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Kosti

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[54] **ANESTHETIC-VASOCONSTRICTOR-ANTIHISTAMINE COMPOSITION FOR THE TREATMENT OF HYPERTROPHIED ORAL TISSUE**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 829,793, July 2, 1969, Pat. No. 3,574,859, which is a continuation-in-part of Ser. No. 742,535, July 5, 1968, abandoned.

[52] **U.S. Cl.** **424/54**

[58] **Field of Search** A61k/7/16; 424/49–58

[56] **References Cited**

UNITED STATES PATENTS

3,514,513	5/1970	Bechtold	424/54
3,574,859	4/1971	Kosti	424/330

FOREIGN PATENTS OR APPLICATIONS

5,885M	3/1968	France	424/54

OTHER PUBLICATIONS

Chemical Abstracts, Vol. 65, entry 9535e, 1966.

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[57] **ABSTRACT**

A composition for the treatment of hypertrophied and hyperplastic oral tissue and the pain phenomena associated with this condition. The composition contains as essential ingredients thereof one or more alkaloids, such as the sympathomimetic amines, which are vasoconstrictors and effect vasoconstriction of the oral tissue, an antihistaminic agent which interfers with the access of histamine to the endothelial cells of the capillary membrane, and a topical anesthetic to relieve pain.

9 Claims, No Drawings

ANESTHETIC-VASOCONSTRICTOR-ANTIHISTAMINE COMPOSITION FOR THE TREATMENT OF HYPERTROPHIED ORAL TISSUE

RELATED APPLICATIONS

This application is a continuation-in-part of my copending application Ser. No. 829,793, filed July 2, 1969, entitled "Process for the Treatment of Hypertrophied Gums" now U.S. Pat. No. 3,574,859, which application is a continuation-in-part of my application Ser. No. 742,535, filed July 5, 1968, now abandoned.

BACKGROUND OF THE INVENTION

Almost all practicing dentists and most physicians, especially those in the field of neurology, otopharyngology, allergy, internal medicine, and related specialties have at one time or another in the normal course of their practice encountered patients exhibiting hypertrophy or hyperplasia of the oral tissue. Enlargement in the size of the oral tissue can be produced either by hypertrophy (increase in the size of each cell) or by hyperplasia (increase in the number of cells) or by both phenomena together. It is usually difficult to differentiate clinically whether tissue is enlarged from hypertrophy or hyperplasia or both, and for this reason the terms are used often interchangeably. Only microscopically may the differentiation be made.

From a clinical point of view, causes of oral tissue enlargement can be considered of two general types of tissue and may be termed "inflammatory hyperplasia" and "fibrous hyperplasia." At the onset of the enlargement there is usually a true inflammatory swelling which microscopically appears as granulation tissue containing varying amounts of polymorphonuclear leucocytes. If the hyperplastic process persists, there is differentiation and proliferation of tissue cells with resultant increase in size or in number of cells; fibrosis of tissue usually takes place, the fibroblasts multiply rapidly, connective tissue is formed, the inflammatory cells disappear and finally the tissue becomes characteristic of dense, avascular tissue. Clinically this transition is characterized by decreasing hyperemia and advancing induration of the hyperplastic tissue. The schematic representation of the pathologic process in transition from initiation of inflammation to fibrosis may be illustrated

inflammation inflammatory hyperplastia
fibrous hyperplasia fibrosis

The chief distinguishing clinical and microscopic signs between the above stages are:

Inflammation is characterized with immediate dilation response of the capillaries to the chemical or physical irritants and the resultant changes in capillary physiology, with increase in the number of open and dilated capillaries supplying the area and increase in capillary filtration of fluids. This state exhibits no cellular change nor increase in size of the tissue and is the beginning of edema. Microscopically, there is increase in number of leucocytes, especially polymorphonuclear neutrophils, in the tissue fluid with no change in the cellular configuration.

Inflammatory hyperplasia is characterized with soft, hyperemic, edematous, or cyanotic, sensitive to touch, easily bleeding tissues which are beginning to enlarge in size clinically. Microscopically, this condition shows

an increase in the number of polymorphonuclear nutrophils and increase in size or number of cells. The number of open or dialated capillaries is also increased. The main feature of this condition is the increase in size of the tissue which is usually not present at the beginning of inflammation.

In fibrous hyperplasia the enlarged tissue is firm, dense, insensitive, resilient, and clinically shows granular appearance. Microscopically, the fibrous tissue is well differentiated with many young fibroblasts present. There is decreased in number of polymorphonuclear neutrophils and open capillaries; the epithelium is slightly hyperplastic and mildly hyperkeratous and hornified. Lamina propria, the submucous layel below the epithelium, shows proliferation of the fibroblasts among which inflammatory cells are present.

Fibrosis is a condition characterized with firm, nodular, fibrous connective tissue. Microscopically, the picture is one of avascular, extremely differentiated bundles of fibrous material with no inflammatory cells or open capillary present, or very few at best, in the tissues.

It becomes apparent now that inflammation and hyperplasia or hypertrophy are different and distinct conditions with inflammation at times, especially at the onset of the pathologic process, being associated with hyperplasia or hypertrophy, inflammation being secondary to hyperplasia or hypertrophy. Hyperplasia or hypertrophy is always manifested in enlargement of tissue whereas inflammation may or may not, and usually is not at the beginning stages, be manifested in enlarged tissues.

Hyperplasia or hypertrophy of the oral tissue may vary in degree from a slight increase in tissue bulk to definitely disfiguring enlargement, and may be grouped into three classes: (1) small enlargement associated with some local irritations on tissues predisposed to fibrous poliferetion, (2) idiopathic fibrous hyperplasia, and (3) those caused by local application or systemic intake of drugs and other chemical agents, such as diphenylhydantoin.

CAUSES OF ORAL TISSUE ENLARGEMENT

A. LOCAL INFLAMMATORY, IRRITATING AND TRAUMATIC FACTORS

1. Poor oral hygiene, accumulations of calculus
2. Malposed teeth, faulty contact points
3. Unusual toothbrush habits
4. Occlusal overfunction
5. Irritation from ill-fitting crowns, clasps, prosthetic or orthodontic appliances
6. Mouthbreathing

B. SYSTEMIC PREDISPOSING FACTORS

1. Endoctrine
   a. Puberty
   b. Menstration and pregnancy
   c. Hypothyroidism and pituitary disfunction
   d. Diabetes
   e. Gonadal disturbances
2. Nutritional
   a. Scurvy
   b. Subclinical nutritional deficiencies of mixed types, including B complex
3. Blood dyscrasias
   a. The Leukemias — particularly monocytic and myelogenous
   b. Polycythemia vera

c. Cooley's amenia
4 Drugs
a. Diphenylhydantoin (Dilantin) sodium
b. Barbituates
5. Idiopathic forms
a. Diffuse fibromatosis of the gums

C. POST EXTRACTION SWELLING

Hypertrophic or hyperplastic oral tissue may be confined to one part of the mouth, such as in the case of post extraction swelling, or it may extend over the entire oral tissue; it may be confined to the gingival margin or enlarge to the extent of the entire oral cavity tissue from the gingiva to the buccal and lingual reflections and to the tonsilar and pharyngeal areas. The initial clinical picture usually exhibits and etiological factor of congestion with edema and hyperemia followed by less of the inflammatory character and thickening and fibrosis of the connective tissue layer if the causes of oral tissue enlargement are allowed to persist.

Many theories have been postulated for the treatment of hyperplasia and hypertrophy of the oral tissue; treatment ranging from the use of diuretics, steroids, anti-inflammatory agents, and other biochemicals with questionable results. The treatment of choice accepted by most clinicians knowledgeable in the art of periodontology is gingivectomy (surgical excission of the hypertrophied or hyperplastic tissue) if the condition is not too severe and complete clearance of teeth (full mouth extraction) if the enlarged tissue interferes with patient's mastication. Heretofore there is no known therapeutic treatment for the cure or control of hyperplasia or hypertrophy, whether associated with diphenylhydantoin sodium or other irritating causative factors, and surgical excission of the enlarged tissue around the teeth is about the only reliable treatment; however, recurrence of hyperplasia or hypertrophy of the oral tissue is certain to reappear after a few months. Complete clearance of the teeth is necessary if the condition is severe. This invention relates to a process and composition for treatment of the enlarged oral tissue which has not been suggested before and is novel in its pharmacodynamic action on the enlarged tissue.

