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ANESTHETIC PREPARATIONS CONTAINING POTENTIATED 4[3-(p-BUTOXYPHENOXY)-PROPYL MORPHOLINE; 3-BUTYL-1-(2-DIMETHYLAMINO ETHOXY) ISOQUINOLINE; 2-DIMETHYLAMINO-2'6'-ACETOXYLIDIDE

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This invention relates to pharmaceutical preparations and more particularly to novel, local anesthetic-containing preparations.

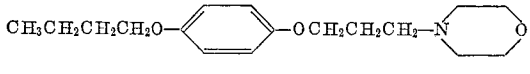
Local anesthetics are pharmaceutical materials useful in the relief of the discomforts of teething, sunburn, pruritus and various dental and surgical procedures. When applied parenterally, local anesthetic preparations usually include a vasoconstrictor such as epinephrine in order to delay the absorption of the material from the site of injection. In this regard, the vasoconstrictor reduces the blood flow to and from the area and thereby sustains a relatively constant concentration of anesthetic in the area desired.

It is known that there are instances in which the combined action of two or more drugs is greater than that which can be anticipated from the sum of their individual actions. This phenomenon is commonly referred to as "potentiation." It is not to be confused with "prolongation," the latter denoting the condition wherein the period of drug action is extended. "Potentiation" denotes the "intensification" of the drug effect.

In the course of our research, it was found that certain materials have a surprising effect upon certain local anesthetics. It was found that, apart from merely prolonging the local effect, the combination of these materials with the anesthetic resulted in a "potentiation" of the latter. This was not in accord with the known effect of these materials and was completely unexpected in the light of the prior knowledge thereof. Another surprising effect noted was that the mucosal tissue irritation by the local anesthetics was reduced.

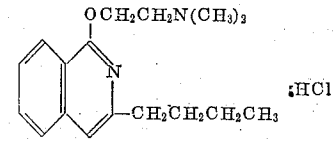
In accordance with the present invention, a potentiated anesthetic preparation comprises a local anesthetic selected from the group consisting of pramoxine, dimethisoquin and xylocaine local anesthetics; and at least one potentiator therefor selected from the group consisting of (A) hydrophilic and water-soluble vinyl polymers, (B) hydrophilic and water-soluble celluloses, (C) copolymers of vinylacetate and crotonic acid, and (D) inorganic polyphosphates, said potentiator being present in an amount sufficient to intensify the anesthetic action of said local anesthetic. In the practice of this invention, therefore, the proportion of said potentiator is correlated with the proportion of local anesthetic to effect a non-toxic but potentiated anesthetic preparation.

Pramoxine local anesthetics are known in the art. The most active salt thereof is described more fully in the article by Schmidt et al.; entitled "The Pharmacology of Pramoxine Hydrochloride: A New Topical Local Anesthetic," appearing in Anest. & Analg. 32, 418 (1953). Therefore, for the practice of this invention, the term "pramoxine" includes the free base and the salts thereof having the anesthetic property. However, pramoxine HCl is preferred for the practice of this invention. This latter compound has the following formula:



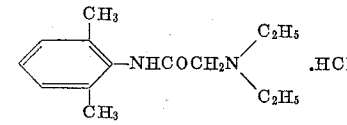
i.e. 4-[3-(p-butoxyphenoxy) propyl] morpholine HCl. For the sake of convenience, this anesthetic usually will hereinafter be referred to as "pramoxine."

Dimethisoquin anesthetics are known in the art and are described more fully in the article by Fellows, E. J. and Macko, E., entitled "The Topical Anesthetic Activity of an Isoquinoline Compound," appearing in the Journal of Pharmacol. Exp. Therap. (1951), 103, 306–309. As used herein the term "dimethisoquin" includes the free base and the salts thereof having the anesthetic property. However, dimethisoquin HCl is preferred for the practice of this invention. This salt has the following formula:



i.e. 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline HCl. For the sake of convenience, this anesthetic usually will be referred to hereinafter as "dimethisoquin."

Xylocaine anesthetics are known materials and are described more fully in the article by N. Löfgren, entitled "Studies on Local Anesthetics: Xylocaine, a New Synthetic Drug," Ivar Hoeggstrom's, Stockholm, Sweden (1948). As used herein, the term "xylocaine" includes the free base and the salts thereof having the anesthetic property. However, xylocaine HCl is preferred for the practice of this invention. This compound may be represented chemically and structurally in the following manner:



i.e. 2-diethylamino 2',6'-acetoxylidide HCl. For the sake of convenience, this anesthetic usually will be hereinafter referred to as "xylocaine."

