

Calcium phosphate mouth rinse for preventing oral mucositis

A new artificial saliva protects the mucosa from damage due to cancer treatment.

What's new, what's important

Side effects from chemotherapy are one of the major concerns for our patients. With the addition of novel antiemetic medicines, we are better equipped to handle nausea and vomiting. Mucositis is still a problem for many of our patients. So far, we have been using salt and baking soda and "miracle or magic mouth wash." But now we have a new option, Caphsol, a supersaturated calcium phosphate rinse. Studies have shown that Caphsol can decrease chemotherapy- and radiation therapy-associated mucositis and its complications. Caphsol should be initiated at the start of chemotherapy along with standard oral care. One dose of Caphsol is made up of two 15 mL ampules of calcium and phosphate mixed together. The recommended dose is 4–10 times per day, depending on the intensity of the mucositis.

— Jame Abraham, MD
Section Editor

Caphsol artificial saliva is a topical oral agent that lubricates the mucosa and helps maintain the integrity of the oral cavity. The agent is a neutral supersaturated calcium phosphate ($\text{Ca}^{2+}/\text{PO}_4^{-3}$) mouth rinse; it is believed that the ions exert a beneficial effect by diffusing into intracellular spaces in the epithelium and permeating mucosal lesions in mucositis.¹

Calcium ions play a central role in inflammation, vasodilation, coagulation, and tissue repair. The inorganic phosphate may be a source of organic phosphates involved in the repair of damaged mucosal surfaces. Caphsol is indicated for dryness of the mouth or throat regardless of the cause or whether the condition is temporary or permanent. It is also indicated as an adjunct to standard oral care in the treatment of mucositis resulting from radiation therapy or high-dose chemotherapy.

Oral mucositis occurs with nu-

merous cancer therapies and is associated with considerable pain, morbidity, and cost. In the setting of chemotherapy and radiation treatment in hematopoietic stem cell transplantation (HSCT), for exam-

ple, oral mucositis is associated with an increased risk of systemic infection and other transplantation complications, increased use of injectable narcotics, and increased length of hospital stay and costs.^{2,3} A 2005

TABLE 1
Caphsol plus fluoride versus fluoride alone in preventing mucositis in HSCT

	Caphsol + fluoride (n = 50)		Fluoride alone (n = 45)		P value
	Mean (SE)	Median (range)	Mean (SE)	Median (range)	
Days to ANC > 200/ μL	11.1 (0.4)	10 (6–18)	12.6 (0.6)	12 (7–28)	< 0.00173
Days to ANC > 500/ μL	13.3 (0.6)	12 (8–25)	14.6 (0.9)	13 (7–38)	< 0.1983
Days of mucositis	3.7 (0.6)	3 (0–15)	7.2 (0.9)	7 (0–20)	< 0.00096
Days of ulceration	2.2 (0.5)	0 (0–13)	5.3 (0.9)	4.5 (0–20)	< 0.0019
Peak mucositis	1.4 (0.2)	1 (0–5)	2.4 (0.3)	3 (0–5)	< 0.004*
Peak pain	19.8 (4.3)	0 (0–100)	50.3 (5.2)	60 (0–100)	< 0.0001*
Days of pain	2.9 (0.6)	0 (0–15)	7.7 (0.8)	7 (0–21)	< 0.0001
Total morphine for mucositis (mg)	34.5 (12.0)	0 (1–400)	122.8 (24.6)	88 (0–812)	< 0.0001*
Days of morphine	1.3 (0.4)	0 (0–11)	4.0 (0.7)	3 (0–22)	< 0.00015*
Hospital days post-transplant	24.5 (2.5)	17 (10–71)	24.8 (2.5)	18 (11–79)	< 0.9447

HSCT = hematopoietic stem cell transplantation; SE = standard error; ANC = absolute neutrophil count

* Nonparametric test (Mann-Whitney U test) used because of non-normality of data; other comparisons based on analysis of variance (ANOVA).

study showed a \$43,000 increase in costs for patients with oral mucosal ulceration compared with no ulceration.³ A randomized, double-blind trial of Caphosol in patients undergoing HSCT showed that treatment with the agent was effective in reducing the frequency, intensity, and duration of oral mucositis.¹

Clinical evidence

In this trial, 95 patients in a single center were randomized to receive Caphosol plus standard fluoride rinsing (n = 50; 52% female; mean age, 43 years) versus fluoride plus placebo rinsing (n = 45; 44% female; mean age, 42 years) and stratified according to autologous or allogeneic transplant.¹ Patients rinsed 4 times daily during transplantation and up to 10 times daily if severe mucositis developed. The groups were balanced with regard to disease category, autologous transplant (27 patients in

the Caphosol-treatment group and 23 in the fluoride-alone group) versus allogeneic transplant, and conditioning regimens. Mucositis was assessed by the National Institute of Dental and Craniofacial Research scale (0–5), and pain was assessed using a 0–100 visual analog scale.

