Study Protocol

Simvastatin 1.2% Topical Dental Gel

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Study Title: The use of topical subgingival application of simvastatin gel in the treatment of peri- implant mucositis: a pilot study

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I. Introduction

Peri-implant mucositis is the precursor to peri-implant diseases [1] , which are responsible for many of the failures that affect dental implants[2]. Bacteria are regarded as the main cause of peri-implant diseases, however the host mediated inflammatory response is what causes the associated tissue destruction via inflammation.[3-7]

Simvastatin (SMV), is a specific competitive inhibitor of 3- hydroxyl- 2- methyl-glutaryl coenzyme A (HMG-CoA) reductase.[8] Research has shown that simvastatin use also reduces periodontal inflammation [9] and it has been shown that simvastatin reduces interleukin IL-6 and IL-8 ,[10] both of which have been associated with diseased implants.[11-12] The use of simvastatin as a subgingivally delivered gel in human subjects has shown reduction of modified bleeding index (mSBI) probing depth (PD), mean clinical attachment loss (CAL) as well as a decreased intrabony defect in patients with periodontitis.[13] Animal studies on the use of topically applied statins resulted in greater bone densities around implants [14-15]

References

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II. Physical, Chemical and Pharmaceutical Properties and Formulation

Simvastatin is a synthetic derivative of a fermentation product of *Aspergillus terreus* and is a methylated form of lovastatin. Like lovastatin, simvastatin is a prodrug which requires hydrolysis for activation as an HMG CoA reductase inhibitor.[1,2,3] Our gel will be used topically for local anti-inflammatory effect.

Lecithin/isopropyl palmitate solution (Lipoil®) , Poloxamer 407 gel (Polox Gel 20%®) will be the gelling agent used. Cellulose derivatives are considered virtually unabsorbed by the human digestive tract and are non-allergenic.[3]

The gel is a yellow, viscous gel.

(Formulations of the study gel and placebo gel are on the following page)

References

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2. Simvastatin. In: American Hospital Formulary Service (AHFS) Drug Information. Hudson, OH : Lexi-Comp; Inc.; [Updated October 15, 2014; Accessed August 28,2014].
3. Select Committee on Gras Substances (SCGOS) Opinion: Methylcellulose. US Food and Drug Administration {Online Database] [Updated 04/18/2013, Accessed 09/02/2014] at http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm260473.htm

MASTER FORMULA SHEET
Dental Pharmacy Compounding Procedure Form

FORMULA NUMBER: *Date compounded*:_____
FORMULA NAME: **Simvastatin 1.2% W/V Dental Gel**
LOT NUMBER: _____

Ingredient	Source	Lot Number	Lot Exp.	Quantity
Simvastatin Powder, U.S.P.				0.024 g
Ethyl Alcohol 200 proof, U.S.P NDC: 51552-0897-05	Fagron			0.06 ml
Methylcellulose 4000 CPS powder, U.S.P.	Fagron			0.2 g
Methylcellulose Gel 3% NDC: 51552-0827-05	Fagron			QS 20.0 ml
Total Qty:				20 ml

Method of Preparation:

1. Weigh 0.2 g methylcellulose 4000 CPS powder
2. Measure 18 ml methylcellulose 3% gel
3. Combine powder and gel in 100 ml beaker and heat to 70 - 90 °C with stirring until powder dissolves. Remove from heat and allow to cool to room temperature. Transfer to 30 ml sterile Luer Lok syringe.
4. Weigh 0.024 grams simvastatin powder on analytical balance, place in capped sterile 30 ml Luer Lok syringe.
5. Draw up 0.06 ml of ethyl alcohol in 0.3 ml volume syringe. Add alcohol to simvastatin powder. Immediately cap syringe.
6. Swirl contents of syringe until powder dissolves.
7. Draw up 5 ml of prepared methylcellulose gel into 30 ml sterile Luer Lok syringe and cap.
8. Connect syringes with Luer Lok connector and transfer between syringes to mix well
9. Add additional prepared methylcellulose gel QS to 20 ml and mix well (syringe to syringe)
10. Transfer prepared gel into one of the 30 ml syringes, add plunger and remove all air.
11. Cap syringe with sterile Luer Lok cap.
12. Label: Product, date, lot. Refrigerate. Use within 48 hours.