Vinyl polymers are the preferred potentiators for the practice of this invention. The instant vinyl polymer potentiators are water soluble, hydrophilic compounds of pharmaceutical grade, non-toxic, inert and capable of being sterilized without changing composition. Illustrative of the vinyl polymers suitable for the practice of this invention are polyvinyl phosphonates such as polyvinyl phosphonic acid, polyvinyl carboxylates such as polyitaconic acid, polyvinyl carboxamides such as polyacrylamides, polyvinyl alcohols and polyvinyl pyrollidone.

For the practice of this invention, the term "vinyl polymers" includes copolymers containing the same. Illustrative of such copolymers are the water soluble copolymers of maleic acid and its water soluble salts which are of pharmaceutical grade, non-toxic, inert and capable of being sterilized without change in composition. These copolymers include styrene-maleic anhydride copolymers, ethylene-maleic anhydride copolymers, and copolymers of vinyl methyl ether and maleic anhydride.

For the practice of this invention, the vinyl alcohol and vinyl pyrollidone polymers are particularly desirable. Illustrative of the polyvinyl alcohols utilized in the compositions described herein are those characterized by a viscosity of four to six centipoises (four percent aqueous solution at twenty degrees centigrade), a pH of 6 to 8 and an 86 to 89 percent hydrolysis from polyvinyl acetate.

It is to be understood, however, that the invention is not limited to the use of the specific polyvinyl alcohols indicated since any other equivalent polyvinyl alcohol of pharmaceutical grade can likewise be used to achieve similar results.

The polyvinyl pyrollidone used in the compositions described herein is characterized by a viscosity coefficient,

i.e. K value, of 15 through 60, e.g. PVP K 15 and PVP K 60. However, it is to be understood that the invention is not to be limited to the use of these specific polyvinyl pyrollidones since any other equivalent polyvinyl pyrollidones of pharmaceutical grade are likewise suitable. (For the sake of convenience, polyvinyl pyrollidone usually will be referred to in the description and examples that follow by the abbreviation PVP.)

The hydrophilic and water soluble celluloses used in the practice of this invention are also of pharmaceutical grade, non-toxic, inert and capable of being sterilized without changing composition. Illustrative of the celluloses employable for the practice of this invention are cellulose derivatives such as carboxymethyl cellulose having a 58% carboxyl substitution and methylated cellulose having a viscosity of about 15 centipoises.

Illustrative of the inorganic polyphosphate potentiators used in the compositions of this invention are water-soluble phosphates having the formula $M_5P_3O_{10}$ wherein M is sodium, potassium or ammonium.

The novel compositions of this invention can be associated in any suitable manner or with any suitable pharmaceutical vehicle. For example, aqueous solutions of anesthetic and potentiator can be mixed together, thereby providing an injectable aqueous solution thereof. The active constituents can also be incorporated in any suitable pharmaceutical vehicle, such as an ointment, a cream, a petrochemical base, or an aliphatic base. The preparations of this invention also can be incorporated in an alcoholic base such as a sprayable carrier consisting essentially of isopropyl alcohol or the like. The sprayable base permits application of the drug to the human body from a pressurized dispensing device having the ability to apply spray in a simple and effective manner.

It will be appreciated that the indicated non-toxic pharmaceutical vehicles act as the carrier for the active ingredients and present a homogeneous medium with the active ingredients thoroughly disposed therethrough. To the preparations there can also be added minor amounts of other materials such as coolants, perfumes, surfactants and other body treating and soothing compounds. It is to be understood also that other materials including other active agents also can be included in the preparations of this invention.

The drug-potentiator preparations of this invention can be applied in any suitable manner commensurate with standard methods of applying local-anesthetics. In general, however, these means of application can be termed topical and parenteral.

As also indicated previously, the proportions of the potentiator are correlated principally with the proportion of local anesthetic so that the desired potentation is effected. It will be understood that this ratio of ingredients will depend on the type of ingredients employed, the type of non-toxic pharmaceutical vehicle or carrier, the purpose and degree of anesthesia intended or required, the manner of application of the preparation to the area, and the like. Generally speaking the ratio of potentiator to local anesthetic can vary from between about 1:1 and about 20:1. Lesser ratios can also be employed but the effectiveness will be sharply reduced thereby. Amounts in excess of 20 parts by weight of potentiator per one part by weight of anesthetic can also be used but no commensurate advantage will be gained thereby.

As a consequence of the potentation effected by the preparation of this invention, the concentration of local anesthetic in the preparations of this invention will be substantially less than that normally employed in inducing the desired anesthesia. Moreover, an "intensification" of the anesthetic effect will be effected per unit of anesthesia employed. Generally speaking, for the practice of this invention, the concentration of local anesthetic can be between .2% and 2% by weight of the preparation, according to the degree of anesthesia desired. Below .2% the drug action diminishes substantially. Drug concentration of above 2% could be employed but normally no commensurate advantage will be gained thereby.

