

Local anesthetic mixture for topical application, and process for its preparation

The present invention relates to a mixture of local anesthetically active compounds in base form in order to obtain topical anesthesia through skin, and process for its preparation.

The object of the present invention is to obtain a possibility of utilizing local anesthetically active compounds in base form and to obtain a maximal concentration of active substance at the site of application on the skin in order to obtain local anesthesia with as low a dose as possible.

It is previously known, e.g. from Swedish Patent No. 352 239, to produce a local anesthetically active film comprising lidocaine in crystalline, microdispersed form in a solid carrier. The film is hereby intended to be used for anesthesia of mucous membranes, especially in the mouth cavity for blocking the nerves around the teeth in order to facilitate smaller incisions. Lidocaine is present in the film in 2 to 40% by weight. The drawback of said solid carrier is that an exactly determined dose can not be administered for penetration as in each case there is no possibility to determine how much of the lidocaine is left in the film carrier. A high concentration of lidocaine in the film carrier cannot be obtained and because penetration is dependent on concentration, more doses than necessary have to be used.

It is further known to combine two or more local anesthetics in the form of acid addition salts in aqueous solutions for injection. (Cf British Patent Specification No. 1 360 820). In such case the active agents are present in water soluble form and do not form a homogenous oil.

Previously, the problem has also been to utilize local anesthetically active compounds in the form of their bases as these are in crystalline form at room temperature and an acceptable effect is not obtained when the substance is applied in crystalline form.

The wish has then been to obtain an oil phase, containing high amount of local anesthetic, which, by means of a simple carrier, can be easily applied on the intended surface.

It has now surprisingly been found that it is possible to obtain such a form by means of the present invention, whereby moreover, a deeper penetrative effect as well as an improved local anesthesia is obtained, whereby the invention is characterized in that it comprises a first local anesthetic agent in the form of its base and as such having a melting point of 30 to 50°C and a second, different local anesthetic agent in the form of its base and as such having a melting point of above 30°C, preferably above 40°C, which agents when brought and heated together form a homogenous oil which has a melting point below 40°C, more preferably below 25°C.

In accordance with the invention

- a) a first local anesthetic agent in the form of its base is mixed with
- b) a second local anesthetic agent in the form of its base, whereby the agent under a) has a melting point of 30 to 50°C and the agent under b) has a melting point of above 30°C preferably above 40°C.

According to a preferred embodiment of the invention prilocaine or tetracaine in base form is mixed with one of benzocaine, lidocaine, bupivacaine, mepivacaine, or etidocaine or tetracaine in base form. It is evident that when tetracaine is used as first base it can not be used as second base.

According to a preferred embodiment prilocaine and benzocaine are mixed in a weight ratio of 63:37 to 96:4, preferably 65:35 to 80:20, most preferably 70:30.

According to a preferred embodiment prilocaine and lidocaine are mixed in a weight ratio of 42:58 to 80:20, preferably 47:53 to 62:38, most preferably 55:45.

According to another preferred embodiment prilocaine and etidocaine are mixed in a weight ratio of 55:45 to 95:5, preferably 60:40 to 80:20, most preferably 70:30.

According to a further preferred embodiment prilocaine and mepivacaine are mixed in a weight ratio of 80:20 to 97:3, preferably 85:15 to 90:10, most preferably 87:13.

According to another, further preferred embodiment prilocaine and bupivacaine are mixed in a weight ratio of 72:28 to 97:3, preferably 78:22 to 88:12, most preferably 85:15.

According to another preferred embodiment of the invention tetracaine and lidocaine in their base forms are mixed in a weight ratio of 40:60 to 70:30, preferably 45:55 to 55:45, most preferably 50:50.

Compounds under a) are prilocaine, tetracaine, butanilicaine and trimecaine.

Compounds under b) are benzocaine, lidocaine, bupivacaine, dibucaine, mepivacaine and etidocaine, as well as tetracaine, butanilicaine and trimecaine.

