

"CHLOROPROCAINE-BASED PHARMACEUTICAL COMPOSITION FOR REPEATED INTRATHECAL ADMINISTRATION"

5 DESCRIPTION

FIELD OF THE INVENTION

The present invention relates to a chloroprocaine-based pharmaceutical composition for repeated intrathecal administration.

10 The present invention originates in the sector of injectable pharmaceutical preparations suitable for spinal or intrathecal anesthesia.

Specifically, the present invention relates to the use of chloroprocaine-based injectable solutions for intrathecal anesthesia.

STATE OF THE ART

15 Spinal anesthesia is a central loco-regional anesthesia technique in which an injection solution containing a local anesthetic as active principle is injected into the dura mater, i.e. the outer meningeal membrane which protects the spinal cord. Typically, the injection is made using special thin needles between the spinous processes of two vertebrae.

20 Once injected, the solution containing the local anesthetic mixes with the cerebrospinal fluid which surrounds the spinal cord and is located between the cord and the dura, blocking the conduction of nerve impulses to the brain and causing the reversible loss of sensitivity, which may or may not be accompanied by motor paralysis. The spinal cord in all cases remains protected by the pia
25 mater, the innermost meningeal membrane.

By mixing with the cerebrospinal fluid the solution containing the local anesthetic determines the anesthesia of the front and rear part of the spinal cord, i.e. the regions from where the motor and sensitive fibers originate. The administration of the anesthetic solution thus determines the absence of sensitivity in territories
30 innervated by the concerned nerve roots and at the same time inhibits muscular activity.

Generally, spinal anesthesia is used for operations on organs of the lower

abdomen and the lower limbs. Typical examples of the use of spinal anesthesia are appendectomy, hernioplasty, Caesarean section, knee arthroscopy, bunion correction etc.

When the anesthetic used for spinal anesthesia is isobaric, i.e. has the same specific weight as the cerebrospinal fluid or liquor, all segments are generally concerned, thus producing a response which is commensurate with the amount of injected drug.

The effect of the spinal anesthesia may last for from one to approximately three hours, according to the type of local anesthetic used.

Local spinal anesthesia techniques may be further divided into epidural injection and intrathecal injection. In the latter case, the solution containing local anesthetic is injected locally into the so-called subarachnoid space.

While the intrathecal technique is more invasive than the epidural technique, because the injection concerns an innermore zone of the spinal cord, it has the advantage of requiring considerably lower doses of local anesthetic, approximately 1/10th. This aspect is generally an advantage because local anesthetics have a given neurotoxicity.

Despite this, the intrathecal administration of local anesthetics may also imply neurotoxicity and is not free from drawbacks. These side effects become even more apparent in the case of repeated doses of local anesthetic.

Furthermore, not all local anesthetics provide an adequate response in case of spinal or intrathecal administration. For example, Hodgson PS, Liu SS, Batra MS et al. (Procaine compared with lidocaine for incidence of transient neurologic symptoms, Reg. Anesth. Pain Med, 2000; 25: 218-22) report a percentage of cases refractory to local anesthesia with procaine equal to 17%.

Other local anesthetics, such as lidocaine, provide more adequate responses for spinal administration. However, its use in spinal cord anesthesia implies given risks for the patient's health in all cases.

For example, it is known from Pollock JE. (Transient neurologic symptoms: etiology, risk factors, and managements, Reg. Anesth. Pain Med. 2002; 27: 581-6) that the use of lidocaine in spinal anesthesiological practice is associated to the onset of transient neurologic syndrome (TNS).

Clinical research has thus addressed the use of alternative local anesthetics, such as bupivacaine. With reference to *in vivo* rat models, Sakura et al. in *Anesth. Analg.* 2005; 101:541-7 observed that bupivacaine induces less severe morphological damage and functional worsening than lidocaine, when both
5 anesthetics are administrated intrathecally, in equipotent concentrations.

However, bupivacaine is a local anesthetic with long-lasting action, and for this reason its use in spinal anesthesia is often associated to phenomena of urinary retention. Its use is thus limited to cases in which long-lasting spinal anesthesia is required.

