Structure / Histotoxicity Relationship of Parenteral Iron Preparations

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Summary

Commercial iron preparations with different chemical structures and stabilities which are indicated for parenteral application were analyzed. After intravenous application in mice, toxic effects were screened by histological examination of liver, kidney, adrenal, lung and spleen. The various iron complexes were classified into four groups according to their physicochemical properties (molecular mass, kinetic and thermodynamic stability). It was found that the toxic effects can be forecasted by the chemical properties. The results clearly show that not all iron preparations tested can be recommended for intravenous application. After injection, the ideal iron preparation is deposited in the reticulo-endothelial system, and not in the parenchyma of the liver, nor mainly in the periportal area. Furthermore, its renal elimination rate should be below 1 % of the dose, and there should be practically no iron detectable in the tubuli. The molecular mass of an optimal product is between 30 000 and 100 000 Daltons, and the preparation does not contain any slowly degradable biopolymers, so that the incidence of allergic side effects is reduced to a minimum. Iron preparations consisting only of weak iron complexes, which liberate iron ions stochastically, should not be used for intravenous application.

Zusammenfassung

Struktur / Histotoxizitäts-Beziehung von parenteralen Eisenpräparaten

Handelsübliche, zur parenteralen Anwendung empfohlene Eisenkomplexe mit verschiedenen chemischen Strukturen und unterschiedlichen Stabilitäten wurden analysiert und nach intravenöser Gabe an Mäuse histologisch auf ihre toxischen Wirkungen auf Leber, Niere, Nebenniere, Lunge und Milz untersucht. Die Eisenkomplexe wurden entsprechend ihren chemisch-physikalischen Eigenschaften (Molmasse, kinetische und thermodynamische Stabilität) in vier Typen eingeteilt. Dabei stellte sich heraus, daß aufgrund der chemischen Eigenschaften die toxischen Auswirkungen gut vorhergesagt werden können. Die Resultate zeigen, daß nicht alle untersuchten Eisenpräparate zur intravenösen Applikation empfohlen werden können. Ein gutes Präparat wird nach Applikation vorwiegend im retikuloendothelialen System, und weder im Parenchym der Leber noch bevorzugt in der periportalen Zone gespeichert. Im weiteren wird es renal unter 1 % ausgeschieden und lagert sich nicht in den Tubuli der Niere ab. Die Molmasse eines optimalen Präparates liegt zwischen 30 000 und 100 000 und enthält keine schlecht abbaubaren Biopolymere, so daß die Möglichkeit zu allergischen Reaktionen möglichst klein bleibt. Eisenpräparate, die nur schwache Eisenkomplexe enthalten und dadurch Eisenionen ungezielt freigeben können, sollten nicht intravenös verabreicht werden.

Key words: *Anaemex® · Ferrum Hausmann® · Iron, structure/histotoxicity relationship of parenteral preparations*

1. Introduction

It is well known that in vitro incubation of divalent iron ions (Fe^{2+}) with the protein apoferritin leads to the formation of ferritin in the presence of oxygen or other oxidizing agents (Spiro et al. 1969). Within this biochemical step, highly toxic iron ions are converted into only slightly toxic, non-ionic, polynuclear iron(III)-hydroxide, which becomes water-soluble through ferritin complex formation (Islam et al. 1989). The formation of non-ionic iron(III)-hydroxide complex ferritin allowed to solve toxicity, tolerance and safety problems of iron stores in the evolution of animals and mammals (Theil et al. 1979).

This can be demonstrated for instance by evaluating the LD_{50}-values of iron salts and mono- and oligonuclear iron complexes on one hand, which have a high toxicity, and of the polynuclear ferric hydroxide carbohydrate complexes on the other hand, which are of low toxicity (Müller 1974, Berenbaum et al. 1960, Hoppe et al. 1955) (Table 1).

The formation of the physiological iron depot ferritin represents a model of the synthesis of different iron prep-

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Table 1: Toxicity of different iron compounds.