When the local anesthetic agents of a) and b) respectively in base, crystalline form are mixed together and heated the mixture shall have a resulting melting temperature of below 40°C and thereby form a homogenous oil. The oil is completely reformed if heated to the melting point even after a storage at low temperature for long time.

The above given weight ratios give mixtures which melt at temperatures below 40°C and are present in the form of an oil. The mixtures form eutectic mixtures with eutectic minima.

The present invention is intended for providing local anesthesia by means of topical application on skin, whereby a mixture of the invention of preferably prilocaine or tetracaine in the form of its base, and any of the compounds benzocaine, lidocaine, bupivacaine, mepivacaine, etidocaine or tetracaine in

a therapeutically effective amount is applied onto the skin surface through which anesthesia is to be obtained.

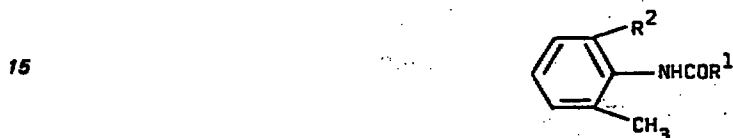
Thereby the mixture is added in a dose of 0.5 to 10 mg/cm² of skin.

The expression skin above relates to mucous membrane as well as intact or wounded skin.

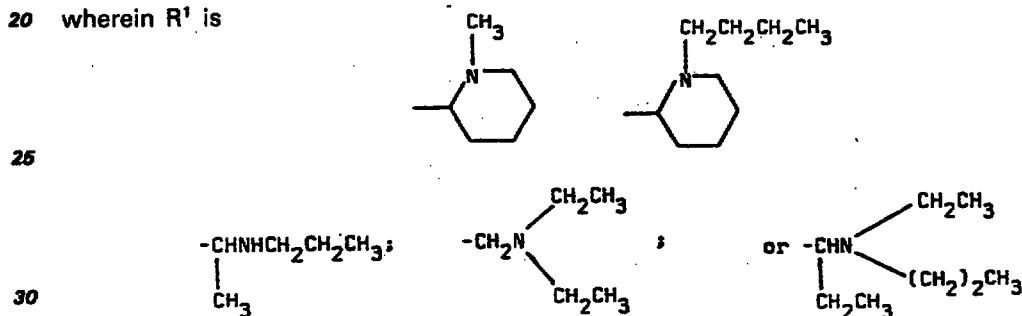
Further, injectable compositions are obtained, which injectable compositions contain in oil form one local anesthetic agent in base form and as such having a melting point of 30° to 50°C, and one other local anesthetic agent in base form and as such having a melting point of above 30°C, preferably above 40°C.

Such a composition will have a potent clinical use in more rapid onset of effect and/or prolonged duration of local anesthetic effect.

Above given compounds except for benzocaine, dibucaine, and tetracaine are represented by the general formula



20 wherein R¹ is



and R² is hydrogen or methyl, whereby R² is hydrogen when R¹ is



or wherein R¹ is —CH₂NH(CH₂)₃CH₃ and R² is chloro.

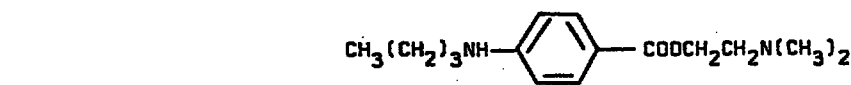
or wherein R¹ is —CH₂N(C₂H₅)₂ and R² is methyl and a further methyl group is present in para-

position to the carbamoyl containing side chain.

Benzocaine, 4-aminobenzoic acid ethyl ester, has the formula



Tetracaine, 2-(dimethylamino)ethylester of p-butylaminobenzoic acid has the formula



Dibucaine, 2-butoxy-N-(2-diethylaminoethyl)cinchonamide, has the formula



1-methyl-2-(2,6-xylylcarbamoyl)piperidine is known under the generic name mepivacaine and is sold under the trade mark Carbocaine®.

1-butyl-2-(2,6-xylylcarbamoyl)piperidine is known under the generic name bupivacaine and is sold under the trade mark Marcaine®.