The preferred composition of this invention will contain a ratio of potentiator to anesthetic of between 1:1 and 10:1. Within these ratios an anesthetic concentration of between .2% and .8% by weight of the preparation is also preferred. For example, where a 1:1 ratio of pramoxine and PVP is employed, a combined concentration of the two ingredients, i.e. pramoxine and PVP, of .4%, will accomplish an anesthetic effect greater than that of a .4% concentration of the drug alone.

In the examples which follow two methods were employed for measuring local anesthesia. The first method is based upon the abolishment of the wink reflex as described in (A) below; the second method is based upon alterations in the response time of an electrically induced skin twitch reflex as described in (B) below.

(A) *Tactile corneal reflex.*—Briefly, this technique consists of a wink response following an application of a cotton swab to the surface of the corneum of the eye of a New Zealand albino rabbit. Anesthetic alone and the anesthetic preparations of this invention are injected into the conjunctival sac, and anesthesia is established by the absence of the wink response.

(B) *Skin twitch reflex.*—This technique involves the eliciting of a skin reflex by electrical stimulation of the shaved integument of the dorsolumbar area of a New Zealand albino rabbit through bipolar platinum electrodes. The potency of the drug preparations are measured in terms of changes in latency (L) (time interval) between stimulation and onset of twitch and duration (t) of the changes. The total effectiveness of the systems investigated is expressed as the area beneath the curve (C.A.) which is represented by the following equation:

$$C.A.=\Sigma\tfrac{1}{2}(t_n-t_n-1)(L_n+L_n-1)$$

C.A. (curve area) represents an absolute value of potency for a particular test substance. In every experiment, the C.A. of the anesthetic alone was compared with the C.A. of the drug-potentiator mixture to give a relative value called the ratio (R). This relationship is expressed below.

$$R=\frac{\text{C.A. of drug-potentiator mixture}}{\text{C.A. of drug}}$$

The following examples will further illustrate the scope and practice of this invention. However, it is to be understood that they are purely by way of illustration and are not to be considered in any way as a limitation of the scope of the compositions forming the subject invention. Except as otherwise indicated, the proportions and percentages employed are by weight.

Example 1

Equal parts by weight of representative potentiators and pramoxine HCl are mixed in aqueous solutions buffered with sodium bicarbonate to a pH of 8.2. In the case of both the potentiators and anesthetic, 0.2% concentrations thereof are employed. The samples are applied to the skin of New Zealand albino rabbits by means of paper disks saturated with the preparations. Changes in latency are determined 5 minutes after the application of the test samples, and thereafter at intervals of 5 minutes for the first 30 minutes, intervals of 15 minutes for the next 30 minutes, and intervals of 30 minutes for the remainder of the time.

In the same animal, preparations containing the drug alone are also applied to the animals and the effects measured as with the drug-potentiator mixtures.

The representative potentiators employed for this series of tests are indicated below:

(1) Polyvinyl alcohol having a degree of hydrolysis of about 88%.

(2) Polyvinyl alcohol having a degree of hydrolysis of about 80%.

(3) Polyvinyl phosphonic acid.
(4) Copolymer of acrylamide and acrylic acid.
(5) PVP K 15.
(6) PVP K 60.
(7) Carboxymethyl cellulose having a degree of substitution of about 0.45.
(8) Carboxmethyl cellulose having a degree of substitution of about 1.2.
(9) A methylether of cellulose having a viscosity (measured in centipoises) of about 154,000.
(10) a methylether of cellulose having a viscosity (measured in centipoises) of about 7000.
(11) Sodium salts of poly (vinylmethyl ether-comaleic anhydrides). (These are 1.1 copolymers having viscosities of from 0.1 to 3.5 centipoises.)
(12) Copolymers of styrene and maleic anhydride solubilized by hydrolysis. (These are of 3 types; an anhydride form having a viscosity (measured as a 12% solution in ammonia at pH 9) of less than 100 centipoises; and two half butyl ester forms converted to their corresponding sodium salts and having viscosities (measured as 5% solutions in ammonia at pH 8.5) of 3.3–4.3 centipoises and 45–80 centipoises respectively.)
(13) Copolymer of ethylene and maleic anhydride. (This is a 1:1 copolymer in either the linear sodium form or the linear or cross-linked anhydride form. Each form is employed.)
(14) Polyitaconic acid having a viscosity of about 0.54 centipoise.
(15) Polyitaconic acid having a viscosity of about 3.4 centipoises.
(16) Copolymer of crotonic acid and polyvinylacetate.
(17) Pentasodium tripolyphosphate.
(18) Pentaammonium tripolyphosphate.

