Drug Review

Succimer, an oral lead chelator

KATHERINE V. MANN AND JOHN D. TRAVERS

Abstract: The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of succimer when used for the treatment of lead poisoning are reviewed.

Succimer is an orally active, heavy-metal chelating agent that forms stable, water-soluble complexes with lead; it also chelates other toxic heavy metals, such as arsenic and mercury. It is a designated orphan drug that is indicated for the treatment of lead poisoning, specifically in children with blood lead concentrations higher than 45 µg/dL. Succimer reverses the adverse metabolic effects of lead on heme synthesis while increasing urinary lead output without adversely affecting essential mineral excretion at the recommended dosage regimen. The rebound in lead concentrations that can occur after short courses of chelating therapies (caused by redistribution of lead from bone stores) may require frequent and multiple courses of chelation therapy.

The most common adverse effects reported in clinical trials of succimer in children and adults were nausea, vomiting, diarrhea, appetite loss, and loose stools; these effects may be related to the drug's unpleasant mercaptan odor. There are no known drug interactions between succimer and other drugs, including iron supplements, although data are limited. The recommended initial dosage in children is 10 mg/kg or 350 mg/sq m every eight hours for five days. The dosage is then reduced to 10 mg/kg or 350 mg/sq m every 12 hours for an additional two weeks.

Clinical studies indicate that succimer is relatively selective for lead and effectively lowers blood lead concentrations. Although clinical experience is limited, an oral lead chelator may offer advantages over currently available agents.

Index terms: Dosage; Drug administration; Heavy metal antagonists; Lead; Pharmacokinetics; Poisoning; Succimer; Toxicity
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Lead toxicity in children is an entirely preventable disease; however, lead toxicity remains an important health problem of U.S. children. Prevention of exposure to environmental lead is essential, and abatement of environmental lead is of primary importance. The 1985 Centers for Disease Control statement on prevention of lead poisoning in young children[1] is currently being updated. The revised document will provide practitioners with current recommendations regarding prevention of, screening for, and degrees of intervention in childhood lead poisoning.

Of importance to many children who already have lead intoxication is access to safe, effective therapy to reduce their body burden of lead. Chelation treatment for lead poisoning decreases the body burden of lead far more rapidly than normal excretory processes can and enhances the removal of the readily mobile soft-tissue fraction of body lead, which is potentially the most toxic fraction of body lead.[2,3]

Succimer (Chemet, McNeil Consumer Products Company) is an orally active chelating agent that was marketed in January 1991 for the treatment of lead poisoning, specifically in children with blood lead concentrations higher than 45 µg/dL. Succimer is a designated orphan drug. Although some clinicians have advocated the use of oral penicillamine for the treatment of lead poisoning, that remains an unlabeled use for penicillamine. The relative lack of specificity of penicillamine for lead, along with the incidence of adverse effects (which approached 33% of treated patients in one recent study[4]), tends to limit the usefulness of penicillamine for the treatment of lead poison-

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ing. Thus, succimer is the first oral medication indicated for the treatment of lead poisoning and the first new chelating agent for lead toxicity in the more than 40 years since the approval of edetate calcium disodium.

This review focuses on the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of succimer when used for the treatment of lead poisoning.

Chemistry and Stability

The succimer molecule was first used by Friedheim and colleagues,[5] who incorporated the molecule into compounds for the treatment of schistosomiasis and trypanosomiasis. Succimer is the stable *meso* isomer of 2,3-dimercaptosuccinic acid; it also has been known as DMSA. The chemical structure of succimer is shown in Figure 1. The empirical formula for succimer is $C_4H_6O_4S_2$; the molecular weight is 182.2.[6] Succimer is a white crystalline powder with a characteristic mercaptan (sulfur) odor and taste; it is practically insoluble in water, very slightly soluble in acetone and ethanol, and very soluble in aqueous alkaline solutions. Succimer has a pKa_1 of 3.0 and a pKa_2 of 3.9. Succimer should be stored at controlled room temperature (15–30 °C).[a]

Figure 1. Succimer is the stable *meso* isomer of 2,3-dimercaptosuccinic acid, also known as DMSA.

