Related Papers
Zinc-containing denture adhesive: a potential source of excess zinc resulting in copper deficiency...
DENTURE CREAM: AN UNUSUAL SOURCE OF EXCESS ZINC, LEADING TO HYPOCUPREMIA AND NEU...
Awareness of zinc toxicity in denture adhesives among dental practitioners in Puducherry - A cross...
Zinc Amount in Dental Enamel can be a Potential Factor of Severe Tooth Wear
View more

Hyperzincemia from ingestion of denture adhesives

Arzu Tezvergil-Mutluay, DDS, PhD,[a] Ricardo M. Carvalho, DDS, PhD,[b] and David H. Pashley, DMD, PhD[c]

Institute of Dentistry, University of Turku, Turku, Finland; Bauru School of Dentistry, University of São Paulo, Bauru, Brazil; School of Dentistry, Medical College of Georgia, Augusta, Ga

The purpose of this article is to review the recent literature that documents the serious adverse systemic effects of prolonged, excessive zinc ingestion from the overuse of denture adhesives. This condition causes elevation of serum zinc levels that result in depression of serum copper. The low serum copper levels cause bone marrow depression and widespread sensory and motor neuropathies. Epidemiologic studies revealed the source of excessive zinc intake to be from overuse of denture adhesives. Denture patients must be advised of the risks of prolonged overuse of denture adhesives. (J Prosthet Dent 2010;103:380-383)

Recently, there have been a number of Internet sites warning denture patients of the poisoning potential from denture adhesives (Fixodent; Procter & Gamble Co, Cincinnati, Ohio, or Poligrip; GlaxoSmithKline Consumer Healthcare, Philadelphia, Pa). The sites all mention pending lawsuits and use phrases such as "zinc poisoning" and "denture cream poisoning" to gain the attention of denture patients.

Since there are millions of denture patients in the US, many of whom use denture adhesives, there is potential for some of those patients to inadvertently ingest more than the recommended daily allowance for zinc, one of the ingredients in denture adhesives. Zinc salts were introduced into copolymer mixtures of lower alkyl vinyl ether-maleic acid blends that were invented by Shah et al[1] in 1988 to stabilize denture adhesives. Procter & Gamble licensed that technology in 1990 when they added zinc to Fixodent denture adhesive. Block Drug Co added zinc to Super Poligrip in 1996. This formulation was retained by GlaxoSmithKline (GSK) when they purchased Block Drug Co in 2001. Three of the GSK denture adhesives contained zinc: Super Poligrip "Original," Super Poligrip "Ultra Fresh," and Super Poligrip "Extra Care." However, because of a recent increase in the number of reported adverse events, and reports in the literature indicating that ingestion of excess zinc can induce copper deficiency in patients that may result in neurological problems, GSK sent a warning letter to all healthcare providers on February 18, 2010, announcing that the company will no longer manufacture or sell zinc-containing denture adhesives, to avoid future potential patient problems. GSK now markets zinc-free alternative denture adhesives: Super Poligrip "Free," Super Poligrip "Comfort Seal Strips," and Super Poligrip "Powder" (Table I).[2] To date, Procter & Gamble has announced no plans to remove zinc from Fixodent, which is purported by the manufacturer to have only half as much zinc as Poligrip.[3]

It is important for dentists to understand the chronology of the discovery that excessive use of zinc-containing denture adhesives may cause bone marrow suppression and polyneuropathy that can result in numbness and paresthesia of the extremities, loss of balance, and walking problems. The purpose of this article is to review the recent literature that documented the adverse systemic effects of prolonged, excessive ingestion of zinc from denture adhesives.

Common nonstroke-related neuropathies

Many elderly patients spontaneously develop numbness or tingling in their extremities and unexplained burning pain as they age. This type of neuropathic pain is commonly seen in long-term type 2 diabetics and is primarily a sensory problem. Neuropathic pain results from dysfunction of nerves rather than stimulation of pain receptors.[4] After gastric bypass surgery, bariatric patients may become deficient in various vitamins and minerals that are required for good health because they can no

[a]Adjunct Professor, Department of Prosthetic Dentistry, Institute of Dentistry, University of Turku.
[b]Associate Professor, Department of Prosthodontics, Bauru School of Dentistry, University of São Paulo.
[c]Regents' Professor, Emeritus, Department of Oral Biology, School of Dentistry, Medical College of Georgia.