2-propylamino-N-(2-tolyl)propionamide is known under the generic name prilocaine and is sold under the trade mark Citanest®.

Diethylaminoacet-2,6-xylylidide is known under the generic name lidocaine and is sold under the trade mark Xylocaine®.

2-(ethylpropylamino)-2',6'-n-butyroxylylidide is known under the generic name etidocaine and is sold under the trade mark Duranest®.

5 2-(butylamino)-6'-chloro-o-aceto-toluidide is known under the generic name butanilicaine.

2-diethylamino-2',4',6'-trimethylacetanilide is known under the generic name trimecaine.

Prilocaine has a melting point of 38°C, lidocaine a melting point of 68°C; etidocaine a melting point of 88°C; mepivacaine a melting point of 155°C; bupivacaine a melting point of 110°C; benzocaine a melting point of 89°C, tetracaine a melting point of 41°C, butanilicaine a melting point of 10 45—46°C, trimecaine a melting point of 44°C, and dibucaine a melting point of 65°C.

The oil formed from the mixture of local anesthetically active compounds in the form of their bases can be administered as such, or be transferred onto a carrier such as paper, or be introduced into a liquid carrier in order to form an emulsion, or as an emulsion in an ointment base. The different forms of preparation, depend on where one wants to obtain anesthesia.

15 After anesthesia through the skin the following incisions can be made.

Mucous membrane: the taking of a punch biopsy, smaller incisions in underlying mucous membrane, e.g. curettage, or gingivectomy or tooth tartar removal, elimination of needle prick pain at an injection. Otolaryngological incisions in nose and throat, e.g., biopsy or trepanation.

Paracentesis of drum-membrane.

20 Sample excision in the urogenitalic area.

Local anesthesia of cervix at delivery.

Intact skin: Smaller cutaneous incisions e.g. biopsy, or excision of naevi, elimination of needle prick pain before injection.

25 The present invention will in the following be described more in detail with reference to a number of examples.

Example 1

30	Prilocaine, base	52 g
	Lidocaine, base	48 g
		100 g

35 The two local anesthetically active compounds in crystalline form were mixed together and heated to 30°C, whereby the two compounds melted and formed a homogeneous oil. The mixture of crystals has a melting point of 22°C. The mixture did not crystallize even after a long storage at low temperature, when reheated to 22°C.

40 Example 2

	Prilocaine, base	70 g
45	Etidocaine, base	30 g
		100 g

50 The two local anesthetically active compounds, in crystalline form, were mixed together and were heated to 35°C, whereby the two compounds melted and formed a homogenous oil. The melting point of the mixture is 29°C.

Example 3

55	Prilocaine, base	85 g
	Mepivacaine, base	15 g
		100 g

The two local anesthetically active compounds in crystalline form, were mixed together and were heated to 40°C, whereby the two compounds melted and formed a homogenous oil. The melting point of the mixture is 33°C.

Example 4

Prilocaine, base	80 g
Bupivacaine, base	20 g
	100 g

The two local anesthetically active compounds, in crystalline form, were mixed together and heated to 40°C, whereby the compounds melted and formed a homogenous oil. The melting point of the mixture is 34°C.

Example 5

Prilocaine, base	70 g
Benzocaine, base	30 g
	100 g

The two local anesthetically active compounds, in crystalline form, were mixed together and were heated to 35°C, whereby the compounds melted and formed a homogenous oil. The melting point is 29°C.

Example 6

Tetracaine, base	50 g
Lidocaine, base	50 g
	100 g

The two local anesthetically active compounds, in crystalline form, were mixed together and were then heated to 25°C, whereby the compounds melted and formed a homogenous oil. The melting point of the mixture is 17°C.

Example 7

A mixture according to Example 1 was applied onto a carrier of paper in an amount of 1.5 mg/cm². The carrier, 1 cm², with the mixture was applied on the teeth gums in the vicinity of the root point of the tooth to be treated, prior to a deep cavity preparation in a vital tooth. After about 5 min the treatment could be carried out without giving the patient any pain sense.

