

ALTHOUGH considerable effort has been invested in the development of new therapeutics for managing iron-overload diseases, the treatment has remained essentially unchanged. Patients with primary hemochromatosis are still treated by frequent phlebotomy, whereas patients suffering from iron overload secondary to blood transfusions, eg, Cooley’s anemia, must be maintained on chelation therapy. Subcutaneous infusion of desferrioxamine B, a hexacoordinate hydroxamate iron chelator produced by Streptomyces pilosus, is still regarded as the method of choice for treating transfusional iron overload. Although the drug’s efficacy and long-term tolerability are well documented, many individuals must be maintained on this regimen for most of their natural lives, and patient compliance can become a major problem. Furthermore, the cost of desferrioxamine treatment renders the population in areas with the greatest need untreated. In principle, both of these difficulties would be overcome with an orally effective iron chelator.

In recent years, several families of orally effective iron chelators have been identified; eg, pyridoxal isonicotinoyl hydrazones (PIHs), hydroxypyridones (CP20, CP94), and the desferrithiocins. Of these compounds, none has yet been shown to be completely satisfactory: All of these ligands have demonstrated severe renal toxicity, whereas drugs 3, 4, and 5 exhibited severe gastrointestinal (GI) toxicity. Under the same experimental protocol, drug 2 did not show significant toxic side effects. In addition, to further evaluate the iron-clearing properties of analogue 2, a dose-response study was performed in the primates that showed that iron excretion increased in a dose-dependent fashion.

Although many chelators that are effective at removing iron in cell culture models have been promoted to the next level of evaluation, the rodent model, many of the compounds that appeared outstanding in both of these screens have failed at the clinical level. Because of the many similarities of the iron-overloaded Cebus monkey to humans, it serves as an excellent intermediate screen for evaluating iron chelators before human studies. The results from this primate study suggest that selected desferrithiocins should now be considered for clinical evaluations.

MATERIALS AND METHODS

Materials. DFO (desferrioxamine B mesylate salt, trade name: Desferal) and the desferrithiocin analogues 1 through 5 were supplied by Ciba-Geigy Ltd (Basel, Switzerland). Cebus apella monkeys were purchased from World Wide Primates (Miami, FL). All reagents and standard iron solutions were obtained from Aldrich Chemical Co (Milwaukee, WI). Atomic absorption measurements were made on a Perkin-Elmer model 5100 PC (Norwalk, CT). Ultrapure salts were obtained from Johnson Matthey Electronics (Rosyton, UK). Imferon, an iron dextran solution, was obtained from Fisons (Bedford, MA). Nalgene metabolic cages, rat jackets, and fluid swivels were purchased from Harvard Bioscience (South Natick, MA). Intramedic polyethylene tubing was obtained from Fisher Scientific (Pittsburgh, PA). All hematologic and serum chemical tests were carried out by Allied Clinical Laboratories (Gainesville, FL). Cremophor RH-40 was obtained from BASF ( Parsippany, NJ), and Multitest 10 SG reagent strips for urinalysis were obtained from Miles Inc, Diagnostics Division (Elkhart, IN).

Drug preparation and administration. Desferrioxamine, desferrithiocin, and the desferrithiocin analogues were administered to the rats at 150 μmol/kg. Desferrioxamine was administered to the monkeys subcutaneously in sterile water for injection at 150 μmol/kg. Desferrithiocin itself was administered orally at a dose of 150 μmol/kg, whereas the desferrithiocin analogues were given at 300 μmol/kg. The reason for the differences in concentration was simply that we were already aware of an effective desferrithiocin dosage in primates, whereas this was not true for the analogues. In the initial treatment rendered the population in areas with the greatest need untreated. In principle, both of these difficulties would be overcome with an orally effective iron chelator.

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measurements, we tested the compounds for their iron-clearing properties. The ligands were given by gavage in a 40% (vol/vol) solution of Cremophor RH-40/water using a No. 8 French infant feeding tube. Before chelator administration, the monkeys were anesthetized with ketamine, 7 to 10 mg/kg, given intramuscularly (IM). In addition, the monkeys receiving the drugs orally were also given Reglan, 2.5 to 5 mg intravenously (IV) to prevent vomiting. Both the rats and the monkeys were fasted for 24 hours before dosing.

