Title: PAIN MANAGEMENT USING LOCALIZED HYPOTHERMIA

Abstract: A method is provided to induce and maintain regional anesthesia or analgesia by localized hypothermia. A cooling solution, such as cooled normal physiological saline, can be injected into the spinal cord or subarachnoid space of a subject to cause localized anesthesia or analgesia without using pharmacological agents.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
PAIN MANAGEMENT USING LOCALIZED HYPOTHERMIA

PRIORITY INFORMATION

This application claims priority to U.S. 60/509,839, filed October 8, 2003, the contents of which are incorporated by reference.

FIELD OF THE INVENTION

This invention is applicable in all fields of medicine, but more particularly, to the fields of anesthesiology, pain medicine, neurology, obstetrics, and cardiology. It relates to the use of a spinal cooling solution such as a physiological saline solution, Ringer’s solution, or cooled cerebrospinal fluid (CSF), or epidural contents to create and maintain, localized hypothermia in the spinal cord or nerve roots in the epidural space of a subject, thus inducing and maintaining regional anesthesia or analgesia.

BACKGROUND OF THE INVENTION

Regional anesthesia and analgesia has been an important component of pain management for many years. However, the induction and maintenance of the regional analgesia or anesthesia has been done almost exclusively with pharmacological approaches. The most frequently used agents for induction and maintenance of regional anesthesia or analgesia are local anesthetics with or without narcotics which all are pharmacological agents. Even though these local anesthetics are potentially toxic, they must remain at the site of administration long enough to allow sufficient time for the localized pain to subside. Therefore, factors such as the choice of pharmacological agent, concentration of pharmacological agent, rate of delivery, and site of administration, all need to be taken into consideration when contemplating their use.

The mechanism by which local anesthetics induce their effect is based upon their ability to interfere with the initiation and transmission of the nerve impulse. Action potentials are generated in nerve by ion currents that pass selectively across membranes through transmembrane ion channels. Local anesthetics exert their effects by specifically binding to Na⁺ channels, thereby inhibiting Na⁺ currents and causing the blockade of Na⁺ channel-dependent impulse conduction. The necessary practical
advantage of local anesthetics is that their action is reversible at clinically relevant concentrations and they are usually followed by complete recovery of nerve function.

By binding to the Na⁺ channel and blocking the inward Na⁺ current in the nerve, any pain stimulus that originates at or below the level of blockage is not conducted to the brain and pain perception is diminished.

However, some complications associated with the use of pharmacological agents may be unavoidable. These include neurotoxicity, seizure, and/or cardiovascular collapse. Furthermore, in pregnant patients there is the potential risk that the pharmacological agent may cross the placenta and adversely affect the fetus or newborn. In addition, the slow recovery from the regional anesthesia may be particularly problematic for ambulatory patients.

Accordingly, a need exists for producing localized anesthesia or analgesia in a subject that avoids using pharmacological agents. A need also exists for an anesthesia or analgesia procedure that is safe and effective for pregnant patients, as well as ambulatory patients. In addition, a need exists for a cost-effective procedure to induce localized anesthesia or analgesia.

SUMMARY OF THE INVENTION

The invention is based on the discovery that a spinal cooling fluid void of pharmacological agents can be injected intrathecally to induce and maintain regional anesthesia or analgesia through the patient's spinal cord. In particular, the invention is directed to cooling the spinal cord or nerve root in epidural space of a subject using a cooling fluid, generally referred to as a "spinal cooling fluid", to produce and maintain localized hypothermia. This localized hypothermia in turn will lead to a reduction of temperature at the nerve root in the epidural space and/or cerebral spinal fluid and the spinal cord to a degree at which the nerve signal conduction is substantially inhibited.
Accordingly, in one aspect, the invention features a method for inducing and maintaining regional anesthesia or analgesia by aspirating a volume of cerebral spinal fluid (CSF) and then infusing intrathecally a volume of a spinal cooling fluid such that the spinal cord is cooled to below normal body temperature and nerve signal conduction is substantially diminished, to thereby provide localized anesthesia or analgesia.

In another aspect, the invention pertains to a device and system for inducing and maintaining regional anesthesia or analgesia. The system includes a hollow tubular member such as a catheter (or needle), with an input and output means. This catheter can be inserted into the subarachnoid space or epidural space of the patient. In one example, the catheter can be inserted between the L3 and L4, or the L4 and L5 vertebrae. The catheter can be used to aspirate a volume of cerebral spinal fluid (CSF) using the output means. A volume of spinal cooling fluid, that has been cooled in a cooling chamber, can be infused into the subarachnoid space or epidural space using the input means, such that the spinal cord or root nerve in the epidural space is cooled to below normal body temperature and nerve signal conduction is substantially inhibited.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graphic representation of the system and device of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods and devices for inducing and maintaining regional analgesia or anesthesia by using spinal cooling fluids that do not contain pharmacological agents.