10 Among short-lasting local anesthetics, the use of chloroprocaine is also known. However, the use of this local anesthetic is limited to intrathecal administration today. Indeed, most chloroprocaine formulations currently available on the market (Chloroprocaine Hydrochloride Injection, USP made by Bedford Laboratories, Boehringer Ingelheim and Nesacain®-MPF made by AstraZeneca) are authorized
15 for epidural but not intrathecal application. Consequently, chloroprocaine is currently used only marginally for intrathecal administration.

The use of a single dose of an aqueous solution of chloroprocaine free of preservatives for intrathecal administration is known from Italian patent no. 1366154 by the Applicant.

20 The presumed neurotoxicity of chloroprocaine has constituted until today a serious deterrent to intrathecal administration of this drug in repeated doses.

Indeed, according to current anesthesiological practice, the repeated spinal or intrathecal administration of chloroprocaine is not only recommended but should be instead avoided in order to limit the risks related to the neurotoxicity of this
25 drug.

For this reason, current medical practice requires to use a different local anesthetic for doses following the first in the cases in which the spinal or intrathecal administration of chloroprocaine must be repeated.

However, in the field of anesthesiology, the recurrent use of spinal and intrathecal
30 anesthesia for one day surgery has increased the demand for drugs with local anesthetic action suitable for repeated intrathecal administration without significantly increasing neurotoxicity risks.

SUMMARY

The applicant of the present invention unexpectedly discovered that 2-chloroprocaine can be repeatedly administrated spinally/intratheally without detecting the neurotoxicity attributed to the drug.

- 5 According to a first aspect, the present invention relates to 2-chloroprocaine and salts and/or derivatives and/or esters thereof for use in central loco-regional anesthesia by intrathecal administration in repeated doses.

Chloroprocaine, or 2-(diethylaminoethyl) 4-amino-2-chlorobenzoate (CAS 3858-89-7), in form of hydrochloride salt (chloroprocaine HCl) is a narcotic substance.

- 10 The pharmaceutical profile of chloroprocaine, in particular in form of hydrochloride, is similar to that of lidocaine, with a typically short onset of 5-15 minutes and a typically short-lasting effect equal to 30-60 minutes.

In the scope of the present invention, 'chloroprocaine' means a substance as-is or in salified form as chloroprocaine hydrochloride or chloroprocaine derivatives.

- 15 The offset of chloroprocaine is rapid; its plasma half-life is indeed comprised in the range from 45 to 60 seconds, which makes it the anesthetic with most rapid offset of those clinically used known today.

According to other aspects, the invention extends to an injectable aqueous solution of chloroprocaine HCl free of preservatives for central loco-regional
20 anesthesia by intrathecal administration in repeated doses

According to another embodiment, the chloroprocaine HCl by intrathecal administration in repeated doses is an injectable aqueous solution having pH from 3 to 4.

- 25 In some embodiments, the chloroprocaine administered in repeated doses according to the invention has a concentration from 0.5 to 1.5% by weight.

In the scope of the present invention, 'repeated doses' mean the intrathecal administration of at least one dose of chloroprocaine after an initial dose.

- 30 In some embodiments, the repeated doses of chloroprocaine are from 2 to 10, e.g. from 3 to 7 subsequent doses, each of which may be typically administered once a day.

In some embodiments, the treatment with repeated doses of chloroprocaine includes the intrathecal administration every day for seven consecutive days.

'Dose of chlorprocaine' means an amount of chlorprocaine and/or salts or derivatives thereof effective to determine a central loco-regional anesthesia when administered intrathecally.