**Dose-response studies with analogue 2 in primates.** To further evaluate the iron-clearing properties of analogue 2, a dose-response study was performed in the primates. The compound was given orally at 150, 300, and 450 μmol/kg. At the 150- and 300-μmol/kg dosages, the drug was administered in a 40% (vol/vol) Cremophor/water solution. At the 450-μmol/kg dose, to more closely mimic potential clinical applications in humans, the compound was administered in gelatin capsules.

**Primate low-iron diet.** A low-iron liquid diet was prepared by first mixing casein, 180 g; sucrose, 194 g; dextrin, 194 g; dextrose, 194 g; cellulose fiber, 90 g; vitamin mix, 5 g; methionine, 5 g; flavoring, 2 g; choline chloride, 2 g; and cholesterol, 1 g. The following liquids were then added to this mixture with stirring: corn oil, 45 g; coconut oil, 45 g; and soy lecithin, 20 g. Finally, the ultrapure salts (sodium chloride, 5.68 g; manganese sulfate, 0.04 g; calcium carbonate, 10.16 g; potassium dihydrogen phosphate, 11.93 g; and magnesium sulfate, 3.45 g) were added to 1,350 mL of distilled deionized water and combined with the nutrient mixture to prepare the final diet. Iron concentrations were determined for each batch of food.

**Primate iron-balance studies.** Animals were maintained on the low-iron liquid diet for 7 days before drug administration. The animals were given food according to their body weight, and intake was carefully monitored.

Three days before drug administration (day –2 to day 0), baseline iron intake and output values were measured. These same measurements were made for day +1 through day +3. Iron-balance status was determined by subtracting the iron output from the iron input. The mixture was then homogenized, freeze-dried, and an aliquot of the resulting sample mixed with (65%) low-iron nitric acid and refluxed for 48 hours. Monkey urine samples were sterilized, acidified, and reconstituted to initial volume after sterilization. Iron concentrations were determined by flame atomic absorption (AA).

**Efficiency calculations.** The efficiency of each ligand was calculated assuming a 1:1 desferrioxamine-iron complex or a 2:1 ligand-iron complex for desferrioxamine and its analogues. In the monkeys, the efficiencies were generated by averaging the iron output for 4 days before the administration of the drug, subtracting this baseline from the 2-day iron clearance after the administration of the drug, and then dividing by the theoretical output. The efficiencies in the rodent model were calculated by subtracting the iron excretion of control animals from the iron excretion of the treated animals. This number was then divided by the theoretical output to obtain the efficiency. In this study, iron output is reported as micrograms of iron excreted per kilogram of animal weight.

**Non-iron overloaded bile duct-cannulated rat.** Male Sprague-Dawley rats, averaging 400 g, were housed in Nalgene plastic metabolic cages during the experimental period and were given free access to water. The animals were anesthetized using sodium pentobarbital (50 mg/kg) given intraperitoneally (IP). The bile duct was cannulated using 22-gauge polyethylene tubing, about 1 cm from the duodenum. The cannula was inserted about 2 cm into the duct, and once bile flow was established, the cannula was tied snugly in place. A skin-tunneling needle was inserted from the shoulder area around to the abdominal incision. The cannula was threaded through the needle until it emerged from the shoulder opening.

The cannula was then passed from the rat to the swivel inside a metal torque-transmitting tether, which was attached to a rodent jacket around the animal’s chest. The cannula was directed from the rat to a Gilson micro fraction collector by a fluid swivel mounted above the metabolic cage. This system allowed the animal to move freely in the cage while continuous bile samples were being collected. Bile samples were collected at 3-hour intervals. Urine samples were taken every 24 hours. Sample collection and handling are as previously described.9,13

**Rodent toxicity studies.** Male Sprague-Dawley rats, averaging 400 g, were housed in individual metabolic cages and fasted overnight. Before the first drug administration, the rats were weighed and evaluated for their general condition and a base-line urine sample was obtained for comparative purposes. The rats were given the drugs once daily for 10 days following an overnight fast. The compounds were administered at 384 μmol/kg and given by gavage in a 40% Cremophor/water solution. The rats were fed 3 hours after drug administration and were given access to food for 5 hours. The amount of food and water consumed and the volume of urine produced were recorded each day. The urine samples were analyzed each morning by dip-stick (Multistix 10 SG) for the presence of white blood cells, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose. In addition, the animals were weighed and their activity level and general condition were noted each day before the administration of the drug. A necropsy was performed whenever an animal died or at the conclusion of the experiment. Control animals were given an equivalent amount of the Cremophor/water solution and were maintained on the same diet schedule as the test animals. In addition, an experiment was carried out with all of the chelators clearing an equivalent amount of iron. In this case, the chelators were administered at 192 μmol/kg (compounds 3, 4, and 5) or 384 μmol/kg (compounds 1 and 2), and the same experimental protocol was followed.

