Hepatic iron in dialysed patients given intravenous iron dextran

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Abstract

Five percutaneous biopsy and 17 necropsy liver specimens were analysed histologically and chemically for iron content in 22 patients receiving dialysis for chronic renal failure, 13 of whom were given intravenous iron-dextran. Brissot scores for assessing histological hepatic iron deposition and chemically measured liver iron concentrations correlated closely. Both variables depended on total cumulative dose of iron, and to a lesser extent, on time since the last dose. Fibrosis (seen in five patients) was minimal and non-specific. Electron microscopic examination showed that there was no generalised damage and confirmed the presence of iron in the hepatocytes in the form of ferritin. High liver iron concentrations, in excess of 1000 µg/100 mg dry weight, were seen in two patients. Four others given comparable cumulated amounts (18-23 g iron) did not have such high concentrations. Plasma ferritin concentrations were high in eight patients, some with and some without fibrosis.

The risk of temporarily high iron deposition in the liver causing damage seemed to be minimal when weighed against the benefit of increased haemoglobin in most of the patients. Intravenous iron treatment merits further evaluation, particularly with the advent of erythropoietin treatment, which requires continuously available iron.

Gastrointestinal blood loss can be as much as 10 ml daily in patients receiving dialysis,¹ in addition to losses in the dialysers and continuous blood sampling, which eventually produces an iron deficiency component to the anaemia of chronic renal failure, unless iron supplementation is given. Controversy continues, however, over the best way to supplement iron.

The high plasma ferritin concentrations seen after intravenous iron dextran treatment in patients given maintenance haemodialysis are temporary, decreasing gradually over several months.^{2,3} Nevertheless, oral iron supplementation is recommended by most investigators^{4,5} in preference to intravenous iron treatment, due to fears of potentially harmful iron overload when the intestinal barrier mechanisms are bypassed. The toxicity of intravenous iron in patients receiving dialysis

remains equivocal because in most series reported to date the issue has been complicated by giving iron by two or more routes—either by multiple blood transfusions, or orally as well as parenterally.^{5,6} The toxicity of monitored and controlled intravenous iron dextran treatment has not been conclusively shown. The advent of erythropoietin treatment means that the provision of adequate stores of available iron is needed constantly and the choice of which source to use becomes increasingly important.

Associations between serum ferritin concentrations and tissue iron assessed at necropsy have been reported⁵ in dialysed patients who had received intravenous iron dextran, but there are few reports on this topic and none has compared liver biopsy results with contemporaneous serum ferritin concentrations. In this report liver iron content and plasma iron, transferrin, and ferritin in patients receiving iron dextran in a renal dialysis unit were measured and compared with the histological variables of iron content and liver damage. The primary purpose was to determine if liver damage occurred to an extent which outweighed the benefit of the iron supplementation for anaemia. Because plasma ferritin concentrations can be high in conditions other than iron overload, measurements of the iron content of liver biopsy specimens are said to be the only reliable method of identifying actual iron overload in patients with high circulating ferritin concentrations.⁷

Methods

Twenty two patients (10 men, 12 women, age range 23 to 70 years, median 46 years) receiving dialysis treatment for end stage chronic renal failure were studied. Seven patients were receiving continuous ambulatory peritoneal dialysis (CAPD) and 15 were receiving maintenance haemodialysis. Nine patients (the seven receiving CAPD and two receiving maintenance haemodialysis) had never received iron supplementation and had been receiving dialysis for between one and 44 months at the time of the study. The patients who received iron had been receiving dialysis for between 15 and 132 months at the time of the study. In five patients liver biopsy samples were taken for analysis after informed consent and in the others tissue samples were obtained at necropsy. A 10-20 mm biopsy core of liver was obtained using a disposable 1.5 mm internal bore Menghini needle on the day following dialysis or from necropsy tissue.