The spinal cooling fluids used in the methods of the invention function to reduce the temperature in the nerve root in the epidural space, and/or CSF and spinal cord, to a temperature that substantially inhibits nerve pulse conduction along an axon to the brain, thereby inhibiting any pain stimulus. In particular, the lower temperature blocks the sodium inward current, which in turn abolishes the action potential and inhibits the nerve pulse being conducted through the blocked region of the axon or at the level of synapses. It may also inhibit the signal conduction across the neuro-synapses.
To reduce the temperature, the CSF can be removed from the spinal cord using one or more catheters or needles, or similar suitable hollow tubular members. The catheters can be inserted, for example, into the epidural space, or the lower region of the subarachnoid space. The volume of spinal cooling fluid infused into the subarachnoid space should be approximately equal to the volume of CSF removed from the subarachnoid space. The spinal cooling fluid can be, for example, cooled physiological saline solution, cooled Ringer's solution, or cooled CSF. The spinal cooling fluid cools the spinal cord to a temperature below 32°C. The spinal cooling solution can be at a temperature of about -4°C to about 10°C, preferably about 0°C to 4°C. It will be appreciated that the presence of a compound that reduces the freezing point of a fluid, e.g., salt, in the spinal cooling fluid reduces the freezing point to prevent the spinal cooling solution from freezing.

The volume of spinal fluid that is infused to decrease the temperature of the spinal cord or epidural space to below 32°C depends upon the temperature of the spinal cooling solution. That is to say, the lower the temperature of the spinal cooling fluid, the lower the volume required to reduce the temperature of the spinal cord or epidural space. The skilled artisan will appreciate that a volume of CSF can be removed before the spinal cooling fluid is infused. A suitable volume of CSF that can be removed is about 1 to about 5 cubic centimeters (cm³). The removal of this volume of CSF is well tolerated and does not cause detrimental effects to the patient, assuming the patient does not have elevated intracranial pressure.

In one embodiment of the invention, "one shot" cooling is used, whereby a volume of CSF can be removed (e.g., 5 cm³), and the same volume of cooling fluid can be infused (i.e., 5 cm³), or double the volume of the spinal cooling fluid can be infused (i.e., 10 cm³). The increased volume of spinal cooling fluid infused is within the tolerance range of a typical patient. In another embodiment, "continuous cooling" is used, where the spinal cooling fluid is infused into the subarachnoid space or epidural space as the CSF is removed in a continuous manner. The effectiveness of the induced anesthesia or analgesia can be tested clinically by a pin-prick test to determine whether the patient responds to pain.
In one preferred example, the cooling fluid can be delivered into the epidural space using an epidural needle. The epidural procedure has been used routinely to deliver agents. In another preferred example, the spinal cooling fluid can be delivered to the lower region of the subarachnoid space using one or more catheters, or needles, that can be inserted into the inter-vetebrate space, for example between the L3 and L4, or the L4 and L5 region of the spine until that the spinal cord is cooled to below normal body temperature and nerve signal conduction is substantially inhibited. It will be appreciated that the method of the invention can be practiced along any region of the spine, and between any two vertebrae in a patient, to induce and maintain regional anesthesia or analgesia in the patient. Alternatively, the CSF is aspirated from the patient and the aspirated CSF will be cooled, and then infused back into subarachnoid space or epidural space. This is preferably performed using a single spinal catheter to aspirate the CSF and infuse the cooled CSF through the same spinal catheter in a continuous manner. A valve may be used to control the direction of fluid flow (CSF or cooling solution).

The general system 10 for inducing regional anesthesia or analgesia through a patient’s spinal cord or epidural space is shown in FIG. 1. In one embodiment, the system 10 comprises a hollow tubular member, such as a catheter 12 with a tip (not shown). The hollow tubular member has a distal end, a proximal end, and an input and output channels 14. In one embodiment, separate input and output catheters can be used. The proximal end of the hollow tubular member can be connected to a cooling chamber 16 comprising a coolant 18, and the distal end can be inserted into a subarachnoid space 20. The cooling chamber 16 receives the spinal cooling fluid 22 from a container or receptacle 24 with an input and output channels (not shown). The output channel delivers the spinal cooling fluid 22 to the cooling chamber 16 where the fluid is cooled to a desirable temperature (e.g., 0°C to 4°C). The temperature of the cooling chamber 16 and the cooling fluid 22 can be monitored using a temperature probe 26. The cooled fluid can be delivered to the subarachnoid space 20 via the hollow tubular member. The CSF pressure can be measured during the procedure using, for example, a manometer (not shown).
The distal end of the hollow tubular member 12 can be inserted into a subarachnoid space 20 between the L3 and L4 region, or between the L4 and L5 region into which the spinal cooling fluid 22 can be infused. Alternatively, the hollow tubular member 12 can be inserted into an epidural space (not shown) into which the spinal cooling fluid can be infused. The analgesia or anesthesia effect can be confirmed by clinical monitoring of a patient’s response to pain, for example, using a pin-prick.

In another embodiment, the device comprises two hollow tubular members such as catheters or needles. The first hollow tubular member can be used as an output channel to remove CSF from the subject. The second hollow tubular member can be used as an input channel to infuse the cooled spinal cooling fluid, or the cooled CSF into the subject.

