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Parenteral iron nephrotoxicity: Potential mechanisms and consequences[1]

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Parenteral iron nephrotoxicity: Potential mechanisms and consequences.

Background. Parenteral iron administration is a mainstay of anemia management in renal disease patients. However, concerns of potential iron toxicity persist. Thus, this study was conducted to more fully gauge iron toxicologic profiles and potential determinants thereof.

Methods. Isolated mouse proximal tubule segments (PTS) or cultured proximal tubular [human kidney (HK-2)] cells were exposed to four representative iron preparations [iron sucrose (FeS), iron dextran (FeD), iron gluconate (FeG), or iron oligosaccharide (FeOS)] over a broad dosage range (0, 30 to 1000 μg iron/mL). Cell injury was assessed by lactate deyhdrogenase (LDH) release, adenosine triphosphate (ATP) reductions, cell cytochrome c efflux, and/or electron microscopy. In vivo toxicity (after 2 mg intravenous iron injections) was assessed by plasma/renal/cardiac lipid peroxidation [malondialdehyde (MDA)], renal ferritin (protein)/heme oxygenase-1 (HO-1) (mRNA) expression, electron microscopy, or postiron injection PTS susceptibility to attack.

Results. In each test, iron evoked in vitro toxicity, but up to 30× differences in severity (e.g., ATP declines) were observed (FeS > FeG > FeD = FeOS). The in vitro differences paralleled degrees of cell (HK-2) iron uptake. In vivo correlates of iron toxicity included variable increases in renal MDA, ferritin, and HO-1 mRNA levels. Again, these changes appeared to parallel in vivo (glomerular) iron uptake (seen with FeS and FeG, but not with FeD or FeOS). Iron also effected in vivo alterations in proximal tubule cell homeostasis, as reflected by the "downstream" emergence of tubule resistance to in vitro oxidant attack.

Conclusion. Parenteral iron formulations have potent, but highly variable, cytotoxic potentials which appear to parallel degrees of cell iron uptake (FeS > FeG ≫ FeD or FeOS). That in vitro injury can be expressed at clinically relevant iron concentrations, and that in vivo glomerular iron deposition/injury may result, suggest caution is warranted if these agents are to be administered to patients with active renal disease.

[1]**See Editorial by Alam et al, p. 457.**

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Administration of parenteral iron has become a mainstay for treating anemia in patients with end-stage renal disease (ESRD). This practice is required in order to offset dialysis-related blood (iron) loss, and the need to optimize hematopoietic responsiveness to exogenous erythropoeitin (Epo) therapy [1–3]. While generally regarded as safe, anaphylactic/oid reactions have been noted following intravenous iron injection, most commonly but not exclusively, with dextran preparations [4]. In addition to allergic reactions, each currently employed parenteral iron formulation [e.g., iron dextran (FeD), iron sucrose (FeS), and iron gluconate (FeG)] has the potential to induce oxidative stress [5–9]. For example, when administered intravenously, these agents may induce free radical generation [10] and lipid peroxidation [5], processes which can induce acute endothelial dysfunction (e.g., as denoted by perturbed forearm endothelial-dependent vasodilation) [10]. Additional support for the concept of iron-induced toxicity comes from a recent report [11] which indicates that clinically achievable concentrations of FeG or FeS can impair polymorphonuclear cell (PMN)/transendothelial migration. This could contribute to infectious complications in dialysis patients.

While the above evidence suggests potential acute toxicities, the long-term consequences of parenteral iron administration remain largely unknown. In this regard, it is noteworthy that iron-mediated oxidative stress can contribute to both atherogenesis [12–17] and chronic inflammation [18–22], each of which are leading causes of morbidity and mortality in ESRD patients [23–25]. Furthermore, because parenterally administered iron has direct glomerular, and as well as tubular access (via peritubular capillaries), it is conceivable that it might contribute to glomerular and/or tubulointerstitial disease progression [26–29]. That intravenous iron + Epo therapy is currently being administered to pre-ESRD patients underscores these concerns.