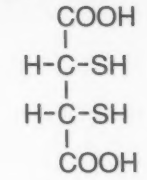
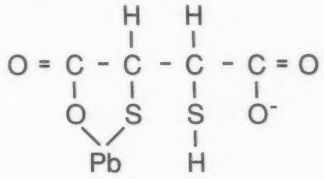


Figure 2. The in vitro succimer–lead complex is a stable five-member heterocyclic ring.[7]



Pharmacology

Succimer is an orally active, heavy-metal chelating agent that forms stable, water-soluble complexes with lead in vitro (Figure 2)[7] and consequently increases the urinary excretion of lead.[8-14] Succimer also has been found to chelate other toxic heavy metals, such as arsenic[15] and mercury.[9,16,17]

Controlled trials of succimer,[11,12] as well as earlier animal studies,[18,a] have examined the effect of succimer administration on urinary excretion of the essential trace minerals calcium, copper, iron, and magnesium. The studies are consistent in that they find succimer specific for lead without clinically important elevations in trace mineral excretion at the doses and durations studied. In one of these trials,[11] a significant increase (1.6-fold to 1.8-fold higher than the pretreatment values) in zinc excretion was observed, and data with respect to copper excretion were conflicting. The effect of succimer on the excretion of essential minerals is small compared with that of edetate calcium disodium, which can induce a more than 10-fold increase in urinary excretion of zinc and a twofold increase in urinary excretion of copper and iron.[19,20] The potential for substantial wasting of the essential mineral zinc is a factor in limiting the course of edetate calcium disodium therapy, but not succimer therapy, to five days. Monitoring of essential minerals is not required during succimer therapy.

Although human clinical data are not available, rat data suggest that intraperitoneal edetate calcium disodium and dimercaprol (British Anti-Lewisite, BAL) may enhance gastrointestinal absorption of lead.[21] In contrast, gastrointestinal absorption of lead and whole body lead retention were markedly reduced by oral administration of succimer in rats.[21] Rat data suggest that therapy with oral succimer, unlike conventional therapy with edetate calcium disodium[22] does not result in redistribution of lead to the brain or other target organs.[23]

In addition to lead, succimer appears to be effective in chelating the toxic heavy metals arsenic and mercury. In various animal studies, succimer has been successful in decreasing the body burden of mercury and increasing its urinary excretion[24-27] and was more effective than equivalent molar doses of *N*-acetyl-D,L-penicillamine[24] or penicillamine.[25] With respect to arsenic, comparative efficacy studies in rodents indicated that succimer provided effective protection against the lethal effects of sodium arsenite and Lewisite.[28-31] In mice, succimer was more effective in providing protection against the lethal effects of sodium arsenite than either penicillamine or *N*-acetyl-D,L-penicillamine at equivalent molar doses[28,29,31] and was more effective than dimercaprol against the lethal effects of Lewisite in rabbits.[28,30] These comparative data have not been confirmed by controlled clinical trials in humans.

Pharmacokinetics

In a preliminary pharmacokinetic study involving 11 healthy adult male volunteers who received a single 16-, 32-, or 48-mg/kg dose of succimer labeled with carbon 14, absorption was rapid but variable, with peak absorption occurring between one and two hours.[a] Both whole blood and plasma concentration data fit a two-compartment model. The apparent elimination half-life was approximately 48 hours. Prelimi-

nary human data from this study indicate that succimer has a small volume of distribution, with the majority of drug remaining in the plasma.[a] It is not known whether succimer passes through the human placental barrier or whether it can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. It is not known whether succimer is excreted in human milk. Because many drugs and heavy metals are excreted in human milk, women receiving succimer therapy should be discouraged from nursing their infants. The exact site of succimer biotransformation has not been determined. Recently, the structures of the major succimer metabolites in humans have been identified as mixed disulfides of L-cysteine.[32] Succimer appears to be rapidly and extensively metabolized, as indicated by the proportion of succimer excreted in the urine as mixed disulfides rather than as unchanged drug.[33]

The complete fate of succimer after oral administration has not been fully elucidated. Preliminary data indicate that renal elimination accounts for the majority of total clearance. Minimal amounts are eliminated by the lungs. Fecal excretion probably represents nonabsorbed drug. Succimer is rapidly excreted by the kidneys; approximately 75% of renal elimination occurs in the first 24 hours.[a] Of the total amount of drug eliminated in the urine, approximately 90% is eliminated in altered form as mixed succimer–cysteine disulfides, with the remaining 10% eliminated as unaltered drug. The majority of mixed disulfides consist of succimer in disulfide linkages with two molecules of L-cysteine; the remaining disulfides contained one L-cysteine molecule per succimer molecule. Peak excretion of altered succimer occurs between two and four hours after ingestion.[33,a]