Compound	LD_{50} in white mice in mg Fe/kg body weight	
	Oral	Intravenous
Salts		
$FeSO_4$	230[2]	11[2]
Fe(II)-gluconate	429[3]	13[3]
Fe(II)-fumarate	630[2]	—
$FeCl_3$	500—840[3]	18.5[3]
Mono- and oligonuclear complexes		
Fe(III)-EDTA	500[1]	40—50[1]
Fe(III)-ammonium-citrate	1000[3]	16.5[3]
Polynuclear complexes		
Ferric hydroxide dextran	> 2500[1]	> 2500[1]
Ferric hydroxide dextrin	> 2500[1]	> 2500[1]
Ferric hydroxide sucrose	> 2500[1]	> 200[1]

References: [1] Müller 1974, [2] Berenbaum et al. 1960, [3] Hoppe et al. 1955.

arations with extremely low toxicity, good tolerance, a wide therapeutical range and a minimal danger of accidental overdosing (Müller 1974).

Parenteral iron therapy is said to be indicated in the following cases:

- known severe problems of intestinal iron absorption,
- absolute intestinal iron intolerance,
- severe or very severe iron deficiency conditions (Hb < 90—100 g/l), where a therapeutical effect must be achieved as quickly as possible, as for instance in the last trimester of pregnancy or in pre-operative iron deficiency conditions (Hallberg et al. 1970),
- cases where regular intake of an oral preparation is not guaranteed,
- iron deficiency where there is no response to oral therapy, e.g. in dialysis patients (Lawson et al. 1971),
- situations where iron stores are scarcely or not at all formed but would be important for further therapy, e.g. in combination with erythropoietin (Van Wyck 1989).

In clinical situations where parenteral iron preparations are indicated, a high safety margin is of paramount importance. This implies that toxic as well as allergic side effects must be avoided.

Nevertheless, the various iron preparations available on the market and used for parenteral application differ strongly in crucial parameters. Not all of them belong to the safest group of polynuclear iron complexes. As their chemical structure is different, a different toxic and histological behavior is observed. This work will demonstrate, analyze and explain the relationship between the chemical structure of iron complexes and their histological properties.

2. Material and methods

2.1. Animals

ICR (Institute Charles River) mice of both sexes (our own breed with animals from the Animal Breeding Institute, University of Zurich, Switzerland) of 20—24 g (about 4 weeks old) were used in all experiments without previous randomization. The animals were kept in stainless steel cages with bottom lattice for the prevention of coprophagia. The light-dark interval was 12 h, temperature 22 °C and humidity 55 %. The animals were fed with a standard diet from Nafag, Gossau (Switzerland) (Nr. 850) containing 250 mg Fe/kg, and iron-free tap water, both ad libitum.

In a test experiment no difference could be found between anemic and non anemic, or between male and female animals, as far as the typical characteristics of the histological findings are concerned. The iron preparations were applied intravenously by injection into the tail vein. Usually a solution, diluted with normal saline, containing 2 w/v % of iron, was used. The standard dose was 200 mg Fe/kg body weight. (Preparations provoking liver necrosis caused apathies and breath troubles after 30 to 60 min, and led to death in some cases within 3—48 h post injectionem). 10 min, 4 h, 4 and 14 d after application the animals were sacrificed and dissected subsequently. Liver, kidney, adrenal, lung and spleen were isolated and placed on a round metal plate and frozen at −12 to −15 °C for 45 min. Two animals were used for each preparation at each check time. A minimum of 2 frozen sections of each type of tissue were prepared per animal with a microtome cryo-cut (American Optical Company, Buffalo, USA; General Representation: Leica AG, Glattbrugg, Switzerland), whereby it proved advantageous to let the lungs thaw at −10 to −12 °C. The thickness of the tissue sections was chosen as 4—5 µm. The following sections were used: liver cross-sections from the upper third and from the middle part of the liver from the lobuli sinister lateralis and dexter medialis, resp.; longitudinal peripheral kidney cross-sections (cortex and medulla) and through the center (cortex — medulla — calix — medulla — cortex); adrenal cross-sections through the middle part; lung cross-sections through the middle part; longitudinal spleen sections through the middle part. The microscope slides were spread with a thin layer of albumen-glycerol before use. Two pieces of tissue sections of each organ were fixed on glass slides. After this they were colored with Berliner blue and Kernecht-red / aluminium sulphate solution, dehydrated and embedded with Eukitt (mounting medium for microscopic preparations) and a cover glass. Three hours after embedding the dry preparations were ready to be examined under the microscope. The microscopic pictures were taken with a Zeiss Axioskop H DIC and a Minolta 7000 camera with Ektachrome 50 EPY and 64 T films.