Given that parenteral iron therapy is likely to remain an integral component of renal disease patient management, it is imperative to better define its potential cytotoxic effects, and to ascertain whether different toxicity profiles exist amongst currently employed parenteral

iron formulations. Indeed, in a recent study performed in this laboratory using suprapharmacologic iron doses [5], a clear gradation of toxicity was apparent amongst four test agents [from most to least severe: FeS ≫ FeG ≫ FeD = Fe oligosaccharide (FeOS)]. However, the reason(s) for this differential in vitro toxicity, if it might be observed with more clinically relevant iron concentrations, whether in vivo toxicologic correlates exist, and the nature of underlying pathogenic mechanisms were not well defined. Hence, the present study was undertaken utilizing a number of experimental models (freshly isolated mouse proximal tubules, cultured human proximal tubular cells, and in vivo mouse experiments) to gain additional insights.

METHODS

Proximal tubule segment (PTS) experiments

Preparation of isolated mouse proximal tubules. Proximal tubules were isolated from normal CD-1 male mice (25 to 35 g) (Charles River, Wilmington, MA, USA), as previously described [30]. In brief, the mice were deeply anesthetized with pentobarbital (4 to 5 mg intraperitoneally), and the kidneys were resected through a midline abdominal incision. They were iced, the cortices were dissected, and the tissues were subjected to collagenase digestion. The tissues were passed through a stainless steel mesh, and then viable PTS were collected after pelleting through 32% Percoll [30, 31]. The recovered tubules were suspended in an experimentation buffer consisting of (in mmol/L): NaCl, 100; KCl, 2.1; $NaHCO_3$, 25; KH_2PO_4, 2.4; $MgSO_4$ 1.2; $MgCl_2$, 1.2; $CaCl_2$, 1.2; glucose, 5; alanine, 1; Na lactate, 4; Na butyrate, 10; 36 kD dextran, 0.6%; and gassed with 95% O_2/5% CO_2, pH 7.44). The final tubule protein concentration was ~2 to 4 mg/mL. Each PTS preparation was rewarmed to 37°C in a heated shaking water bath and divided into four to six equal aliquots (1.25 mL) in 10 mL Erlenmyer flasks, depending on the needs of individual experiments (see below).

Comparative effects of iron preparations on proximal tubule adenosine triphosphate dehydrogenase (ATP) content.

Dose response experiments. The purpose of this study was to compare dose-response toxicity effects of four test iron preparations. Given that previous studies demonstrated that mitochondrial dysfunction, as assessed by reductions in tubule ATP production, is a sensitive marker of iron toxicity [5, 31], tubule ATP concentrations, as well as lethal cell injury [% lactate dehydrogenase (LDH) release], were chosen as test biologic end points. Twelve individual sets of PTS were prepared, each was divided into five equal aliquots, and these were incubated ×30 minutes in a 37°C shaking water bath in the presence of 95% O_2/5% CO_2, under the following conditions: (*1*) control incubation; (*2*) 1000 μg/mL iron addition; (*3*) 500 μg/mL iron addition; (*4*) 250 μg/mL iron addition; and (*5*) 125 μg/mL iron addition. Each individual tubule preparation was used to test one of the four iron preparations: (1) FeS (Venofer) (American Regent, Shirley, NY, USA); (*2*) FeD (INFeD) (Watson Pharmaceuticals, Morristown, NJ, USA); (*3*) FeG (Ferrlecit) (Watson Pharmaceuticals); and (*4*) FeOS, an iron preparation currently in clinical trials (Pharmacosmos, Copenhagen, DK). In all, each of these preparations were tested in three separate dose-response experiments. After completing the 30-minute incubations, a sample of each aliquot was removed, adenine nucleotides were extracted in trichloroacetic acid, and then the samples were analyzed for ATP by high-performance liquid chromatography (HPLC) (nmol/mg tubule protein) [32]. An aliquot of each tubule suspension was also used to determine % LDH release.

pH control experiment. Because FeS stock solution has a pH of approximately 10.5, and because a high pH can induce cytotoxicity [33], a control for the above FeS additions was conducted with an equivalent amount of sucrose (300 mg/mL) with its pH adjusted to 10.5 by 1 N NaOH addition. Aliquots from four sets of tubules were incubated either under control conditions or with 62.5 μL of the alkaline sucrose solution (equivalent to the volume of the 1000 μg/mL FeS dosage). After 30-minute incubations, ATP concentrations and % LDH release were assessed.