Prepared by: _____ **Checked by: _____**

MASTER FORMULA SHEET

Dental Pharmacy Compounding Procedure Form

FORMULA NUMBER: *Date compounded*:_____
FORMULA NAME: **Placebo Gel: 4% Methylcellulose W/V Dental G**el
LOT NUMBER: _____

Ingredient	**Source**	**Lot Number**	**Lot Exp.**	**Quantity**
Methylcellulose 4000 CPS powder, U.S.P.	Fagron			0.2g
Ethyl Alcohol 200 proof, U.S.P NDC: 51552-0897-05	Fagron			0.06 ml
Methylcellulose Gel 3% NDC: 51552-0827-05	Fagron			QS 20.0 ml
Total Qty:				20 ml

Method of Preparation:

1. Weigh 0.2 g methylcellulose 4000 CPS powder.
2. Measure 18 ml methylcellulose 3% gel.
3. Combine powder and gel in 100 ml beaker and heat to 70- 90 °C with stirring until powder dissolves. Remove from heat and allow to cool to room temperature. Transfer to 30 ml sterile Luer Lok syringe.
4. Draw up 0.06 ml of ethyl alcohol in 0.3 ml volume syringe. Transfer to 30 ml sterile Luer Lok syringe. Immediately cap syringe.
7. Draw up 5 ml of prepared methylcellulose gel into 30 ml sterile Luer Lok syringe and cap
8. Connect syringes with Luer Lok connector and transfer between syringes to mix well.
9. Add additional prepared methylcellulose gel QS to 20 ml and mix well (syringe to syringe).
10. Transfer prepared gel into one of the 30 ml syringes, add plunger and remove all air.
11. Cap syringe with sterile Luer Lok cap.
12. Label: Product, date, lot.
13. Place in light resistant ziplock bag. Label. Refrigerate. Use within 48 hours.

Prepared by: _____ **Checked by: _____**

III. Nonclinical Studies

Sakoda et al. studied the anti-inflammatory effect of simvastatin in oral tissues, specifically the effect of simvastatin on a human epithelial cell line KB which has been extensively used as a model for the study of gingivalepithelial cells stimulated by IL-1. Simvastatin was found to reduce IL-1_-induced production of inflammatory cytokines IL-6 and IL-8 by human oral epithelial cells [1]

References

1- Sakoda K, Yamamoto M, Negishi Y, Liao JK, Node K, Izumi Y. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. Journal of Dental Research. 2006;85(6):520-3.

IV. Effects in Humans

a. Pharmacokinetics and Product Metabolism in Humans

Simvastatin is FDA approved in therapeutic doses of 5-80 mg/day per os as a hypolipidemic agent. Simvastatin is a methylated derivative of lovastatin, both of which are prodrugs that must be activated in the liver. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form.[1] This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.[1]

Orally administered simvastatin is metabolized in the liver via CYP3A4 with an extensive first-pass effect. Bioavailibility is <5%. Simvastatin and its active metabolite are 95% bound to plasma proteins. Approximately 60% of an orally absorbed dose is excreted in the feces and 13% in the urine. The half-life is 1.9 hours.[2,3]

Simvastatin is a substrate of CYP3A4 and CYP2D6 hepatic metabolism. Other drugs that inhibit CYP3A4 can result in increased HMG-CoA reductase inhibition and toxicity. This is a dose-related phenomenon which usually occurs with repeated dosing of both interacting drugs and in the higher dosage range (maximum of 80 mg/day) of simvastatin. Simvastatin does not affect the metabolism of other CYP3A4 substrates.[2,3] Simvastatin is also a substrate and inhibitor of the P-gp transport system.[2,3]

Strong inhibitors of CYP3A4 can cause at least a 5-fold increase in plasma AUC values or more than an 80% decrease in clearance. These include protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir), some macrolide antibiotics (clarithromycin, telithromycin), some azole antifungals (ketoconazole, itraconazole), an antidepressant (nefazodone).[4]