Each of the anesthetic-potentiator mixtures has an anesthetic effectiveness substantially greater than that of the anesthetic alone. In general, the ratio of effectiveness of the inventive preparations over the anesthetic alone is greater than 3. In this regard, low viscosity polyvinyl alcohols having a degree of hydrolysis of about 88% and 80% respectively (hereinafter referred to as PVA (1) and PVA (2); polyvinyl pyrrolidone having a K value of 60 (hereinbefore referred to as PVP K 60); low viscosity (0.1–0.5 centipoise) copolymer of vinyl methyl ether and maleic anhydride hereinafter referred to as PVM (0.1–0.5); and pentasodium tripolyphosphate, evidence the greatest effectiveness in potentiating the local anesthetic, i.e., in all cases these preferred potentiators reveal an effectiveness ratio (R) of greater than 9.0.

Example 2

The potentiation of pramoxine HCl in a .2% aqueous solution thereof by various potentiators at concentrations in the aqueous solutions of .4% and .8%, is determined by means of the tactile corneal reflex and the skin twitch reflex test methods. The potentiators employed are pentasodium tripolyphosphate, PVM (0.1–0.5), PVA (1), PVA (2) and PVP K 60.

It is observed that an increased intensification of the anesthetic is effected by all the potentiators at all the concentrations indicated. Moreover, an increase in the concentration of potentiators "prolongs" the anesthesia of the corneum accordingly.

Example 3

A comparable study is also made of the anesthetic potencies of 0.2%, 0.4% and 0.8% concentrations of dimethisoquin, xylocaine and pramoxine HCl, when employed in an aqueous medium alone and in combination with equal parts by weight of the representative potentiators indicated in Example 2. The skin twitch method is the test medium. The results of these tests indicate that increasing the drug concentration when such is employed without a potentiator has minimal effects upon the latency threshold. On the other hand in admixture with the potentiators, there is a general elevation in the latency threshold and a prolongation of the duration of the anesthetic effect.

Example 4

The anesthetic effects of pramoxine HCl and pramoxine base, alone, and in combination with equal parts by weight of a copolymer of crotonic acid and vinyl acetate are measured. Water as a carrier therefor is employed. Latency, duration of activity and total activity (C.A.) are significantly increased by the addition of the potentiator even though the potentiator employed is pharmacologically inert when employed topically. There is no significant difference noted between the latency values observed for pramoxine HCl and pramoxine free base-treated animals. However, the pramoxine HCl-potentiator-treated animals exhibit increased latency corresponding with the pramoxine concentration used. The pramoxine free base-potentiator mixture also exhibits an increase in latency but such is less than that with the salt-potentiated mixture. Duration of anesthesia for pramoxine HCl-treated rabbits is clearly dose-related. The duration of anesthesia for pramoxine base-treated rabbits is also dose-related but is less perceptible than with the salt. However, combinations of the potentiator with the salt or free base clearly produces significantly increased dose-effect changes in both instances. The total activity (C.A.) is analogous to the values for latency. Depending upon the parameters employed, (within the limits indicated heretofore) the drug is potentiated 10 to 80 times by the copolymer.

Example 5

The inventive preparations of this invention can be incorporated in a cream formulation. In the manufacture of a cream, suitable fatty material and emulsifying agent are combined with the anesthetic and potentiator in water to form an aqueous phase and an oily or fatty phase. These are then combined in the form of a cream.

A typical sterile formulation for a potentiated anesthetic-containing cream is (in percent by weight):

	Percent
Glycerol monostearate	11.0
Stearic acid	5.0
Spermaceti	3.0
Pluronic F–68[1]	0.5
Mineral oil	1.5
Polyoxyethylene sorbitan monolaurate	1.0
70% sol, of sorbitol, N.F.	6.0
Methyl para-hydroxy benzoate	0.18
Propyl para-hydroxy benzoate	0.02
Isopropyl myristate	5.0
Pramoxine HCl	1.0
PVP K 60	1.0

With the balance being primarily water.

[1] A polymeric condensation product of ethylene oxide and polyoxypropylene containing 80% polyoxyethylene in the total molecule and in which the molecular weight of the polyoxypropylene base is approximately 1750.

This formulation exhibits a C.A. of 190 using the skin twitch reflex test, which contrasts favorably with a C.A. of 101 for the identical formulation without the potentiator (PVP K 60).