Effects of low dose FeS and FeG on tubule ATP concentrations. The above dose-titration experiments indicated that FeS and FeG had the greatest suppressive effects on tubule ATP concentrations, with reductions being apparent at the lowest test concentration (125 μg iron/mL) (see **Results** section). The following experiment ascertained whether ATP reductions could be induced by even lower iron concentrations (i.e., within clinically achievable plasma iron concentrations). Four sets of tubules were prepared, each was divided into five equal aliquots, and incubated ×30 minutes as follows: group 1, control conditions; groups 2 and 3, with 30 or 60 μg/mL FeS iron; and groups 4 and 5, with 30 or 60 μg/mL FeG iron. ATP levels and LDH release were then assessed.

In vivo mouse experiments

Assessment of lipid peroxidation following intravenous iron treatment. The following experiments were undertaken to ascertain the relative degrees of lipid peroxidation induced by three representative test iron compounds: FeD, FeS, and FeG. These three compounds were selected because they manifested the greatest differential toxicity in the above described proximal tubule experiments (see **Results** section). Mice ($N = 18$) were placed in non-traumatic restraining cages, and they were injected via

Table 1. Mouse primers for quantitating heme oxygenase 1 (HO-1) mRNA in renal cortex

Genes	Primer sequences	Polymerase chain reaction conditions	Product size
Mouse GAPDH	5′-CTG CCA TTT GCA GTG GCA AAG TGG-3′ 5′-TTG TCA TGG ATG ACC TTG GCC AGG-3′	94°C – 45 sec; 57°C – 45 sec; 72°C – 45 sec; 28 cycles	437 bp
Mouse HO-1	5′-AAC ACA AAG ACC AGA GTC CCT CAC-3′ 5′-CAA GAG AAG AGA GCC AGG CAA GAT-3′	94°C – 45 sec; 57°C – 45 sec; 72°C – 45 sec; 28 cycles	288 bp

Primer sequences used for quantitating HO-1 mRNA in mouse renal cortex 4 hours following intravenous iron treatment (see text). Glyeraldehyde-3-phosphate dehydrogenase (GAPDH) was quantified as a "housekeeping gene."

the tail vein with either 2 mg of iron ($N = 4$ of each of the above iron preparations), or with a sham tail vein saline injection ($N = 6$). The mice were then released from the restrainers and, 90 minutes later, they were deeply anesthetized with pentobarbital, as above. The abdominal cavities were opened, a plasma sample was obtained from the inferior vena cava, and then one kidney per animal was resected. The thorax was opened and the heart was removed. The tissues were placed on an iced plate. A piece of renal cortex and of cardiac apex were resected, the tissues rinsed in iced saline to remove contaminating blood, and then ~75 mg of renal cortex or heart tissue were homogenized in 1 mL of iced phosphate-buffered saline (PBS) containing 25 mmol/L desferrioxamine (DFO) to chelate any free iron which may have been generated during this process. Samples of tissue homogenates (200 μL) were then assayed for malondialdehyde (MDA) concentrations by the thiobarbituric acid method [34]. Tissue MDA concentrations were expressed as nmol/mg tissue protein. Plasma samples (200 μL), to which 25 mmol/L DFO was added, were also assayed for MDA with values being expressed as nmol/mL.

Parenteral iron effects on renal ferritin and heme oxygenase-1 (HO-1) expression. The following experiments were conducted to ascertain whether, and to what degree, the four test iron preparations impact renal cortical homeostasis, as assessed by the potential induction of ferritin and HO-1 proteins (redox-sensitive indicators). To this end, mice received every other day tail vein injections of 2 mg iron, administered as either FeS ($N = 5$), FeG ($N = 5$), INFeD ($N = 5$), or FeOS ($N = 4$). Each group of mice had their own simultaneous control groups which received equal volume tail vein saline injections. Approximately 24 hours following the last of the three injections, the mice were anesthetized with pentobarbital, the kidneys were removed, and the cortices were dissected on an iced plate.