**RESULTS**

**Rodent drug toxicity.** A 10-day toxicity study was carried out on compound 1 as well as on four of its analogues. At the dosage investigated, compound 1 appeared to be highly nephrotoxic. Urinalysis indicated a drug that induced several
renal disorders: glucosuria, persistent proteinuria, decreased urinary pH, and cessation of urine production. Necropsy revealed discoloration of the kidneys with areas of necrosis further attesting to renal impairment. In addition, tremors and ataxia were noted in all of the dying animals. All of the animals in this study were dead by day +5.

Although compound 1 was found to be nephrotoxic, analogues 3, 4, and 5 were found to be severe gastrointestinal irritants. At necropsy, the animals' GI tracts were hemorrhagic. The stomachs of all of the animals were grossly distended with gas and fluid. The stomach walls were paper thin and translucent; obvious musculature was noted only at the esophageal and duodenal junctures. In addition to the observed GI toxicity, several of the animals also had slight to profuse purulent ocular and/or nasal discharges indicating a systemic infection, which was further supported by the presence of white blood cells in the animals' urine samples, as well as a "left shift" when a peripheral blood smear was performed. Although some of the urinalysis findings, i.e., glucosuria and proteinuria, may be associated with renal failure, at necropsy, the animals' kidneys did not display any obvious macroscopic lesions, and the condition of the GI tracts in these animals is suggestive of glucosuria secondary to acute pancreatitis and not due to renal failure. Finally, all of these animals were dead by day +6.

When compound 2 was evaluated using the same experimental protocol, no significant toxic side effects were found. All of the rodents survived the 10-day exposure to the drug. The animals ate well and had normal urine and fecal production throughout the experiment. In addition, a peripheral blood smear was performed that was comparable to that obtained from control animals. Postmortem examination and kidney histology revealed no significant abnormalities. This compound has emerged as the most promising analogue tested to date.

In addition to the above study, an experiment was performed in which all of the animals were given the compounds at a dosage at which the total iron excretion was equivalent. To determine the iron clearance, the compounds were first tested in the non-iron-overflowed bile duct-cannulated rats. It was determined that when compounds 3, 4, and 5 were administered at 192 μmol/kg, their iron clearance was 295 ± 60, 331 ± 23, and 376 ± 61 μg/kg, respectively, and when compounds 1 and 2 were given at 384 μmol/kg, their iron clearance was 308 ± 56 and 278 ± 44 μg/kg, respectively. A 10-day toxicity study was then performed as before. Once again, all of the rats except for those given compound 2 died. Necropsy results were essentially the same as those observed previously. This suggests that the toxicity of the desferriothiocins does not correlate with their ability to remove iron.

Drug toxicity in primates. For all treated and untreated animals, complete blood counts (CBC) and kidney and liver profiles fell within the accepted normal range of the human values. Monkey ferritin could not be determined using the commercially available human ferritin antibody assay. The animals were alert, active, ate well, and had normal urine and feces production both before and after drug administration. However, it must be emphasized that this was a single dosage and that none of the monkeys were exposed to the drugs chronically.

Comparison of chelator-induced iron clearance in primates and rodents. Six iron chelators (Fig 1) were evaluated: desferriothiocin B (DFO) administered subcutaneously, desferriothiocin sodium salt (1), desmethyl desferriothiocin (2), desazadesmethyl desferriothiocin sodium salt (3), desazadesmethyl desferriothiocin pivaloyloxymethyl ester (4), and desazadesmethyl-5,5-dimethyl desferriothiocin (5) administered orally. The efficiency of orally administered desferriothiocin and its analogues was compared with subcutaneously administered DFO as a positive control. The efficiencies of the drugs were calculated based on the assumption that desferrioxamine forms a 1:1 complex with iron and that the desferriothiocin analogues form a 2:1 complex with the metal. The Cebus monkeys responded differently to the ligands than did the rats. Although the variability in ligand-induced iron clearance was higher in the monkeys than in the rats, with each primate serving as its own control, effective chelators were easily identified (Figs 2 and 3; Tables 1 and 2). The order of efficiency in the monkey model was 5 > 1 > 4 > 3 > 2 > DFO.