In one embodiment of the invention, the spinal cooling fluid is cooled physiological saline that is injected into the epidural space to produce regional anesthesia or analgesia. The regional anesthesia or analgesia can be maintained by adding additional cooling fluid at regular time intervals, e.g., every 30 minutes. Other examples of suitable cooling solutions include, but are not limited to, cooled Ringer’s solution and cooled CSF.

In another embodiment, a volume of CSF can be removed from the subarachnoid space by aspiration using a catheter or needle, the withdrawn fluid volume can be replaced with cooled physiological saline. The volume of cooled saline that is added to the subarachnoid space should be the same as that withdrawn. This cooled physiological saline can be infused into the subarachnoid space of the subject using a catheter or needle such that the cooled physiological saline cools the spinal cord to below normal body temperature and substantially inhibits nerve signal conduction.

In another embodiment, the regional anesthesia or analgesia is effected by cooling the patients own CSF. That is a volume of CSF is removed from the subarachnoid space by aspiration using a catheter or needle. This aspired CSF can be cooled down to a temperature that blocks nerve signal conduction (e.g., 4°C) by a
cooling system, and the cooled CSF can be infused back into the subarachnoid space of the subject using a catheter or needle, such that the cooled CSF blocks nerve signal conduction. The blockage of nerve signal conduction can be determined clinically by monitoring the patient's response to pain using, for example, a pin-prick test. The method can further comprise monitoring the nerve signal conduction to determine when it is substantially diminished by blocking an inward sodium flux in an axon. The nerve conduction can be measured using known techniques.

The method of the invention provides a simple, cost-effective procedure for inducing regional anesthesia or analgesia without using pharmacological agents. Therefore, the many complications associated with local anesthetics, such as local and systemic toxicity arising from the pharmacological anesthetics, can be avoided. Other advantages provided by the methods of the invention are the elimination of the danger of pharmacological anesthetics crossing the placenta and adversely affecting the fetus or newborn in a pregnant woman. Furthermore, the duration and depth of the anesthesia or analgesia produced with the method of the invention can be more readily controlled, and the recovery time from anesthesia is much shorter than that produced with local pharmacological anesthetics. This property is particularly important for ambulatory patients.

One skilled in the art will appreciate further features and advantages of the invention based on the above-described embodiments. Accordingly, the invention is not to be limited by what has been particularly shown and described, except as indicated by the appended claims. All publications and references cited herein are expressly incorporated herein by reference in their entirety.
What is claimed is:

1. A method for inducing and maintaining regional anesthesia or analgesia through a patient's spinal cord, comprising:
   - aspirating a volume of cerebral spinal fluid (CSF) from a subarachnoid space;
   - infusing a volume of a cooling fluid into the subarachnoid space such that the spinal cord is cooled to below normal body temperature and nerve signal conduction is substantially inhibited, to thereby provide localized anesthesia or analgesia.

2. The method of claim 1, wherein the step of aspirating the cerebral spinal fluid (CSF) comprises aspirating with a first hollow tubular member having a lumen.

3. The method of claim 1, wherein the step of infusing the spinal cooling fluid comprises infusing with a second hollow tubular member having a lumen.

4. The method of claim 1, wherein the volume of the spinal cooling fluid infused into the subarachnoid space is approximately equal to the volume of CSF removed from the subarachnoid space.

5. The method of claim 1, wherein the spinal cooling fluid is a physiological saline solution.

6. The method of claim 1, wherein the spinal cooling fluid is Ringer's solution.

7. The method of claim 1, wherein the spinal cooling fluid is the patient's own CSF.

8. The method of claim 1, wherein the spinal cord is cooled to a temperature below 32°C.
9. The method of claim 1, further comprising the step of measuring CSF pressure using a manometer.

10. The method of claim 1, further comprising the step of measuring the cooling solution temperature.

11. The method of claim 1, wherein the nerve signal conduction is substantially diminished by blocking an inward sodium flux in an axon and blocking signal transmission across synapses.

12. The method of claim 1, wherein the analgesia and anesthesia effect are measured clinically by monitoring the patient's response to pain.

13. A system for inducing and maintaining regional anesthesia or analgesia through a patient's spinal cord, comprising:
   a hollow tubular member with a distal end, a proximal end, and input and output channels, wherein the distal end of the hollow tubular member is connected to a cooling chamber, and the proximal end is inserted into a subarachnoid space; and
   a container with input and output channels comprising a cooling fluid, wherein the output channel delivers the cooling fluid to the cooling chamber to cool the cooling fluid, wherein the cooled fluid is delivered to the subarachnoid space via the hollow tubular member.

14. The system of claim 13 wherein the cooling chamber further comprises a temperature probe to monitor the temperature.

15. The system of claim 13, wherein the hollow tubular member is a catheter.

16. The system of claim 13, further comprising the step of measuring CSF pressure using a manometer.
17. The system of claim 13, wherein the spinal cooling fluid is selected from the group consisting of a physiological saline solution, Ringer's solution, and the patient's own CSF.

18. The system of claim 13, wherein the proximal end is inserted into a subarachnoid space between the L3 and L4 region.

19. The system of claim 13, wherein the proximal end is inserted into a subarachnoid space between the L4 and L5 region.
FIG. 1