The mode of diphenylhydantoin sodium action on the enlarged tissue is diversified and complicated and certain cytologic actions are not clearly elucidated. However, the resultant enlargement of the oral tissue due to this drug is similar clinically to the enlargement caused by other chemical and physical irritants. For this obvious reason the pharmodynamic action of the drug diphenylhydantoin on the oral tissue is emphasized in this patent application but in no way it should restrict the use of this invention only to the enlargement caused by this drug.

Many studies have been made in regard to the causal relationship of diphenylhydantoin sodium with oral tissue hyperplasia or hypertrophy and the resultant fibrosis of the said tissues with all investigators agreeing that diphenylhydantoin hyperplasia is essentially the result of irritation of the gingival tissue around the teeth by the drug when taken systemically. Hyperplasia or hypertrophy does not occur in the edentulous areas which indicates that the teeth serve as nodi of diphenylhydantoin sodium irritation. Almost all investigators agree that there is no relationship between the amount of diphenylhydantoin intake and the degree of resultant fibrous hyperplasia. Perhaps this fact indicates that the action of diphenylhydantoin on the tissues works on the "all or none" principle — even a small amount of diphenylhydantoin will exert the same irritating effect on the tissues or it will not effect the tissues at all. Therefore, some metabolic changes occur at the tissue level that prevents reabsorption of the diphenylhydantoin by the venous circulation and consequent elimination by the kidneys in the urine, making possible the retention of the diphenylhydantoin sodium complex in the intercellular substance to initiate fibrosis. Hypertrophy and hyperplasia of the oral tissues continues to attract interest in the dental profession especially in periodontology, because of the lack of treatment for this condition and the high percent of occurrence in patients under treatment with diphenylhydantoin for the control of convulsive seizures. The overwhelming gingival oral tissue reaction to this drug necessitates more and more effect on the dental profession to treat this condition as a serious one since heretofore there are no biochemicals available to aleviate this condition thereapeutically; only surgical intervention or taking the drug away from the patient; will provide temporary relief. Complete removal of the teeth will usually result in total elimination of this problem.

Local or systemic irritation, be it chemical such as diphenylhydantoin sodium or physical such as faulty dental restorations and prosthesis, will initially start in edema and gradually progress to fibrosis unless there is some sort of thereapeutic intervention between the two points to prevent the extreme — fibrosis. Edema can, and usually does, precede hypertrophy and hyperplasia and finally fibrosis, but it is not a part of the fibrous process itself, edema being a condition characterized with unusual accumulation of extravascular fluid in the tissues. The causative factor in production of edema is the apparent imbalance between the transudation of fluid from the circulation and its return by the vascular system. Exchange of water and solutes across the capillary membrane occurs by filtration at the artetiolar end of the capillary bed and reverse flow, or absorption, at the venous end. The two most important factors that influence the rate of fluid and solutes across the capillary membrane are tissue tension and capillary permeability.

Diphenylhydantoin sodium was introduced into medicine for symptomatic treatment of epileptic seizures and has become the drug of choice for treatment and control of convulsive conditions due to its non hypnotic effect on the central nervous system. The primary concern of the dental profession to this drug is the effect it has on the oral gingival tissue causing fibrous proliferation which results in fibrous enlargement of the gums. Gingiva is that portion of the oral mucous membrane which surrounds the teeth and is not attached to the underlying alveolar bone. It differs from the mucous membrane in that the epithelium is thicker and hornified to better resist the constant stresses applied to the tissue during mastication. Once the teeth are removed the gingiva ceases to exist; then it becomes attached to the alveolar bone and the epithelium looses its hornification. Some periodontists hold the gingiva to be different tissue from mucous membrane and this differentiation is particularly true in case of fibrous hyperplasia due to dilantin since the drug affects only the gingiva, the tissue around the teeth, and has no effect on the rest of the mucous membrane of the mouth.

Diphenylhydantoin sodium when taken orally, in either flavored or oil vehicle, is partially dissolved in the

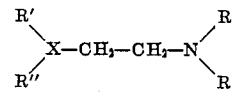
intestine and readily absorbed by the circulation and carried throughout the body, especially in the areas demonstrating high metabolic rate of the tissues such as brain, the hair follicle, the oral gingiva etc. Since the alkalinity of the gastric fluid and of the oral tissues is not high enough to provide complete dissolution of diphenylhydantoin sodium (the pH must be about 11.7 to obtain saturated solution) the unchanged drug, due to its affinity for the tissues in high metabolic rate, finds its way into the extracellular ground substance of the oral gingiva. Once in the ground substance of the gingiva diphenylhydantoin conjugates with glucuronic acid — a metabolite of hyaluronic acid, and in this form it is excreted in the urine. The metabolites found in the urine are conjugated with glucuronic acid. The conjugation reaction involves combination of a metabolite of diphenylhyantoin with some other substance, such as the metabolite of hyaluronic acid - glucuronic acid, followed by the elimination of the resulting conjugate. The dissolved diphenylhydantoin in the ground substance of the oral gingiva is easily dissociated even by weak acids such as carbon dioxide (CO_2), which is the biproduct of metabolism in the tissues whenever the tissues are active in response to a chemical or physical stimulant, with the regeneration of 5,5-diphenylhydantoin. The metabolities of diphenylhydantoin, hydantoic acid and amino acid, by the action of carbon dioxide and the subsequent increase of carbonic acid (H_2CO_3) are regenerated to the 5,5-diphenylhydantoin which is made available for more conjugation with glucuronic acid and therefore binding in the ground substance of the gingiva. This complex, unless eliminated by the urine, will prolong the irritation of the fibroblasts resulting in secretion of collagen for formation of fibrous tissue bundles. It now becomes apparent that diphenylhydantoin in the oral tissues undergoes a vicous cycle of disassociation and regeneration.

Another important characteristic of diphenylhydantoin action in the gingival tissue is that it stimulates liberation of histamine and histamine-like substances and reduces the amount of serotonin. Histamine is found in the cells of most connective tissue and its primary function upon liberation is to vasodialate the arterioles and capillaries thereby bringing more circulation to the injured area and to lower the capillary permeability. Diphenylhydantoin in regard to the capillary membrane has dual effect; initially it stimulates the chemoreseptors of the endothelical cells to secrete histamine and secondly it acts directly on the smooth muscle of the arteries and arterioles causing lowering of membrane permeability. Diphenylhydantoin and histamine both jointly vasodialate the capillaries and increase the capillary membrane permeability allowing diffusion of not only crystalloids but also colloidal substances from the vascular system and into the tissue spaces. This particular action of diphenylhydantoin, vasodilation and alteration of capillary membrane permeability, is essentially the reason why edema is preceding or superimposed condition to fibrosis of the gingiva in diphenylhydantoin therapy.

The outer layer of the mucous membrane — the hornified epithelium, is acidophil in character and the underlying submucous layer is alkaline having pH of approximately 7.4. The alkalinity of the submucous layer, where the ground substances are found, maintains the consistency of the hyaluronic acid gel-like and stable. Alkalinity having pH (or more precisely pOH) of 7.4 is not high enough to keep the diphenylhydantoin sodium present in the tissues in solution but is high enough to prevent disaggregation of hyaluronic acid by the carbonic acid which is produced during tissue metabolism. The viscous consistency of the ground substance keeps the conjugate of the diphenylhydantoin - glucuronic acid bound or captured within the tissue spaces preventing the conjugated complex from being absorbed and subsequently excreted by the venous circulation. Retention of the diphenylhydantoin complex in the ground substance enables the drug to prolong and intensify its stimulatory effect on the fibroblasts resulting in gingival fibrosis.

SUMMARY OF THE INVENTION

This invention pertains to compositions uniquely suited for the treatment of hypertrophied or hyperplastic tissue and the pain associated therewith and which comprise in combination a vasoconstricting alkaloid, an antihistamine, and an anesthetic. The preferred alkaloids for use in this invention are aromatic amines having between about 6 to 10 carbon atoms and aliphatic amines having between about 4 to 7 carbon atoms. The preferred antihistaminics are those of the skeletal structural formula:



wherein X may be oxygen, nitrogen or carbon, and R, R′ and R″ are either aryl, alkyl or aralkyl groups.