BRIEF DESCRIPTION OF THE DRAWINGS

5 The present invention will be described in detail below with reference to the figures, in which:

Figure 1 is a chart showing the motor function score for a group of rats to which a daily dose of vehicle, chlorprocaine 0.5%, chlorprocaine 1%, chlorprocaine 2% and bupivacaine 0.5% was administered for seven consecutive days intrathecally according to the protocol illustrated in Example 1 below;

10 Figure 2 is a chart showing the weight variation of the rats treated for seven consecutive days by intrathecal administration with repeated daily dose of vehicle, chlorprocaine 0.5%, chlorprocaine 1%, chlorprocaine 2% and bupivacaine 0.5% according to the test in Example 1. The data are presented as $\pm$ SEM average of 6 rats;

Figure 3 is a chart showing the tail flick latency of rats treated for 7 consecutive days by intrathecal administration with daily dose of vehicle, chlorprocaine 0.5%, chlorprocaine 1%, chlorprocaine 2% and bupivacaine 0.5% according to the test in Example 1. The data are presented as $\pm$ SEM average of 6 rats;

20 Figure 4 is a chart showing the nerve injury score in sections obtained from a 10 mm caudal portion of conus medullaris (cauda equina) in rats treated for 7 days by intrathecal administration with repeated doses of vehicle, chlorprocaine 0.5%, chlorprocaine 1%, chlorprocaine 2% and bupivacaine 0.5% according to the test in Example 1. An injury score from 0 to 3 was attributed to each section. The injury score for each cross section was calculated as average score of all clusters in each section. The data are presented as $\pm$ SEM average of 6 rats.

The present invention will now be described with reference to the following examples which are supplied by way of examples only without limiting the invention in any manner.

30 DETAILED DESCRIPTION OF THE INVENTION

Some embodiments of the invention include the use of an injectable aqueous solution of chlorprocaine or derivatives/salts thereof, in particular chlorprocaine

hydrochloride, wherein the aqueous solution is essentially free of preservatives, antioxidants and the pH of which is from 3 to 4.

In particular, the applicant has discovered that, contrary to expectations, the repeated intrathecal administration of chloroprocaine HCl does not determine
5 detectable neurotoxicity and a significant increase in the typical side effects of repeated spinal and intrathecal administration of the local anesthetic.

This discovery is surprising because the indications contained in scientific literature induced anesthesiologists to administer a different type of local anesthesia if needing to administer a second dose of chloroprocaine close to the
10 first.

The essential absence of neurotoxicity of the repeated intrathecal administration of chloroprocaine HCl in aqueous solution, e.g. with pH 3 - 4, is further surprising. Indeed, one would expect that the repeated administration in the spinal column of a potentially neurotoxic active principle, such as chloroprocaine in a very acid
15 solution, to show evident signs of cell toxicity. On the contrary, there was no clinical evidence of such toxicity using repeated doses of chloroprocaine in accordance with the embodiments of the invention.

Specifically, the inventors have found that contrary to expectations on the basis of common general knowledge, 12 hours after a first intrathecal administration of
20 chloroprocaine HCl even repeated doses of the drug may be injected, without increasing neurotoxicity in statistically significant manner.

In accordance with some embodiments, the invention relates to the intrathecal administration in a human being over 24 hours of at least one dose of an injectable chloroprocaine-based aqueous solution of the afore-described type, repeated
25 every day for a time period from two to ten days.

In accordance with certain embodiments, the present invention provides an injectable pharmacological composition comprising chloroprocaine or the salts and/or derivatives thereof for central loco-regional anesthesia by intrathecal administration of a daily dose of 5-150 mg of chloroprocaine or of a salt and/or
30 derivatives thereof repeated for a time period from 2 to 10 days, typically from 3 to 7 days. In some of these embodiments, the daily dose may be single or fractioned into two-three doses.

In some embodiments, the chloroprocaine dose which may be administered intrathecally ranges from 10 to 100 mg/day, from 15 to 80 mg/day, from 30 to 60 mg/day, repeated for a time period from 2 to 10 days, typically from 3 to 7 days.

In accordance with some embodiments, a low-dose solution of chloroprocaine HCl typically of 5-15 mg/ml is administered intrathecally in repeated doses, for example 1-3 a day, for 2-10 days or 3-7 days.