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For light microscopical examination, tissue was fixed in buffered formalin. Paraffin wax sections were stained by the following techniques: haematoxylin and eosin, reticulin, and Perl's stain for iron. The amount of stainable iron in the liver was scored by the method described by Brissot *et al* and the final grade calculated.⁸ Brissot scores were also established for 17 age and sex matched control subjects, who showed no evidence of renal or liver disorder at necropsy. Tissue for electron microscopical examination was fixed in cacodylate-buffered 3% glutaraldehyde. Thin sections were stained with lead citrate and uranyl nitrate and examined with a JEOL 100 XC electron microscope at 60 kV.

Average weights of wet tissue used for hepatic iron estimation were about 20 mg from necropsy specimens and 5 mg from percutaneous biopsy specimens. These were processed and tissue iron assessed chemically by the methods described by Barry and Sherlock.⁹ The same method of measuring iron concentrations (ICSH recommended method¹⁰) was also used for all plasma iron estimations.

Blood samples taken before dialysis were taken either at the dialysis treatment session before the biopsy or within four weeks of death for estimation of plasma total iron, transferrin, and ferritin. Plasma transferrin was measured by immunodiffusion (M-Partigen immunoplates, Hoechst, West Germany) and total iron binding capacity (TIBC) was calculated assuming the binding of 2 Fe⁺⁺⁺ per transferrin molecule (molecular weight 81 000). Plasma ferritin was estimated by radioimmunoassay (Travenol, England).

Blood samples for haematological indices were taken after dialysis from the pre-dialyser (arterial) blood line just before disconnection in patients receiving maintenance haemodialysis, and at the end of the first dwell-time of the day in patients receiving CAPD (four exchanges per 24 hours).

Patients were given courses of iron dextran injection BP (Imferon; Fisons, England), in amounts providing either 600 mg elemental iron once monthly for nine months, or 200 mg once weekly for 30 weeks, until 5.4 or 6.0 g

iron had been given. The infusions were temporarily discontinued if plasma iron (monitored before the next infusion was due) rose above 20 $\mu\text{mol/l}$. The infusions were given in 5% saline over four to five hours during dialysis, into the pre-dialyser blood line. No toxic reactions were seen.

Results

The causes of death are listed for those patients whose specimens were obtained at necropsy (table 1). No patient died of causes related to iron overload.

Chemically measured liver iron in the nine patients not given intravenous iron was 42 (SD 19) $\mu\text{g}/100\text{ mg}$ dry weight. This is at the lower end of the reported⁹ reference range of 30 to 140 $\mu\text{g}/100\text{ mg}$ dry weight for this method. The Brissot grade ranged from nil to II (range of scores 0 to 6, mean (SD) 2.3 (2.3)) and no fibrosis was seen (table 2).

In the 13 patients given intravenous iron at varying time spans before necropsy or percutaneous biopsy (table 2), the measured liver iron ranged from 28 to 1846, with all but two below 754 $\mu\text{g}/100\text{ mg}$ dry weight (median 345 $\mu\text{g}/100\text{ mg}$ dry weight). The highest liver iron of 1846 $\mu\text{g}/100\text{ mg}$ dry weight was found in a patient given 22.0 g iron from iron dextran over five years, the last dose being seven months before assessment. The other patient with concentrations of > 1000 $\mu\text{g}/100\text{ mg}$ dry weight had been given 23.4 g iron over 10 years, the last dose 21 months previously, and he had also received blood transfusions. Although both these patients had been good responders to iron supplementation in the past in terms of improved blood haemoglobin concentrations, neither responded well to their last course of iron supplementation. Liver iron did not exceed 2% of dry weight in any patient.

LIGHT MICROSCOPY

There was a mild periportal fibrosis in five patients, mostly in those with high iron concentrations in their livers (table 2). There was no evidence of cirrhosis. The biopsy specimens showed no evidence of active