In previous studies, we demonstrated that the efficiency of DFO dosed at 150 μmol/kg increased from 2.8% ± 0.7% in the rats to 5.5% ± 0.9% (range 4.4% to 6.6%), in the iron overloaded primates (P < .001), whereas the efficiency of compound 1, also administered at 150 μmol/kg, increased from 2.5% ± 1.2% in the rodent to 18.6% ± 9.3% (range 10.3% to 33.9%) in the primates (P < .005). The mode of excretion for both ligands was different in the monkeys, with a larger percentage of iron being excreted in the urine than was observed in the rats.

Analogue 4 was approximately 2.7 times more efficient in the primates than it was in the rats, 8.4% ± 3.9% (range, 4.5% to 12.9%) in the monkeys versus 3.1% ± 1.8% in the rodents (P < .03), and it was as efficient as DFO given subcutaneously (P > .15). The mode of excretion was similar in both animal models, with the majority of the iron being excreted in the bile/feces; 94% in the rats and 67% in the monkeys. The efficiency of analogue 5 was also higher in the monkeys than it was in the rats, 6.7% ± 1.8% in the rodent and 21.9% ± 3.4% (range, 18.6% to 25.8%) in the primates (P < .001), and, in the primates, was found to be nearly 4 times as efficient as DFO given subcutaneously (P < .001). Once again, the majority of the induced iron was excreted in the bile/feces; 100% in the rodents and 89% in the primates. Although the efficiency of ligand 3 was higher in the monkeys than it was in the rats, 4.2% ± 1.6% in the rodents versus 8.2% ± 3.2% (range, 4.7% to 13.3%) in the primates (P < .04), the distribution of cleared iron was similar to that seen in the rat. In the monkeys, 20% of the iron was excreted in the urine and 80% was excreted in the feces, whereas in the rodent, 4% of the iron was excreted in the urine and 96% was excreted in the bile. In the primates, this ligand was also found to be as efficient as DFO (P > .11). Finally, the efficiency of ligand 2 was also greater in the primates than in the rodents: 8.0% ± 2.5% (range, 4.4% to 10.4%) in the primates versus 2.4% ± 0.6% (range, 1.4% to 2.9%) in the rats (P < .001) and was as efficient as DFO (P > .07). In the monkeys, 42% of the iron...
iron clearing properties of DFO, DFT, and DFT analogues

Fig 1. Structures of the iron chelators chosen for evaluation: DFO, desferrithiocin sodium salt (1), desmethyl desferrithiocin (2), desazadesmethyl desferrithiocin sodium salt (3), desazadesmethyl desferrithiocin pivaloyloxymethyl ester (4), and desazadesmethyl-5,5-dimethyl desferrithiocin (5).

was excreted in the stool and 58% in the urine, whereas in the rats, 82% of the iron was excreted in the bile and 18% in the urine.

Dose-response studies with analogue 2. To further evaluate the iron-clearing properties of analogue 2, a dose-response study in the primates was performed. When the compound was administered orally at 150 μmol/kg in 40% Cremophor, it was found to have an efficiency of 4.8% ± 2.7%. Approximately 52% of the induced iron was excreted in the urine and 48% was excreted in the feces. At 300 μmol/kg, also administered orally in 40% Cremophor, the efficiency was 8.0% ± 2.5%. Again, the iron excretion was nearly equally distributed between the urine and the feces; 58% in the urine and 42% in the feces. Finally, to more closely mimic potential clinical applications in humans, the compound was administered in gelatin capsules at 450 μmol/kg. At this dose, the efficiency was 10.8% ± 3.2%. However, this time the majority of the iron (86%) was excreted in the stool, with only 14% excreted in the urine. This shift in iron distribution may well be associated with the Cremophor vehicle. Although the efficiencies are close to within experimental error of each other, there is a def-
Fig 2. Chelator-induced iron excretion in the urine (left panels) and feces (right panels) of iron-overloaded Cebus monkeys given DFO 150 μmol/kg subcutaneously; compound 1 administered at 150 μmol/kg orally; and compound 2 dosed at 300 μmol/kg orally. The iron excretion is reported in micrograms of iron excreted per kilogram of monkey weight.
Fig 3. Chelator-induced iron excretion in the urine (left panels) and feces (right panels) of iron-overloaded Cebus monkeys given compound 3 at 300 μmol/kg orally; compound 4 administered at 300 μmol/kg orally; and compound 5 dosed at 300 μmol/kg orally. The iron excretion is reported in micrograms of iron excreted per kilogram of monkey weight.
Experimental dose response; the iron output increases almost linearly with chelator dose (Table 3).