Lead Poisoning

Succimer has been used safely and effectively outside of the United States (primarily in China) as a treatment modality for heavy-metal poisoning in more than 300 adult patients during the past 25 years.[34] In the United States, information on succimer is available from clinical pharmacology studies, clinical trials, and compassionate-use cases involving more than 300 adults and children, primarily patients with lead toxicity. Succimer has been available in the United States only as an orphan investigational drug; therefore, published literature is limited. Described herein are the results of published controlled clinical trials of succimer in children and adults, as well as clinical data establishing the duration of the treatment course. In addition to controlled studies, approximately 250 patients with lead poisoning have been treated with succimer either orally or by injection in open domestic and foreign studies, and similar results have been reported.[8-10,14,a]

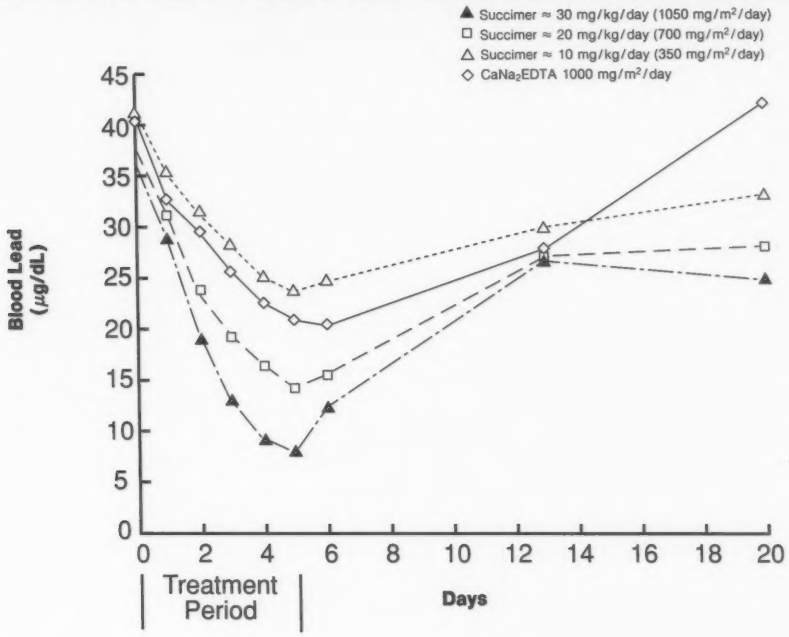
Clinical studies indicate that succimer is a relatively selective and highly effective medication that lowers blood lead concentrations.[8-12,14,a] Succimer reverses the adverse metabolic effects of lead on heme synthesis while increasing urinary lead output without adversely affecting essential mineral excretion at the recommended dosage regimen. The primary indicators of drug efficacy in the controlled trials of oral succimer were lowered blood lead concentrations and increased urinary lead excretion. Secondary indicators of efficacy included restoration of red blood cell aminolevulinic acid dehydratase (ALA-D) activity, an enzyme necessary for heme synthesis, and a reduction in urinary aminolevulinic acid (ALA) and coproporphyrin.[11,12,a] Measurement of coproporphyrin and ALA-D provides clinical investigators with an indication of the effects of lead on heme biosynthetic pathways and the degree to which these effects are reversed during chelation therapy. ALA-D activity and urinary excretion of ALA are sensitive indicators of exposure to lead.

Studies Establishing Effective Dosage Level. The dose-ranging studies described below evaluated the efficacy of five days of succimer therapy in both children and adults. Graziano et al.[12] described their experience with 21 children aged two to seven years who had blood lead concentrations of 31–49 µg/dL and who also had a positive edetate calcium disodium mobilization test result (defined as urinary excretion of >0.6 µg of lead per milligram of edetate calcium disodium administered). Of the 21 patients (14 Hispanic, six black, and one white), six children were treated with edetate calcium disodium and 15 received succimer therapy. Succimer-treated children were randomly assigned to receive succimer 350, 700, or 1050 mg/sq m/day orally in three divided doses (every eight hours) for five days . These doses correspond to approximately 3.3, 6.7, and 10.0 mg/kg/dose or 10, 20, and 30 mg/kg/day, respectively. Succimer was administered orally by emptying the contents of the succimer capsules into either a fruit drink or ice cream. Edetate calcium disodium (1000 mg/sq m/day) was administered intravenously in two divided doses, also for five days.