Table 1 Necropsy findings and causes of death

Case No	Renal disease	Causes of death	
		Contributory	Immediate
1	Polycystic kidneys	Recurrent pancreatitis	Septicaemia
2	Polycystic kidneys	Left ventricular hypertrophy; hepatic congestion and gross polycystic change	Unexplained postoperative (sacral mass)
3	Chronic glomerulonephritis	Protein depletion; pleural effusions; hepatic congestion	Multiple pulmonary infarcts
4	Chronic pyelonephritis	Biventricular hypertrophy; recurrent pancreatitis	Unidentified
5	Chronic glomerulonephritis	Hypertensive heart disease; hepatic congestion	Myocardial infarction
6	Obstructive	Left ventricular hypertrophy; obstructive uropathy; peritonitis	Uncertain
7	Chronic glomerulonephritis	Peritonitis; pelvic abscess	Myocardial infarction
8	Vasculitic	Congestive heart failure; hepatic congestion; pulmonary thrombo-emboli	Suppurative bronchopneumonia;
9	Hypoplasia	Left ventricular hypertrophy; pelvic abscess	Myocardial infarction
10	Chronic glomerulonephritis	Renal isograft rejection; calcific arteriosclerosis	Bronchopneumonia associated with immunosuppression
11	Chronic pyelonephritis	Mitral stenosis/incompetence; biventricular heart failure; hepatic congestion	Endocarditis; septicaemia
12	Hypertensive	Multiple granulomata; hepatic congestion	Subarachnoid haemorrhage
13	Hypoplasia	Pulmonary emboli	Unidentified
14	Chronic glomerulonephritis	Left ventricular hypertrophy; septicaemia	Rupture of left ventricular abscess; endocarditis
15	Hypoplasia	Cardiac conduction defect; dysrhythmia; hepatic congestion	Biventricular heart failure postoperative parathyroidectomy
16	Hypoplasia	Left ventricular hypertrophy; aortic valve prosthesis	Gastroenteritis; hypokalaemia
17	Chronic glomerulonephritis	Peritonitis; pulmonary oedema; effusions; hepatic congestion	Apical pneumonia

Table 2 Chemically measured and histologically assessed liver iron state in dialysed patients receiving intravenous iron

Patients receiving dialysis	Biopsy/ Necropsy	Intravenous iron total dose g	Time since last dose (months)	Blood transfusions units	Liver iron $\mu\text{g}/100\text{ mg}$ dry weight	Liver histology: Brissot score				
						Hepatocytes	Kupffer cells	Fibrosis	Score	Grade
No intravenous iron given:										
1 CAPD	Necropsy	0	—	0	16	0	1	0	1	I
2 CAPD/MD		0	—	0	17	0	0	0	0	0
3 CAPD		0	—	0	20	0	0	0	0	0
4 CAPD		0	—	0	46	3	0	0	3	I
5 CAPD		0	—	0	53	0	0	0	0	0
6 CAPD		0	—	0	61	3	1	0	4	I
7 CAPD		0	—	8	63	3	1	0	4	I
8 MD		0	—	0	46	3	3	0	6	II
9 MD		0	—	0	55	—	—	—	—	—
Mean (SD)					43 (9)					
Intravenous iron given:										
10 MD	Necropsy	5.4 in 10 m	110	4	21	0	0	0	0	0
11 MD		2.0 in 4 m	2	8	28	3	3	0	6	II
12 MD		6.0 in 8 m	34	0	104	6	1	0	7	II
13 MD		6.0 in 10 m	16	0	130	6	2	0	8	II
14 MD		18.0 in 9 y	15	0	255	—	—	—	—	—
15 MD		6.0 in 8 m	14	0	330	6	3	0	9	II
16 MD		12.0 in 17 m	18	8	345	9	4	0	13	III
17 MD		22.8 in 8 y	11	0	380	9	4	1	14	III
18 MD		22.8 in 7 y	15	0	616	12	3	2	17	IV
19 MD	Necropsy	11.4 in 4 y	32	0	738	9	3	1	13	III
20 MD	Biopsy	18.0 in 3 y	12	2	753	9	4	1	14	III
21 MD	Biopsy	23.4 in 10 y	21	3	1528	12	4	1	17	IV
22 MD	Biopsy	22.0 in 5 y	7	0	1846	12	4	0	16	IV
Median					345					
Reference range*		—	—	—	30 to 140 ^a	0 to 3	0 to 2	0	0–4	0–I

*Age and sex matched controls without liver or renal disease; m = months; y = years.

damage or degeneration in the hepatocytes, although there was an apparent increase in lipofuscin granules and haemosiderin, especially in those patients with a high liver iron content. The necropsy specimens showed a variety of changes, including small and large cytoplasmic vacuoles. Three of the patients with high liver iron had some double plating of the hepatocytes, suggesting some recent regeneration. Excess mitoses were not seen.