Western blotting. The above noted renal cortical tissue samples were extracted for protein and probed by Western blot for ferritin and HO-1, using previously described general methodologies [35]. In the case of ferritin, 25 μg of protein extract were electrophoresed through a 12% Bis-Tris acrylamide Nupage gel (Invitrogen Life Technologies, Carlsbad, CA, USA) and probed with goat antiferritin antibody (catalog number SC-14416) (Santa Cruz Biotechnology, Santa Cruz, CA, USA), according to manufacturer's instructions. For HO-1 detection, 50 μg of protein extract was electrophoresed as described above, and probed with rabbit anti-HO-1 antibody (catalog number SC-10789) (Santa Cruz Biotechnology) as the primary antibody as per manufacturer's instructions. Secondary detection of the anti-ferritin and anti-HO-1 antibodies was performed with either horseradish peroxidase (HRP)-labeled donkey antigoat IgG (catalog number SC-2020) (Santa Cruz Biotechnology) for ferritin or with HRP-labeled donkey antirabbit IgG (catalog number NA 934) (Amersham-Pharmacia, Piscataway, NJ, USA) for HO-1. Detection was by enhanced chemiluminescence (ECL Kit) (Amersham-Pharmacia). Western blot semiquantitative analysis was performed by band optical density scanning. Nonspecific secondary antibody staining was ruled out by the fact that the secondary antibody, in the absence of the primary antibody, did not identify the relevant protein bands (ferritin, ~25 kD; HO-1, ~32 kD). Equal protein loading/transfer was verified by India ink staining. A positive control consisted of renal cortical protein samples from mice 18 hours postinduction of glycerol induced-acute renal failure (which upregulates both HO-1 and ferritin) [36].

HO-1 mRNA expression following iron treatment. Stress induced changes in tissue ferritin concentrations are largely determined by posttranslational events, whereas HO-1 expression is regulated via oxidant stress-induced HO-1 gene transcription [37]. Therefore, to gain further insights into relative degrees of iron-induced oxidant stress, mice were injected with either FeD, FeG, FeS, or FeOS, as noted above ($N = 4$ to 6 per group). Controls consisted of ten mice subjected to tail vein saline injections. Four hours later, the mice were anesthetized with pentobarbital, and the kidneys resected. The renal cortical tissues were immediately placed into TRIzol reagent (Invitrogen Life Technologies) and total RNA was extracted according to the manufacturer's instructions. The final RNA pellet was brought up in RNase-free water to an approximate concentration of 3 mg/mL.

Reverse transcription (RT) and polymerase chain reaction (PCR) were performed using the 1st-Strand Synthesis Kit for RT-PCR (Ambion Inc., Austin, TX, USA), as previously described in detail [38]. The specific primers for HO-1 and glyceraldehyde-3-3-phosphate dehydrogenase (GAPDH) were designed with 50% to 60% GC composition (see Table 1). The similarity in annealing

temperature, but dissimilarity in PCR products, enabled a multiplexed reaction whose products were analyzed by agarose gel electrophoresis and ethidium bromide staining. cDNA bands were visualized and quantified by densitometry with a Typhoon 8600 scanner (Amersham Pharmacia Biotech). HO-1 cDNA bands were expressed as ratios to the simultaneously obtained GAPDH cDNA bands, the latter used as a housekeeping gene.

Renal histology. To assess whether parenteral iron treatment might induce structural renal alterations, mice which were subjected to the above intravenous iron treatment protocols (2 mg iron every other day × 1 week; $N = 2$ for each test agent) or to sham saline injections ($N = 3$). One day following the last injection, the kidneys were harvested, and prepared for either light or electron microscopy. For light microscopy, a midline slice of kidney (cortex to papilla) was fixed in 10% formalin and 4 μ paraffin-embedded sections prepared and stained with hematoxylin and eosin. For electron microscopy, 1 mm cubes of renal cortex were fixed by immersion in $^1/_2$ strength Karnovsky's fixative. Tissue sections were cut and evaluated by transmission electron microscopic analysis, as previously described [39]. At least four glomeruli from two different kidneys were extensively examined by electron microscopy.

Cultured proximal tubular [human kidney (HK-2)] cell experiments

Cytotoxicity and cellular loss of cytochrome c. The following experiment was undertaken to further ascertain relative degrees of iron-mediated cytotoxicity, as assessed by % LDH release and extracellular cytochrome c release (a marker of mitochondrial damage) [31]. To these ends, immortalized human proximal tubular (HK-2) cells were cultured in T-75 flasks with keratinocyte serum-free medium (K-SFM) and passaged by trypsinization every 5 to 6 days, as previously described [40]. For experimentation, the cells were seeded into 18 T-25 flasks. After an overnight postseeding recovery period, the cells were divided into six groups of three flasks each: (*1*) control cells ($N = 3$); (*2*) incubation with 100 μg/mL FeS iron; (*3*) incubation with 100 μg/mL FeG iron; (*4*) incubation with 100 μg/mL FeD iron; (*5*) incubation with 100 μg/mL FeOS iron; and (*6*) a second group of control incubated cells. The cells were maintained under routine culture conditions for 3 days. At the completion of the incubations, % LDH release was determined. Then, the cells which remained attached to the flasks were recovered by scraping with a cell scraper, and washed with Hanks' balanced salt solution (HBSS), and pelleted. The pellets were photographed with a digital camera. Then, cell protein extracts were prepared and probed for cytochrome c by Western blotting [31]. An equal amount of protein (8 μg) from each cell sample was applied.