The antihistamine should have a minimum molecular weight of about 150, and each of the aryl, alkyl or aralkyl groups should contain in the range of about 2 to 16 carbon atoms. If X in the structure shown above is nitrogen, the resulting compound may be viewed as an ethyleadiamine derivative; if oxygen, as an aminoalkyl ether; and if carbon as an alkylamine. Attached through the carbon, oxygen or nitrogen is the so-called nucleus of the antihistaminic drug. Preferably, this nucleus should consist of a minimum of two aryl or aralkyl groups.

The anesthetics preferred for use in this invention are the amino esters of aromatic acids and aminoacyl amides of aromatic acids. Such compounds will generally contain a maximum of about 26 carbon atoms.

The compositions of this invention should contain the vasoconstricting alkaloidal and antihistaminic each in an amount of about 0.0125 to 5.0 percent by weight based on the weight of the entire composition. When the alkaloid is present in an amount in excess of about 1.0 weight percent then the weight ratio of alkaloid to antihistamine is preferably about 1:05, that is, the amount of antihistamine employed is about half that of the alkaloid. When the concentration of alkaloid is less than about 1.0 percent, then good results have been found using an equal amount of the antihistamine, or an alkaloid to antihistamine ratio of 1:1. These ratios are not absolute and are being set forth only as a guide.

The amount of anesthetic compound employed is, of course, very dependent on the compound selected. For example, tetracaine hydrochloride because of its rapid absorption by the blood and relative toxic reaction

when ingested in large amounts, should be used in minimal amounts. Good results have been achieved in the treatment of pain associated with hyperplasia or hypertrophy with concentrations in the range of about 0.0125 to 5.0 weight percent. On the other hand, benzocaine is relatively free of any side effects and toxic reactions, even when used in high concentrations, and has been used successfully at concentrations in the range of 0.0125 to 20.0 weight percent. Accordingly, the anesthetic compound should be present in an amount of about 0.0125 to 20.0 weight percent based on the weight of the entire composition.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Application of the composition of this invention to the oral tissues, for example, either in mouthwash or toothpaste formulations, will readily penetrate the outer keratinous epithelial layer, break the electrical polarization that exists between the acidic epithelium and the alkaline submucosa and diffuse into the deeper submucous tissues. Brushing or massaging of the gums will express the air bubbles from the epithelium, particularly the air bubbles in the ducts of the secretory glands which extend deep into the submucosa, providing entrance and facilitate absorption of the drug. Once the composition gains entrance in the ground substance of the enlarged tissue its alkalinity will readily neutralize the acid present during the tissue activity resulting in metabolic alkalosis. This neutralization tends to increase the pH of the tissue fluid from 7.4 to about 10–12, depending on the dissociation of the alkaline composition to free hydroxyl group and the amount of carbonic acid present in the tissues for neutralization. Increased alkalinity of the tissue fluid, especially around pH 11–12, results in increased dissolution of diphenylhydantoin either in the conjugated or metabolic form, thusly eliminating the drug by the venous capillary system. The change of tissue acidity affects the hydrolysis of ground substance — hyaluronic acid. On hydrolysis, hyaluronic acid yields equimolar amounts of d-glucoseamine, d-glucuronic acid, and acidic acid and is believed to contain a repeating disaccharide unit comprising N-acetyl glucoseamine glucuronide. Hydrolysis of the glucuronic acid decreases the viscosity of the ground substance freeing the diphenylhydantoin portion from the diphenylhydantoin-glucuronic acid conjugate to be dissolved by the alkaline composition, particularly when the pH is 11–12, and subsequently eliminated by the kidneys. The dissolution of the drug diphenylhydantoin in the tissue fluid will result in decrease of stimulatory effect the drug has on the fibroblasts therefore lessening the chance for fibrosis.

Another important function of this invention, in acid as well as alkaline formulations, is the effect it has on the collagen material of the oral tissues. Collagen is the most abundant protein material in any connective tissue. The fibrous connective tissue contains 63 percent water, and 31.6 percent collagen with small amount of elastin and mucoids. Collagen is a tough, inert, insoluble in water fiber but slowly converted to gellatin by boiling water, dilute acids and alkalies. Diphenylhydantoin, being an irritant, stimulates the fibroblasts to secrete collagenous material which is precipitated outside the cells forming interconnected bundles of the insoluble threads. This process of fiber formation is called fibrosis. The acid or alkaline character of my composition will retard the excretion of the collagen material by the fibroblasts (fibroblasts are germinating cells, or precursors, giving rise to new fibers) thusly minimizing, if not completely eliminating the possibility of fibrosis. The acidity, or the alkalinity, of the composition of this invention will gradually convert the newly formed collafenous fiber into more easily reactive gelatin which is readily digestable by tissue enzymes and removed by the circulation. The composition of this invention will further gradually break the bonds linking parallel polypeptide chains to single peptide chains of gelatin. The compensatory alkalinity of the tissue fluid during the treatment with the compositions of this invention is opposed by the buffering system of the intercellular fluid and the excess alkalinity will be neutralized by the carbonic acid of the tissue fluid in order to keep the proper bicarbonate/carbonic acid ratio 20:1 at pH 7.4.

The vasoconstrictor component of the compositions of this invention, such as the sympathomimetic amine phenylephrine hydrochloride, upon entrance into the ground substance of the tissue acts directly on the chemoreseptors of the endothelical cells of the capillary membrane. It causes swelling of the cells thereby decreasing the lumen of the capillaries and restoring the patency of the membrane. This vasoconstriction of the arterioles and capillaries (the venuoles are not affected to an appreciable degree) stops the escape, or leakage, of the larger molecules of proteins and the unchanged diphenylhydantoin sodium from the circulation and into the tissues thereby restoring the normal balance of vascular and extravascular fluid and electrolytes exchange. The prevention of diphenylhydantoin escape into the tissues and the subsequent elimination of the metabolites of diphenylhydantoin from the tissues by the venous circulation, reduces the amount of the drug available for stimulation of the fibroblasts to secrete collagenous material and form the insoluble fibers. Decrease of diphenylhydantoin metabolites from the tissues liberates the calcium ions from the complex diphenylhydantoin-calcium conjugate allowing it to return to the cement material of the endothelial cells of the capillary membrane and active cells. The vasoconstriction of the capillaries deprives the hypertrophied or hyperplastic cells from nutrition and subsequent decrease either in the size of the cells themselves or the number of cells. In hypertrophy or hyperplasia, especially at the initial stages, there is increase in the number of capillaries which is evident under microscopic examination. The vasoconstrictor, for example, phenylephrine hydrochloride, by virtue of its action on the endothelial cells of the capillary membrane decreases and sometimes virtually eliminates, particularly the newly formed capillaries, from being able to supply the hypertrophied or hyperplastic cells with nutritious materials therefore practically "starving" the new cells to death. This event is especially true before fibrosis is allowed to proceed.

The antihistamine, as for example, antazoline hydrochloride, upon entrance into the ground substance of the oral tissues prevents the access of histamine liberated by the excitatory effect of diphenylhydantoin on the tissue cells, to its receptor site in the endothelial cells of the capillary membrane and thereby blocks the response of the effector cell to the amine. The antihistamine possesses no pharmacodynamic action; it does not react to have antagonistic action with the hista-

mine. The antihistamine occupies the receptor site of the endothelial cells without causing a cellular response. This characteristic of the antihistamine used in my formulations potentiates the physiological antagonism of the sympathomimetic amine to the effects of the histamine on the capillary membrane resulting in more profound vasoconstriction. The pharmacodynamic action of, for example the phenylephrine hydrochloride - antazoline hydrochloride combination is more intense than that produced by either agent used alone. Phenylephrine hydrochloride gives a very rapid onset of reduction of local oral tissue swelling while antazoline hydrochloride prolongs the reduction in the size of the oral tissue by its direct action on the capillary membrane.

The most beneficial advantage of vasoconstrictor-antihistamine combination is virtually elimination of any side effects produced by either agent used alone. The sedative effect of the antihistamine will counteract the stimulant effect of the sympathomimetic agent.