Lidocaine and prilocaine alone do not give such an anesthetic effect.

Biological effect

The biological effect of the local anesthetic mixture of the present invention was determined in an experimental investigation of dermal analgesia by epidermal application of different local anesthetic formulations.

In the present investigation it was shown in 12 volunteers that the pain response, induced by pin-pricking, was partly blocked by epidermal application of different local anaesthetic formulations. Dermal analgesia (tested by pin-pricking) was most pronounced with a formulation consisting of a eutectic mixture of lidocaine base and prilocaine base, in a total concentration of 10%, as an aqueous emulsion. The other two tested formulations, containing 10% lidocaine and 10% prilocaine base respectively, were less effective, with regard to dermal analgesia, even if these produced some demonstrable effects, different from a placebo emulsion.

Material and method

12 healthy medical students from the Uppsala University Hospital took part in the study.

Pre-formed pads, consisting of cellulose fibres, 2 times 2 centimetres, were soaked by a standardized procedure in either an emulsion containing 5% lidocaine base + 5% prilocaine base, an emulsifying agent and water, 10% lidocaine base in the same vehicle, 10% prilocaine bases in the same

vehicle, or a placebo emulsion containing the emulsifying agent and water only. On one forearm of the volunteer the four different emulsions were applied under occlusive dressings consisting of impervious tape, while on the other arm the four emulsions were applied under a non-occlusive dressing, using surgical tape (3M). A certain distance between the application areas was chosen in order to avoid any risk of interference between them.

On the arms of the volunteers 11 and 12 the emulsions were applied directly to the skin, with no cellulose pads, but with occlusive and non-occlusive dressings applied as in the other volunteers.

The application time for the pads was 60 minutes.

Immediately after removal of the pads, the square areas under the two types of dressing were marked at the edges. A line was also marked within each applied area dividing them into two identical triangles. One of these surfaces were then used for the pin-prick experiments, the other for studying other effects.

Testing of dermal analgesia

The pin-pricking procedure was carried out with disposable dental needles. In each of the test areas 10 pin-pricks were made. 10/10 represents full analgesia, 0/10 no analgesia.

Results

The lidocaine-prilocaine emulsion was found to be significantly more effective than the lidocaine emulsion, the prilocaine emulsion and the placebo emulsion in producing dermal analgesia. By the XX test it was found that:

	Lidocaine-prilocaine versus placebo: $p = 0.001$	} Under occlusive bandage
	Lidocaine-prilocaine versus lidocaine: $p = 0.001$	
	Lidocaine-prilocaine versus prilocaine: $p = 0.01$	

	Lidocaine-prilocaine versus placebo: $p = 0.01$	} Under non occlusive bandage
	Lidocaine-prilocaine versus lidocaine: $p = 0.01$	
	Lidocaine-prilocaine versus prilocaine: $p = 0.01$	

The lidocaine and prilocaine emulsions were found to be insignificantly more effective than the placebo emulsion under occlusion as well as insignificantly different in effect to placebo under a non-occlusive bandage, as evident from Table I, statistical data, below.

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Table I

		<u>Pin-prick</u>							
5		<u>Occlusion</u>				<u>Non-occlusion</u>			
		L-P	L	P	Placebo	L-P	L	P	Placebo ¹¹
10	1	10/10	2/10	0/10	0/10	7/10	0/10	0/10	0/10
	2	10/10	0/10	0/10	0/10	10/10	0/10	0/10	0/10
	3	2/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
15	4	10/10	5/10	10/10	0/10	10/10	0/10	6/10	0/10
	5	9/10	3/10	1/10	0/10	7/10	1/10	0/10	0/10
20	6	8/10	2/10	0/10	0/10	9/10	0/10	0/10	0/10
	7	8/10	0/10	—	0/10	2/10	0/10	1/10	0/10
25	8	10/10	0/10	2/10	0/10	8/10	0/10	0/10	0/10
	9	7/10	2/10	0/10	4/10	0/10	0/10	0/10	0/10
	10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10
30	M ₁₋₁₀	7.40	1.40	1.44	0.40	5.10	0.10	0.70	0.20
	11	10/10	8/10	7/10	0/10	5/10	0/10	2/10	0/10
35	12	10/10	6/10	9/10	0/10	3/10	0/10	0/10	0/10
	M ₁₋₁₂	7.82	2.33	2.64	0.30	4.92	0.08	0.75	0.17

