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Nitrosative Stress and Apoptosis by Intravenous Ferumoxytol, Iron Isomaltoside 1000, Iron Dextran, Iron Sucrose, and Ferric Carboxymaltose in a Nonclinical Model.

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Abstract

Iron is involved in the formation as well as in the scavenging of reactive oxygen and nitrogen species. Thus, iron can induce as well as inhibit both oxidative and nitrosative stress. It also has a key role in reactive oxygen and nitrogen species-mediated apoptosis. We assessed the differences in tyrosine nitration and caspase 3 expression in the liver, heart, and kidneys of rats treated weekly with intravenous ferumoxytol, iron isomaltoside 1000, iron dextran, iron sucrose and ferric carboxymaltose (40 mg iron/kg body weight) for 5 weeks. Nitrotyrosine was quantified in tissue homogenates by Western blotting and the distribution of nitrotyrosine and caspase 3 was assessed in tissue sections by immunohistochemistry. Ferric carboxymaltose and iron sucrose administration did not result in detectable levels of nitrotyrosine or significant levels of caspase 3 vs. control in any of the tissue studied. Nitrotyrosine and caspase 3 levels were significantly ($p<0.01$) increased in all assessed organs of animals treated with iron dextran and iron isomaltoside 1000, as well as in the liver and kidneys of ferumoxytol-treated animals compared to isotonic saline solution (control). Nitrotyrosine and caspase 3 levels were shown to correlate positively with the amount of Prussian blue-detectable iron(III) deposits in iron dextran- and iron isomaltoside 1000-treated rats but not in ferumoxytol-treated rats, suggesting that iron dextran, iron isomaltoside 1000 and ferumoxytol induce nitrosative (and oxidative) stress as well as apoptosis via different mechanism(s).