In obtaining the new and novel treatment, this invention makes use of certain alkaloid compounds or substances which are sympathomimetic amines, and which possess among other properties those of serving as decongestants or vasoconstrictors effecting shrinkage of the overgrown oral tissues. Preferred are aromatic amines having been 6 to 10 carbon atoms, and aliphatic amines having a total of between 4 to 7 carbon atoms. Some examples of useful compounds are:

A. Aromatic Nucleus:

I. Unsubstituted:

1. Phenylethylamine — $C_6H_5.CH_2.CH_2.NH_2$
2. Phenylethanolamine — $C_6H_5.CHOH.CH_2.NH_2$
3. Amphetamine — $C_6H_5.CH_2.CHCH_3.NH_2$
4. Dextro-amphetamine — Isomer of amphetamine.
5. Methamphetamine — $C_6H_5.CH_2.CHCH_3.NHCH_3$
6. Mephentermine — $C_6H_5.CH_3.CHCH_3H.CH_3$
7. Phenylpropanolamine — $C_6H_5.CHOH.CHCH_3.NH_2$
8. Ephedrine — $C_6H_5.CHOH.CHCH_3.NHCH_3$
9. Naphazoline — $C_{10}H_7.CH_2C{-}NH{-}CH_2$ (N——CH$_2$)
10. Phenylpropylmethylamine — $C_6H_5CHCH_3.CH_2.NHCH_3$

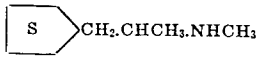
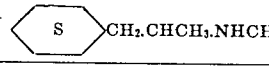
II. Monosubstituted:

1. Tyramine — $HO.C_6H_4.CH_2.CH_2.NH_2$
2. 5-hydroxytriptamine
3. Synephrine — $HO.C_6H_4.CHOH.CH_2.NHCH_3$
4. Phenylephrine — $C_6H_4OH.CHOH.CH_2.NHCH_3$
5. Hydroxyamphetamine — $HO.C_6H_4.CH_2.CHCH_3.NH_2$
6. Paredrinol — $HO.C_6H_4.CH_2.CHCH_3.NHCH_3$
7. Methoxyphenamine — $CH_3O.C_6H_4.CH_2.CHCH_3.NHCH_3$

III. Disubstituted:

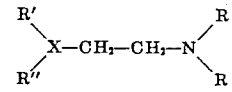
1. Epinine — $(HO)_2.C_6H_3.CH_2.CH_2.NHCH_3$
2. Levarterenol — $(HO)_2.C_6H_3.CHOH.CH_2.NH_2$
3. Epinephrine — $(HO)_2.C_6H_3.CHOH.CH_2.NHCH_3$
4. Methoxamine
5. Oxymetazoline — 6-5345-butyl-3(2-imidazoline-2-yl methyl)2,4-dimethylphenol.

B. Aliphatic Nucleus:

1. Tuaminopheptane — $CH_3(CH_2)CHCH_3.NH_2$
2. Methylhexaneamine — $CH_3CH_2.CHCH_3.CH_2.CHCH_3.NH_2$
3. Cyclopentamine —  $CH_2.CHCH_3.NHCH_3$
4. Propylhexedrine —  $CH_2.CHCH_3.NHCH_3$

Ephedrine sulfate, phenylephrine hydrochloride, cyclopentamine hydrochloride, methylhexaneamine hydrochloride, and oxymetazolin hydrochloride, are the preferred sympathomimetics because they can be employed in aqueous, oil and alcohol solutions and in mixtures thereof. They are readily available, relatively stable, do not decompose readily to light, heat or air. They can be boiled for sterilization, have a long duration of action and are substantially free of aftercongestion.

The antihistamine employed in the compositions of this invention may be any of the commercially available compounds, the majority of which have the structural formula:



in which it is apparent that core of the structure is a substituted ethylamine, which is also present in histamine. It is most likely that it is this portion of the molecule which competes with histamine for cell receptors. In most instances, the ethylamine grouping is present as a straight chain, but in a few it is part of a ring structure.

Nearly always, the substituted ethylamine of histamine antagonists is teritary, with the activity of secondary or primary amines being greatly attenuated. Furthermore, optimal substituent groups on the amine in most senses is N-dimethylalkyl. Generally N-diethyl compounds are less active and more toxic. Occasionally, the substituted amine is incorporated in a heterocyclic ring without loss of activity. Quarternization of the tertiary amine diminishes but does not abolish activity.

As noted earlier in this application, X in the structure may be oxygen, nitrogen or carbon and it is not possible to make any great distinction between these with respect to antihistaminic activity. In addition, the following can be associated with antihistaminic activity; aminoketones, secondary aminoalcohols, alkylesters and haloalkylamines.

Attached through the carbon, oxygen or nitrogen is the socalled nucleus of the antihistamine which should consist of a minimum of two aryl or aralkyl groups or their equivalent in a polycyclic ring system, with the nucleus having a minimum molecular weight of 150.

Some of the typical antihistaminics are the hydrochlorides, citrates, maleates and succinates such as:

antazoline hydrochloride	$C_{17}H_{19}N_3.HCL$
tripelennamine hydrochloride	$C_{16}H_{21}N_3.HCL$
tripelennamine citrate	$C_{16}H_{21}N_3.(C_6H_8O_7)2$

thonzylamine hydrochloride	$C_{16}H_{23}CLN_4O{\cdot}HCL$
methapyriline hydrochloride	$C_{14}H_{19}N_3S{\cdot}HCL$
methapheniline hydrochloride	$C_{15}H_{20}N_2S{\cdot}HCL$
pyrilamine maleate	$C_{17}H_{23}N_3O{\cdot}C_4H_2O_3$
chlorphenamine maleate	$C_{16}H_{19}CLN_2{\cdot}C_4H_2O_3$
chlorothen	$C_{14}H_{16}CLN_3S$
pheniramine	$C_{16}H_{20}N_2$
pheniramine maleate	$C_{16}H_{20}N_2{\cdot}C_4H_2O_3$
chlorcyclizine hydrochloride	$C_{18}H_{21}CLN_2{\cdot}HOL$
diphenhydramine hydrochloride	$C_{17}H_{21}NO{\cdot}HCL$
doxylamine succinate	$C_{21}H_{28}N_2O_5$
phenyltoloxamine citrate	$C_{17}H_{21}NO$
diphenylpyraline hydrochloride	$C_{19}H_{23}NO{\cdot}HCL$
phenindamine tartrate	$C_{19}H_{19}N$
thenyldiamine hydrochloride	$C_{14}H_{19}N_3S$

Antazoline hydrochloride, diphenhydramine hydrochloride thonzylamine hydrochloride, and chlorphenamine maleate are the preferred antihistaminics in this invention due to their lack of incidence of side action and low tissue irritancy; however, any of the above named antihistaminics may be used in this invention without lowering the potency and the effectiveness of the fluid and toothpaste compositions.

As indicated above, this invention is concerned with reducing the size of enlarged oral tissue and alleviation of pain associated with hyperplasia. The reduction in size of the tissue is effected by the action of the sympathiomimetic amine directly on the chemoreseptors of the endothelial cells of the capillary membrane causing vasoconstriction of the capillaries and arterioles, and by the competitive inhibition of the antihistaminic drug on the histamine by occupying the receptor site of the endothelial cells without causing cellular response. The pain is alleviated by the action of the anesthetic or the analgesic on the nerve endings of the enlarged tissue.

The anesthetic employed must be capable of blocking nerve conduction when applied locally to nerve tissue and should not be irritating and must produce anesthesia without causing damage to nerve structure.

Generally, topical anesthethics are weak organic bases which are poorly soluble in water. However, these bases will react with acids, particularly hydrochloric acid, to form water soluble salts which are suitable for topical application. There is abundant evidence to show that the neutralization of the acid salt and the liberation of the free base are essential for anesthetic activity.

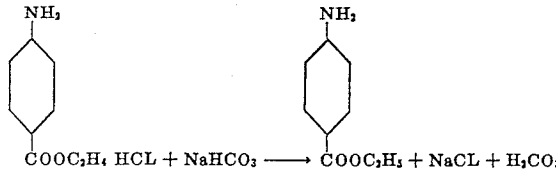
Little is known regarding the pharmacodynamics of the topical anesthetics. The drug appears to have a selected affinity for voluntary muscle nerves, proprioseptors, cold and hot, and pressure nerves, etc. The anesthetic apparently passes through the neurilemma and into the axon where it combines with the nerve fiber chemically, altering its function of conductivity. The topical anesthetic will also affect the synaptic transmission of nerve impulses possibly by affecting the metabolism of acetylcholine or competing with it in an enzyme system. The topical anesthetics are fat-soluble and to make the alkaloids water soluble they are dispensed as acid salts.