The Kupffer cells were generally increased in number, practically all showing some ferritin or lipofuscin, or both. This was more noticeable in the patients with high iron concentrations in their livers. In some of these latter patients there were scattered aggregates of Kupffer cells and macrophages containing iron (fig 1) in their portal tracts. There was no iron in the bile duct epithelium. Seven patients showed a mild non-specific reactive hepatitis, which followed no particular pattern.

The Brissot grade ranged from II to IV (scores 6 to 17, mean (SD) 11.2 (5.2)). The Perl's stain showed variable iron in hepatocytes and in Kupffer cells. Fibrosis, seen in five patients, was score 1 (minimal) in four patients and score 2 in one patient, extending variably from the portal tracts. Fibrosis was not seen in the patient with the highest chemically measured liver iron (table 2). The fibrosis was seen in the patients with liver iron between 380 and 1528 $\mu\text{g}/100\text{ mg}$ dry weight, given total doses between 11.4 and 23.4 g iron intra-

venously over a three to 10 year period, 11 to 32 months before assessment.

ELECTRON MICROSCOPY

In percutaneous needle biopsy specimens there was little damage to the hepatocytes, confirming results of light microscopy. Iron was seen as electron dense material in the residual bodies in the form of granules with a regular pattern. There was an excess of residual bodies in the livers containing excess iron but the other organelles showed little sign of damage. Ferritin could be seen in the residual bodies. The necropsy specimens had the typical cytoplasm seen after death, but an excess of residual bodies could still be made out in those patients with a high iron content in their livers. At high resolution the ferritin cores were resolved.

CORRELATIONS

There were significant positive correlations (table 3) between hepatic iron, Brissot score, and cumulative iron dose, and significant negative correlations between Brissot score and time since last dose in the 11 patients treated with iron supplementation. The relation between liver iron and the time interval since last dose (fig 2) indicates a wide individual scatter at equivalent dose loads within 12 to 21 months after the last dose. For example, patients given the highest doses of iron (22–23 g) had hepatic iron concentrations ranging from 380 to 1528 $\mu\text{g Fe}/100\text{ mg}$ dry weight.

There was no significant correlation between hepatic iron and plasma iron, ferritin, or transferrin (table 4). Plasma ferritin concentrations in excess of 1000 ng/ml were seen in six patients who had liver iron concentrations ranging from 345 to 1846 $\mu\text{g}/100\text{ mg}$ dry weight.

The five percutaneous biopsy specimens were performed in patients given the largest cumulative amounts of intravenous iron over the preceding years, in whom anaemia was increasing, to ascertain whether further doses

Table 3 Correlations between variables related to iron storage

Variables	n =	r	p Value
Hepatic iron/Brissot score	20	+0.79	<0.001
Hepatic iron/cumulative iron dose	22	+0.78	<0.001
Hepatic iron/cumulative iron dose, patients given iron	13	+0.70	<0.01
Brissot score/cumulative iron dose	20	+0.92	<0.01
Brissot score/time since last dose	11	-0.77	<0.01
Hepatic iron/time since last dose	12	-0.29	>0.30
Hepatic/plasma iron	22	+0.22	>0.30
Hepatic iron/plasma ferritin	19	+0.42	<0.05
Hepatic iron/plasma transferrin	20	-0.43	<0.05
Plasma iron/plasma ferritin	19	+0.63	<0.005

Figure 1 Perls's stain of typical liver under light microscopy. Iron can be seen in hepatocytes with a lysosomal distribution. Iron is also present in Kupffer cells (arrows). Groups of Kupffer cells may be seen both in sinusoids (S) and portal tracts (P).

of iron could be justifiably given. For that reason blood haemoglobin concentrations tended to be low at the time of the biopsy (table 4). Two (cases 11 and 16) of the eight necropsy specimens in the group treated with iron supplements were from patients who failed to show a haemoglobin response to previous iron supplementation, and in others a considerable period of time had elapsed since the last dose, which also contributed to low haemoglobin concentrations before death. Most of the patients were normocytic but four of the patients given iron were still macrocytic (MCV

> 96fl), and they also had high plasma ferritin concentrations. No patients were hypochromic (table 4).

