Chelation Therapy for Off-Label Uses

Policy Number: 8.01.02  
Last Review: 7/2014
Origination: 10/1988  
Next Review: 9/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Chelation Therapy for Off-Label Uses. This is considered investigational.

When Policy Topic is covered

When Policy Topic is not covered

Off-label applications of chelation therapy (See Considerations for FDA-approved uses) are considered investigational, including, but not limited to:
- Atherosclerosis (i.e., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
- Multiple sclerosis
- Arthritis (includes rheumatoid arthritis)
- Hypoglycemia
- Autism
- Alzheimer’s disease
- Diabetes

Considerations

There are a number of indications for chelation therapy that have received FDA approval and for which chelation therapy is considered standard of care treatment. These include:
- extreme conditions of metal toxicity;
- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NTDT);
- Wilson's disease (hepatolenticular degeneration); and
- lead poisoning
- control of ventricular arrhythmias or heart block associated with digitalis toxicity;
- emergency treatment of hypercalcemia;

For the last two bullet points, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. The FDA removed the approval for NaEDTA as chelation therapy due to safety concerns, and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

Description of Procedure or Service

Chelation therapy, an established treatment for treating heavy metal toxicities, has been investigated for a variety of other off-label applications including treatment of atherosclerosis, Alzheimer’s disease and autism.
Background

Chelation therapy is an established treatment for the removal of metal toxins by converting them to a chemically inert form that can be excreted in the urine. Chelation therapy consists of the intravenous or oral administration of chelating agents that remove metal ions such as lead, aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body.

Specific chelating agents are used for particular heavy metal toxicities. For example, desferoxamine (not FDA approved) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning. (Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia. (1) Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer's disease, which is associated with the disequilibrium of cerebral metals. Unlike traditional systemic chelators that bind and remove metals from tissues systemically, MPACs have subtle effects on metal homeostasis and abnormal metal interactions. In animal models of Alzheimer's disease, they promote the solubilization and clearance of beta amyloid protein by binding its metal-ion complex, and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt two putative pathogenic processes of Alzheimer's disease. However, no MPACs have received U.S. Food and Drug Administration (FDA) approval for the treatment of Alzheimer's disease. Chelation therapy has also been discussed as a treatment for other indications including atherosclerosis and autism. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

Regulatory Status

FDA approved calcium-EDTA (Versenate) for lowering blood lead levels among both pediatric and adult patients with lead poisoning. Succimer is approved for the treatment of lead poisoning in pediatric patients only. FDA approved disodium-EDTA for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with the drug, digitalis. In 2008, FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used. (2)

Several iron chelating agents have received are FDA approved:

- Deferoxamine for subcutaneous, intramuscular, or intravenous injections was approved to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia.
- Deferasirox, approved in 2005, is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients age 2 years and older. Under the accelerated approval program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 10 years and older with chronic iron overload due to nontransfusion-dependent thalassemia (NTDT).
- In 2011, the FDA approved the iron chelator deferiprone (Ferriprox®) for the treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form for oral use.

Rationale

This policy was created in 1995 and updated regularly with literature searches using MEDLINE. The most recent literature review covered the period through May 21, 2014. Chelation therapy is an established treatment for metal toxicity and transfusional hemosiderosis. These uses are not covered in this policy. Literature searches have focused on the use of chelation therapy for off-label conditions including, but not limited to, atherosclerosis, autism, Alzheimer disease, diabetes, and other conditions, such as multiple sclerosis.

Atherosclerosis

In 2002, Villarruz et al published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease. (3) Five placebo-controlled randomized-controlled trials (RCTs) were identified, none of which reported
mortality, non-fatal events, or cerebrovascular vascular events. Four of the 5 studies (total \( N=250 \)) found no significant benefit of EDTA chelation therapy on reported outcomes, including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study, which included only 10 patients, was apparently stopped early due to benefit, but relevant outcome data were unavailable. The Cochrane reviewers concluded that evidence was insufficient to draw conclusions about the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were needed.

Among published RCTs, Knudtson et al (2002) randomized 84 patients with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo. (4) Treatment was administered for 3 hours twice weekly for 15 weeks and then monthly for 3 months. Outcome measures included change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the 2 groups. Another double-blind, placebo-controlled RCT of EDTA chelation showed no difference between groups in short- or long-term improvement in vasomotor response. (5) Two small RCTs from the 1990’s also reported no benefit of chelation therapy as a treatment for peripheral arterial disease. (6, 7)

**Section summary**

Several RCTs of chelation therapy for treating atherosclerosis generally have reported intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs that report health outcomes are needed to establish the efficacy of this treatment.

**Autism**

Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard et al (2001) hypothesized a link between environmental mercury and autism. (8) This theory was rejected by Nelson and Bauman (2003), who found that many characteristics of mercury poisoning such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children. (9) A 2007 systematic review by Ng et al concluded that there was no association between mercury poisoning and autism. (10)

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and identified no controlled studies. (11) The author stated that case series suggested a potential role for chelation in treating some autistic individuals with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

**Section summary**

There is a lack of controlled studies on the effect of chelation therapy on health outcomes in patients with autism.