In each treatment group, blood lead concentrations declined during the five-day treatment period. Treatment with succimer 10.0, 6.7, and 3.3 mg/kg/dose resulted in a 78%, 63%, and 42% decline in blood lead concentrations, respectively. The decline in blood lead concentrations in the edetate calcium disodium control group was 47%. As shown in Figure 3, succimer 1050 mg/sq m/day (approximately 30 mg/kg/day) was significantly more effective in reducing blood lead concentrations (78% decrease) than either conventional intravenous edetate calcium disodium therapy (47% decrease) or lower dosages of succimer. The decline in blood lead concentrations in response to succimer 700 and 350 mg/sq m/day (63% and 42% decrease, respectively) did not differ significantly from the decline in response to conventional edetate calcium disodium therapy.

Rebound in blood lead concentrations often occurs after short courses of all chelating therapies because of

Figure 3. Mean blood lead concentrations of children receiving succimer at approximately 10, 20, or 30 mg/kg/day or edetate calcium disodium ($CaNa_2EDTA$) 1000 mg/sq m/day for five days as a function of time. (Reprinted with permission from reference 12.)



the relatively large lead burden associated with chronic lead ingestion and the subsequent re-equilibration phenomenon.[35] This rebound is thought to be caused by lead mobilization from the skeleton and re-equilibration into blood and soft tissues. As expected, blood lead concentrations rebounded after cessation of drug therapy in all treatment groups.

A significant increase in ALA-D activity occurred in all treatment groups; succimer 30 mg/kg/day was significantly more effective in restoring ALA-D activity than either lower dosages of succimer or conventional therapy with edetate calcium disodium (Figure 4).[12] No adverse reactions or changes in essential mineral excretion were reported in the succimer treatment groups. In the edetate calcium disodium treatment group, the urinary excretion of copper, iron, zinc, and calcium was significantly increased, the last perhaps because the drug contains calcium. As described by the authors, the mean urinary mineral excretion per milligram of creatinine was low for copper (from a baseline pretreatment value of 0.65 μg to a high of 1.16 μg during therapy) and iron (from a baseline pretreatment value of 1.8 μg to a high of 2.5 μg) but was large and clinically important for zinc (from a baseline pretreatment value of 3.8 μg to a high of 13.5 μg).

The results of this pediatric study are in accordance with a study in adult patients (aged 24–58 years) who had occupational lead poisoning from exposures to lead sources such as house and bridge painting and pigment mixing.[11] This multiple-dose, single-blind, randomized trial evaluated 18 men with blood lead concentrations between 44 and 96 μg/dL. Patients were randomly assigned to receive succimer 30, 20, or 10 mg/kg/day orally in three divided doses (every eight hours) for five days. In each patient, a linear decline in blood lead concentrations was observed over time (Figure 5). After five days, the mean blood concentrations of the three groups decreased by 72.5%, 58.3%, and 35.5%, respectively. The mean urinary lead excretions in the initial 24 hours were 28.6-fold, 18.6-fold, and 12.3-fold, respectively, higher than the pretreatment 24-hour urinary lead excretion. As the amount of lead available for chelation was reduced during therapy, urinary lead output decreased. Symptoms such as headache and colic improved. Metabolic indexes of lead toxicity also responded favorably to succimer treatment; red blood cell ALA-D activity, which was markedly depressed before treatment, increased in a linear, dose-dependent manner, which paralleled a decrease in urinary ALA excretion in each dosage group. Additionally, urinary excretion of coproporphyrin also decreased during succimer treatment, indicating rejuvenation of coproporphyrinogen oxidase, an enzyme necessary for heme synthesis. After cessation of therapy, blood lead concentrations rebounded, again probably indicating mobilization of lead from bone. There was no significant effect on the urinary elimination of calcium, iron, or magnesium.

Figure 4. Mean erythrocyte aminolevulinic acid dehydratase (ALA-D) activities measured as nanomoles of porphobilinogen per gram of hemoglobin per hour (nm PBG/g Hgb/hr) of children receiving oral succimer or intravenous edetate calcium disodium ($CaNa_2EDTA$) 1000 mg/sq m/day as a function of time. (Reprinted with permission from reference 12.)