A semiquantitative standard measure (relative unit = rU) was selected in order to estimate the distribution of colored particles in the tissues. The values represent grades of severity and were estimated as integers from the above mentioned tissue sections; they indicate the mean of at least 5 different microscopic pictures (sectors) per section. The severity grades were defined as follows:

0 rU: no iron:	No iron detectable with this method.
1 rU: very little:	Only traces of iron, sometimes detectable only locally. Very fine-grained iron deposit or only individual iron particles.
2 rU: little:	Several clearly detectable fine to medium-sized iron deposits or only few medium-sized iron particles.
3 rU: moderate:	Iron is distributed over the whole tissue; local agglomerations can appear. Fine to medium-sized iron particles.
4 rU: distinct:	Clear iron deposits everywhere. Fine to coarse-grained iron particles.
5 rU: much:	Further increase in the frequency of iron particles and in the density of the agglomerations; often with coarse-clotted iron deposits.
6 rU: very much:	Maximum iron deposit in the whole region of the tissue.

Relative amounts of iron found in selected tissue areas and cells (e.g. reticulo-endothelial system (RES) and parenchyma) are expressed as proportions with integers for the description of the relative quantities. The same tissue sections and microscopic pictures (sectors) were used for each section.

With 0.9 % NaCl as test solution, all tissue sections show a relative iron concentration of 0—1 rU.

Undue toxicity tests in white mice were carried out according to BP guidelines (British Pharmacopoeia 1988) relating to iron dextran injection and iron sorbitol injection.

2.2. Materials and method of analysis

The iron preparations were taken from the market or from our own manufacturing lines. All preparations were reanalyzed with respect to their iron content. Further determinations of the carbohydrate content, the point of zero charge, the degradation kinetics, and the molecular mass by gelchromatography were carried out (the results are given in Table 3). All preparations were used in parenteral iron therapy, except for Fe-AA and the low molecular mass iron dextrin complex Fe-Ma, which has been chosen for comparison with Fe-Am.

2.2.1. Determination of the iron content

Complex bound iron was mineralized with hydrochloric acid (10 ml of HCl 37 w/w % for 5 ml iron complex solution), oxidized with 1 g potassium persulfate, diluted with 100 ml distilled water

and 10 ml glacial acetic acid, adjusted with NaOH 30 w/w % at pH 2.2–2.5 and titrated at 40–50 °C with 0.1 mol/l $EDTANa_2$ and pyrocatecholdisulphonic acid disodium salt (trade name = Tiron) as indicator until the color changed from red to green, and finally to yellow.

2.2.2. Determination of the carbohydrate content

2 × 1 ml distilled water, 2 × 1 ml standard solution (145 mg sucrose dissolved with distilled water to a volume of 100 ml solution) resp. 2 × 1 ml test solution (0.5–2.5 ml iron complex solution, depending on the expected carbohydrate content, dissolved with distilled water to a volume of 100 ml solution) were added into 2 × 3 test tubes with ground glass stoppers by means of a 1 ml Hamilton syringe. Thereafter 10 ml anthrone reagent were added and mixed thoroughly (200 mg anthrone weighed into a 100 ml volumetric flask, rinsed down with 20 ml distilled water; 60 ml concentrated sulfuric acid were slowly added while continuous cooling was ensured. After complete dissolution it was filled up to 100 ml with conc. sulfuric acid). The test tubes were placed into a boiling water bath; the stop watch was started and the test tubes closed with glass stoppers. The rack was placed in cold running water after exactly 10 min. After cooling, the content of the test tubes was mixed thoroughly. The absorption spectrum was measured with a spectrophotometer in the range of 600–650 nm in 10 mm glass cuvettes. The carbohydrate content was calculated from the measured absorption and the calibration curve.

