Adis Evaluation

Key points in the overall evaluation of cyclosporin in the treatment of immunoregulatory disorders

CLINICAL BENEFITS

- Potential first-line choice in primary biliary cirrhosis and primary aplastic anaemia
- Firm evidence of efficacy in Behçet's disease, psoriasis vulgaris and rheumatoid arthritis refractory to other therapy
- Some evidence of efficacy in a variety of other immunoregulatory disorders
- Does not cause myelosuppression

POTENTIAL LIMITATIONS

- Firm evidence of lack of efficacy in insulin-dependent diabetes mellitus, multiple sclerosis and long term maintenance of Crohn's disease
- Chlorambucil or cyclophosphamide likely to be more effective in children with nephrotic syndrome
- Nephrotoxicity is dosage-limiting

Careful monitoring with appropriate dosage adjustment is required during concomitant therapy with drugs known to affect cyclosporin plasma concentrations.

Nursing mothers must stop breastfeeding during cyclosporin therapy as the drug passes into breastmilk.

Prescribing and formulary considerations

Table 1 summarises the relative efficacy of cyclosporin in various immunoregulatory disorders. It should be borne in mind that cyclosporin has often been studied in patients with severe disease refractory to other treatment. The drug is an appropriate choice in conditions in which it has good/excellent activity, especially those in which efficacy has been confirmed in comparative trials.

In psoriasis vulgaris, Behçet's syndrome or RA, cyclosporin is likely to be reserved for those patients whose disease is refractory to established therapy.

It may be a suitable as a first-line drug in patients with primary biliary cirrhosis or primary aplastic anaemia, for which there are few other effective treatments. However, in children with nephrotic syndrome, chlorambucil or cyclophosphamide should be tried before considering cyclosporin.

Cyclosporin should be limited to patients who have severe disease. It is not appropriate for treating cosmetic conditions such as alopecia areata.[1] In those indications in which it has moderate efficacy, cyclosporin is worth considering for patients who have not responded to established therapy.

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Succimer shows short term efficacy in children with lead poisoning

IN BRIEF Succimer is an orally active chelating agent that is worthy of consideration in children with elevated blood lead concentrations and without encephalopathy.

In the short term, it appears well tolerated and has similar efficacy to other agents used in mild to moderate lead poisoning.

As with other agents, succimer produces a rapid reduction in blood lead concentrations during therapy, but concentrations rebound towards pretreatment values following discontinuation of the drug. Experience with the drug is limited and it has not been evaluated in children with encephalopathy, for whom other agents are preferred.

For less serious cases of lead poisoning, succimer cannot be routinely recommended in place of more established agents. Rather, physicians should consider likely efficacy, contraindications, patient preference, blood lead concentrations and personal experience with the available agents on an individual basis.

Lead poisoning is still a concern of paediatricians, despite reductions in the use of paints and fuels containing lead.[1]

Symptoms of acute lead poisoning include abdominal pain, vomiting, diarrhoea, paralysis, convulsions and encephalopathy. These are generally associated with blood lead concentrations >70 μg/dl.‡ Ingestion of paint chips remains the most common cause of symptomatic lead poisoning in the US.[1]

Blood lead concentrations lower than those resulting in overt symptoms are now recognised as being hazardous to children's health. Reduced intelligence, altered behaviour, short stature, and decreased bodyweight and chest circumference have all been associated with elevated blood lead concentrations.[1]

The US Centers for Disease Control and American Academy of Pediatrics now define childhood lead poisoning as being a whole blood lead concentration ≥25 μg/dl in association with an erythrocyte protoporphyrin level of ≥35 μg/dl.[1]

Chelation therapy in lead poisoning

The aim of chelation therapy is to remove lead from the body. The chelating agent binds to the heavy metal and the

‡ Conversion factor for blood lead concentrations: 1 μg/dl = 0.048 μmol/L.

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Differential Features

Comparison of the features of succimer with those of other chelating agents used in the treatment of children with lead poisoning[2-4]