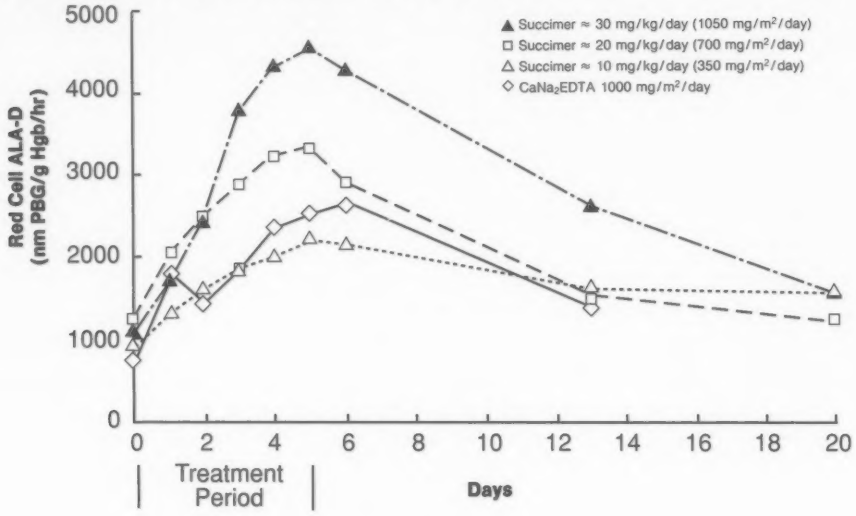
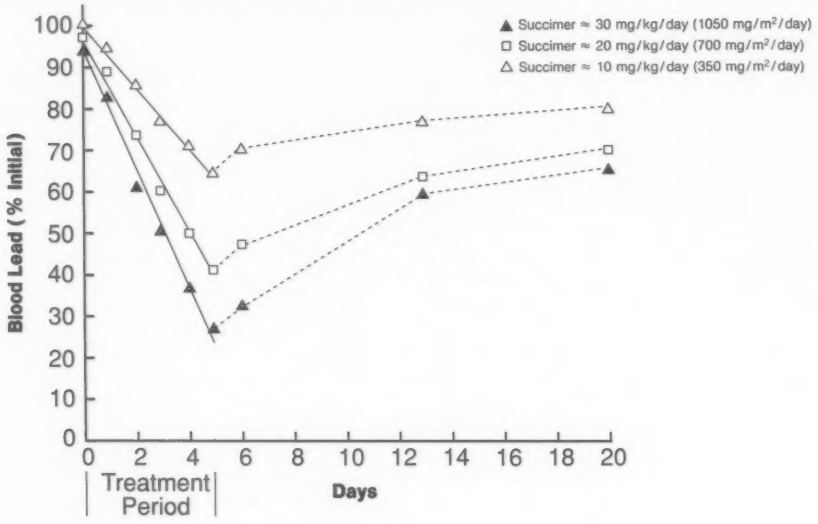


Figure 5. Mean blood lead concentrations expressed as a percentage of pretreatment values in adult male patients receiving five days of succimer therapy at 10, 20, or 30 mg/kg/day. (Reprinted with permission from reference 11.)



Urinary zinc excretion increased significantly ($p \leq 0.01$) in a dose-dependent fashion, but was clinically unimportant in the groups receiving 20 and 30 mg/kg/day (1.6-fold to 1.8-fold higher than the pretreatment values).

Data Establishing Treatment Course. The blood lead concentration declines in response to chelation therapy for lead intoxication and then rises, or rebounds, after the cessation of chelation therapy because of the redistribution of lead from bone stores. This phenomenon, due to the compartmental kinetics of lead, is primarily a function of body lead burden. In some patients, the rebound can be steep, requiring frequent and multiple courses of chelation therapy before the blood lead concentration stabilizes in a clinically acceptable range. The possibility of re-expo-

sure to a lead-containing environment should be considered in a child who does not respond with an appropriate decline or has an excessive rebound in blood lead concentrations, and further efforts should be taken to ensure abatement. Further studies were conducted to determine the optimal therapeutic course of succimer, with the goal of minimizing or reducing the rebound in blood lead concentrations caused by the re-equilibration phenomenon.