The intrathecal administration of repeated doses of chloroprocaine HCl, e.g. one dose over 24 hours for three-seven days has the following advantages:

i) a rapid recovery of the organic functions of the patient after the anesthetic treatment. The favorable pharmacological profile of chloroprocaine, which combines fast onset with fast offset, allows the patient to perambulate a short time period after the treatment and to limit the risks of urinary retention found after repeated use of the common local anesthetics having a longer half-life.

ii) a high comfort for patients even after repeated dose administration, e.g. one injection/day for 7 days.

iii) low systematic toxicity because the half-life of chloroprocaine HCl is lower than one minute. This advantage is consequent to the rapid offset of chloroprocaine by virtue of plasma pseudo cholinesterase.

iv) a reduced incidence of typical side effects of the local anesthetics. In particular, the concomitant administration of medium-long-lasting action local anesthetics with opioids, commonly performed to complete the analgesic action, determines the onset of collateral effects, such as itching and skin rashes. With the repeated intrathecal administration of chloroprocaine HCl, the onset of these side effects found with the use of conventional local anesthetics is considerably limited.

In accordance with an embodiment, the present invention includes the intrathecal administration of repeated doses of an injectable aqueous solution comprising 5.0-15 mg of chloroprocaine HCl, 4-12 mg NaCl per 1 ml of water and HCl in an amount sufficient to give a pH from 3.0 to 4.0 to the solution.

An embodiment includes the repeated intrathecal use of an injectable chloroprocaine-based aqueous solution having osmolarity from 270 to 300 mOsm/kg.

According to a further embodiment, the aqueous solution of chlorprocaine HCl used for repeated intrathecal administration has a relative density at 37°C of 1.0003 to 1.0020 g/ml.

According to some embodiments, the injectable aqueous solution for repeated intrathecal administration comprises an amount of chlorprocaine HCl from 0.5 to 1.5% by weight, preferably 1% ca.

For example, a lumbar trunk anesthesia for short surgery can be obtained by intrathecal administration of a variable amount of chlorprocaine HCl variable from 30 to 50 mg and the administration of the same amount of drug can be repeated the following day with essentially with no side effects.

In some embodiments, the invention relates to a pharmaceutical composition comprising chlorprocaine or salts and/or derivatives thereof for use in central loco-regional anesthesia by intrathecal administration in repeated doses either separate, sequential or simultaneous with an analgesic drug and/or with adrenaline. Typically the dose may be repeated every 2-10 days, preferably every 3-7 days.

Typically, the administration of chlorprocaine in repeated doses may be required whenever the therapeutic need arises, e.g. in the case of repeated surgery, endoscopy, localized persistent pain treatment and further clinical indications, or as palliative cure.

In accordance with another aspect, the present invention relates to a central loco-regional anesthesia method comprising the intrathecal administration in repeated doses of an injectable chlorprocaine-based pharmaceutical composition according to any one of the described or exemplified embodiments.

In certain embodiments, the method of the invention includes the intrathecal administration of at least 5-150 mg dose/day of chlorprocaine HCl every 1-10 days, 3-7 days.

By way of example, it is possible to infuse by intrathecal administration an injectable aqueous solution with an acid pH from 3 to 4, containing from 5 to 15 mg/ml of chlorprocaine HCl, preferably free of preservatives and/or stabilizers, repeated for 2-10 days or 3-7 days.

In some embodiments, a pharmaceutical composition containing chloroprocaine or salts thereof is either administered or infused in repeated doses by means of a spinal catheter. The infusion of the composition or solution of chloroprocaine or a salt thereof according to conventional anesthesiological techniques known by persons skilled in the art.

EXAMPLES

Example 1

A pre-clinical trial was carried out to assess the neurotoxicity of 2-chloroprocaine by intrathecal administration in repeated doses using a saline solution as control.

Results

Group treated with saline solution (vehicle)

A first group of six rats was repeatedly treated with 20 µl of an injectable saline solution by intrathecal administration once a day.