Feature	Succimer	Calcium disodium edetate†	Dimercaprol† (British antilewisite)	Penicillamine
Route of administration	Oral	IV/IM	Deep IM	Oral
Indications				
Biochemical toxicity (BPb 25-39 µg/dl)	✓[a]	✓[a]		✓[a]
Symptoms possible (BPb 40-69 µg/dl)	✓	✓		✓
Symptoms present[b] (BPb 70-90 µg/dl)	✓	✓[c]	✓[c]	
Encephalopathy present (BPb >90 µg/dl)		✓[d]	✓[d]	
Contraindications	Not fully established Use with caution in renal or hepatic impairment	Anuria	G6PD deficiency Peanut allergy[e]	Penicillin allergy
Adverse effects	GI disorders, skin rash, flu-like syndrome, drowsiness, dizziness	Nephrotoxicity, mucocutaneous reactions, fever	Severe pain on injection, fever, tachycardia, GI disorders, sweating, convulsions	Anaphylaxis, GI disturbances, skin rash, leucopenia, thrombocytopenia, eosinophilia, angiodema, nephrotoxicity
Administration with iron possible?[f]	Yes	No (chelation of iron reduces chelation of lead)	No (a chelate forms, which is a potent emetic)	No (may reduce blood penicillamine concentrations)

† Calcium disodium edetate is not available in Germany; in Spain, dimercaprol is available through the Department of Foreign Drugs.
a There is no consensus about the value of chelation at these blood lead concentrations. May be worthwhile if blood lead concentrations remain elevated and biochemical toxicity persists despite identification and removal of the source of lead.
b Symptoms not including encephalopathy.
c Calcium disodium edetate may be used in combination with dimercaprol.
d Calcium disodium edetate must be used in combination with dimercaprol when encephalopathy is present.
e Dimercaprol is formulated in peanut oil.
f Iron deficiency predisposes to lead poisoning.
Abbreviations and symbol: BPb = blood lead concentration; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; IM = intramuscular; IV = intravenous; ✓ = consider in this indication.

resulting complex is excreted in the urine and/or faeces.[2] However, there is a lack of evidence that chelation therapy prevents or reverses lead neurotoxicity.[2]

In the absence of evidence that chelation therapy reduces the neurological sequelae of elevated blood lead concentrations, it is very important to consider the potential toxicity of available chelating agents. As shown in the *Differential Features* table, calcium disodium edetate ($CaNa_2EDTA$), dimercaprol (2,3-dimercapto-1-propanol; British antilewisite) and penicillamine are associated with significant toxicity.

Succimer† (2,3-dimercaptosuccinic acid; DMSA), a water-soluble derivative of dimercaprol, appears to be a relatively well tolerated drug that may be used as a chelating agent in some situations.[2,5]

Succimer

Animal studies

In mice and rats, intraperitoneal or oral administration of succimer has generally produced reductions in lead concentrations in tissues (e.g. liver, kidney, brain, spleen, bone) compared with control animals.[5] However, not all results have been consistent, with some showing increases in lead concentrations in some tissues (e.g. bone, spleen).[5]

Six months' administration of succimer was well tolerated by mice, rats and beagle dogs, with no clinical or histological adverse effects observed.[5] Succimer does not appear to enhance the absorption or retention of lead.[5]

† Succimer is investigational in Canada, and is not available in The Netherlands, Denmark, Germany, Spain or the UK.

Studies in adults

In adults with occupationally acquired severe and/or symptomatic lead poisoning, succimer administration has:

- reduced blood lead concentrations and improved clinical symptoms of lead poisoning
- promoted urinary excretion of lead
- increased δ-aminolevulinic acid dehydratase activity (a measure of red blood cell function)
- not promoted urinary excretion of calcium, magnesium or iron.[5]

However, blood lead concentrations have generally rebounded following discontinuation of a 5-day course of succimer in these studies.[5]

Adverse effects reported in these patients included gastrointestinal upset and mild transient elevations of liver enzyme levels. Long term tolerability data are lacking.[5]

Efficacy in children

In one study involving 21 children aged 2 to 7 years with blood lead concentrations of 30 to 49 µg/dl and no symptoms of serious lead poisoning, patients received 5 days' treatment with either $CaNa_2EDTA$ 1000 mg/m^2/day or succimer (350, 700 or 1050 mg/m^2/day).[6]

Blood lead concentrations declined progressively during each of the treatments, but rebounded once treatment was completed.[6] The highest dosage of succimer reduced blood concentrations by significantly more than each of the lower dosages of succimer or $CaNa_2EDTA$.

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Urinary lead excretion and erythrocyte δ-aminolevulinic acid dehydratase activity increased during treatment, but declined once treatment was completed. The highest dosage of succimer was the most effective treatment in terms of improving δ-aminolevulinic acid dehydratase activity, but $CaNa_2EDTA$ produced the greatest increase in urinary lead output.[6] These encouraging results have prompted the assessment of succimer in patients with higher blood lead concentrations.