Table I. Brand names, manufacturers, and composition of denture adhesives

Manufacturer	Brand Names of Products with Zinc	Composition
GlaxoSmithKline Consumer Healthcare, Philadelphia, Pa	Super Poligrip Original Super Poligrip Ultra Fresh Super Poligrip Extra Care	30% methyl vinyl ether/maleic acid, Ca and Zn salt copolymer; 24% carboxymethyl cellulose, 16% mineral oil, 30% inert ingredients
Procter & Gamble Co, Cincinnati, Ohio	Fixodent Original Fixodent Fresh Fixodent Control Fixodent Complete Fixodent Comfort Fixodent Control Plus Scope Flavor	53 wt% karaya gum, 16% sodium carboxymethyl cellulose, 16% 2.6:1 Ca; Na partial salt of polyvinyl methyl-maleic acid copolymer, 8% Zn partial salt of polyvinyl methyl-maleic acid copolymer
Wick Pharma/P&G GmbH, Schwalbach, Germany	Super-Haftcreme Extra Stark	27% poly(methyl vinyl ether), 10% polymaleic acid, 3% calcium zinc salt, paraffin, petrolatum, silicon dioxide, 1.9% carnellose sodium, menthol
	Products without Zinc	
GlaxoSmithKline Consumer Healthcare	Super Poligrip Free Super Poligrip Comfort Seal Strips Super Poligrip Powder	Same as Super Poligrip Original with calcium but without zinc salts
Queisser Pharma GmbH, Flensburg, Germany	Protefix Adhesive Cream, Extra-Strong	30% calcium salt of copolymer of methyl vinyl ether/maleic acid, 23% carboxymethyl cellulose, paraffin, petrolatum
Fittydent Intl GmbH, Pinkafeld, Austria	Fittydent Super Adehesive Cream	Undefined quantities of sodium carboxymethyl cellulose, polyvinyl acetate, hydroxypropyl cellulose

longer absorb these nutrients from normal diets. They should take special vitamin and mineral supplements. In the absence of such supplements, many patients develop copper insufficiency that results in neurological symptoms.[5-9] One of the hallmarks of copper insufficiency is low plasma copper (hypocupremia).

Zinc-induced neuropathies

Unlike the sensory problems associated with long-term diabetes, prolonged hypocupremia can produce both motor and sensory problems. Another recently discovered cause of hypocupremia is excessive oral zinc consumption, particularly associated with excessive use of zinc-containing denture adhesives.[3,7,10-17] In patients with this condition, high concentrations of zinc in the small intestine induce increased expression of metallothioneins, proteins that bind zinc in a futile attempt to prevent its excessive absorption into the body. The problem, however, is that metallothioneins have a higher affinity for copper than zinc.[3] Dietary copper is so firmly attached to the intestinal cells that it cannot be absorbed into the body.[18] Although the metallothioneins cannot bind all of the excess ingested zinc, they can bind all dietary copper. The dietary copper bound to metallothioneins is lost in the stool via intestinal epithelial turnover rather than being absorbed as it normally is in the absence of excessive ingested zinc.[17] This leads to hypocupremia.

Since many critical enzymes in nerves require copper as a cofactor, deficiencies in copper can result in abnormal nerve function. Hedera et al[16] examined 11 patients with the signs of hyperzincemia and hypocupremia. The authors reported that 9 of the 11 patients exhibited bone marrow suppression (pancytopenia) and both sensory and motor neuropathies. Although the authors recognized the patients were overloaded with zinc, the actual source of zinc could not

be identified. To treat the hypocupremia, the 11 patients were given oral supplements of 6 mg of copper/day (range 2-8 mg/day) to correct their hypocupremia. Their hematologic abnormalities resolved faster than did their neurologic deficits, even in the presence of hyperzincemia. More recently, the detection of the high zinc content in denture adhesives identified a possible dietary source of excessive zinc intake[3] in hyperzincemia patients suffering from polyneuropathics associated with hypocupremia. With this information available, Hedera et al[17] reevaluated the hypocupremic subjects and observed that 100% (11 of 11) of the patients with copper deficiency syndrome had ingested large amounts of zinc from denture adhesives. This suggested that most such patients with the diagnosis of idiopathic hyperzincemia, if not all, developed that condition due to probable overuse of denture adhesives.