No significant changes were observed in the behavior of the rats after seven consecutive days of treatment. The rats treated with repeated doses with the vehicle did not show signs of sleepiness, tendency to bite or scratch, regurgitation or vomiting, altered defecation or abnormal salivation.

The motor functions remained entirely unchanged. Only on the seventh day did two of the six rats show partial unilateral paralysis which only slightly influenced normal posture.

The body weight was not influenced by the administration in repeated doses and showed an increasing physiological trend.

The tail flick latency before injecting the vehicle was in line with historical laboratory data and appropriate to the test system. The basic latency indicates a tendency to reduction over the seven days of the test, although in non-significant manner. No evident signs of inflammation or irritation were found in the caudal regions subject to stimulation by heating.

A 10 mm portion of the *conus medullaris* (*cauda equina*) was analyzed seven days after the intrathecal injection. The histological score was 0.809 ± 0.067 . The results are summarized in the chart shown in Fig. 4.

2-chloroprocaine 0.5% group (C0.5)

No appreciable changes in behavior were observed after injecting 20 µl of 2-chloroprocaine 0.5% until the seventh day of the trial. The rats treated repeatedly by intrathecal administration of a dose of 2-chloroprocaine 0.5% a day did not show signs of sleepiness, tendency to bite or scratch, regurgitation or vomiting, altered defecation or abnormal salivation. Motor functions remained unchanged. Signs of partial unilateral paralysis (score 1), which only partially influenced normal posture, appeared on the sixth day in one rat and on the seventh day in two rats.

Body weight was not altered by the administration of 20 µl of 2-chloroprocaine 0.5% and showed a physiologically increasing trend.

No statistically significant difference was observed by comparing the administration of 20 µl of 2-chloroprocaine 0.5% with the group treated with the vehicle ($F=0.12$ $DFn=1$, $DFd=70$ $Pvalue = 0.7337$).

The tail flick latency before injecting 20 µl of 2-chloroprocaine 0.5% was comparable with the values of rats treated with vehicle. The basic latency indicated a reduction tendency over the seven days of the test although in non-significant manner. No evident signs of inflammation or irritation were found in the caudal regions subject to stimulation by heating.

The administration of 20 µl of 2-chloroprocaine 0.5% caused a slight increase of tail flick latency after 20 minutes of exposure, although this effect was not significant from the statistic point of view.

The histological score did not show statistic differences when 2-chloroprocaine 0.5% compared with the control group (0.764 ± 0.083).

2-chloroprocaine 1% group (C1)

No appreciable changes in behavior were observed after injecting 20 µl of 2-chloroprocaine 1% until the seventh day of the trial. The rats were treated repeatedly by intrathecal administration of a dose of 2-chloroprocaine 1% a day did not show signs of sleepiness, tendency to bite or scratch, regurgitation or vomiting, altered defecation or abnormal salivation.

Motor functions: signs of partial unilateral paralysis (score 1), which only partially influenced normal posture, appeared on the fifth day in one rat and on the sixth and seventh day in two rats.

Body weight was not altered by the administration of 20 µl of 2-chloroprocaine 1%.

No statistically significant difference was observed by comparing the administration of 20 µl of 2-chloroprocaine 1% with the group treated with the vehicle ($F=0.05$ P value = 0.8353).

Tail flick latency before injecting 20 µl of 2-chloroprocaine 1% was comparable with the values of rats treated with vehicle.

A significant increase of tail flick latency was observed 20 minutes after injecting 20 µl of 2-chloroprocaine 1% and this effect was statistically significant in the trial ($P<0.05$).

The histological score did not show statistic differences when 2-chloroprocaine 1% was compared with the control group (0.954 ± 0.122). A moderately inflammatory infiltrate in some fibers was identified in two rats.

2-chloroprocaine 2% group (C2)

No appreciable changes in behavior were observed after injecting 20 µl of 2-chloroprocaine 2% until the seventh day of the trial, including a single rat with diarrhea on the sixth and seventh day.