2.2.3. Determination of the point of zero charge

0.2–1.0 ml (depending on the iron content) of iron complex solution was transferred into a 200 ml beaker and diluted with 100 ml of distilled water. 0.1 mol/l hydrochloric acid or 0.1 mol/l sodium hydroxide solution was slowly added from a burette while magnetic stirring, potentiometric pH measurement and horizontal illumination through the beaker with a microscopic lamp were carried out in a darkened room, until a distinct, permanent turbidity appeared. At this point the pH was read. 'None' means that no turbidity or precipitation occurred (complexes which are stable enough not to precipitate still have a point of zero charge).

2.2.4. Determination of the degradation kinetics

The degradation kinetics were determined according to the method of Erni et al. (1984) at 25 °C. The k-values [$k \cdot 1000 \cdot min^{-1}$] given in Table 3 were calculated at $\theta = 0.1$, 0.5 and 0.9. The k-values at $\theta = 0.5$ for monodisperse systems, and those at $\theta = 0.1$ and 0.9 for mixtures were used respectively for the correlation diagram with the molecular masses as shown in fig. 30 (cf. discussion).

2.2.5. Determination of molecular masses

The method is based on the application of HPLC to permeation chromatography on poly(methylmethacrylate) gel. The following equipment was used: Waters HPLC-station, consisting of Waters 590 programmable pump, WISP 710B autosampler, column oven connected with Waters 410 differential refractometer and a Waters system interface module. For operation and data evaluation, MAXIMA 820 software was used. The following columns were used: HEMA-Bio 100, 10 µ, 8 × 30 mm, and HEMA-Bio 1000, 10 µ, 8 × 300 mm, by Stagroma AG (Wallisellen, Switzerland). These two columns were connected in series and thermostated at 45 °C. An aqeuous solution of 0.02 mol/l Na_2HPO_4 and 0.02 mol/l NaH_2PO_4 was used as solvent. The solvent flow was 0.5 ml/min at a pressure of max. 2000 psi. The refractometer was set to a sensitivity of 32 and a scale factor of 50.

A Shodex standard kit (Showa Denko K. K., Tokyo, Japan; Distributor Switzerland: Macherey and Nagel, Oensingen), containing pullulanes (polymaltotriose-polymer) with different M_w values was used for calibration (Table 2).

The pullulanes had been calibrated by the supplier by means of an ultracentrifugal sedimentation equilibrium method. The first and last point of the calibration curve was performed with a mixture of dextran T 2000 (Pharmacia, Uppsala, Sweden) with a M_w of approx. 2.000.000, and glucose with a M_w of 180. A calibration curve was obtained from the relationship log M_w versus retention time. By means of this curve, the molecular masses of the iron complexes were calculated after integration of the relevant peaks.

Values of the calibration curve:

Curve Type = cubic; $r^2 = 0.99948$; Standard Error = 0.03313

Table 2: Pullulan standard kit characteristics.

Grade	M_w	M_w/M_n
P-800	853.000	1.14
P-400	380.000	1.12
P-200	186.000	1.13
P-100	100.000	1.10
P- 50	48.000	1.09
P- 20	23.700	1.07
P- 10	12.200	1.06
P- 5	5.800	1.07

Equation of the Curve:

$\log M_w = +3.09E+01 - 2.07E+00 \times R + 5.72E-02 \times R^2 - 5.73E-04 \times R^3$

(R = retention time)

3. Characterization of the analyzed iron preparations

3.1. Compilation of the results

The results are shown in Table 3.

3.2. Description of the tested preparations

(cf. Table 3 and Discussion)

3.2.1. Fe-Da-BP/USP, Fe-Da5, Fe-Da20, Fe-Am

These iron complexes are composed of a polynuclear iron hydroxide complexed with dextran (polyisomaltose) or with dextrin (polymaltose); (amylum has a higher molecular mass than maltrin of Fe-Ma). The molecular mass and the complex stability are higher in comparison to all other tested iron preparations (cf. Table 3). This leads to the observed low toxicity (Müller 1974). Thus the iron dextranates and dextrinates are suited especially for intramuscular application, but they are also used for intravenous injection or infusion (Fe-Da-BP/USP, Fe-Da5, Fe-Am) or for TDI (total dose infusion) (Fe-Da-BP/USP, Fe-Da5, Fe-Am) (Hallberg et al. 1970, Dresch 1976).