Upon application of the composition of this invention on the oral tissue, the anesthetic salt undergoes three separate but interdependent stages: (1) neutralization, (2) hydrolysis, and (3) resynthesis. NEUTRALIZATION:

The neutralization of the anesthetic salt, which is strongly acid in reaction, is affected by the sodium bicarbonate ($NaHCO_3$) present in the tissue. The anesthetic salt is hydrophilic in nature and reacts with the sodium bicarbonate from the tissue raising the pH of the environment to over 7.5. The reaction may be represented as follows:

$$\underset{\text{acid salt}}{R':N'HCL} + NaHCO_3 \longrightarrow \underset{\text{free base}}{RN} + NaCL + H_2CO_3$$

or as in case of Benzocaine



The ability of the undissociated free base to penetrate cellular membranes is the first requisite for anesthetic activity. Once the neutralization is satisfied the anesthetic is further dissociated to cationic form which reacts readily with the intracellular constituents of the nerve fiber, principally the lipids. This ionization reaction may be represented as

$$RN + HOH \rightarrow RNH^+ + OH^-$$

where now the free base is in form of cations and has the tendency to escape from solution into the state of absorption on cellular constituents. Once the equilibrium of the neutralization reaction is reached, the free anesthetic base becomes hydrophobic and lipophilic to form a temporary lebile union with the axoplasm. This complex temporary lebile structure interferes with breakdown of acetylchloline by the enzyme cholinesterase. Acetylcholine is a chemical mediator present in the nerve tissue as a non diffusable, physiologically inactive form and not susceptible to hydrolysis. In this form it is referred to as a procursor or bound acetylcholine which is found in the individual nerve fibers and at the synapse. Upon stimulation of a nerve to conduct an impulse, acetylcholine is liberated by each individual cell of the nerve fiber to conduct and transmit an impulse from one cell to another all along the axon and across the myoneural junction to the muscle affected by that particular nerve causing excitation. To prevent continuous and rapid firing of stimuli along the axon, acetylcholine is almost immediately destroyed by the enzyme acetylcholine esterase, or simply cholinesterase. This complex biochemical reaction may be represented

$$\underset{\text{Acetylcholine}}{CH_3{\cdot}C{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}N^+(CH_3)_3} \xrightleftharpoons[\text{+ CoA acetate}]{\text{ACH-esterase + HOH}} \underset{\text{Choline}}{HOCH_2{\cdot}CH_2{\cdot}N^+(CH_3)_3} + \underset{\text{Acetic acid}}{CH_3COOH}$$

OH^- OH^-

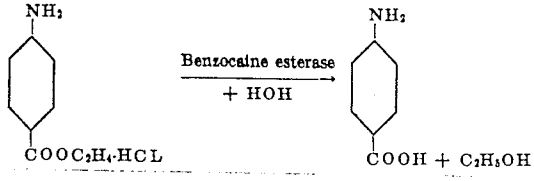
This reaction is reversable under normal tissue conditions so that subsequent to the stimulation of the nerve fiber, resynthesis of the end products (choline and acetic acid) to the original substance (acetylcholine) occurs in the presence of enzyme choline acetylase and coenzyme acetase.

The free base, which has now penetrated the neurilemma, reacts directly with potassium and magesium ions in the axoplasm preventing the resynthetization of acetylcholine by denying enzyme choline acetylase its activators. The potassium and magnesium ions are necessary to be present in the substrate for the enzyme choline acetylase to be effective. They are referred to as activators. The enzyme choline acetylase catalyses the transfer of acetyl radical from CoA-acetate to choline which is essential for synthesis of acetylcholine. The free anesthetic base in effect acts as an anticholinesterase by the nature of its interference with cholinesterase in breaking down of acetylcholine re-

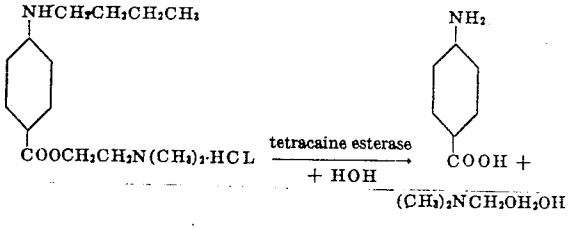
sulting in prolonged parasympathetic activity. The anesthetic effect will last as long as the union of the free base and the lipid constituents of the axoplasm is left intact or until the enzymatic accumulation in the nerve tissue, the substrate, is concentrated enough to reverse the reaction and change the direction of the equilibrium to the side of the hydrolysis of the drug.

HYDROLYSIS:

Following the absorption, benzocaine and tetracaine are hydrolysed to ethanol and para-aminobenzoic acid and dimethylaminoethanol and para-amino benzoic acid respectively by the enzyme esterase. The hydrolysis reaction within the nerve axoplasm of benzocaine hydrocloride may be represented as



and the hydrolysis of tetracaine hydrochloride may be represented as

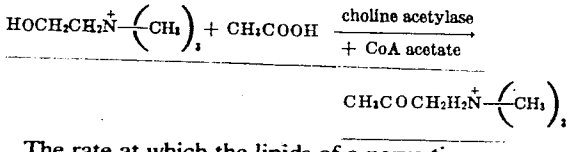


The biproducts ethanol and para-amino benzoic acid and dimethylaminoethanol and para-amino benzoic acid of benzocaine and tetracaine respectively, are inert compounds and are removed from the tissue by routine channels of elimination. Eighty percent of para-amino benzoic acid is excreeted in the urine and only 30 percent of ethanol and dimethylaminoethanol is recovered in the urine. The low percentage of the recovered alcohols is due to some being changed to aldehyde or ketone by the nerve cell protein and as such carbohydrates are used by the nerve as a source of energy during transmission of an impulse. The respiratory quotient of a metabolizing nerve is very close to 1.0 which suggests that the nerve is utilizing carbohydrates almost exclusively.

The unhydrolysed benzocaine and tetracaine which enter the blood circulation are rapidly detoxified chiefly by the liver and excreted in the urine by the kidneys.

RESYNTHESIS

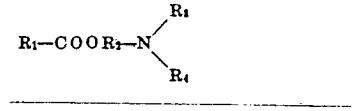
This phase deals primarily with resynthesis of the enzyme acethylcholine and the return of the nerve constituents to their normal biochemical equilibrium. Clinically, this is the so-called wearing-off period; chemically, it may be represented as



The rate at which the lipids of a nerve tissue are exchanged are relatively slow in comparasion to that of an active organ such as the liver. Tracer studies with deutorium indicate that while 50 percent of the liver fats may be exchanged in 24 hours, only 20 percent of the fat in nerve tissue is replaced in 7 days. This explains the slow hydrolysis of the anesthetic solution in the nerve tissue and its rapid destruction in the liver.

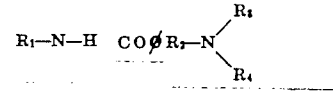
Instillation of the composition of this invention in either fluid, paste, or tablet form on the oral tissue will have three distinct and yet coordinated functions. (1) the action of the sympathomimetic amine on the endothelial cells of the capillary membrane resulting in vasoconstriction of the said capillary membrane, (2) the action of the antihistaminic on the histamine in the tissues potentiating the effect of the sympathomimetic amine, and (3) the action of the analgesic agent on the nerve fibers of the affcted hyperplastic or hypertrophied and enlarged oral tissue resulting in blockage of the sensory pain impulses and temporary anesthesia. In addition, the vasoconstriction caused by the sympathomimetic amine will prolong the effect of the topical anesthetic due to the resultant decrease in the absorption of the anesthetic drug. This decrease in the absorption of the anesthetic drug is significant since it will require less amount of the anesthetic to obtain the necessary degree of analgesia, decreases the possibility of toxicity, and prolongs the duration of the analgesia.

