Title: USE OF NITROGLYCERIN TO REVERSE LOCAL ANESTHESIA

Abstract: Methods of reversing local anesthesia are disclosed. The methods comprise administering a local anesthetic and vasoconstrictor to induce local anesthesia followed by reversing anesthesia with nitroglycerin. Also disclosed are kits comprising a local anesthetic, a vasoconstrictor and nitroglycerin.
USE OF NITROGLYCERIN TO REVERSE LOCAL ANESTHESIA

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention is in the field of medicinal chemistry. The invention relates in particular to a method of reversing local anesthesia induced by a local anesthetic and a vasoconstrictor, comprising administering an effective dose of nitroglycerin.

Background Art

[0002] Local anesthesia is widely used by dentists to provide pain relief to patients during dental procedures. To provide pain relief, a drug formulation containing a local anesthetic compound such as lidocaine is injected into the gum tissue surrounding the tooth or teeth on which the dental procedure is to be performed. There are short-acting and long-lasting local anesthetic drug formulations. Short-acting local anesthetic drug formulations contain lidocaine or a related local anesthetic drug dissolved in saline or other suitable injection vehicle. Typically, local anesthesia with short-acting local anesthetics lasts approximately 20-30 minutes, which is not long enough for many dental procedures. To obtain long-lasting local anesthesia, dentists often use lidocaine or other local anesthetic formulations which, in addition to the local anesthetic drug itself, contain low concentrations of epinephrine or another adrenergic receptor agonist such as levonordefrin. More than 90% of the local anesthesia procedures performed by dentists involve local anesthetic formulations containing alpha-adrenergic receptor agonists. The vasoconstrictor is necessary because local anesthetics without vasoconstrictor are too short-acting for most dental procedures. The added epinephrine stimulates alpha-adrenergic receptors on the blood vessels in the injected tissue. This has the effect of constricting the blood vessels in the tissue. The blood vessel constriction causes the local anesthetic to stay in the tissue much longer, resulting in a large increase in the duration of the anesthetic effect (from 20 minutes for the short-acting formulation to 3-6 hours for the long-lasting formulation).
A major problem with the use of epinephrine-containing local anesthetics is soft-tissue anesthesia (lip, cheek, tongue) which usually lasts many hours longer than anesthesia and analgesia of the tooth pulp. Tooth pulp anesthesia and analgesia are the desired effects of local anesthesia from a dental procedural perspective while soft-tissue anesthesia is usually an undesirable side effect. Soft tissue anesthesia results in a number of problems and inconveniences, such as a prolonged and uncomfortable feeling of numbness in and around the mouth, inability to smile, difficulty eating, drinking and swallowing, and loss of productivity by missing work hours or meetings. Lingering soft-tissue anesthesia can be the cause of injuries due to biting of the tongue or lips. Furthermore, lingering soft-tissue anesthesia is an inconvenience and it is perceived as an annoyance by many patients. Lingering soft-tissue anesthesia can lead to injury especially in children who often bite into the anesthetized tissue out of curiosity. It would therefore be desirable to have a drug that could be used at will by dentists to rapidly reverse local anesthesia after it is no longer needed.

**BRIEF SUMMARY OF THE INVENTION**

The present invention provides compositions and formulations of nitroglycerin and use thereof for reversing the effects of long-lasting local anesthetic agents containing vasoconstrictors such as alpha-adrenergic receptor agonists.

In one embodiment, the present invention relates to a method of reversing soft tissue anesthesia resulting from injection of an anesthetic agent and a vasoconstrictor in a mammal, comprising administering to the mammal an effective amount of nitroglycerin at the site of the injection.