Moderate inhibitors of CYP3A4 may cause at least a 2 fold increase in the plasma AUC values or a 20-50% decrease in clearance. Moderate inhibitors include some calcium channel blockers (verapamil, diltiazem), a macrolide antibiotic (erythromycin), an azole antifungal (fluconazole), an antiemetic (aprepitant), valerian and bergamottin (found in grapefruit juice).[4]

b. Safety and Efficacy

Simvastatin was first approved by the FDA in July 1998 and initially marketed under the trade name Zocor® by Merck and Company, Inc.[1] The first generic versions were approved in December 2006. Simvastatin is listed as a core medication on the current World Health Organization's List of Essential Medicines for the global patient population.[6]

Allergic reactions to HMG-CoA reductase inhibitors are rare, estimated to be 0.1% and the incidence of cross-reactivity is unknown.[2,3.7] Allergic reactions to this drug when taken orally can include face and mouth swelling or severe skin rash. Other adverse reactions of simvastatin when taken in the normal oral dosage range include eczema, headache, edema, myalgia, nausea, gastritis and vertigo. These are most likely dose-related reactions and not anticipated in this study.[2.3]

It is anticipated that the topical application of 1.2 mg of simvastatin (0.15% of the maximum recommended daily dose) will not produce an allergic reaction. In case of an immediate allergic reaction, the subjects will be escorted to the University of Iowa Hospitals and Clinics emergency room, which is in close proximity to the College of Dentistry. In addition, all UI Dental Clinics are equipped with standard emergency supplies/devices should they become necessary, and ACLS trained practitioners will be on site.

Simvastatin is considered a pregnancy category X drug and should not be used in women of childbearing age unless conception is highly unlikely. It is unknown if simvastatin is excreted in breast milk and the drug's use in women who are breast-feeding is contraindicated by the manufacturer.[1-3]

This study will administer a single topical dose of 1.2 mg simvastatin (0.15% of the maximum recommended daily dose) to healthy adult subjects, so we do not anticipate any toxicity issues. Limited information is available on the acute toxicity of statins.[8] If any reaction does occur, supportive and symptomatic treatment will be initiated and the patient will be closely observed and sent to the UIHC emergency room for evaluation and management.

Simvastatin has toxic potential similar to other statins. Increases in serum aminotransferase concentrations (AST [SGOT], ALT [SGPT] more than 3 times upper limits of normal have been reported with statins. These increases are dose related and often transient, resolving in the majority of patients without a change in drug or dose. [2,3,8]

Myopathy occurs in less than 0.7% of patients receiving statins and the risk is dose related and also higher in patients with renal or hepatic disease, uncontrolled hypothyroidism and geriatric patients.[2,3]

A study by Pradeep et al. used subgingival 1.2% simvastatin gel along with scaling and root planning on 60 patients with periodontitis (inflammation of both bone and gums around natural teeth). The study showed that on 1, 2, 4 and 6 month recalls, a statistically significant reduction in bleeding on probing, probing depths, clinical attachment loss, as well as increased bone regeneration.[9]

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V. Summary of Data

Recent research has shown that simvastatin (SMV); a specific competitive inhibitor of 3- hydroxyl- 2- methyl-glutaryl coenzyme A (HMG-CoA) reductase FDA approved for lowering cholesterol, also reduces periodontal inflammation(1,2,3, 4) . Simvastatin is has rare allergic reactions (5,6), and other complications are mainly dose dependent (6) . The use of Simvastatin results in reduction of the clinical parameters of gingival inflammation, like modified Bleeding index (mSBI) probing depth (PD) and mean clinical attachment loss (CAL) in patients with periodontitis (7). Moreover, Simvastatin reduces the crevicular levels of interleukin IL-6 and IL-8 (8) both of which have been associated with implants with peri implant disease (9, 10).
The anti- inflammatory effect of simvastatin on implants with peri-implant mucositis has not yet been tested, thus the purpose of the present study is to assess the anti-inflammatory action of locally delivered simvastatin in subjects with implants affected by peri-implant mucositis (defined as BOP and/or purulence but not signs of mesial/distal bone loss greater than 1mm from the accepted reference point on the implant system).the gel used will be used at 0.15% of the maximal recommended dose thus any adverse effects are not expected.

References

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