A multiple-dose, open-label study evaluated succimer treatment regimens for the control of rebound in blood lead concentrations.[a] Nineteen children, aged one to seven years, with blood lead concentrations of 42–67 µg/dL, were treated for five days with succimer 1050 mg/sq m/day (30 mg/kg/day) and then randomly assigned to one of three groups. Group one was followed for two weeks with no further therapy; group two was treated for two weeks with succimer 350 mg/sq m/day (once daily); and group three was treated for two weeks with succimer 700 mg/sq m/day (in two divided doses). After the initial five days, the mean percent decline in blood lead concentration in all groups was 61%. The untreated group and the group receiving 350 mg/sq m/day had a rebound in blood lead concentrations during the ensuing two weeks of treatment. In contrast, the group that received 700 mg/sq m/day had no such rebound during treatment and had less severe rebound after cessation of therapy.

Montalvan and colleagues[14] described 24 patients with lead poisoning who were treated with succimer on an ambulatory basis. This open-label study of eight adults (aged 17–53 years) and 16 children (aged 19 months to 8 years) included all patients with blood lead concentrations in excess of 41 µg/dL, as well as symptomatic patients (e.g., polyuria, abdominal colic, hyperactivity, a learning disability) with blood lead concentrations higher than 25 µg/dL. Succimer was administered at a dosage of 30 mg/kg/day for five days; patients then received a 16-day course of succimer 20 mg/kg/day. Succimer therapy resulted in a decline in blood lead concentrations in all patients; this decline was most dramatic in patients with pretreatment concentrations between 40 and 60 µg/dL. At the end of therapy, the average decline from pretreatment blood lead concentrations was reported as 40 µg/dL. Urinary lead excretion averaged 2–4 mg/24 hours in cases in which adequate urine was collected.

Lead Encephalopathy. Three adults with lead encephalopathy were reported to have improved in response to succimer therapy.[9] However, data are not available regarding the use of succimer for the treatment of this rare and sometimes fatal complication of lead poisoning in children.

Other Heavy-Metal Poisoning

No controlled, randomized clinical studies of succimer have been conducted in cases of poisoning with other heavy metals. A limited number of patients have received succimer for mercury poisoning[16,17,a] or arsenic poisoning[15,a] through compassionate-use protocols. These patients showed increased urinary excretion of the heavy metal and various degrees of symptomatic improvement. Bluhm et al.[16] compared succimer (30 mg/kg/day) and *N*-acetyl-D,L-penicillamine (250 mg every six hours) for four days in 12 patients exposed to elemental mercury vapor during an industrial accident. Therapy was initiated between 73 and 116 days after exposure. With both drugs, the increase in the urinary excretion rate of mercury depended on the pretreatment mercury levels. Succimer induced a threefold increase in mercury excretion compared with a twofold increase induced by *N*-acetyl-D,L-penicillamine.

Adverse Effects

Few adverse events have been observed in clinical trials and compassionate-use cases, and those that have been observed have generally been mild and transient.[8-12,a] However, clinical experience with succimer has been limited. Consequently, the full spectrum and incidence of adverse reactions, including the possibility of hypersensitivity or idiosyncratic reactions, have not been determined.

The most common adverse effects reported in clinical trials in children and adults were primarily gastrointestinal and included nausea, vomiting, diarrhea, appetite loss, and loose stools.[36] At times, these events have been believed to be related to the unpleasant mercaptan odor of succimer; administration in such a way as to minimize the odor may overcome some of these reactions. Rashes, some necessitating discontinuation of therapy, have been reported in about 4% of patients, primarily adults. If rash occurs, other causes (e.g., measles) should be considered before ascribing the reaction to succimer. Rechallenge with succimer may be considered when blood lead concentrations are high enough to warrant retreatment. Mild, transient elevations of serum aminotransferase concentrations have been observed in 6–10% of patients, primarily adults, receiving succimer therapy. The importance of these increases is currently unknown.[36]

Drug–Disease Interactions

A small number of children with glucose-6-phosphate dehydrogenase deficiency and sickle-cell anemia have been successfully treated with succimer without incident. Dimercaprol has reportedly caused hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[37] A small number of patients receiving hemodialysis for renal failure have been treated with succimer. All patients tolerated the drug treatment.