Primate iron balance studies. It is critical to point out that in each experiment, the level of iron in the food was measured with atomic absorption spectroscopy. It was clear from these data that the animals absorb rather substantial amounts of iron under normal circumstances. In previous experiments,13 it was demonstrated that DFO can hold the monkeys in negative iron balance (Table 3). For this family of compounds, the non-iron-overloaded bile duct-cannulated rat forecast the behavior of the ligands in the primates. Although there were quantitative differences (the chelators were more efficient in the primates), the order of effectiveness was essentially the same in both animal models.

There were also clear trends regarding the compounds’ toxicities. Desferrithiocin was primarily nephrotoxic, whereas the major toxicity associated with the desaza compounds was GI toxicity. Because of their capacity to shut down ribonucleotide reductase inhibitors,15-17 it is somewhat surprising that more iron chelators do not present with intestinal epithelial cells are turning over so quickly that they are good targets for ribonucleotide reductase inhibitors. It would be interesting to determine if the IC50 values of the chelators in cell culture could predict the toxicity of the chelators in animals. However, the fact that the least toxic desferrithiocin, analogue 2, was as efficient as analogues 3, 4, or 5, suggests that the toxicity of the desferrithiocins does not weigh heavily on their ability to remove iron. Furthermore, it is certainly notable that the removal of the desferrithiocin aromatic nitrogen and the methyl group (compound 3) resulted in a shift from nephrotoxicity to GI toxicity, whereas the removal of the desferrithiocin methyl group (analogue 2) resulted in an analogue with substantially reduced toxic effects. The precise reason for the differences in toxicity among the various analogues of course still remains to be addressed. We are pursuing two approaches: a comparative study of the metabolic products and a comparative study of the clearance and organ distribution of the radiolabeled drugs. Nevertheless, the results from the primate study suggest that selected desferrithiocins should now be considered further as credible clinical targets.

### Table 1. Drug-Induced Iron Excretion in the Urine and Feces of Iron-Overloaded Cebus Monkeys

<table>
<thead>
<tr>
<th>Iron Excretion</th>
<th>Compound</th>
<th>Efficiency (%</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical total</td>
<td>DFO (150 μmol/kg SC)</td>
<td>8.37 (100)</td>
<td>4.19 (100)</td>
</tr>
<tr>
<td>Experimental total</td>
<td>1 (150 μmol/kg PO)</td>
<td>0.471 ± 0.073 (6.5)</td>
<td>0.799 ± 0.401 (18.6)</td>
</tr>
<tr>
<td></td>
<td>2 (300 μmol/kg PO)</td>
<td>0.666 ± 0.206 (7.9)</td>
<td>0.674 ± 0.265 (8.2)</td>
</tr>
<tr>
<td></td>
<td>3 (300 μmol/kg PO)</td>
<td>0.704 ± 0.323 (8.4)</td>
<td>1.834 ± 0.289 (21.9)</td>
</tr>
<tr>
<td></td>
<td>4 (300 μmol/kg PO)</td>
<td>0.206 (7.8)</td>
<td>0.233 ± 0.156 (33.1)</td>
</tr>
<tr>
<td></td>
<td>5 (300 μmol/kg PO)</td>
<td>0.210 ± 0.214 (11.5)</td>
<td>0.668 ± 0.282 (81.5)</td>
</tr>
</tbody>
</table>

Values are in milligrams per kilogram, with percentages in parentheses.