Discussion

An understanding of the interrelations between iron storage and liver damage will eventually come from studies of liver iron and histological data in various iron deficient and iron replete conditions.⁹ In this paper we reported the interrelations in dialysed patients given

Table 4 Plasma iron and related concentrations and haematological indices at or near the time of biopsy

Case no	Plasma					Whole blood			
	Fe μmol/l	TIBC μmol/l	Saturation (%)	Transferrin (mg/dl)	Ferritin (ng/dl)	Haemoglobin (g/dl)	MCV (fl)	MCH (pg)	MCHC (g/dl)
No intravenous iron given:									
1	12.0	59.3	20	240	10	13.9	92	30.9	33.5
2	12.7	42.0	30	170	158	7.3	74	23.9	32.3
3	22.0	55.7	39	225	97	11.6	96	32.2	33.4
4	15.7	58.2	27	236	274	9.6	92	30.5	32.9
5	6.8	40.0	17	162	27	6.6	83	27.2	31.7
6	16.3	56.8	29	230	375	6.9	91	31.1	33.2
7	7.5	31.0	24	126	258	7.6	95	30.5	31.5
8	—	—	—	—	—	7.2	93	27.9	29.6
9	—	—	—	—	—	—	—	—	—
Mean (SD)	13.3 (5.3)	49.0 (11.2)	26 (7)	198 (45)	158*	8.8 (2.7)	89.5 (7.4)	29.3 (2.7)	32.3 (1.3)
Intravenous iron given:									
10	25.9	49.4	52	200	28	11.3	91	30.1	33.2
11	19.3	30.9	62	125	146	5.3	78	26.8	32.9
12	12.2	50.6	24	205	292	6.9	74	24.3	32.1
13	12.0	59.3	20	240	778	6.5	87	26.3	30.4
14	8.0	42.0	19	170	103	11.5	80	25.2	31.1
15	12.5	52.5	24	213	> 500	11.2	82	27.2	32.7
16	34.7	33.4	104	135	7162	5.0	95	33.7	33.6
17	12.5	48.0	26	194	—	11.6	97	32.1	33.1
18	11.6	37.1	31	150	1110	7.4	103	33.7	31.9
19	10.4	35.8	29	145	1640	14.7	86	28.3	33.2
20	35.6	46.9	76	190	2171	7.8	97	34.9	34.6
21	16.5	37.8	44	153	1707	7.4	95	31.4	33.0
22	21.8	33.4	65	135	2548	5.4	99	33.0	32.2
Mean (SD)	17.9 (9.1)	42.9 (8.9)	44 (26)	173 (36)	944*	8.6 (3.1)	89.5 (9.1)	29.8 (3.6)	32.6 (1.1)

*Median.

Figure 1 is a scatter plot showing liver iron levels (µg/100mg dry weight) on the y-axis (0 to 1800) versus months since iron treatment on the x-axis (0 to 42). The plot includes data points for five groups: No Fe³⁺ given (filled circles), 2g Fe³⁺ given over 0-0.5y (open circles), 5-6g Fe³⁺ given over 0-1.0y (filled circles), 11-12g Fe³⁺ given over 1.5-2y (filled triangles), and 18-23g Fe³⁺ given over 3-9y (filled squares). Two horizontal dashed lines indicate control levels at approximately 50 and 150 µg/100mg. The 18-23g group shows the highest peak at 6 months (~1850 µg/100mg). The 11-12g group shows a peak at 33 months (~750 µg/100mg). The 5-6g group shows a peak at 15 months (~350 µg/100mg). The 2g group shows a peak at 0 months (~50 µg/100mg). The No Fe³⁺ group shows a peak at 0 months (~50 µg/100mg).