Drug–Drug Interactions

There are no known drug interactions between suc-

cimer and other drugs, including iron supplements[38,a]; however, data on concomitant drug use are limited and drug combinations have not been systematically studied. Many children with elevated lead concentrations are also iron deficient, and some data suggest that iron deficiency results in increased gastrointestinal absorption of lead[39]; therefore, iron supplementation is often considered in these children. Dimercaprol reportedly forms a toxic (emetogenic) complex with iron, and concurrent therapy is not recommended.[37] In the small number of children who have been treated with succimer and iron supplements, there has been no evidence of the formation of a similar toxic chelate. In the children who have been so treated, oral iron and succimer were not administered simultaneously but were separated by two to three hours. Because there are data suggesting that the bioavailability of oral penicillamine may be decreased by concomitant administration of iron and antacids,[40,41] it may be prudent to avoid concomitant administration of succimer with these agents pending definitive studies. Data are not available on the concomitant use of succimer with edetate calcium disodium, with or without dimercaprol, and such use is not recommended.[36] Currently, after therapeutic courses of edetate calcium disodium (with or without dimercaprol), an interval of four weeks is recommended before initiation of a subsequent course of therapy with succimer, because of the lack of data regarding the sequential use of these agents.

Drug–Laboratory Test Interactions

In vitro studies indicate that succimer may cause false-positive results of ketone urinalysis that uses nitroprusside reagents (e.g., Ketostix). Succimer also may falsely decrease measurements of serum uric acid and creatine phosphokinase.[a]

Recommended Monitoring Variables

As with any drug used to treat a serious illness such as lead toxicity, monitoring for therapeutic efficacy as well as safety is recommended in patients receiving succimer. A diagnostic blood lead concentration should be determined before therapy is begun, and patients should be monitored for rebound in blood lead concentrations after therapy. Severity of the toxicity (as measured by the pretreatment blood lead concentration and the exposure history) should be used as a guide to the frequency of blood lead monitoring after a therapeutic course, but monitoring should be done at least once weekly until blood lead concentrations are stable. Reinstitution of therapy should be considered when blood lead concentrations rebound secondary to lead redistribution from bone stores. It is recommended that two weeks elapse between courses of chelation therapy unless blood lead concentrations indicate that more rapid retreatment is necessary.

Succimer heavy-metal chelates are excreted in the urine; therefore, all patients undergoing treatment should be adequately hydrated. Caution should be exercised when succimer therapy is considered in patients who have compromised renal function. Limited data suggest that succimer is dialyzable but that the lead chelates are not.[a]

Because transient elevations of serum aminotransferase levels have been observed in 6–10% of patients, primarily adults, during the course of succimer therapy, serum aminotransferases should be monitored before the initiation of therapy and at least weekly during therapy, particularly in patients with a history of liver disease. No data are available regarding the metabolism of succimer in patients with liver disease.

The possibility of allergic or other mucocutaneous reactions to the drug should be considered when succimer is readministered (as well as during initial courses). Patients requiring repeated courses of succimer should be monitored during each treatment course. One adult patient treated in Europe had a recurrent mucocutaneous reaction during the third, fourth, and fifth courses of succimer therapy; it is unclear whether this was an allergic, fixed drug reaction.[42] If rash occurs, patients should consult their physician; rechallenge with succimer may be considered when lead levels are high enough to warrant retreatment. One adult patient may have had a febrile reaction to succimer with a maximum temperature reached at two hours (39.2 °C oral); the patient's temperature returned to normal over the ensuing seven hours. This reaction was associated with chills, diaphoresis, hypertension, and slight tachycardia that resolved within one hour.[a]

FDA-Approved Labeling and Availability

Succimer is indicated for the treatment of lead poisoning in children with blood lead concentrations above 45 µg/dL. There is no clinical experience with the use of succimer in children less than one year of age. As with any type of chelation therapy, succimer is not indicated for the prophylaxis of lead poisoning in a lead-containing environment; the use of succimer should always be accompanied by identification and removal of the source of the lead exposure. Identification of the source of lead in the child's environment and its abatement are critical to a successful therapy outcome.

Chemet (succimer) is supplied as opaque white gelatin capsules of medicated beads containing 100 mg of succimer. The average wholesale cost of a bottle of 100 capsules is $230.