### Table 2. Comparison of Chelator Efficiencies in Rats and Monkeys

<table>
<thead>
<tr>
<th>Rats</th>
<th>Efficiency (%)</th>
<th>Range (%)</th>
<th>Monkeys</th>
<th>Efficiency (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFO (150 μmol/kg SC)</td>
<td>2.8 ± 0.7</td>
<td>2.1-4.1</td>
<td>DFO (150 μmol/kg SC)</td>
<td>5.5 ± 0.9</td>
<td>4.4-6.6</td>
</tr>
<tr>
<td>1 (150 μmol/kg) PO</td>
<td>2.5 ± 1.2</td>
<td>1.2-4.5</td>
<td>1 (150 μmol/kg) PO</td>
<td>18.6 ± 9.3</td>
<td>10.3-33.9</td>
</tr>
<tr>
<td>2 (150 μmol/kg) PO</td>
<td>2.4 ± 0.6</td>
<td>1.4-2.9</td>
<td>2 (300 μmol/kg) PO</td>
<td>8.0 ± 2.5</td>
<td>4.4-10.4</td>
</tr>
<tr>
<td>3 (150 μmol/kg) PO</td>
<td>4.2 ± 1.6</td>
<td>1.9-5.9</td>
<td>3 (300 μmol/kg) PO</td>
<td>8.2 ± 3.2</td>
<td>4.7-13.3</td>
</tr>
<tr>
<td>4 (150 μmol/kg) PO</td>
<td>3.1 ± 1.8</td>
<td>1.0-4.8</td>
<td>4 (300 μmol/kg) PO</td>
<td>8.4 ± 3.9</td>
<td>4.5-12.9</td>
</tr>
<tr>
<td>5 (150 μmol/kg) PO</td>
<td>6.7 ± 1.8</td>
<td>3.9-8.7</td>
<td>5 (300 μmol/kg) PO</td>
<td>21.9 ± 3.4</td>
<td>18.6-25.8</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The more highly alkylated compounds were consistently shown to be more effective as oral iron chelators in the primate model when comparing the relative activities among the desferrithiocins and the desazadesferrithiocins. For the desferrithiocins, the order was 1 > 2, whereas for the desazadesferrithiocins, the order was 5 > 4 > 3. In the case of the desazadesferrithiocins, we are assuming, of course, that the pivaloyloxy ester of compound 4 was cleaved by the non-specific serum esterases to compound 3. This assumption is in keeping with the fact that on a molar basis the efficiencies of compounds 3 and 4 are essentially identical: 8.2% ± 3.2% versus 8.4% ± 3.9% in the primates (P > .95) and 4.2% ± 1.6% versus 3.1% ± 1.8% in the rodents (P > .34). With this family of compounds, the non-iron-overloaded bile duct-cannulated rat forecast the behavior of the ligands in the primates. Although there were quantitative differences (the chelators were more efficient in the primates), the order of effectiveness was essentially the same in both animal models.

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Iron Clearing Properties of DFO, DFT, and DFT Analogues

Table 3. Net Iron Balance in Cebus Monkeys

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (μmol/kg)</th>
<th>Route</th>
<th>Vehicle</th>
<th>48 h Induced Fe (μg/kg)</th>
<th>Predrug (μg/kg)</th>
<th>Postdrug (μg/kg)</th>
<th>Significance of T-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFO</td>
<td>150</td>
<td>SC</td>
<td>dH2O</td>
<td>471 ± 73</td>
<td>217 ± 128</td>
<td>−245 ± 142</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>PO</td>
<td>40% Cremophor</td>
<td>799 ± 401</td>
<td>230 ± 50</td>
<td>−500 ± 225</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>PO</td>
<td>40% Cremophor</td>
<td>203 ± 111</td>
<td>88 ± 41</td>
<td>−300 ± 145</td>
<td>P &lt; .03</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>PO</td>
<td>40% Cremophor</td>
<td>666 ± 206</td>
<td>237 ± 59</td>
<td>−456 ± 242</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>2</td>
<td>450</td>
<td>PO</td>
<td>None</td>
<td>1,358 ± 404</td>
<td>211 ± 70</td>
<td>−1,146 ± 370</td>
<td>P &lt; .003</td>
</tr>
</tbody>
</table>

The amount of iron absorbed by the untreated animals over a 3-day period is compared with the amount of iron absorbed by the treated animals over a 3-day period. Net iron balance = dietary iron intake − (urinary iron + fecal iron). Animals in a negative iron balance are excreting more iron than they are absorbing.

However, it must be emphasized that further preclinical testing of analogue 2 involving long-term studies at a range of dosages as well as administration to a nonrodent species must be completed before its introduction into humans.

REFERENCES
A comparative study of the iron-clearing properties of desferrithiocin analogues with desferrioxamine B in a Cebus monkey model

RJ Bergeron, RR Streiff, EA Creary, RD Jr Daniels, W King, G Luchetta, J Wiegand, T Moerker and HH Peter

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