**Alzheimer Disease**

A 2008 Cochrane review evaluated metal protein attenuating compounds (MPAC) for treating Alzheimer disease (12) The review identified 1 placebo-controlled RCT. This study, by Richie et al, was published in 2003. Patients were treated with PBT1, an MPAC also known as clioquinol, an anti-fungal medication that crosses the blood-brain barrier. (13) FDA withdrew clioquinol for oral use in 1970 because of its association with subacute myelo-optic neuropathy. Richie et al administered oral clioquinol to 16 Alzheimer disease patients in doses increasing to 375 mg twice daily, and compared this group with 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog). One patient in the treatment group developed impairments in visual acuity and color vision during weeks 31 to 36 during treatment with clioquinol 375 mg twice daily. Her
symptoms resolved on treatment cessation. A 2012 update of this review included trials through December 2011. Only the Lannfelt et al trial discussed below was identified. (14)

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt et al (2008) completed a double-blind, placebo-controlled RCT of 78 Alzheimer disease patients who were treated for 12 weeks with 50 mg PBT2 (n=20), 250 mg PBT2 (n=29), or placebo (n=29). (15) There was no statistically significant difference in ADAS-Cog or Mini-Mental Status Exam scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis and transient ischemic event) were reported, both by patients receiving placebo.

Ongoing investigations in chelation therapy for the treatment of Alzheimer disease and other neurodegenerative diseases include linking a carbohydrate moiety to drug molecules to enhance drug delivery across the blood-brain barrier; this strategy may solve the potential problem of premature and indiscriminate metal binding. In addition, multi-function drugs that not only bind metal but also have significant antioxidant capacity are in development. (16)

Section summary

There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published RCTs did not find that the treatment was superior to placebo for improving health outcomes.

Diabetes

Cardiovascular Disease in Patients With Diabetes
A 2009 trial by Cooper et al in New Zealand evaluated the effect of copper chelation using oral trientine on left-ventricular hypertrophy in 30 patients with type 2 diabetes. (17) Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area (LVM) in the active treatment group compared with the placebo group (–10.6 g/m² vs –0.1 g/m², p=0.01). The study was limited by the small sample size and high drop-out rate.

Diabetic Nephropathy
Chen et al (2012) in China conducted a single-blind RCT of chelation therapy effects on the progression of diabetic nephropathy in patients with high-normal lead levels. (18) Fifty patients with diabetes, high-normal body lead burden (80-6,000 mcg), and serum creatinine 3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 mcg/dL in the treatment group and 7.1 mcg/dL in the control group, and baseline mean body lead burden was 151 mcg in the treatment group and 142 mcg in the control group. According to the U.S. Occupational and Health Safety Administration (OSHA), maximum acceptable blood lead level in adults is 40 mcg/dL. (19) Patients were randomized to 3 months of calcium disodium EDTA or placebo. During 24 months of treatment, patients in the chelation group received additional chelation treatments as needed (ie, for serum creatinine level above pretreatment levels or body lead burden >60 mcg), and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate (eGFR). Mean (SD) yearly rate of decrease in eGFR was 5.6 mL/min/173 m² (5.0) in the chelation group and 9.2 mL/min/173 m² (3.6) in the control group, a statistically significant difference (p=0.04). Secondary end point was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine patients (36%) in the treatment group and 17 (68%) in the control group attained the secondary end point, a statistically significant difference (p=0.02). There were no reported side effects of chelation therapy during the 27-month trial period.

Section summary
Two small RCTs with limitations represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients that report health outcomes such as cardiovascular events, end-stage renal disease, and mortality are needed.

**Myocardial Infarction (MI)**

In 2013, results of the multicenter, randomized, double-blind Trial to Assess Chelation Therapy (TACT) were published. (20) The trial included 1708 individuals, age 50 years or older, who had a history of myocardial infarction at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to receive 40 infusions of disodium EDTA (n=839) or placebo (n=869). The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. Primary end point was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years. The threshold for statistical significance was adjusted for multiple interim analyses to a p-value of 0.036. A total of 361 patients in the chelation group (43%) and 464 patients in the placebo group (57%) discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary end point were 33% (95% confidence interval [CI], 29 to 37) in the chelation group and 39% (95% CI, 35 to 42) in the control group, a statistically significant difference (log-rank test, p=0.035). The most common individual clinical end point was coronary revascularization, which occurred in 130 (15%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=0.08). The next most frequent end point was death, which occurred in 87 patients (10%) in the chelation group and 93 patients (11%) in the placebo group (p=0.64). No individual component of the primary outcome differed statistically between groups; however, the study was not powered to detect differences in individual components. Four severe adverse events that were definitely or possibly related to study therapy occurred. There were 2 events each in the treatment and control groups, including 1 death in each group.