The rats treated repeatedly by intrathecal administration of a dose of 2-chloroprocaine 2% a day did not show signs of sleepiness, tendency to bite or scratch, regurgitation (except for one) or vomiting, altered defecation or abnormal salivation.

Motor functions: two rats showed partial unilateral paralysis (score 1) on the third day which only partially influenced normal posture. The symptoms became bilateral for one rat on the fourth day. A change of posture (score 1) was observed in all rats on the sixth day, while two rats showed bilateral weakness which influenced perambulation on the seventh day (score 2).

The body weight decreased after administering 20 µl of 2-chloroprocaine 2%, showing a clear reduction trend along the study period. The effect did not reach statistic significance when compared with the group treated with vehicle in an experiment of these proportions ($F=1.37$ value $P=0.2691$).

Tail flick latency before injecting 20 µl of 2-chloroprocaine 2% was comparable with the values of rats treated with vehicle.

A significant increase of tail flick latency was observed 20 minutes after the administration by injecting 20 µl of 2-chloroprocaine 2% and this effect was statistically significant in the trial ($P < 0.001$).

The histological score showed no statistic differences when 2-chloroprocaine 2% was compared with the control group (1.034 ± 0.1170). A moderately inflammatory infiltrate in some fibers was identified in three rats.

Bupivacaine 0.5% group (B0.5)

Changes of behavior were observed after injecting 20 µl of bupivacaine 0.5% to the seventh day of the study included modest sleepiness in one rat on the fifth day and in two rats on the sixth and seventh days. Excluding these rats, the other animals of the group repeated by intrathecal administration of a dose of bupivacaine 0.5% a day did not show signs of sleepiness, tendency to bite or scratch, regurgitation (except for one) or vomiting, altered defecation or abnormal salivation.

Motor functions: two rats showed partial unilateral paralysis (score 1) on the third and fourth day which only partially influenced normal posture. A change of posture (score 1) could be observed in all rats on the sixth day. Furthermore, two rats on the sixth day and three rats on the seventh day showed bilateral limbic weakness which influenced perambulation (score 2).

Body weight decreased by 0.5% during the administration of bupivacaine, showing a clear reduction trend during the study period compared with that shown for group C2. The effect did not reach statistic significance when compared with the group treated with vehicle in an experiment of these proportions ($F = 0.54$ P value = 0.4785).

Tail flick latency before injecting 20 µl of bupivacaine 0.5% was comparable with the values of rats treated with vehicle.

A significant increase of tail flick latency was observed 20 minutes after the administration by injecting 20 µl of bupivacaine 0.5% and this effect was statistically significant in the trial ($P < 0.001$).

The histological score did not show statistic differences by comparing bupivacaine 0.5% (0.979 ± 0.110) with the control group. A moderately inflammatory infiltrate in some fibers was identified in one rat.

Conclusions

The test frequency and the repeated injection tended to make some rats irritable, but this aspect appeared to be independent from the drug because it was also observed in animals treated with the vehicle.

- 5 The increased variability of the measurements observed during the study is likely referred to this.

Furthermore, rats have a high learning capacity and this explains the basic tail flick latency observed over the 7 day period.

- 10 This trial, including the post-surgery recovery period, uses the maximum period of time for which rats could be maintained easily and safely with spinal catheter.

- Only minor alterations in behavior was observed in all trial groups. With regards to the worsening of motor functions, it is apparent that the repeated administration of effective doses of local anesthetics produces an increased incidence of alterations, evaluated as abnormal posture and in some cases as limbic weakness.

- 15 On the other hand, concentrations of 2-chloroprocaine 2% and bupivacaine 0.5% appeared less tolerated than other administered concentrations in nearly equivalent manner; it is not instead possible to establish substantial differences between the treated groups of animals in terms of neurological damage after carrying out behavior and motor functionality tests.

- 20 The histo-pathological assess of a 10 mm caudal portion of the conus medullaris (cauda equina) confirmed the behavioral observations. No obvious alterations were observed in the treatment groups. In some cases, it was possible to identify a moderately inflammatory infiltrate in some fibers after repeated administrations of 2-chloroprocaine 1 and 2% and of bupivacaine 0.5%.