Statistical data

40	Patients No. 1—10	L-P/-placebo:t = 5.78***	L-P/placebo:t = 3.40**
		L-P/L:t = 5.87***	L-P/L:t = 3.70**
45	1—12	L-P/P:t = 11.33**	L-P/P:t = 3.50**
		L-P/placebo:t = 7.11***	L-P/placebo:t = 3.96**
50		L-P/L:t = 6.03***	L-P/L:t = 4.29**
		L-P/P:t = 4.30**	L-P/P:t = 3.97**

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60

65

Table I

	<u>Pin-prick</u>	
	<u>Occlusion</u>	
5		
	Patients No.	
	1—10	L/placebo:t = 1.58 n s
10		P/placebo:t = 0.80 n s
	1—12	L/placebo:t = 2.32*
		P/placebo:t = 1.71 n s
15	<u>Non-occlusion</u>	
	1—10	L/placebo:t = 0.42 n s
20		P/placebo:t = 0.76 n s
	1—12	L/placebo:t = 0.43 n s
		P/placebo:t = 1.05 n s
25	1)	
	L-P = lidocaine-prilocaine comp	
	L = lidocaine comp	
	P = prilocaine comp	

It has also been shown that the present combinations of local anesthetics possess worthwhile properties in inhibiting perspiration. They can thus be used in antiperspirant compositions as emulsions for roll-on, or emulsions or solutions for spraying.

35 Claims

1. Local anesthetic preparation for topical or parenteral application characterized in that it comprises as active component a first local anesthetic agent in the form of its base and as such having a melting point of 30 to 50°C, and a second, different local anesthetic agent in the form of its base and as such having a melting point of above 30°C, preferably above 40°C which agents when brought and heated together form a homogenous oil, which has a melting point below 40°C, more preferably below 25°C.
2. Process for the preparation of local anesthetically active preparations according to claim 1, characterized in that a first local anesthetic agent in the form of its base and as such having a melting point of 30 to 50°C is mixed with a second, different local anesthetic agent in the form of its base, and as such having a melting point of above 30°C, preferably above 40°C.
3. Process according to claim 2 characterized in that the first local anesthetic agent is prilocaine or tetracaine in the form of its base and the second local anesthetic agent is benzocaine, lidocaine, bupivacaine, mepivacaine, etidocaine, or tetracaine in the form of its base.
4. Process according to claims 2—3, characterized in that prilocaine and benzocaine are mixed with each other in a weight ratio of 63:37 to 96:4.
5. Process according to claim 4, characterized in that the weight ratio is 65:35 to 80:20, preferably 70:30.
6. Process according to claims 2—3, characterized in that prilocaine and lidocaine are mixed with each other in a weight ratio of 42:58 to 80:20.
7. Process according to claim 6, characterized in that the weight ratio is 47:53 to 62:38, preferably 55:45.
8. Process according to claims 2—3, characterized in that prilocaine and etidocaine are mixed with each other in a weight ratio of 55:45 to 95:5.
9. Process according to claim 8, characterized in that the weight ratio is 60:40 to 80:20, preferably 70:30.
10. Process according to claims 2—3, characterized in that prilocaine and mepivacaine are mixed with each other in a weight ratio of 80:20 to 97:3.
11. Process according to claim 10, characterized in that the weight ratio is 85:15 to 90:10, preferably 87:13.

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35 Claims

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2. Process for the preparation of local anesthetically active preparations according to claim 1, characterized in that a first local anesthetic agent in the form of its base and as such having a melting point of 30 to 50°C is mixed with a second, different local anesthetic agent in the form of its base, and as such having a melting point of above 30°C, preferably above 40°C.