The topical anesthetics, which are analgesic, used in this invention are generally secondary or tertiary amino esters of aromatic acids, or secondary or tertiary aminoacyl amides of aromatic acids, the ester type having the benzoic acid, parabenzoic acid or meta-benzoic acid as the nucleus of the structure with aromatic or aliphatic substutions of up to 14 carbons atoms each, and the amide type having the xylene or toluene radical as the nucleus of the structures with, again, aromatic or aliphatic substitutions of up to 14 carbons each. The ester type has the general structural formula:



where R_1 with its carboxyl group may be benzoic acid, para-amino benzoic acid, or meta-amino benzoic acid and R_2, R_3 and R_4 are aromatic or aliphatic radicals of up to 14 carbon atoms each.

The amide type has the general structural formula



where R_1 is either xylene or toluene substituted and R_2, R_3 and R_4 are aromatic or aliphatic radicals of up to 14 carbon atoms.

Some of the typical local and topical anesthetics employed today are the synthetic products such as

cocaine hydrochloride	$C_{17}H_{21}NO_4$·HCL
procaine hydrochloride	$C_{13}H_{20}N_2O_2$·HCL
lidocaine hydrochloride	$C_{14}H_{22}N_2O$·HCL
mepivacaine hydrochloride	(Carbocaine hydrochloride)
	$C_{15}H_{22}N_2O$·HCL
prilocaine hydrochloride	(Citanest hydrochloride)
	$C_{13}H_{19}N_2O$·HCL
pyrrocaine hydrochloride	$C_{14}H_{20}N_2$·HCL
butethamine hydrochloride	(Monocaine hydrochloride)
	$C_{13}H_{20}N_2O_2$·HCL
metabutethamine hydrochloride	(Unicaine hydrochloride)
	$C_{13}H_{20}N_2O_2$·HCL
isobucaine hydrochloride	$C_{15}H_{23}N_2O$·HCL
tetracaine hydrochloride	(Pontocaine hydrochloride)
	$C_{15}H_{24}N_2O_2$·HCL
propoxycaine hydrochloride	(Ravocaine hydrochloride)
	$C_{16}H_{26}N_2O_3$·HCL

-Continued

benzocaine	$C_9H_{11}N_2O$
BUTACAINE SULFATE	(Butyn Sulfate) $C_{18}H_{30}N_2O_2 \cdot H_2SO_2$
dyclonine hydrochloride	(Dyclone hydrochloride) $C_{18}H_{27}NO_2 \cdot HCL$
dibucaine hydrochloride	(Nupercaine hydrochloride) $C_{20}H_{29}N_3O_2 \cdot CHL$
piperocaine hydrochloride	(Neothesin hydrochloride) $C_{16}H_{23}NO_2 \cdot HCL$
phenacaine hydrochloride	(Holocaine hydrochloride) $C_{18}H_{22}N_2O_2 \cdot HCL \cdot H_2O$
diperodon hydrochloride	(Diothane hydrochloride) $C_{22}H_{27}N_3O_4 \cdot HCL$
dimethisoquin	(Prulargan, Quinisocaine, Quotane, Prulargin) $C_{17}H_{24}N_2O$
naepane	(Naepaine, Amylsine) $C_{14}H_{22}N_2O_2$

The combination of Benzocaine and Tetracaine hydrochloride was found to be most effective in producing topical anesthesia due to Tetracaine's high activity even in very low concentrations and its rapid onset of anesthesia and Benzocaine's low solubility. There is a group of local or topical anesthetics characterized by the fact that its members are poorly soluble in water, and Benzocaine is one of them. Due to its insolubility, the compounds are not absorbed with sufficient rapidity to be toxic and therefore can be applied directly to the wounds and open surfaces on the mucous membrane. For the same reason they remain localized at the site of application for long periods of time, which accounts for their sustained anesthetic action. In my formulations Tetracaine will produce a very rapid onset of anesthetic action even in concentrations of less than 1.0 percent without any toxic effects and Benzocaine will give a sustained anesthetic effect. The vasoconstrictor phenylephrine hydrochloride adds to the sustained actions of both topical anesthetic agents by prolonging the absorption of the drugs by the circulation.

Any one, or any combinations, of the above named topical anesthetics may be used in lieu of Benzocaine and Tetracaine to produce topical analgesia without departing from the intent and the scope of the invention; however, the solubility, toxicity, potency, and activity of each individual drug must be considered in the selection of the topical anesthetic.

Some other compounds that may be employed as topical anesthetics are some aromatic alcohols such as Benzyl Alcohol and Saligenin; quinine salts such as Quinine and Urea Hydrochloride; chlorobutanol; ethyl chloride; phenolic compounds such as amyltricresol, parachlorophenol, cresol, creosote, eugenol, guaiacol, phenol, thymol and other related organic compounds.

The compositions of this invention may be fluid, paste, spray or tablet preparations of the vasoconstrictor-antihistamine-analgesic combination. The following examples illustrate such preparations.

EXAMPLE I

Each cc of a fluid composition contains:

phenylephrine hydrochloride U.S.P.	10.00	mg	1.00	%
diphenhydramine hydrochloride U.S.P.	5.00	mg	0.5	%
benzocaine hydrochloride	50.00	mg	5.00	%
tetracaine hydrochloride	10.00	mg	1.00	%
benzalkonium chloride	2.00	mg	0.2	%
saccharine sodium	0.18	mg	0.018	%
spearmint oil	0.15	mg	0.015	%
sodium chloride	3.90	mg	0.39	%
sodium thiosulfate	0.20	mg	0.02	%
alcohol	80.00	mg	0.8	%
distilled water q.s. 1 cc				

This composition is intended to be used as a mouthwash, rinse, or gargle. The patients are instructed to swish about one to one half fluid ounce of the solution in the mouth for approximately 1 to 2 minutes and expel the remainder. Rinsing with water after usage is discouraged for at least 1 hour for the obvious reason of better absorption of the drug. The procedure should be repeated two to four times daily, depending on the severity of the condition, or as recommended by the physician or dentist.

EXAMPLE II

Each cc of a spray composition contains:

phenylephrine hydrochloride	10.00 mg	1.00 %
diphenhydramine hydrochloride	5.00 mg	0.5 %
benzocaine hydrochloride	10.00 mg	1.00 %
tetracaine hydrochloride	5.00 mg	0.5 %
zirconium oxide	10.00 mg	1.00 %
menthol	0.09 mg	0.009 %
camphor	0.98 mg	0.098 %
calamine	9.80 mg	0.98 %
isopropyl alcohol	95.00 mg	9.5 %
methylparaben	0.80 mg	0.08 %
propylparaben	0.20 mg	0.02 %
propellants	873.33 mg	87.33 %

This cool, soothing, composition is intended to be used as a spray. The patients are instructed to spray the affected area approximately six times (1 cc) with the solution and are discouraged to rinse with water for approximately 1 hour after usage. The procedure should be repeated two to four times daily, depending on the severity of the condition, or as recommended by the physician or dentist.

EXAMPLE III

Each tablet or cone of the composition contains:

phenylephrine hydrochloride	50.00 mg	1.00	%
diphenhydramine hydrochloride	25.00 mg	0.5	%
benzocaine hydrochloride	750.00 mg	15.00	%
tetracaine hydrochloride	20.00 mg	0.4	%
sodium chloride	19.50 mg	0.39	%
glucose	1.00 mg	0.02	%
polyethylene glycol 6000	3000.00 mg		
dl-leucine q.s. 5 Gm			

This water soluble tablet or cone composition is intended to be used as an insert or a packaging of the affected areas. In post extraction and post surgical cases the patient is instructed to insert the tablet or the cone into the tooth socket or the incission for the effective treatment of hypertrophy or hyperplasia and tissue enlargement and the associated pain. The procedure should be repeated four times daily or as required for pain.

EXAMPLE IV

Each one Gram (1 Gm) of a cream composition constains:

phenylephrine hydrochloride	10.00 mg	1.00	%
diphenhydramine hydrochloride	5.00 mg	0.5	%
benzocaine hydrochloride	20.00 mg	2.00	%
tetracaine hydrochloride	10.00 mg	1.00	%
zirconium oxide	10.00 mg	1.00	%
menthol	7.00 mg	0.7	%
camphor	3.00 mg	0.3	%
methylparaben	0.80 mg	0.08	%
propylparaben	0.20 mg	0.02	%
isopropyl alcohol	88.00 mg	8.8	%

This cool, soothing, cream composition is intended to be used as a topical application of the affected areas. The patients are instructed to apply the cream on the affected areas two to four times daily, depending on the severity of the condition, or as recommended by the physician or dentist. The base of this composition is very slightly soluble in water for better penetration of the drug in the affected areas.