DISCUSSION

Several authors,[19,20] in letters to editors, speculated that patients with both hypocupremia and hyperzincemia might be more susceptible than the general population of denture users to the exposure to zinc-containing denture adhesives, either by increased absorption or reduced elimination of zinc. The average use of denture adhesives by patients in one study[17] was more than 2 tubes per week, containing approximately 80 g of material. The shortest duration of denture adhesive use was 7 years. The estimated daily zinc exposure was between 350-1700 mg/day. This zinc exposure can be compared to the oral therapeutic administration of zinc in patients with Wilson's disease[21,22] to slowly remove tissue accumulations of copper. Such patients are given 75 mg of zinc per day in 2 or 3 divided doses. The estimated zinc intake from denture adhesives was 5-23 times the amount the FDA approves for Wilson's disease.[23] Because of the excessive zinc ingestion by the 11 patients studied by Hedera et al,[17] it is unlikely that their symptoms were due to an increased susceptibility to zinc.

The root cause of excessive zinc ingestion from denture adhesives in patients is poorly fitting dentures. Dentists often advise their denture patients that their prostheses will require periodic relining or remaking as residual ridge resorption occurs over time. Too often, patients resort to the use of denture adhesives to compensate for the space that develops over time between denture bases and the underlying mucosa. As more alveolar supporting bone is lost, such patients may use more adhesive. Instead, they need to have loose-fitting dentures relined or remade to regain the retention they seek. This message needs to be better communicated to the public, along with the dangers of overuse of denture adhesives. The recent paper by Hedera et al[17] concludes with the following statement: "Poorly fitting dentures requiring large amounts of denture cream to provide a sufficient seal appear to be the common characteristics of patients with idiopathic hypocupremia, hyperzincemia, bone marrow suppression and a combination of polyneuropathy with spinal cord degeneration. Patients presenting with this constellation of neurologic and hematological signs need to be immediately screened for abnormal blood copper and zinc levels, and the use of large amounts of denture cream."

Thus, although there are many causes of hypocupremia (low plasma copper), nearly all of those conditions would be associated with normal serum zinc levels. When hypocupremia is associated with hyperzincemia, the cause of that condition is thought to be ingestion of excessive zinc. This was the observation made by Hedera et al.[16] The authors had seen a group of patients exhibiting hyperzincemia associated with hypocupremia and symptoms of progressive myelopolyneuropathy (widespread peripheral sensory and motor deficits, usually due to abnormal metabolic or toxic origins). The authors knew that the patients had somehow consumed excess zinc, but they did not know the source of that zinc.[6,12-14,16] Denture adhesives as a possible source of hyperzincemia was first reported by Nations et al[17] and then later by Spinazzi et al in a letter to the editor.[20] This encouraged Hedera et al[17] to reevaluate the use of denture adhesives in a group of 11 patients in which myelopolyneuropathy was combined with hypocupremia and hyperzincemia. Their investigation showed that all 11 patients had a history of excessive use of denture adhesives for poorly fitting dentures.

SUMMARY

As formulations and frequency of use of denture adhesives vary widely, it is difficult to establish a safe amount to be consumed. Apparently, "zinc overload" and its consequences will not occur by occasional or moderate use of denture adhesives. The consequences reported by some authors were associated with the use of large amounts of denture adhesive over years. As a number of issues have yet to be determined, such as bioavailability of zinc from denture adhesives and the effects of gastric pH on zinc absorption, the best advice is to recommend zinc-free denture adhesives to denture patients. Dentists need to stress the need for periodically relining denture bases to minimize the need for denture adhesives. Endosseous implants can also improve denture stability.

REFERENCES

1. Shah NB, Gounaris MC, Holeva KT, inventors; Richardson-Vicks, Inc, assignee. Denture stabilizing zinc and strontium salts of AVE/MA copolymer. US patent 4 758 630. July 19, 1988.
2. Al RH, Dahl JE, Morisbak E, Polyzois GL. Irritation and cytotoxic potential of denture adhesives. Gerodontology 2005;22:177-83.
3. Nations SP, Boyer PJ, Love LA, Burritt MF, Butz JA, Wolfe GI, et al. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology 2008;71:639-43.

