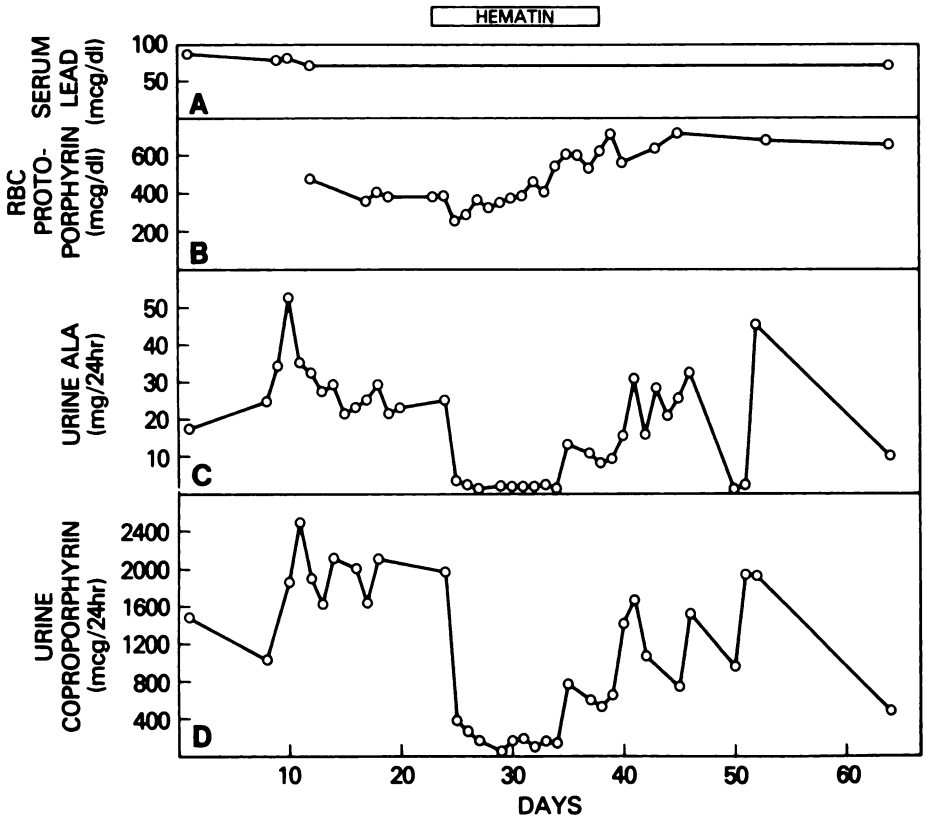

Fig. 1. Serum lead (A), red cell protoporphyrin (B), urinary ALA excretion (C), and urinary porphobilinogen excretion (D) during the duration of intensive observation (64 days). The period of intravenous hematin administration is indicated by the rectangle at the top of the figure.

tration. The diminution of ALA and coproporphyrin by hematin was achieved independent of an alteration in serum lead or in red cell protoporphyrin concentrations. There are only a few hypotheses to explain this observation. First, hematin might catabolize the excess ALA and coproporphyrin to unidentified metabolites. Presumably the excess protoporphyrin in the erythrocytes would be protected from such a heme effect. Second, hematin might chelate or in some way remove the lead molecule from exposure to the heme pathway. Third, a biochemical effect of hematin on heme biosynthesis is possible in the presence of lead. Hematin has repressed the activity of ALA synthase in bacteria[6] and rats,[7] and this effect is implied in its effect in humans with acute attack forms of porphyria.[8,9]

Measurements of ALA and PBG in urine are not altered by the addition of hematin.[17] There is no basis to consider that hematin might remove lead or reverse enzyme inhibition in the face of excess tissue lead. The red cell protoporphyrin data are not compatible with the expected outcome of reversing inhibition of ferrochelatase, which is also inhibited by excess tissue lead. The third possibility is favored. This explanation requires that hematin repress the activity of hepatic ALA synthase, analogous to the concept in AIP.[8,9] However, there is no evidence at this time that hepatic ALA synthase is induced in chronic lead intoxication. Furthermore, the necessary attendant concept of altered hepatic heme metabolism as the

major source of excess urinary ALA and coproporphyrin in lead intoxication would be novel. Since the liver is considered to be the primary site of hematin clearance,[3-5,18] these data would be consistent with that possibility. The presumption that red cell protoporphyrin is produced in the erythron is also consistent with the failure of hematin to diminish erythrocyte protoporphyrin concentration in the face of lowered urinary ALA and coproporphyrin excretion.

This failure to observe changes referable to heme biosynthesis in the erythron secondary to hematin administration has two possible explanations. Either the 16-day trial was insufficient to observe changes in protoporphyrin production over the red cell life span or intravenous hematin at the in vivo concentration achieved does not affect the heme biosynthetic pathway in that tissue. Considering the first possibility, normally about 16% of red cells will turn over during a 16-day period; however, there was evidence that the turnover rate was increased in this patient. His ^{51}Cr red cell survival was decreased, and his reticulocyte count was 6.1% (5.1% corrected). Thus, probably in excess of 40% of his red cell mass turned over during the period of hematin administration. In addition, the diagnostic phlebotomies performed during the trial may have enhanced this turnover further. Therefore, it is unlikely that the duration of the hematin trial was a factor in the failure to observe a decrease in red cell protoporphyrin concentration. The second possibility appears more probable, on the basis of previous studies on hematin metabolism in vivo.[3-5,18] The increase in red cell protoporphyrin concentration that occurred during the study is attributed to the further increase in red cell turnover stimulated by frequent phlebotomies.

This report is not intended to suggest that intravenous hematin is an alternative to the removal of lead for the treatment of lead intoxication. The biochemical similarities of AIP and lead intoxication, and the known biochemical effects and safety of intravenous hematin in AIP, provided a sound basis for examining the pathobiochemistry of lead intoxication with this unique approach. These data demonstrate that some aspects of abnormal heme biosynthesis in lead intoxication can be corrected by hematin without removing lead, and they suggest that an extraerythropoietic site of excess ALA and coproporphyrin production exists in lead intoxication.

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