In another embodiment, the invention relates to a method of providing local anesthesia to a mammal, comprising:

(a) administering to the mammal in need thereof an anesthetic agent and a vasoconstrictor to the site to be anesthetized, wherein said anesthetic agent is administered in an amount effective to provide local anesthesia and said vasoconstrictor is administered in an amount effective to constrict the blood vessels at the site and prolong the local anesthesia, and then

(b) administering nitroglycerin to said site to reduce the prolongation.
The invention also relates to a kit comprising a carrier having in close confinement therein two or more containers, wherein a first container contains an anesthetic agent and optionally a vasoconstrictor and a second container contains nitroglycerin.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention relates to a method of reversing soft tissue anesthesia resulting from injection of an anesthetic agent and a vasoconstrictor in a mammal, comprising administering to the mammal an effective amount of nitroglycerin at the site of the injection.

In another embodiment, the invention relates to a method of providing local anesthesia to a mammal, comprising:

(a) administering to the mammal in need thereof an anesthetic agent and a vasoconstrictor to the site to be anesthetized, wherein said anesthetic agent is administered in an amount effective to provide local anesthesia and said vasoconstrictor is administered in an amount effective to constrict the blood vessels at the site and prolong the local anesthesia, and then

(b) administering nitroglycerin to said site to reduce the prolongation.

The anesthetic agent and vasoconstrictor may be administered together as part of a unitary pharmaceutical composition or as part of separate pharmaceutical compositions so long as the vasoconstrictor acts to constrict the blood vessels in the vicinity of where the anesthetic agent has been administered to result in a prolonging of anesthesia. In a preferred embodiment, the anesthetic agent and vasoconstrictor are administered together in solution. The anesthetic agent and vasoconstrictor may be administered by injection, by infiltration or by topical administration, e.g., as part of a gel or paste.

In a preferred embodiment, a solution comprising the anesthetic agent and vasoconstrictor is administered by injection directly into the site to be anesthetized, e.g., prior to a dental procedure.

Examples of local anesthetics that may be used in the practice of the invention include without limitation lidocaine, polocaine, lignocaine, xylocaine, novocaine, carbocaine, etidocaine, procaine, prilocaine, bupivacaine, cinchocaine and mepivacaine.
Examples of vasoconstrictors that can be used according to the invention include alpha adrenergic receptor agonists, such as catecholamines and catecholamine derivatives. Particular examples include without limitation levonordrephin, epinephrine, and norepinephrine.

In order to reverse the local anesthesia after a medical procedure according to the present invention, nitroglycerin is administered at a dose effective to cause vasodilatation in the area around the site of administration of the local anesthetic. An effective dose of nitroglycerin may be in the range of about 0.01 mg to about 100 mg, e.g., about 0.05 mg to about 10 mg, e.g., about 0.1 mg to about 1 mg. An effective dose may be about 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 mg. When administered as a liquid (e.g., by injection) the concentration of nitroglycerin in the liquid may be about 0.01 mg/mL to about 10 mg/mL, e.g., about 0.1 mg/mL to about 5 mg/mL. When administered as a solid (e.g., as a gel or paste or as a unit dose form) the amount of nitroglycerin per dose may be about 0.01 mg to about 100 mg, e.g., about 0.05 mg to about 10 mg, e.g., about 0.1 mg to about 1 mg. The concentration of nitroglycerin in a gel or paste may be about 0.01% to about 10%, e.g., about 0.1% to about 1%, e.g., 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, or 1%.