Months since iron treatment	No Fe ³⁺ given (µg/100mg)	2g Fe ³⁺ given over 0-0.5y (µg/100mg)	5-6g Fe ³⁺ given over 0-1.0y (µg/100mg)	11-12g Fe ³⁺ given over 1.5-2y (µg/100mg)	18-23g Fe ³⁺ given over 3-9y (µg/100mg)
0	~50	~50	~50	~50	~50
6					~1850
12					~780
15			~350		~630
18			~150	~350	~270
21					~1550
33				~750	
36					

There have been several attempts to relate chemically estimated iron content of the liver to the amount of iron shown histochemically.^{8 17-19} The earliest attempt graded only the iron detectable in parenchymal cells. Later investigators reported difficulties using this assessment, because only grades III and IV were associated with a significant increase in iron concentration.¹⁸ Brissot *et al* tried to overcome these shortcomings by additionally taking into account iron deposits in the reticuloendothelial system (Kupffer cells) and the presence or absence of fibrosis, and weighting each of these observations to give a total score.⁸ They recommended liver biopsy as the only definitive way of obtaining a precise measurement of iron stores. The close correlation between chemically measured liver iron concentrations and Brissot score in our patients was similar to

It has been suggested that transfusional iron may be less prone to cause liver damage than iron absorbed through the gut.²¹ Others suggest

that the iron from iron dextran is potentially more harmful and less available than transfusional iron.⁴ Our results, overall, do not support this. The two patients with the highest liver iron have been receiving maintenance haemodialysis for 103 and 118 months, respectively, and are among our longest treated patients. Although their plasma ferritin concentrations were also high and exceeded 1000 ng/ml, similar or higher plasma ferritin concentrations were seen in three other patients. Neither of these patients had HLA antigens A3, B7, or B14. Their high liver iron was not therefore associated with the presence of histocompatibility enzymes linked to idiopathic haemochromatosis, adding weight to the evidence that these antigens are not relevant to the iron overload state in dialysed patients.²²

Liver iron values in transfusional iron overload are very much higher²³ than those seen in our patients, ranging from 1.4 to 4.9% with a mean of 2.2% (2200 µg/100 mg dry weight).²³ Focal portal fibrosis and inflammation were present in seven of these 10 patients²³ and early cirrhosis was present in one. These were all non-thalassaemic patients with normal renal function and various anaemias, who had received between 60 and 210 units of transfused blood. Serum ferritin concentrations in these patients were also higher than in our series, with nine of 15 patients having values of 2000 ng/ml or more.²³ Most transfused patients with thalassaemia have liver iron values between 1.5 and 5.5%.²⁴ Hepatic iron concentrations between 3000 and 10 000 µg/100 mg dry weight (3% to 10%) have been seen in other patients receiving multiple blood transfusions.¹⁸ None of our patients exceeded 2% and only two were above 1%.

Previous studies have indicated that plasma ferritin values decrease towards normal over a period of months after iron supplementation is discontinued.²⁵ The correlation between plasma ferritin and liver iron was less close in our patients than in other series.⁴ Poor correlation between chemical or histochemical indices of hepatic iron stores and plasma indices of iron state has been noted before in several conditions⁷ and is particularly relevant to patients receiving dialysis.

In conclusion, iron deposition in the liver after iron supplementation is to be expected, and the increased deposition found in our patients was not out of line with expectations. The risk of damage from the iron deposition seems low, particularly when weighed against the benefit in terms of increased blood haemoglobin in most patients. The minimal fibrosis noted in a few patients may not necessarily be related to the treatment. The results indicate that fears about intravenous iron dextran administration may be unwarranted when it is used under carefully monitored conditions. The intravenous route should not be ruled out as a method of choice for maintenance of adequate iron stores during

erythropoietin treatment. In view of the rapidity with which some dialysed patients use up iron stores under these circumstances the intravenous route may have substantial advantages over the oral route,²⁶ including elimination of compliance difficulties and ease of administration.

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