3.2.2. Fe-Su-I, Fe-Su-II, Fe-SU-III, Fe-Ma

These iron complexes are composed of a polynuclear iron hydroxide, complexed with sucrose (Fe-Su-I, Fe-Su-II, Fe-Su-III), and with dextrin (Fe-Ma). The molecular mass and the complex stability are lower in comparison to iron dextran, resulting in the observed higher toxicity (Müller 1974). But iron saccharates are still suited especially for intravenous application (cf. Discussion).

The molecular mass and the complex stability of Fe-Ma, an iron complex used for oral application, are lower in comparison to Fe-Am, resulting in the higher toxicity observed (cf. Table 3).

3.2.3. Fe-DiSoCi, Fe-SuGl, Fe-AA, Fe-ChS

The first two of these iron complexes are composed of an oligonuclear iron hydroxide complexed with dextrin, sorbitol and citric acid (Fe-DiSoCi), and with sucrose and gluconic acid (Fe-SuGl). The molecular masses and complex stabilities are very low in comparison to iron dextran and iron saccharates. Citric acid and gluconic acid yield a substantially better complex with iron hydroxide than do sorbitol and sucrose, so that in these mixtures mainly low molecular mass iron(III)-hydroxide citric acid complex and partially gluconic acid complex respectively are present (cf. Table 3). This results in a comparatively higher toxicity (Müller 1974).

Fe-AA is composed mainly of mononuclear iron(II)- and iron(III)-ascorbate and -dehydroascorbate. The complex stability with alloxanic acid is neglectable in comparison to ascorbic acid. The system iron(II)/(III) / ascorbic acid, which generates radicals, becomes toxic for liver and mucosa cells (Zglinicki et al. 1990, Hiraishi et al. 1991).

Table 3: Compilation of the results.

Iron preparation	Iron content [mg/ml]	Ligand content [mg/ml]	pH of the solution	Point of zero charge [pH]	Degradation kinetics [k × 10 min^{-1}] θ = 0.1/0.5/0.9	Molecular mass of complex [Dalton]	Undue toxicity in white mice, i.v. [mg Fe/kg body weight]	Points in correlation diagram (Fig. 30)
Fe-Da-BP/USP (Lot 015109)	48.6	206	6.0	none[4]	20/34/67	103 000	> 500	1
Fe-Da5 (Lot 911308)	49.3	64	6.0	none[4]	23/34/66	523 000	> 1 000	2
Fe-Da20 (Lot 985108)	198.0	205	6.0	none[4]	12/27/50	445 000	> 1 000 > 10 000 (i.p.)	3
Fe-Am (Lot 962208)	50.3	56 dextrin	5.8	none[4]	9/20/42	462 000	> 1 000	4
Fe-Su-I (Lot 750208)	20.2	318 sucrose	10.8	5.0	107/89/117	43 300	> 200	5
Fe-Su-II (Lot 951108)	20.0	383 sucrose	9.6	4.5	110/87/129	31 100	> 200	6
Fe-Su-III (Lot Y 288)	20.3	392 sucrose	9.7	5.3	77/81/107	48 200	180[5]	7
Fe-Ma (Lot 919218)	50.4	67 dextrin	6.0	none[4]	51/73/118	52 300	> 400	8
Fe-DiSoCi (Lot 09.109.431)	50.5	160[1]	7.3	2.2	449/320/204	8 700	> 50	9
FeSuGl (Lot 91145701)	12.5	197[2]	8.4	3.6	136/130/130	37 500 < 1 000[2]	> 50	10
Fe-AA (Lot NN 348.102)	2.0	5 mg Asc.a.[3] 5 mg All.a.[3]	7.3	2.6	615/608/96	< 1 000	> 50	11
Fe-ChS (Lot 91.1.55101)	3.8	—	7.4	none[4]	144/98/8	47 800 1 400 000	250[5]	12 13

[1] As sorbitol and dextrin (cf. Methods of analysis); contains also citric acid, which is not included. [2] As sucrose (cf. Methods of analysis); contains also 23 mg sodium gluconate/ml (value from the declaration) with a molecular mass of < 1000 Daltons. [3] Ascorbic acid and alloxanic acid (values from the declaration). [4] For the explanation of 'none' cf. methods of analysis. [5] LD_{50}-value in white mice as indicated in the leaflet.