The study is limited by the high number of withdrawals, with differential withdrawals between groups. The primary end point included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary end point barely met the significance threshold; if more patients had remained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the publication, 60% of patients were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in a population that is not generalizable to that seen in general clinical care. (21)

Escolar et al (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. (22) In TACT, there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes: Among 538 self-reported diabetics (31% of the trial sample), those randomized to EDTA had a 39% reduced risk of the primary composite outcome compared with placebo (hazard ratio [HR], 0.61 [95% CI, 0.45 to 0.83]; log rank test, p=0.02); among 1170 nondiabetic patients, risk of the primary outcome did not differ statistically between treatment groups (HR, 0.96 [95% CI, 0.77 to 1.20]; log rank test, p=0.73). (20) For the subsequent subgroup analysis, the definition of diabetes mellitus was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose ≥126 mg/dL at trial entry. Of 1708 patients in TACT, 633 (37%) had diabetes mellitus by this definition; 322 were randomized to EDTA, and 311 to placebo. Compared with all other trial participants, this subgroup of diabetic patients had higher body mass index, fasting blood glucose, and prevalence of congestive heart failure, stroke, hypertension, peripheral artery disease, and hypercholesterolemia. Within this subgroup, baseline characteristics were similar between treatment groups. With approximately 5 years of follow-up, the primary composite end point occurred in 25% of the EDTA group and 38% of the placebo group (HR, 0.59 [99.4% CI adjusted for multiple subgroups, 0.39 to 0.88]; log rank test, p=0.002). In adjusted analysis of the individual components of the primary end point, there were no statistically significant differences between treatment groups. There were 36
adverse events attributable to study drug that led to trial withdrawal, 16 in the EDTA group and 20 in the placebo group.

This substudy has the same limitations as the parent study described above, namely, high and differential withdrawal and heterogeneous composite end point. Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

**Section summary**

One RCT with limitations, including high dropout with differential drop-out between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes mellitus. However, this was not a high-quality trial and therefore results may be biased. Further trials of high quality are needed to corroborate whether chelation therapy improves outcomes in patients with prior MI.

**Other Potential Indications**

No RCTs or other controlled trials that evaluated safety and efficacy of chelation therapy for other conditions, such as multiple sclerosis or arthritis, were identified. Iron chelation therapy is being investigated for Parkinson disease (23) and endotoxemia. (24)

**Ongoing Clinical Trials**

A search of online site, ClinicalTrials.gov, for randomized trials of chelation therapy in heavy metal intoxication returned 14 actively-recruiting trials. All identified trials examined iron toxicity. Investigational indications are listed in Table 1 and include pantothenate kinase-associated neurodegeneration (PKAN) (NCT01741532), Parkinson disease (NCT01539837), hypotension (NCT00870883), and multiple sclerosis (NCT01627938).

**Table 1. Ongoing Randomized Trials of Chelation Therapy for Investigational Uses (Current May 2014)**

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<td>A Pilot Clinical Trial With the Iron Chelator Deferipron in Parkinson's Disease (DeferipronPD) (NCT01539837)</td>
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<td>140</td>
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* Estimated.
Summary

Chelation therapy is an established treatment for metal toxicities and transfusional hemosiderosis. There is insufficient evidence that chelation therapy improves health outcomes for patients with other conditions that are off-label for FDA-approved chelating agents, including, but not limited to, atherosclerosis, autism, Alzheimer disease, and diabetes. One RCT, the TACT study, reported that chelation therapy reduced cardiovascular events in patients with a previous MI, and that the benefit was greater in diabetic patients compared to non-diabetic patients. However, this study had significant limitations, including high dropout rates, and therefore the conclusions are not definitive. Thus, chelation therapy for these off-label applications is considered investigational.

Practice Guidelines and Position Statements

ACP/ACCF/AHA/AATS/PCNA/STS

In 2012, the American College of Physicians, American College of Cardiology Foundation, American Heart Association, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, and Society of Thoracic Surgeons published a clinical practice guideline on management of stable ischemic heart disease (IHD). (25) The guidelines recommended that “chelation therapy should not be used with the intent of improving symptoms or reducing cardiovascular risk in patients with stable IHD. (Grade: strong recommendation; low-quality evidence)”

American College of Cardiology

In 2005, ACC (26) stated that chelation “is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.)”

American College of Physicians

A 2004 clinical practice guideline from ACP (27) stated that chelation “should not be used to prevent myocardial infarction or death or to reduce symptoms in patients with symptomatic chronic stable angina. (Level of evidence B: Based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.)”

National Institute for Health and Care Excellence

NICE issued clinical guidance on autism in children and young people in 2013 (28) and autism in adults in 2012. (29) Both documents specifically recommend against the use of chelation therapy for the management of autism.

References


Billing Coding/Physician Documentation Information

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| J0470 | Injection, dimercaprol, per 100 mg, |
| J0600 | Injection, edetate calcium disodium, up to 1000 mg, |
| J0895 | Injection, deferoxamine mesylate, 500 mg |
| J3520 | Edetate disodium, per 150 mg |
| M0300 | IV chelation therapy (chemical endarterectomy ; (a local carrier Medicare code that is specific to ‘chemical endarterectomy) |
| S9355 | Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem |

Additional Policy Key Words

N/A

Policy Implementation/Update Information

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<td>2/1/09</td>
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