The nitroglycerin may be administered by any method known in the art which provides a sufficient dose to the site of anesthesia to cause vasodilation. In certain embodiments, the nitroglycerin may be administered by injection into the site of anesthesia, by infiltration or by topical administration. In one embodiment, the nitroglycerin is administered by injection at the site of anesthesia. The nitroglycerin may be in a solution with a pharmaceutically acceptable carrier, e.g., water, 5% dextrose, or saline. In one embodiment, the nitroglycerin is administered to mucosal tissue. In this embodiment, the nitroglycerin may be applied to the site in the form of a gel or paste (e.g., U.S. Patent Nos. 7,074,424, 7,048,912, 6,464,961, 6,315,987, and 6,287,588), or as part of an impregnated wafer, pellet or cotton ball, whereby the nitroglycerin is taken up by the mucosal tissue resulting in reversal of the anesthesia. In a further embodiment, the nitroglycerin may be delivered by a resorbable or non-resorbable patch. Patches for trans-mucosal delivery of pharmaceutical agents are well known in the art, and include,
e.g., patches described in U.S. Patent Nos. 7,001,609, 6,893,656, 6,867,342, 6,838,078, 6,796,429, 6,767,935, 6,706,728, 6,632,522, 6,630,238, 6,627,216, 6,624,200, 6,592,280, 6,590,059, 6,552,024, 6,399,610, 6,264,981, 6,248,358, 5,985,317, 5,942,243, 5,900,247, 5,863,555, 5,849,322, 5,750,136, 5,750,134, 5,736,553, 5,672,356, 5,298,256, 5,225,196, and 4,983,392. In other embodiments, the nitroglycerin may be delivered as part of a gum or lozenge, as part of a lollipop (e.g., U.S. Patent No. 6,103,257), as part of a foam, in an osmotic device which is placed in the mouth (e.g., U.S. Patent Nos. 5,869,096, 5,776,493, 5,053,032 and 5,869,096), as part of a sustained release delivery device (e.g., U.S. Patent No. 7,052,719, 6,932,983, 6,730,322, 6,319,520, 6,007,843, and 5,512,293), as part of a gas-filled microsphere (e.g., U.S. Patent No. 5,733,572), as part of an oral-dissolving tablet (e.g., U.S. Patent Nos. 7,022,340, 6,004,581, 5,922,680, 5,888,534, 5,780,434, 5,624,677, 5.1 12,616, and 5,073,374), or as a spray or liquid (e.g., U.S. Patent Nos. 7,070,799, 6,998,110, 6,977,070, 6,969,508, 6,849,263, 6,676,931, 6,451,286, 6,436,367, 6,110,486, 5,958,379, 5,955,098, 5,487,898, and 5,284,657).

[0016] Examples of medical procedures that may be carried out according to the present invention include, without limitation, both major and minor surgery, dental procedures, cosmetic surgery, tissue grafting (e.g. hair and bone grafting) and cesarean section. In one embodiment, reversal of anesthesia according to the present invention is carried out by medical personnel to mitigate any mistakes that are made, and which may lead to the loss of extremities such as fingers, as well as ears and tips of noses.

[0017] The invention also relates to a kit comprising a carrier such as a carton or box having in close confinement therein two or more containers such as CARPULES, vials, tubes, jars and the like. A first container contains an anesthetic agent and optionally a vasoconstrictor and a second container contains nitroglycerin. Alternatively, the vasoconstrictor may be present in a separate container. In a preferred embodiment, the anesthetic agent, vasoconstrictor, and nitroglycerin are present in a container (such as a CARPULE that has a volume of about 1.6 to about 1.8 mL) that fits into a standard dental local anesthetic syringe. Such CARPULES are available commercially from a variety of suppliers, e.g., Henry Schein, Port Washington, N.Y. In this embodiment, a CARPULE containing the local anesthetic and vasoconstrictor is placed into the syringe, and the mixture is injected. The CARPULE may then be removed and a second CARPULE inserted which contains the nitroglycerin. In one embodiment, the containers are part of a
prefilled dual cartridge syringe in which two components (e.g., the anesthetic agent and the vasoconstrictor) are mixed prior to injection. In another embodiment, the container containing the nitroglycerin may be a patch or other device that is placed at the site of the anesthesia.


[0019] Mammals which may be treated according to the present invention include all mammals that may experience the beneficial effects of the present invention. Such mammals include without limitation humans and veterinary mammals such as cattle, pigs, sheep, horses, dogs, and cats. When applied to children and veterinary animals, the prompt reversal of anesthesia inhibits the child or animal from biting their lip or tongue when numb.

[0020] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

[0021] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections may set forth one or more but not all exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.
WHAT IS CLAIMED IS:

1. A method of reversing soft tissue anesthesia resulting from injection of an anesthetic agent and a vasoconstrictor in a mammal, comprising administering to the mammal an effective amount of nitroglycerin at the site of the injection.