Patients undergoing autologous transplantation had a shorter time to onset of neutrophil engraftment (absolute neutrophil count [ANC] > 200/ μ L) and time to engraftment (> 500/ μ L) and shorter hospital stays after stem cell infusion. Findings for the Caphosol group versus fluoride-alone group showed similar trends in the autologous and allogeneic subgroups. Overall, Caphosol treatment was associated with numerous significant benefits (Table 1), including reductions in time to ANC > 200/ μ L, days of mucositis, days of ulceration, peak level of mucositis, peak pain level, days of pain, total milligrams

of self-administered morphine, and days of morphine use. No mucositis was observed in 40% of Caphosol-treated patients versus 19% of fluoride-alone patients. No morphine was required by 74% of the Caphosol group, compared with 34% of those who received fluoride treatment only. There were no differences between groups with regard to length of hospital stay or days of fever following stem cell infusion.

References

1. Papas AS, Clark RE, Martuscelli G, O'Loughlin KT, Johansen E, Miller KB. A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003;31:705–712.
2. Spijkervet FK, Sonis ST. New frontiers in the management of chemotherapy-induced mucositis. *Curr Opin Oncol* 1998;10(suppl I): S23–S27.
3. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol* 2001;19:2201–2205.

From the Community Oncologist's Perspective

Caphosol reduces the severity of mucositis when started at the onset of cancer therapy

Athena Papas, DMD, PhD

Department of Oral Medicine, Tufts University School of Dental Medicine, Boston, MA

Caphosol (supersaturated calcium phosphate rinse) is a supersaturated electrolyte solution resembling human saliva, designed in part to replace the normal ionic and pH balance in the oral cavity. Healthy functioning mouths naturally produce saliva, which includes calcium and phosphate that perform many important functions.

Calcium ion plays an important role in the inflammatory process, the pathogenesis of pain and fever, leukocyte influx and adhesion, platelet aggregation, production of fibrin, and tissue repair in damaged mucosal surfaces. Inorganic phosphate is an essential component of the organic phosphates present both extracellularly and intracellularly, affecting mucosal surfaces. These important nat-

ural functions are rendered weak or impossible when cancer treatment induces severe saliva hypofunction and oral mucositis.

A key component in preventing and treating oral mucositis is helping to augment or replace the important functions of saliva. Keeping the mouth healthy in cancer patients has a positive cascading effect, as demonstrated by Caphosol when started at

the inception of cancer therapy.

As noted in the accompanying article, the pivotal trial conducted on Caphosol in bone marrow transplant patients demonstrated significant benefits for patients, including reductions in the time to onset of engraftment, days of mucositis, days of ulceration, peak level of mucositis, peak pain level, days of pain, total milligrams of self-administered morphine, and days of morphine use. No mucositis was observed in 40% of Caphosol-treated patients versus 19% of patients who rinsed with fluoride alone in this double-blinded randomized clinical trial. Further, no morphine was required by 74% of Caphosol-treated patients versus 34% of patients in the fluoride-alone group.

A recent reanalysis of the Caphosol pivotal trial data was done for the Cochrane review on preventing oral mucositis in patients receiving cancer therapy. Comparing Caphosol with

placebo in regard to the absence or presence of mild, moderate, and severe mucositis demonstrated that all three comparisons significantly favored Caphosol over placebo: mild (relative risk [RR]: 0.75; 95% confidence interval [CI], 0.58–0.99); moderate (RR = 0.63; 95% CI, 0.42–0.94); and severe (RR = 0.42; 95% CI = 0.23–0.76).¹

One dose of Caphosol comprises two ampules (one calcium ampule and one phosphate ampule), each 15 mL; the ampules are mixed together by the patient at home. Caphosol should be initiated at the start of cancer therapy in conjunction with standard oral care. The recommended dose of Caphosol during high-dose chemotherapy or radiation treatment is 4 doses per day, beginning with the onset of cancer treatment, and may be increased up to 10 doses per day if pain from mucositis is experienced.

Caphosol should be used for the duration of the treatment. The recommended dose for the relief of dry mouth is 2–10 times per day. There are no known interactions with medicinal or other products.

Several studies on oral mucositis in head and neck cancer, as well as outcomes in graft-versus-host disease, are in development. In randomized clinical trials where many products did not show a significant change, the availability of Caphosol is an important development for patients who are at risk of developing oral mucositis and xerostomia.

Reference

1. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2007;4: CD000978.

E-mail comments to Dr. Papas at [athena.papas@tufts.edu](mailto:papas@tufts.edu).