Dosage and Administration

The recommended initial dosage in children is 10 mg/kg or 350 mg/sq m every eight hours for five days (Table 1 provides a dosage schedule based on weight). After the initial five days of therapy, the dosage is reduced to 10 mg/kg or 350 mg/sq m every 12 hours (two thirds of initial daily dosage) for an additional

Table 1.
Succimer Pediatric Dosage Schedule

Weight			
Pounds	Kilograms	Dose (mg)[a]	No. Capsules[a]
18–35	8–15	100	1
36–55	16–23	200	2
56–75	24–34	300	3
76–100	35–44	400	4
≥100	≥45	500	5

[a] To be administered every eight hours for five days followed by doses every 12 hours for 14 days.

two weeks of therapy. A course of treatment lasts 19 days. Repeated courses may be necessary when indicated by weekly monitoring of blood lead concentrations after each course. A minimum of two weeks between courses is recommended unless blood lead concentrations indicate the need for more prompt treatment. Clinical experience with repeated courses is limited. The safety of uninterrupted therapy for longer than three weeks has not been established and it is not recommended.

For young children who cannot swallow capsules, succimer can be given by separating the capsule and administering it immediately by sprinkling the beads on soft food or by putting them in a spoon and following with a fruit drink, which may help to mask the characteristic sulfur odor. The drug should be mixed with soft food immediately before administration; stability data are not available and stability cannot be ensured when the beads are mixed in various foods over a longer period of time. Parents should be discouraged from premixing doses of succimer hours or days in advance.

Use in Pregnancy

Succimer is classified as a category C agent, indicating that animal studies have demonstrated adverse effects on the fetus; there are no controlled studies in pregnant women. Succimer should not be administered to women who are pregnant or who may become pregnant during therapy unless the potential benefit outweighs the potential risk to the fetus.[36] A disodium salt of dimercaptosuccinic acid was shown to be teratogenic and fetotoxic in pregnant mice when given subcutaneously in a dose range of 410–1640 mg/kg during the period of organogenesis.[43] A more recent study reported the absence of observed teratogenicity of succimer in fetal rats exposed to oral maternal doses of succimer up to 1000 mg/kg/day during the period of organogenesis.[44]

Toxicology

A number of animal studies evaluating acute, subacute, and chronic toxicity demonstrate that the toxic effects of succimer appear only at doses well in excess of the recommended doses. Single doses of 2300 mg/kg in rats and 2400 mg/kg in mice produced ataxia, convulsions, labored respiration, and frequently death. The median lethal single dose of succimer in mice and rats is more than 3000 mg/kg.[a]

In dogs, only minimal signs of toxicity (e.g., diarrhea, emesis, or weakness) were observed with single oral (up to 300 mg/kg) or intravenous (100 mg/kg) doses of succimer. Six-day and 28-day oral toxicity studies in dogs have shown that doses of 300 mg/kg/day or higher were toxic and lethal to some dogs; the kidneys and gastrointestinal tract were the major target organs for toxicity, and deaths were due to renal failure.[a] In one ongoing, six-month chronic toxicity study of oral succimer in dogs, thrombocytopenia was observed in animals receiving succimer at 80 or 140 mg/kg/day after three months of dosing. Ecchymoses were noted on pathology of affected animals. Depressed platelet counts were not observed in dogs receiving 10 mg/kg/day for three months.[a]

Succimer has been evaluated by various methods, and no mutagenic activity has been observed.[a]

Overdosage Management

No case of overdosage has been reported in humans. Limited data indicate that succimer is dialyzable. In case of acute overdosage, induction of vomiting or gastric lavage followed by administration of an activated charcoal slurry and appropriate supportive therapy is recommended.[36]

Conclusion

Succimer represents innovative drug therapy for the treatment of lead poisoning. Clinical studies indicate that succimer is relatively selective for lead and effectively lowers blood lead concentrations. Succimer reverses the adverse metabolic effects of lead on heme synthesis while increasing urinary lead output without adversely affecting essential mineral excretion. In addition to selectivity, efficacy, and safety benefits, as an oral agent succimer offers ease of administration and may permit physicians the option of treating children as outpatients. Although clinical experience is limited, the benefit of an oral lead chelator may offer advantages over currently available agents.

[a]Data on file, McNeil Consumer Products Company, Fort Washington, PA. 1991 Feb.

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