2. The method according to claim 1, wherein said vasoconstrictor is an alpha adrenergic receptor agonist.

3. The method according to claim 2, wherein the alpha adrenergic receptor agonist is a catecholamine or a catecholamine derivative.

4. The method according to claim 3, wherein the alpha adrenergic receptor agonist is levonordefrin, epinephrine or norepinephrine.

5. The method according to claim 1, wherein the nitroglycerin is administered in solution, by injection into the site.

6. The method according to claim 1, wherein the nitroglycerin is administered topically to the site.

7. The method according to claim 1, wherein the nitroglycerin is administered by application of a patch comprising the nitroglycerin.

8. A method of providing local anesthesia to a mammal, comprising:

   (a) administering to said mammal in need thereof an anesthetic agent and a vasoconstrictor to the site to be anesthetized, wherein said anesthetic agent is administered in an amount effective to provide local anesthesia and said vasoconstrictor is administered in an amount effective to constrict the blood vessels at the site and prolong the local anesthesia, and then

   (b) administering nitroglycerin to said site to reduce the prolongation.

9. The method according to claim 8, wherein anesthetic agent and vasoconstrictor are administered together in solution.
10. The method according to claim 9, wherein said solution is administered by injection into the site.

11. The method according to claim 8, wherein the anesthetic agent and vasoconstrictor are administered together in solution, by injection into the site.

12. The method according to claim 8, wherein said anesthetic agent is selected from the group consisting of lidocaine, polocaine, etidocaine, lignocaine, xylocaine, novocaine, carbocaine, procaine, prilocaine, bupivacaine, cinchocaine and mepivacaine.

13. The method according to claim 8, wherein said vasoconstrictor is an alpha adrenergic receptor agonist.

14. The method according to claim 13, wherein the alpha adrenergic receptor agonist is a catecholamine or a catecholamine derivative.

15. The method according to claim 14, wherein the alpha adrenergic receptor agonist is levonordefrin, epinephrine or norepinephrine.

16. The method according to claim 8, wherein the nitroglycerin is administered in solution, by injection into the site.

17. The method according to claim 8, wherein said alpha adrenergic receptor antagonist is administered topically to the site.

18. The method according to claim 8, wherein the nitroglycerin is administered by application of a patch comprising the nitroglycerin.

19. A kit comprising a carrier having in close confinement therein two or more containers, wherein a first container contains an anesthetic agent and optionally a vasoconstrictor and a second container contains nitroglycerin.

20. The kit according to claim 19, wherein said anesthetic agent and said vasoconstrictor are in said first container.

21. The kit according to claim 19, wherein said anesthetic agent and said vasoconstrictor are in separate containers.
22. The kit according to claim 19, wherein said container is a CARPULE.

23. The kit according to claim 19, wherein said vasoconstrictor is an alpha adrenergic receptor agonist.

24. The kit according to claim 19, wherein said nitroglycerin is contained by a patch.
**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 08/02979

A. **CLASSIFICATION OF SUBJECT MATTER**

USPC - 514/509, 514/645; 424/400

According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/509, 514/645; 424/400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/509, 579, 645; 424/400 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT,PGPB,EPAB,JPAB); DialogWeb; Google Scholar
Search Terms Used: nitroglycerin, anesthesia, anesthetic, vasoconstrictor, adrenergic receptor agonist, catecholamine, levonordefrin, epinephrine, patch, inject, CARPULE.

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 3,742,951 A (AFFARONI) 03 July 1973 (03.07.1973); col 2, ln 14-17; col 3, ln 42-45; col 6, ln 55-67; col 10, ln 4-12.</td>
<td>1-24</td>
</tr>
<tr>
<td>Y</td>
<td>US 4,879,308 A (ALAM et al.) 07 November 1989 (07.11.1989); col 5, ln 43-46.</td>
<td>5, 16</td>
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</tbody>
</table>

1. Further documents are listed in the continuation of Box C.

- Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

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