From the Nurse's Perspective

Mucositis often overlooked and undertreated

Angela Price, RN, BSN, OCN

Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV

Mucositis can be a serious problem in cancer patients. It is sometimes overlooked by healthcare providers as a potential side effect of cancer treatment until it is too late, and patients are already having problems with their oral mucosa. Mucositis is seen in as many as 35%–40% of all patients receiving cytotoxic chemotherapy and in an even higher percentage of patients undergoing hematopoietic stem cell transplantation.¹

Whether a patient experiences problems with mucositis or not depends upon many factors: the patient's tolerance, the specific chemotherapeutic agents used and their dosage, the regimen, whether chemotherapy and radiation therapy are being used, and the area being treated with radiation. Certain chemotherapeutic agents have a higher incidence of causing mucositis, such as cytarabine, doxorubicin, etoposide, 5-fluorouracil, methotrexate, bleomycin, and cis-

platin. Almost all patients who are undergoing hematopoietic stem cell transplantation experience some degree of mucositis.²

Mucositis can start—or be as minimal—as erythema of the oral mucosa and progress to mouth sores and even severe ulcerations and breakdown of the oral cavity. The National Cancer Institute's Common Toxicity Criteria define the grade of mucositis based on the finding on clinic examination (Table 1).

When there is breakdown of the

TABLE 1

Grading of oral mucositis severity

Grade	Clinical findings	Functional or symptomatic features
1	Erythema of the mucosa	Minimal symptoms, normal diet
2	Patchy ulcerations or pseudomembranes	Symptomatic but can eat and swallow modified diet
3	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Symptomatic and unable to adequately aliment or hydrate orally
4	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Symptoms associated with life-threatening consequences
5	Death	Death

Source: National Cancer Institute Common Toxicity Criteria, version 3.0, 2003

oral mucosa, it provides an opportunity for infection. Seventy percent of oral infections in relationship to mucositis are caused by *Candida albicans*; however in transplant patients, herpes simplex virus is more common.²

Treating oral mucositis

Over the years, everyone in the oncology community has struggled with how to treat patients with oral mucositis. Most of us have tried different solutions such as a fluoride rinse; a rinse made up of table salt and baking soda; or a form of “magic mouthwash,” a solution containing lidocaine, diphenhydramine, and an antacid. Nothing has been proven to help patients with their symptoms or prevent the oral side effects from chemotherapy and radiation therapy. Patients may obtain only temporary relief from what we have all been using to date.

Now there is something that is US Food and Drug Administration approved for the prevention and treatment of oral mucositis and that

actually has clinical data to support the benefits of using this medication. Although the studies mainly focused on patients undergoing hematopoietic stem cell transplantation, Caphosol can benefit any patient having problems with oral mucositis and xerostomia.

Whether our patients are receiving chemotherapy or radiation therapy, at the first sign of their mouth being sore, they want something to help “fix it.” Caphosol actually works up front by preventing oral mucositis or at least reducing the length of time patients will need pain medication to relieve their mucositis.

Caphosol is an aqueous solution of dibasic sodium phosphate (0.032% w/w), monobasic sodium phosphate (0.009% w/w), calcium chloride (0.052% w/w), and sodium chloride (0.569% w/w). Its composition resembles that of human saliva, and it works by infiltrating into the intercellular spaces of the epithelium to prevent and treat oral mucositis.

Caphosol is simple to use, so any

patient should be able to self-administer it. Patients merely have to empty the two ampules into a clean cup or glass and then mix them. Then they swish half the solution around in their mouth for 1 minute, spit it out, and repeat rinsing their mouth with the remaining solution. For best results, patients should wait 15 minutes before eating or drinking. Patients should not wait to develop mucositis before they start rinsing with Caphosol; they should begin using the solution when they first start their cancer treatment and use it anywhere from 4 to 10 times a day, depending upon the severity of their symptoms.

I have seen Caphosol decrease the incidence of oral mucositis in my patients who were receiving adjuvant therapy for breast cancer, concurrent radiation therapy, and chemotherapy for gastric cancer and autologous stem cell transplants. Many chemotherapeutic agents have the potential to cause patients to experience some grade of oral mucositis. Finally, there is something that can help our patients prevent and/or reduce the pain and discomfort of this side effect.

References

1. Papas AS, Clark RE, Martuscelli G, O’Loughlin KT, Johansen E, Miller KB. A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003;31:705–712.
2. Toljanic JA, Bedard J-F, Joyce RM. Oral toxicity associated with chemotherapy. Available at: <http://patients.uptodate.com/topic.asp?file=chemagen/2886>. Accessed March 20, 2008.

E-mail comments to Ms. Price at pricean@wvuh.edu.