EXAMPLE V

Each one Gram (1 Gm) of a cream composition contains:

phenylephrine hydrochloride	10.00 mg	1.00	%
diphenhydramine hydrochloride	5.00 mg	0.5	%
benzocaine hydrochloride	100.00 mg	10.00	%
tetracaine hydrochloride	10.00 mg	1.0	%
oxyquinoline sulfate	10.50 mg	1.05	%
menthol	4.80 mg	0.48	%
ichthamol	10.00 mg	1.00	%
zinc oxide	10.00 mg	1.00	%
petrolatum, lanolin q. s.			

This cool, soothing, water insoluble cream composition is intended for use as a topical applicant on the affected areas. The patients are instructed to apply the cream on the affected areas two to four times daily, depending on the severity of the condition, or as recommended by the physician or dentist. Rinsing with water after use is discouraged for about 1 hour for better absorption of the drug by the tissues.

EXAMPLE VI

Each 90 cc (3 fl. oz.) of a toothpaste composition contains:

phenylephrine hydrochloride	900.00 mg	1.00%
diphenhydramine hydrochloride	450.00 mg	0.5 %
benzocaine hydrochloride	4,500.00 mg	5.00%
tetracaine hydrochloride	900.00 mg	1.00%
glycerin (glycerol)!	1,000.00 mg	1.10%
propylene glycol	18,000.00 mg	19.80%
mineral oil	1,000.00 mg	1.10%
peppermint oil	300.00 mg	0.33%
saccharine sodium solution 50%	100.00 mg	1.10%
sodium lauryl sulfate	1,500.00 mg	1.65%
dicalcium phosphate (in fine powder)	54,000.00 mg	59.40%
sodium carboxymethylcellulose 120 H	900.00 mg	1.00%
methylparaben	100.00 mg	0.11%
sodium thiosulfate	20.00 mg	0.02%
distilled water q.s. 90 cc.		

This composition is intended to be used as a toothpaste. The patients are instructed to squeeze approximately 1 inch of the toothpaste on a toothbrush and gently massage the affected areas as teeth are brushed for about 1 to 2 minutes, and expel the remainder without rinsing the mouth for about 1 hour. The procedure should be repeated three to four times daily, depending on the severity of the condition, or as recommended by the physician or dentist.

The described tablet or cone composition of Example III was used by the inventor, Carl M. Kosti, D.D.S., in the treatment of 10 patients who had hyperplasia or hypertorphy associated with severe pain as a result of extraction of impacted molars. The cone was inserted into the tooth socket immediately after the extractions on five patients and other five patients were used as control group without medication. The patients under treatment with the drug exhibited no hypertrophy or hyperplasia nor was there any pain associated with the post extraction healing of the tooth socket. The control patients exhibited hypertrophy and hyperplasia on the second day post extraction and pain after the first day. On the third day the control patients were placed on therapy with this invention. They were instructed to place the cone into the tooth socket three times daily and were examined each day for one week. The second day of therapy showed significant reduction in size of the traumatized area and almost absence of pain. On the fifth day of therapy the tissue returned to its pre-extraction, normal size without any pain and the patients were dismissed.

In the foregoing examples, glycerin is used as a sweetening agent or vehicle in place of syrups (syrups are contraindicated in toothpastes due to their high carbohydrate content increasing the incidence of tooth decay) and to maintain the consistency of the toothpaste; propylene glycol is used in the formulation as a diluent and binder and may serve as a substitute for glycerin and alcohol; methylparaben is used as a preservative due to its inhibitory action on the microorganisms; saccharine sodium solution is used as a sweetening agent; pepermint oil is one of the many essential oils that can be used as flavoring agents; mineral oil in this invention is used as a diluent; sodium lauryl sulfate is used as an emulsifier and foaming agent; dicalcium phosphate, due to its fineness is employed as an abrasive; sodium carboxymethylcellulose is used as an emulsifier and thickening and suspending agent; and distilled water in the context of this invention is used as a vehicle and dilutant.

EXAMPLE VII

A toothpaste was prepared as in Example VI with the addition of the following ingredient:

Stannous flouride 1 ppm (one part per million)

Stannous flouride and other flouride derivatives such as sodium flouride, monoflourophosphate, potassium flouride, etc. are effective anticariogenic substances used in toothpaste to control tooth decay by their action on the protein portion of the enamel and dentin making the said protein portions harder and subsequently more resistent to acid desolution and bacterial invasion. Such substances are generally used in concentrations of 0.25 to 10 ppm.

Other preservatives and their concentrations that can be used in lieu of methylparaben in the context of this invention are:

sodium bisulfite	0.05	– 0.25	weight percent
sodium benzoate	0.05	– 0.25	do.
sodium thiosulfate	0.01	– 0.20	do.
chlorobutanol	0.01	– 1.0	do.
thimerosal	0.001	– 0.01	do.
phenylmercuric acetate	0.001	– 0.01	do.

The following substances are wetting and foaming agents which can be used to reduce the surface tension of the mucous membrane to improve penetration of the basic active ingredients. Except as noted, one or more can be used in place of the sodium lauryl sulfate of Example VI or as added ingredients in the formulations:

*benzalkonium chloride
*benzethonium chloride
thonzonium bromide
sulfocolaurate
dioctyl sodium sulfosuccinate
sodium alkyl sulfoacetate
sodium lauryl sarcocinate
*cetyl pyridinium chloride
sodium tetradecyl sulfate

*These compounds are preferably not used in same formulations with other soaps and detergents. They are cathionic surface active agents and in solution inactivate anionic surface active agents, for example soaps and detergents such as sodium lauryl sulfate. These compounds are also mildly antiseptic and bacteriostatic. Hence, they can be used where a preservative is employed.

The essential components of the toothpaste composition of this invention are the alkaloid and the antihistamine each in a concentration of from about 0.0125 to 5.0 weight percent, the anesthetic in an amount of from about 0.0125 to 20 weight percent, an alkaloid preservative in an amount from about 0.001 to 0.5 weight percent, a suspending agent in an amount of about 0.002 to 2.0 weight percent and from about 1 to 21 weight percent of a moisture retainer, with the balance of the composition being water.

Suitable compounds for use as the alkaloid preservative are methylparaben, propylparaben, sodium bisulfate, sodium benzoate, sodium thiosulfate, chlorobutanol, thimersol and phenylmercuric acetate. Preferred suspending agent materials are sodium carboxymethylcellulose, methylcellulose, bentonite, acacia, sterculia gum and tragacanth. Preferred moisture retainer materials are glycerin, propylene glycol, sorbital, polyethylene glycol, diethylene glycol monoethyl ether, polysorbate, monolaurate and polyoxyethylene sorbitan.

While the toothpaste composition of this invention need only employ the alkaloid, antihistamine, anesthetic preservative, suspending agent and moisture retainer components, excellent results have been obtained from a more balanced toothpaste formulation which included, in addition to the above components, from about 0.01 to 0.5 weight percent of a sweetening agent, about 0.01 to 1.5 of a foaming agent and about 30 to 65 weight percent of an abrasive.

Examples of abrasive materials which can be used in this invention are pumice, calcium carbonate, stannic oxide, dibasic calcium phosphate, magnesium carbonate and tribasic calcium phosphate. Suitable sweeteners include sodium cyclamate, calcium cyclamate, saccharines and sodium saccharine. Suitable foaming agents include sodium lauryl sulfate, sodium tetradecyl. sulfate, sodium lauryl sarcocinate, dioctyl sodium sulfosuccinate sulfocolaurate, thonzonium bromide, methyl benzathonium chloride, dichlorobenzalkonium chloride, dichlorobenzathonium chloride, and cetyl pyridinum chloride.

Because the vasoconstrictor-antihistamine-anesthetic combination of this invention has a long duration of action, administration in the morning and at bedtime is generally recommended. Some patients may require treatment more frequently, especially where hypertrophy or hyperplasia or tissue enlargement is of severe nature or where more rapid reduction in size of tissue is indicated. In that case typical application of the drug three times a day is suggested: in the morning, at noon, and at bedtime.