Although the present invention has been described with reference to particular embodiments and examples, it will be apparent to those skilled in the art that variations and modifications of this invention can be made without departing from the principles and true spirit of the invention.

What is claimed is:

1. A potentiated anesthetic preparation which comprises a local anesthetic selected from the group consisting of 4-[3-(p-butoxyphenoxy) propyl] morpholine, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline and xylocaine local anesthetic; and a potentiator therefor selected from the group consisting of (A) hydrophilic

and water-soluble vinyl polymers, (B) hydrophilic and water-soluble celluloses, (C) copolymers of vinylacetate and crotonic acid and (D) inorganic polyphosphates, said potentiator being present in an amount sufficient to intensify the anesthetic action of said local anesthetic.

2. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, a local anesthetic selected from the group consisting of 4-[3-(p-butoxyphenoxy) propyl] morpholine, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline and xylocaine local anesthetics; and a potentiator therefor selected from the group consisting of (A) hydrophilic and water-soluble vinyl polymers, (B) hydrophilic and water-soluble celluloses, (C) copolymers of vinylacetate and crotonic acid, and (D) inorganic polyphosphates, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of local anesthetic.

3. A preparation according to claim 2, in which the potentiator is present in amounts of from one to ten parts by weight per part by weight of the local anesthetic.

4. A preparation according to claim 2, in which said local anesthetic constitutes between .2% and 2% by weight of said preparation.

5. A preparation according to claim 2, in which the local anesthetic concentration is between .2% and .8% by weight of the preparation.

6. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, and, as a potentiator for said 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, polyvinyl pyrrolidone, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and the concentration of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride being from .2% to 2% by weight of the preparation.

7. A preparation according to claim 6, in which the concentration of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride is between .2% and .8% by weight and the potentiator is present in amounts of from one to ten parts by weight per part by weight of the 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride.

8. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, and, as a potentiator for said 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, polyvinyl alcohol, the potentiator being present in amounts of from one to twenty parts by weight of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and the concentration of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride being from .2% to 2% by weight of the preparation.

9. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and, as a potentiator for said 4-[3-(p-butoxphenoxy) propyl] morpholine hydrochloride, a copolymer of vinyl methyl ether and maleic anhydride, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and the concentration of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride being from .2% to 2% by weight of the preparation.

10. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and, as a potentiator for said 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, pentasodium tripolyphosphate, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and the concentration of 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride being from .2% to 2% by weight of the preparation.

11. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and, as a potentiator for said 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride, polyvinyl pyrrolidone, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and the concentration of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride being from .2% to 2% by weight of the preparation.

12. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and, as a potentiator for said 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride, polyvinyl alcohol, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and the concentration of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride being from .2% to 2% by weight of the preparation.

13. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and, as a potentiator for said 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride, a copolymer of vinyl methyl-ether and maleic anhydride, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and the concentration of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride being from .2% to 2% by weight of the preparation.

14. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and, as a potentiator for said 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride, pentasodium tripolyphosphate the potentiator being present in amounts of from one to twenty parts by weight per part by weight of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride and the concentration of 3-butyl-1-(2-dimethylamino ethoxy) isoquinoline hydrochloride being from .2% to 2% by weight of the preparation.

15. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, xylocaine hydrochloride and, as a potentiator for said xylocaine hydrochloride, polyvinyl pyrrolidone, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of xylocaine hydrochloride and the concentration of xylocaine hydrochloride being from .2% to 2% by weight of the preparation.

16. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, xylocaine hydrochloride and, as a potentiator for said xylocaine hydrochloride, polyvinyl alcohol, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of xylocaine hydrochloride and the concentration of xylocaine hydrochloride being from .2% to 2% by weight of the preparation.

17. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, xylocaine hydrochloride and, as a potentiator for said xylocaine hydrochloride, a copolymer of vinyl methyl ether and maleic anhydride, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of xylocaine hydrochloride and the concentration of xylocaine hydrochloride being from .2% to 2% by weight of the preparation.

18. A potentiated anesthetic preparation which comprises a pharmaceutical vehicle, xylocaine hydrochloride and, as a potentiator for said xylocaine hydrochloride, pentasodium tripolyphosphate, the potentiator being present in amounts of from one to twenty parts by weight per part by weight of xylocaine hydrochloride and the

concentration of xylocaine hydrochloride being from .2% to 2% by weight of the preparation.

19. A potentiated anesthetic cream preparation which comprises a cream base and 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and, as a potentiator for said 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride, polyvinyl pyrrolidone, the 4-[3-(p-butoxyphenoxy) propyl] morpholine hydrochloride and potentiator each being present in amounts of 1 percent by weight of the preparation.

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