4. Chen H, Lamer TJ, Rho RH, Marshall KA, Sitzman BT, Ghazi SM, Brewer RP. Contemporary management of neuropathic pain for the primary care physician. Mayo Clin Proc 2004;79:1533-45.
5. Kumar N, McEvoy KM, Ahlskog JE. Myelopathy due to copper deficiency following gastrointestinal surgery. Arch Neurol 2003;60:1782-5.
6. Kumar N, Gross JB Jr, Ahlskog JE. Myelopathy due to copper deficiency. Neurology 2003;61:273-4.
7. Kumar N, Gross JB Jr, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology 2004;63:33-9.
8. Kumar N, Crum B, Petersen RC, Vernino SA, Ahlskog JE. Copper deficiency myelopathy. Arch Neurol 2004;61:762-6.
9. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc 2006;81:1371-84.
10. Brewer GJ, Schoomaker EB, Leichtman DA, Kruckleberg WC, Brewer LF, Myers N. The uses of pharmacologic doses of zinc in the treatment of sickle cell anemia. In: Brewer GJ, Prasad AS, editors. Zinc metabolism: current aspects in health and disease. New York: Allan R. Liss, Inc. 1977. p. 241-58.
11. Prasad AS, Brewer GJ, Schoomaker EB, Rabbani P. Hypocupremia induced by zinc therapy in adults. JAMA 1978;240:2166-8.
12. Hoffman HN 2nd, Phyliky RL, Fleming CR. Zinc-induced copper deficiency. Gastroenterology 1988;94:508-12.
13. Broun ER, Greist A, Tricot G, Hoffman R. Excessive zinc ingestion. A reversible cause of sideroblastic anemia and bone marrow depression. JAMA 1990;264:1441-3.
14. Gyroffy EJ, Chan H. Copper deficiency and microcytic anemia resulting from prolonged ingestion of over-the-counter zinc. Am J Gastroenterol 1992;87:1054-5.
15. Prodan CI, Holland NR, Wisdom PJ, Burstein SA, Bottomley SS. CNS demyelination associated with copper deficiency and hyperzincemia. Neurology 2002;59:1453-6.
16. Hedera P, Fink JK, Bockenstedt PL, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome. Arch Neurol 2003;60:1303-6.
17. Hedera P, Peltier A, Fink JK, Wilcock S, London Z, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin. II. The denture cream is a primary source of excessive zinc. Neurotoxicology 2009;30:996-9.
18. Yuzbasiyan-Gurkan V, Grider A, Nostrant T, Cousins RJ, Brewer GJ. Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. J Lab Clin Med 1992;120:380-6.
19. Hedera P, Brewer GJ. Letter to the Editor. Reply. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown source: further support for existence of a new zinc overload syndrome. Arch Neurol 2004;61:604-5; author reply 605.
20. Spinazzi M, Armani M. Letter to the Editor. Reply. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology 2009;73:76.
21. Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. Treatment of Wilson's disease with zinc: XV long term follow-up studies. J Lab Clin Med 1998;132:264-78.
22. Roberts EA, Schilsky ML; American Association for Study of Liver Disearses (AASLD). Diagnosis and treatment of Wilson disease: An update. Hepatology 2008;47:2089-111.
23. Brewer GJ. Neurologically presenting Wilson's disease: epidemiology, pathophysiology and treatment. CNS Drugs 2005;19:185-92.

Corresponding author:
Dr David H. Pashley
School of Dentistry, Medical College of Georgia
Department of Oral Biology
1120 15th St, CL-2112
Augusta, GA, 30912-1129
Fax: 706-721-6252
E-mail: dpashley@mcg.edu

Copyright © 2010 by the Editorial Council for *The Journal of Prosthetic Dentistry.*

Receive JPD Tables of Contents by E-mail

To receive tables of contents by e-mail, sign up through our Web site at http://www.journals.elsevierhealth.com/periodicals/ympr.

Instructions
Log on and click "Register" in the upper right-hand corner. After completing the registration process, click on "My Alerts," then "Add Table of Contents Alert." Select the category "Mosby" or type *The Journal of Prosthetic Dentistry* in the search field and click on the Journal title. You may add tables of contents alerts by accessing an issue of the Journal and clicking on the "Add TOC Alert" link.

You will receive an e-mail message confirming that you have been added to the mailing list.

Note that tables of contents e-mails will be sent when a new issue is posted to the Web site.