Electron microscopic analysis of iron effects on HK-2 cell morphology. The following experiment was undertaken to ascertain the effect of the four test iron preparations on HK-2 cell morphology. To this end, a 6-well Costar plate was seeded with HK-2 cells and allowed to grow to near confluence. One well each was subjected to the following conditions: (*1*) control incubation; (*2*) incubation with 100 μg FeS iron; (*3*) incubation with 100 μg FeG iron; (*4*) 100 μg FeD iron; (*5*) 100 μg of FeOS iron; and (*6*) additional control culture. After an 18-hour incubation, the cell culture medium in each well was removed, and then a mixture of 1 part of $^1/_2$ strength Karnovsky's fixative/1 part fresh culture medium was added to the adherent cells. The cells were allowed to fix overnight. After dehydration and alcohol fixation, groups of cells were randomly lifted off the plates by applying small resin blocks to the monolayers. These blocks were then cut and processed for transmission electron microscopy, as previously described [41].

Combination in vivo/in vitro experiments

Intravenous iron injection with subsequent in vitro analysis of cytoresistance. A feature of acute sublethal renal tubular injury is the subsequent emergence of partial cell resistance to further attack [42–45]. In particular, iron-mediated injury induces resistance to further oxidative damage [36, 42]. Hence, the goal of this experiment was to ascertain whether parenteral iron administration can induce sublethal proximal tubular injury, and that this prior injury is denoted by the emergence of cytoresistance to subsequent iron-mediated tubular attack. To this end, four mice were injected with 2 mg of FeS via the tail vein (0.1 mL). Four mice subjected to equal saline tail vein injections served as controls. The mice were then provided with free food and water access (preliminary data indicated that no difference in food intake/body weight resulted from the iron injection). Eighteen hours postinjections, they were anesthetized with pentobarbital, the kidneys resected, and cortical proximal tubules were isolated, as above. The eight preparations (four postiron injection; four postsaline injection) were each divided into five equal tubule aliquots as follows: (*1*) control incubation (95% O_2/5% CO_2); (*2*) hypoxic incubation (95% N_2/5% CO_2); (*3*) exposure to 100 μmol/L antimycin A (a mitochondrial inhibitor); or (*4*) addition of 25 μmol/L ferrous ammonium sulfate (iron), complexed to the siderophore hydroxyquinoline (FeHQ), permitting iron to gain intracellular access [42]. After completing 15-minute incubations under each of these conditions, the extent of lethal cell injury was gauged by % LDH release. The results for the control and Venofer pretreatment groups were compared.

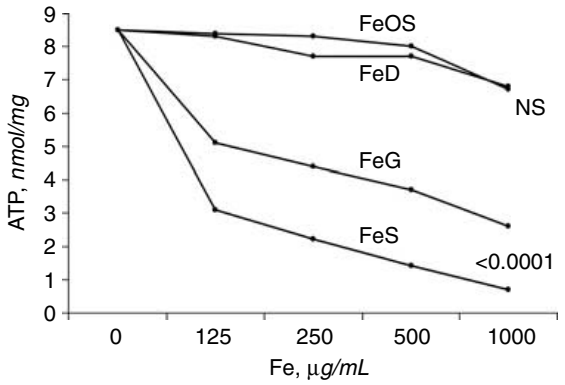

Fig. 1. Proximal tubular segment adenosine triphosphate (ATP) concentrations following 30-minute incubations with four test iron preparations: iron dextran (FeD), iron oligosaccharide (FeOS), iron gluconate (FeG), and iron sucrose (FeS). ATP concentrations are presented as nmol/mg tubule protein. FeD and FeOS caused only minimal ATP declines, and these were apparent at only the 1000 µg/mL iron concentration. In contrast, steep ATP declines were observed with both FeS and FeG, with the degree of ATP reductions being statistically greater with FeS vs. FeG ($P < 0.0001$; all dose-paired comparison). Standard error bars are not shown for clarity sake, but were all <0.4 nmol/mg protein.