Key to the abbreviations of the preparations: Fe-Da BP/USP: iron dextran BP/USP manufactured by Hausmann Laboratories; Fe-Da5: iron dextan 5 % human: Ferrum Hausmann® i.m.: Dexferrum; Fe-Da20: iron dextran 20 %, Anaemex® (Hausmann); Fe-Am: iron dextrin (amylum) complex, Ferrum Hausmann® i.m.: Amyloferrum; Fe-Su-I: iron sucrose complex, Ferrum Hausmann® i.v.: Venoferrum; Fe-Su-II: iron sucrose complex, Feppsol, manufactured by Hausmann Laboratories, distributed by Green Cross, Japan; Fe-Su-III: iron sucrose complex; Fe-Ma: iron dextrin (maltrin) complex, Maltoferrum (active ingredient of Ferrum Hausmann® chewable tablets, syrup and drops); Fe-DiSoCi: iron dextrin/sorbitol/citric acid complex; Fe-SuGl: iron sucrose/gluconic acid complex; Fe-AA: iron ascorbic acid/alloxanic acid; Fe-ChS: iron chondroitinsulphate.

Fe-ChS is a mixture of iron(III)-chondroitinsulphates with very different molecular masses (cf. Table 3). The high molecular mass fraction has a similar complex stability as iron dextran, resulting in the fact that this complex is present in the serum for a long time after application (half-life time in rats: approx. 4 h).

4. Results

4.1. General remarks about histology

Histological tests were carried through in order to determine the distribution of intravenously applied iron in liver, kidney, adrenal, lung and spleen. At the same time the tissue sections involved were carefully checked for damages such as necrosis. It is to be noted that with certain iron preparations the selected standard dose of 200 mg Fe/kg b.w. was already close to the LD_{50}-value (cf. Table 3), so that cell damages were likely to appear.

4.2. Results in detail

The deposited quantities of iron (in relative units, cf. Methods) in liver, kidney, adrenal, lung and spleen, in correlation with the time after application (10 min, 4 h, 4 d and 14 d) are shown in Fig. 1—5.

4.2.1. Comments on liver sections

Fe-Da5, Fe-Da20, Fe-Am (cf. Table 4)

The distribution and relative concentrations of iron deposits correspond largely to the picture of iron dextran BP/USP (Fig. 6—9).

Fe-Su-II, Fe-Su-III

The distribution and relative concentrations of iron deposits correspond largely to the picture of Fe-Su-I (Fig. 10—12).

Fe-Ma

After 4 d (Fig. 13) and 14 d, necroses were found over the whole tissue. After 14 d a phase of regeneration was observed.

Fe-AA

Dose: The following doses had to be selected for toxicological reasons: 200 mg Fe/kg b.w. (acute toxic region) for 10 min and 4 h. 100 mg Fe/kg b.w. for 4 d and 14 d.

Necrotization began 10 min post injectionem. After 4 h there were severe necroses in the periportal region with the most part of deposited iron in the parenchyma (Fig. 16).

Fe-ChS

Necrotization began 4 h post injectionem. After 4 d there were already some necroses in the periportal region (Fig. 17).

In those mice which survived only 2 days because of the high toxicity of the iron injected, 4 rU of iron were found in the liver: homogeneously distributed, partly coarse-grained, generally more in the RES than in parenchyma. The proportion between periportal and central area was about 1 : 1. Small to medium-sized necroses were visible all over the tissue.

4.2.2. Comments on kidney sections

Fe-DiSoCi (cf. Table 5)

A dark brown coloration of the urine appearing 10 min after the i.v. application is the most noticeable phenomenon and is caused by the excretion of low molecular iron complexes, which are detectable in the histological preparation of the calix (Fig. 21). All tested organs are free from iron after 4 days already.