Example 2

Standard protocol

- 30 The repeated anesthiaprotocol included the slow injection by intrathecal administration of an injectable solution containing chloroprocaine HCl 0.5%, 1.2% NaCl, and HCl in amount sufficient to give a pH of 4.

The chloroprocaine solution was injected once a day for three consecutive days.

Example 3

Standard protocol

The repeated anesthesiaprotocol included the slow injection by intrathecal administration of an injectable solution containing chloroprocaine HCl 1.5%, 0.4 % NaCl, and HCl in amount sufficient to give a pH of 3.

- 5 The chloroprocaine solution was injected once a day for 7 consecutive days.

Example 4**Standard protocol**

The repeated anesthesiaprotocol included the slow injection by intrathecal administration of an injectable solution containing chloroprocaine HCl 1.0%, 0.72%
 10 NaCl, and HCl in amount sufficient to give a pH of 3.5, to which dexamethasone phosphate 0.4% as corticosteroids anti-inflammatory was added.

The combined chloroprocaine/dexamethasone solution was injected once a day for 3 consecutive days.

Example 5

- 15 **Standard protocol**

The repeated anesthesiaprotocol included the slow injection by intrathecal administration of an injectable solution containing chloroprocaine HCl 1.0%, 0.72 % NaCl, and HCl in amount sufficient to give a pH of 3.5, to which a 2% solution of acetaminophen was added.

- 20 The combined chloroprocaine/acetaminophen solution was injected once a day for 7 consecutive days.

Example 6

Anesthetic pharmaceutical composition for intrathecal use having the following mg/ml formula:

- | | |
|-----------------------|---------------------------|
| 25 Chloroprocaine HCl | 5 mg |
| NaCl | 7 mg |
| Water | 1 ml |
| HCl | to adjust pH from 3 to 4. |

Example 7

- 30 Anesthetic pharmaceutical composition for intrathecal use having the following mg/ml formula:

Chloroprocaine HCl	15 mg
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NaCl	4 mg
Water	5 ml
HCl	enough to adjust pH from 3 to 4.

5 Example 8

Anesthetic pharmaceutical composition for intrathecal use having the following mg/ml formula:

Chloroprocaine HCl	75 mg
NaCl	2.3 mg
10 Water	5 ml
HCl	to adjust pH from 3 to 4.

CLAIMS

1. Use of chlorprocaine or salts thereof, for the manufacture of an injectable solution which is free of preservatives and antioxidants and has a pH
5 from 3 to 4 for central loco-regional anesthesia by intrathecal administration of at least a dose of 15-80 mg per day repeated for a time period of 2 to 10 days.
2. Use as claimed in claim 1, characterized in that said chlorprocaine salt is chlorprocaine HCl.
- 10 3. Use as claimed in claim 1 or 2, characterized in that it comprises the intrathecal administration of a daily dose of 30-60 mg of chlorprocaine or a salt thereof.
- 15 4. Use as claimed in any one of the claims 1-3, characterized in that the intrathecal administration comprises the administration of a daily dose repeated for a period of 3 to 7 days.
- 20 5. Use as claimed in any one of the claims 1-4, characterized in that it comprises chlorprocaine HCl, sodium chloride, sterile water and hydrochloric acid.
- 25 6. Use as claimed in any one of the claims 1-5, characterized in that it comprises 5-15 mg of chlorprocaine HCl/ml of water, 4-12 mg of NaCl, and HCl in an amount sufficient to reach a pH of 3.0-4.0.
7. Use as claimed in any one of the claims 1-6 in central loco-regional anesthesia in combination with adrenaline by intrathecal administration in repeated doses.

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8. Use as claimed in any one of the claims 1-7 in central loco-regional anesthesia in combination with an analgesic drug by intrathecal administration in repeated doses.
- 5 9. Use as claimed in claim 8, characterized in that said analgesic drug is selected from acetaminophen, NSAIDs, corticosteroids and opiate drugs.