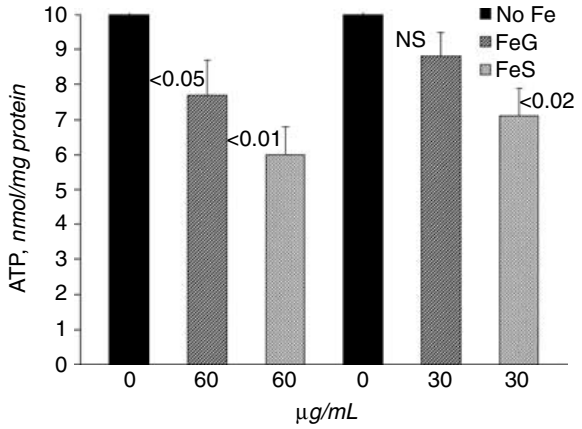

Fig. 2. Proximal tubular segment adenosine triphosphate (ATP) concentrations with low dose (30 and 60 µg/mL) iron sucrose (FeS) and iron gluconate (FeG) exposures. Both drugs caused significant ATP depressions at the 60 µg/mL concentration. Each drug also tended to depress ATP concentrations even at the 30 µg/mL dosage, but only the FeS result achieved statistical significance ($P < 0.02$ vs. controls).

Calculations and statistics

All values are presented as means ± 1 SEM. Statistical comparisons were made by paired or unpaired Student *t* testing, as per the nature of the experiment. If multiple comparisons were made, the Bonferroni correction was applied.

RESULTS

Isolated tubule experiments

Proximal tubule ATP concentrations in response to 125 to 1000 µg/mL iron exposures. As shown in Figure 1, each of the test iron preparations caused dose dependent reductions in tubule ATP concentrations. The FeOS and FeD curves did not significantly differ, and statistically significant ATP reductions were observed at only the highest tested concentration (1000 µg/mL of iron; $P < 0.04$ vs. their respective controls). In contrast, FeS and FeG each induced steep dose-response curves, clearly much more severe than those observed with either FeOS or FeD. FeS caused the most severe ATP depressions, with ~50% greater ATP losses being observed vs. their corresponding FeG results ($P < 0.0001$ in an overall comparison between paired concentrations).

% LDH release with the 125 to 1000 µg/mL iron dosage range. The 95% confidence band for % LDH release for control tubules was 8% to 13%. In the above-described 30-minute titration experiments, only FeS raised % LDH release above this normal range, but this was observed only at the two highest test concentrations (41 ± 3%, 14 ± 1%, and 13 ± 1% with 1000 µg/mL, 500 µg/mL, and 250 µg/mL iron doses, respectively) (data not shown). Each of the other test compounds (FeD, FeG, and FeOS) failed to raise % LDH release above control values (≤13%) even with application of 1000 µg/mL iron concentrations.

pH controls for high dose Venofer additions. Addition of alkaline sucrose solution (pH 10.5), did not reproduce FeS cytotoxic effects. First, it tended to *raise*, rather than lower, tubule ATP concentrations (pH 10.5, 8.4 ± 0.6; controls, 8.0 ± 0.5 nmol/mg protein). Second, % LDH release was 14 ± 1% with alkaline sucrose incubation, compared to 41 ± 3% with the 1000 µg/mL FeS addition. Third, even the highest test dose of FeS (1000 µg/mL) had only a small effect on tubule suspension pH, raising it from 7.44 to 7.8. Lesser amounts of FeS addition had no discernible pH effect.

ATP concentrations and LDH release with "low dose" (30 and 60 µg/mL) iron concentrations. As shown in Figure 2, even when added in a 30 or 60 µg iron/mL dose, FeS still caused statistically significant reductions in tubule ATP concentrations, compared to co-incubated control tubules. FeG also lowered ATP at these two iron concentrations, but the result was statistically significant only at the 60 µg/mL concentration (Fig. 2). None of these incubations caused a significant increase in LDH release (range for controls and iron compounds, 9% to 11%).

In vivo experiments

MDA levels following parenteral iron treatment. As shown in Figure 3A, each of the iron compounds induced statistically significant plasma MDA increments, rising well above the upper 95% confidence limit (shown by horizontal line) for normal plasma MDA values. The plasma MDA increase was ~2× as great with FeD, compared

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