The suggested dosage of the vasoconstrictor is between 0.0125 percent and 5 percent and that of the antihistamine ranges from one half to equal concentration of the vasoconstrictor employed. The ratio of vasoconstrictor to antihistamine in a typical example of this invention is either 1:0.5 or **1:1.** The concentration of anesthetic should be between 0.0125 percent and 20.0 percent by weight of the composition.

The recommended dosages of the vasoconstrictors are:

For adults and children over six years of age:

Severe hypertrophy or enlargement		
Fluid composition	0.5	– 2.5%
Paste composition	1.0	– 5.0%
Mild to moderate hypertrophy or enlargement		
Fluid composition	0.125	– 0.5%
Paste composition	0.25	– 0.75%
Daily oral hygiene and prophylaxis		
Fluid composition	.015	– 0.125%
Paste composition	0.015	– 0.125%

For children six years of age or younger:

Severe hypertrophy or enlargement		
Fluid composition	0.0125	– 0.25%
Paste composition	0.05	– 0.25%
Mild to moderate hypertrophy or enlargement		
Fluid composition	0.0125%	– 0.025%
Paste composition	0.0125%	– 0.125%
Daily oral hygiene and prophylaxis		
Not generally recommended		

These concentrations of the vasoconstrictor are only by way of example and recommended dosage and do not limit the percentage concentrations within the limits of the given examples. People knowledgeable in the arts of compounding pharmaceuticals may with few trials arrive to a preferred concentration of the active ingredients falling within the range of 0.0125 percent and up to 5 percent.

The use of sympathominetic amines in combinations with antihistaminic agents for treatment of hyperplastic or hypertrophied and enlarged tissue has never been suggested or implied before; the mode of action of this combination is different than that obtained from either agent used alone. While the sympathomimetic amines have pharmacodynamic action on the chemoreceptors of the endothelial cells of the capillary membranes resulting in a physiological antagonism of the effects of the histamine on the effector cells, the antihistaminics prevent the access of histamine to its receptor site in the cells by competetive inhibition without causing a cellular response or chemical reaction or antagonism between the histamine and the antihistaminic agent. Further, vasoconstrictor-antihistamine combination employed in this patent virtually eliminates any side effect produced by either agent used alone; the sedative effect of the antihistaminic agent will counteract the stimulant effect of the vasoconstrictor. Finally, I am not aware of employing vasoconstrictor-antihistamine combination in high acid or high alkaline pH as described herein due to the precipitation of the alkaloids and the antihistamines, by the alkaline compounds; however, I have discovered that concentration of more than 10 percent of alcohol or glycols such as glycerin

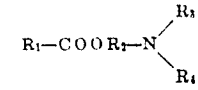
or propylene glycol, will prevent the said precipitation in either the fluid or paste compositions.

In addition to the foregoing, I am not aware of anyone suggesting or advocating a process or a composition for the treatment of pain associated with hypertrophy or hyperplasia and oral tissue enlargement. Treatment of the pain symptom is just as important to the comfort and the well being of the patient as is the treatment of the condition itself. This invention deals not only with the therapeutic treatment and the prevention of oral tissue enlargement but it also relates to the aleviation of the pain phenomena which is an important and integral part of the entire process of tissue differentiation and proliferation expected with this condition. Needless to say, pain is the first symptom most patients afflicted with this condition will experience and the need for its treatment is obvious. Topical anesthetics used alone are not as effective in the treatment of pain associated with tissue enlargement as would two topical anesthetics such as benzocaine and tetracaine combined with a sympathomimetic amine and a antihistamine. Local anesthetic agents such as benzocaine and tetracaine although are classified as anesthetic drugs they are in their pharmacologic action analgesic since by definition anesthesia is a state of depressed consciousness with inhibition or abolishment of pain and analgesia is a state of inhibition and abolishment of pain without loss of consciousness when the drugs are used systemically. Topical application of an anesthetic agent will produce insensitivity or insensibility to pain in a circumscribed area without central nervous system depression even when high concentrations of the drug is employed, therefore the terms anesthesia and analgesia or anesthetic drug, or analgesic drug are used interchangeably to indicate insensibility or abolishment to pain when these drugs are used topically on the oral tissue.

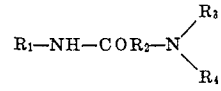
This invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention. The disclosure therein is by way of example and included in the invention are all modifications and equivalents falling within the scope of the appended claims.

I claim:

1. A composition for the treatment of hypertrophied or hyperplastic oral tissue comprising (a) an alkaloid selected from the group consisting of aromatic amines having between about 6 to 10 carbon atoms and aliphatic amines having between about 4 to 7 carbon atoms, (b) an antihistaminic component selected from the group consisting of antazoline hydrochloride, tripelennamine hydrochloride, tripelennamine citrate, thonzylamine hydrochloride, methapyriline hydrochloride, methapheniline hydrochloride, pyrilamine maleate, chlorphenamine maleate, chlorothen, pheniramine, pheniramine maleate, chlorocyclizine hydrochloride, diphenhydramine hydrochloride, doxylamine succinate, phenyltoloxamine citrate, diphenylpyraline hydrochloride, phenindamine tartrate, and thenyldiamine hydrochloride, and (c) an anesthetic component selected from the group consisting of secondary and tertiary amino esters of aromatic acids and secondary and tertiary aminoacyl amides of aromatic acids, said amino esters having the structure



wherein R_1 with its carbonyl group may be benzoic and paramino benzoic acid or meta-amino benzoic acid, R_2 is selected from the group consisting of aliphatic or aromatic radicals having up to 14 carbon atoms each and R_3 and R_4 are selected from the group consisting of hydrogen and aliphatic or aromatic radicals having up to 14 carbon atoms each, and said aminoacyl amides having the structure



wherein R_1 is selected from xylene or toluene, R_2 is selected from the group consisting of aliphatic or aromatic radicals having up to 14 carbon atoms each and R_3 and R_4 are selected from hydrogen and aliphatic or aromatic radicals having up to 14 carbon atoms each, said alkaloid and antihistaminic compounds each being present in said composition in an amount of from about 0.0125 to 5.0 per cent by weight of the composition, and said anesthetic component being present in an amount of from about 0.0125 to 20.0 per cent by weight of the composition.

2. A composition according to claim 1 wherein said antihistaminic compound is selected from the group consisting of antazoline hydrochloride, diphenhydramine hydrochloride thonzylamine hydrochloride, chlorphenamine maleate, pyrilamine maleate, pheniramine maleate and mixtures thereof.

3. A composition according to claim 1 wherein said anesthetic compound is selected from the group consisting of benzocaine hydrochloride, tetracaine hydrochloride and mixtures thereof.

4. A treatment for tissue which is hypertrophied or hyperplastic comprising applying to the area to be treated the composition of claim 1.

5. A toothpaste composition according to claim 1 comprising said alkaloid, anesthetic and said antihistaminic compounds, from about 0.001 to 0.5 percent of a preservative, from about 0.002 to 2.0 percent of a suspending agent and from about 1 to 21 percent of a moisture retainer, the remainder of said composition being water and said percentages being based on the weight of the total composition.

6. A toothpaste composition according to claim 5 wherein said suspending agent is selected from the group consisting of sodium carboxymethylcellulose, methylcellulose, bentonite, acacia, sterculia gum and tragacanth, and wherein said moisture retainer is selected from the group consisting of glycerin, propylene glycol, sorbital, polyethylene glycol, diethylene glycol monoethyl ether, polysorbate, monolourate and polyoxyethylene sorbitan.

7. A composition according to claim 1 further including from about 0.001 to 0.5 weight percent of a preservative selected from the group consisting of methylparaben, propylparaben, sodium bisulfite, sodium benzoate, sodium thiosulfate, chlorobutanol, themersoal and phenylmercuric acetate.

8. A mouthwash composition according to claim 7 comprising an aqueous solution of said alkaloid, antihistaminic compound, anesthetic compound and preservative.

9. A water soluble tablet composition according to claim 7 comprising a suspension of said alkaloid, antishistaminic compound, anesthetic compound and preservative in a suspending agent selected from the group consisting of sodium carboxymethylcellulose, methylcellulose, bentonite acacia, sterculia gum and tragaconth.

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