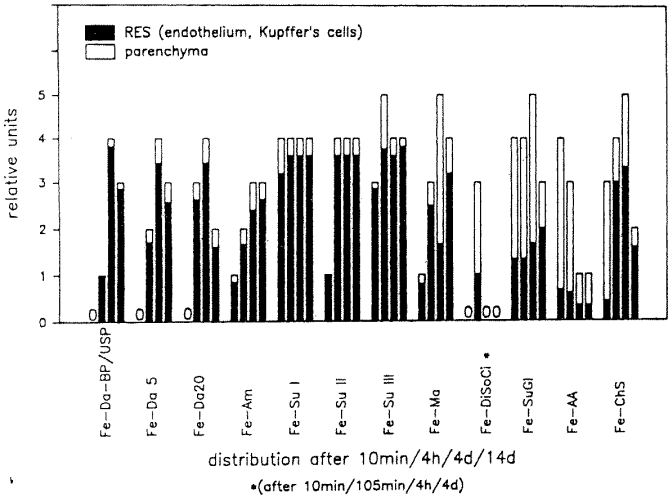

Fig. 1: Distribution of iron deposits in histological sections of the liver. The distribution is given in relative units after 10 min, 4 h, 4 d and 14 d (* corresponds to 10 min, 105 min, 4 h and 4 d). For further details cf. 4.2. These details apply also to Fig. 2—5. For a clinically safe iron preparation the iron deposit should mainly be in the RES (cf. Discussion).

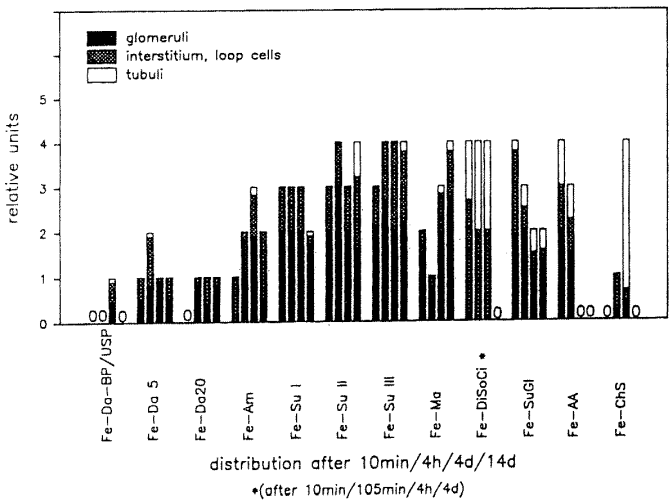

Fig. 2: Distribution of iron deposits in histological sections of the kidney. For a clinically safe and well utilized iron preparation the iron deposit should not be in the tubuli (cf. Discussion).

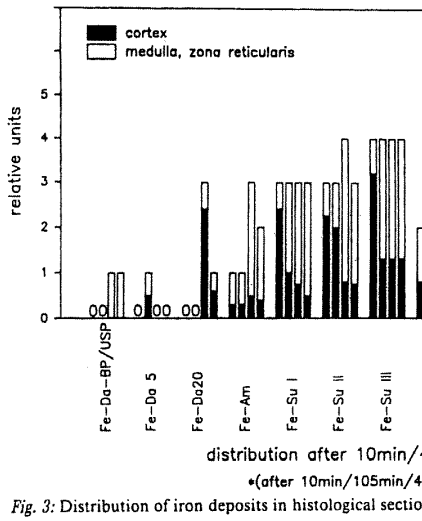

Fig. 3: Distribution of iron deposits in histological sectio

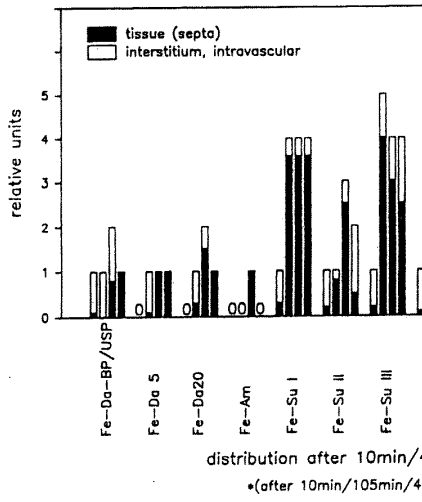

Fig. 4: Distribution of iron deposits in histological sectio

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