In children with blood lead concentrations of 50 to 69 μg/dl, oral succimer 1050 mg/m^2/day for 5 days reduced blood lead concentrations by 61%, compared with a 45% decrease observed in patients receiving 5 days' intravenous $CaNa_2EDTA$ treatment.[4] Succimer also produced greater increases in erythrocyte δ-aminolevulinic acid dehydratase activity than $CaNa_2EDTA$, but urinary lead excretion was similar in both groups of children.[4]

Of the children initially treated with succimer in this study, some received no further chelation therapy while others received succimer 350 or 700 mg/m^2/day for 2 weeks as outpatients. One week after discharge, mean blood lead concentrations had rebounded to at least 66% of pretreatment values in patients receiving no outpatient chelation therapy or succimer 350 mg/m^2/day. In contrast, the patients receiving succimer 700 mg/m^2/day had blood lead concentrations that were 50% of pretreatment values until discontinuation of succimer, after which lead concentrations rebounded to 77% of pretreatment values within 2 weeks.[4]

Succimer 1050 mg/m^2/day for 5 days was compared with a combination of $CaNa_2EDTA$ 1000 mg/m^2/day for 5 days plus dimercaprol 300 mg/m^2/day for 3 days in children with blood lead concentrations of ≥70 μg/dl. No outpatient chelation therapy was administered after either of these regimens.[4]

Blood lead concentrations followed similar courses with both regimens, although the nadir was reached sooner and the rebound was less pronounced in patients receiving $CaNa_2EDTA$ + dimercaprol.[4]

In these studies, $CaNa_2EDTA$ promoted increased urinary excretion of zinc, copper, iron and calcium compared with baseline, with the increase in zinc excretion being considered clinically significant by the study authors.[4,6] In contrast, succimer had only modest and clinically insignificant effects on the excretion of these minerals.[4,6]

Tolerability in children

Adverse events observed in paediatric studies included transient and reversible elevations of liver enzyme levels, 'flu-like symptoms, rash and vomiting.[4,6]

Notably, 9 children received iron supplementation during succimer therapy without experiencing adverse effects. Iron supplements cannot be administered with other agents. Also, 2 children with glucose-6-phosphate dehydrogenase deficiency have received succimer without precipitating haemolysis,[4] an advantage over dimercaprol.

Other authors have reported anaphylaxis during a second course of succimer, and dramatic rises in serum alkaline phosphatase levels.[2]

The drug has an unpleasant sulphurous taste and smell, which may limit compliance.[2,5]

Dosage and administration

Succimer is administered orally in a dosage of 10 mg/kg or 350 mg/m^2 every 8 hours for 5 days and then every 12 hours for 2 weeks.[3,7] Repeat courses may be administered, usually at least 2 weeks after the initial course.[3,7]

Adis Evaluation

Key points in the overall evaluation of succimer

CLINICAL BENEFITS

- Reduces blood lead concentrations at least as well as calcium disodium edetate in the short term
- Orally administered
- Well tolerated in the short term
- Does not produce significant increases in urinary excretion of metals such as iron and zinc

POTENTIAL LIMITATIONS

- Inadequate data on long term tolerability and in patients with symptomatic lead poisoning
- No evidence that treatment prevents neurological sequelae long term
- Unpleasant taste and smell

The drug is formulated only as 100mg capsules, which may mean that dosages must be approximated rather than calculated exactly according to the recommendations.[2]

Capsules may be opened and the contents administered with soft food or fruit juice to facilitate administration to young children and to disguise the unpleasant taste.[7]

The drug should not be administered unless all sources of lead can be removed from the child's environment.[2]

Nutritional deficiencies of minerals such as iron predispose to lead poisoning, and should be corrected.[1] It appears that iron supplements can be given safely during treatment with succimer.[4]

Prescribing and formulary considerations

The US FDA has approved succimer for the treatment of children with blood lead concentrations ≥45 μg/dl who do not have encephalopathy.[2]

Recent data indicate that the drug may be useful in patients with blood lead concentrations in excess of 70 μg/dl.[4] However, the US Centers for Disease Control states that clinicians contemplating the use of succimer in place of parenteral chelation therapy in such children should be aware that experience is limited.[7]

As yet, there are insufficient data to support recommending succimer in preference to the traditional parenteral therapies in children with encephalopathy. In addition, oral agents may be difficult to administer to children with encephalopathy.

Compared with the only other orally administered agent, penicillamine, succimer is well tolerated.[5] It also appears well tolerated compared with the available parenteral agents.

However, data regarding the efficacy and tolerability of the drug in the longer term are lacking. Thus, the drug may be considered an alternative to more established agents at present, rather than as a first-line drug.[5,7]

There is no role for succimer as prophylaxis of lead poisoning.[2]

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