3. Process according to claim 2 characterized in that the first local anesthetic agent is prilocaine or tetracaine in the form of its base and the second local anesthetic agent is benzocaine, lidocaine, bupivacaine, mepivacaine, etidocaine, or tetracaine in the form of its base.

4. Process according to claims 2—3, characterized in that prilocaine and benzocaine are mixed with each other in a weight ratio of 63:37 to 96:4.

5. Process according to claim 4, characterized in that the weight ratio is 65:35 to 80:20, preferably 70:30.

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7. Process according to claim 6, characterized in that the weight ratio is 47:53 to 62:38, preferably 55:45.

8. Process according to claims 2—3, characterized in that prilocaine and etidocaine are mixed with each other in a weight ratio of 55:45 to 95:5.

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10. Process according to claims 2—3, characterized in that prilocaine and mepivacaine are mixed with each other in a weight ratio of 80:20 to 97:3.

11. Process according to claim 10, characterized in that the weight ratio is 85:15 to 90:10, preferably 87:13.





12. Process according to claims 2—3, characterized in that prilocaine and bupivacaine are mixed with each other in a weight ratio of 72:28 to 97:3.

13. Process according to claim 12, characterized in that the weight ratio is 78:22 to 88:12, preferably 85:15.

14. Process according to claims 2—3, characterized in that tetracaine and lidocaine are mixed with each other in a weight ratio of 40:60 to 70:30.

15. Process according to claim 14, characterized in that the weight ratio is 45:55 to 55:45, preferably 50:50.

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Patentansprüche

1. Lokalanästhetisches Präparat für örtliche oder parenterale Anwendung, dadurch gekennzeichnet, daß es als aktive Komponente ein erstes lokalanästhetisches Mittel in der Form seiner Base, das als solches einen Schmelzpunkt von 30 bis 50°C besitzt, und ein zweites, hiervon verschiedenes lokalanästhetisches Mittel in der Form seiner Base, das als solches einen Schmelzpunkt oberhalb 30°C, vorzugsweise oberhalb 40°C besitzt, enthält, wobei die Mittel, wenn sie zusammengebracht und zusammen erhitzt werden, ein homogenes Öl bilden, welches einen Schmelzpunkt unterhalb 40°C, bevorzugt unterhalb 25°C besitzt.

2. Verfahren zur Herstellung von lokalanästhetisch wirksamen Präparaten nach Anspruch 1, dadurch gekennzeichnet, daß ein erstes lokalanästhetisches Mittel in der Form seiner Base, das einen Schmelzpunkt von 30 bis 50°C besitzt, mit einem zweiten, hiervon verschiedenen lokalanästhetischen Mittel in der Form seiner Base, das einen Schmelzpunkt oberhalb 30°C, vorzugsweise oberhalb 40°C besitzt, vermischt wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das erste lokalanästhetische Mittel Prilocain oder Tetracain in der Form ihrer Base und das zweite lokalanästhetische Mittel Benzocain, Lidocain, Bupivacain, Mepivacain, Etidocain oder Tetracain in der Form ihrer Base ist.

4. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Prilocain und Benzocain miteinander in einem Gewichtsverhältnis von 63:37 bis 96:4 miteinander vermischt werden.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das Gewichtsverhältnis 65:35 bis 80:20, vorzugsweise 70:30 ist.

6. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Prilocain und Lidocain miteinander in einem Gewichtsverhältnis von 42:58 bis 80:20 vermischt werden.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß das Gewichtsverhältnis 47:53 bis 62:38, vorzugsweise 55:45 ist.

8. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Prilocain oder Etidocain miteinander in einem Gewichtsverhältnis von 55:45 bis 95:5 vermischt werden.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß das Gewichtsverhältnis 60:40 bis 80:20, vorzugsweise 70:30 ist.

10. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Prilocain und Mepivacain miteinander in einem Gewichtsverhältnis von 80:20 bis 97:3 vermischt werden.

11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß das Gewichtsverhältnis 85:15 bis 90:10, vorzugsweise 87:13 ist.

12. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Prilocain und Bupivacain miteinander in einem Gewichtsverhältnis von 72:28 bis 97:3 vermischt werden.

13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, daß das Gewichtsverhältnis 78:22 bis 88:12, vorzugsweise 85:15 ist.

14. Verfahren nach Anspruch 2 bis 3, dadurch gekennzeichnet, daß Tetracain und Lidocain miteinander in einem Gewichtsverhältnis von 40:60 bis 70:30 vermischt werden.

15. Verfahren nach Anspruch 14, dadurch gekennzeichnet, daß das Gewichtsverhältnis 45:55 bis 55:45, vorzugsweise 50:50 ist.

Revendications

1. Préparation à action anesthésique locale pour une application topique ou parentérale, caractérisée en ce qu'elle comprend comme constituant actif un premier agent à action anesthésique locale sous la forme de sa base et ayant comme tel un point de fusion de 30 à 50°C et un second agent à action anesthésique locale sous la forme de sa base et ayant comme tel un point de fusion supérieur à 30°C, de préférence supérieur à 40°C, lesquels agents lorsqu'ils sont mélangés et chauffés ensemble forment une huile homogène qui a un point de fusion inférieur à 40°C, de préférence inférieur à 25°C.

2. Procédé pour l'obtention de préparations à action anesthésique locale selon la revendication 1, caractérisé en ce qu'un premier agent à action anesthésique locale sous la forme de sa base et ayant comme tel un point de fusion de 30 à 50°C est mélangé avec un second agent à action anesthésique locale, différent du premier, sous forme de sa base, et ayant comme tel un point de fusion supérieur à 30°C, de préférence supérieur à 40°C.

3. Procédé selon la revendication 2, caractérisé en ce que le premier agent à action anesthésique locale est la prilocaïne ou la tétracaïne sous la forme de leur base et le second agent à action anesthésique locale est la benzocaïne, la lidocaïne, la bupivacaïne, la mépivacaïne, l'étidocaïne ou la tétracaïne sous forme de leur base.

5 4. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la prilocaïne et la benzocaïne sont mélangées ensemble dans un rapport pondéral de 63:37 à 96:4.

5. Procédé selon la revendication 4, caractérisé en ce que le rapport pondéral est compris entre 65:35 et 80:20, et est de préférence de 70:30.

10 6. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la prilocaïne et la lidocaïne sont mélangées ensemble dans un rapport pondéral de 42:58 à 80:20.

7. Procédé selon la revendication 6, caractérisé en ce que le rapport pondéral est compris entre 47:53 et 62:38, et est de préférence de 55:45.

8. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la prilocaïne et l'étidocaïne sont mélangées ensemble dans un rapport pondéral de 55:45 à 95:5.

15 9. Procédé selon la revendication 8, caractérisé en ce que le rapport pondéral est compris entre 60:40 et 80:20, et est de préférence de 70:30.

10. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la prilocaïne et la mépivacaïne sont mélangées ensemble dans un rapport pondéral de 80:20 à 97:3.

20 11. Procédé selon la revendication 10, caractérisé en ce que le rapport pondéral est compris entre 85:15 et 90:10 et est de préférence de 87:13.

12. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la prilocaïne et la bupivacaïne sont mélangées ensemble dans un rapport pondéral de 72:28 à 97:3.

13. Procédé selon la revendication 12, caractérisé en ce que le rapport pondéral est compris entre 78:22 et 88:12, et est de préférence de 85:15.

25 14. Procédé selon l'une des revendications 2 ou 3, caractérisé en ce que la tétracaïne et la lidocaïne sont mélangées ensemble dans un rapport pondéral de 40:60 à 70:30.

15. Procédé selon la revendication 14, caractérisé en ce que le rapport pondéral est compris entre 45:55 et 55:45, et est de préférence de 50:50.

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