

UNITED STATES PATENT OFFICE

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SPINAL ANÆSTHETIC SOLUTION

No Drawing.

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Our invention relates to improvements in spinal anæsthetic solutions and methods of preparing the same. It relates more particularly to spinal anæsthetic solutions which have as a base an alkamine ester of an aromatic acid adapted for use as a spinal anæsthetic agent such as the monohydrochloride of para-amino benzoyl-diethyl-amino-ethanol which is generally known as "Novocaine" or "Procaine". One of its objects is to provide a solution which does not mix with the spinal fluid when employed clinically for the production of spinal anæsthesia until the anæsthetic agent has been absorbed, thereby regulating the time, extent and intensity of anæsthesia. Further and more specific objects, features and advantages will more clearly appear from the detailed description given below.

Spinal anæsthesia (sometimes called spinal analgesia) is a method of anæsthesia used extensively for surgical operations below the diaphragm. It is produced by injecting a solution of a spinal anæsthetic agent directly into the spinal fluid contained in the subarachnoid space of the spinal canal. The injection is made through one of the vertebral interspaces of the lower dorsal or lumbar region of the spine.

The spinal anæsthetic solutions as heretofore employed by different surgeons are prepared by dissolving the spinal anæsthetic agent in a vehicle such as water, physiological salt solution, spinal fluid or dilute alcohol solution; the purpose being to produce a fluid of the same, heavier or lighter specific gravity compared with the spinal fluid.

A great objection to the spinal anæsthetic solutions hitherto used is the absolute commitment of the surgeon to the consequences of these solutions when injected into the spinal fluid. Once injected the anæsthetic solution mixes with the spinal fluid and as a result its action cannot be controlled by the surgeon. Despite all precautions the anæsthetic solution may rapidly disseminate through the spinal fluid towards the brain and produce untoward symptoms such as pallor, nausea, vomiting, a tremendous drop in blood pressure and at times even death from paralysis of the nerves controlling respiration.

In addition there is also uncertainty as to the time, extent and intensity of anæsthesia due to dilution of the spinal anæsthetic solution by the spinal fluid and not infrequently the anæsthesia wears off before the operation is completed.

In order to prevent uncertainty as to the extent of anæsthesia, to stabilize the intensity and to regulate the time of anæsthesia, to diminish the tremendous drop in blood pressure and to prevent nausea and vomiting, we have devised a spinal anæsthetic solution that will not mix with the spinal fluid until the spinal anæsthetic agent has been absorbed by the intradural nerve trunks and nerve roots. The spinal anæsthetic solution has the additional characteristic that it floats in the spinal fluid, not unlike the air bubble in a spirit level, and as a result, anæsthesia can be produced higher or lower on the body surface as the surgeon desires by merely adjusting the position of the patient. Also, according to our improvements, a spinal anæsthetic solution is produced which is stable and sterile and may be kept for long periods of time as a ready-to-use solution.

To ascertain the intradural action of our spinal anæsthetic solution as compared with ordinary spinal anæsthetic solutions prepared with water, normal salt solution or spinal fluid as a vehicle, methylene-blue was added to the respective solutions and the solutions were then injected into glass tubes shaped to conform with the human spine and filled with salt solution having approximately the same specific gravity as spinal fluid. The extent and rapidity of dissemination of the solutions were observed and timed. This was further checked by the use of miniature glass tubes filled with spinal fluid, the results of dissemination being practically the same. As a final check, methylene-blue was added to the various anæsthetic solutions and injected directly into the spinal fluid in the subarachnoid space of the spinal canal. Postanæsthetic taps were then made at definite intervals and the extent and amount of dissemination was determined by the use of a colorimeter.

We have discovered that stable control-

lable anæsthetic solutions can be produced by including therein a gluelike adhesive substance preferably in the nature of gliadin dissolved in alcohol which so affects the spinal anæsthetic solution as to increase its viscosity and not inhibit the absorption of the spinal anæsthetic agent. The gliadin is insoluble in spinal fluid and precipitates on contact with spinal fluid forming a semipermeable membrane between the spinal anæsthetic solution and the spinal fluid. When we refer to gliadin or a solution of gliadin it will be understood that this includes the alcohol-soluble protein found in most of the cereals such as wheat, rye, maize, etc. For the spinal anæsthetic agent we prefer to use the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol (novocaine or procaine). However, other alkamine esters of aromatic acids adapted for use as spinal anæsthetic agents may be employed, for example the hydrochloride of diethyl-amino-propyl-cinnamate (apothesine) and the hydrochloride of para-amino-benzoyl-dimethyl-amino-methyl-isobutanol (tutocaine).

In producing the spinal anæsthetic solution the proportions may be greatly varied depending upon the various conditions to be met, etc., but we prefer solutions in which the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol varies from 5% to 10%, gliadin from 0.03% to 0.06% and ethyl alcohol from 10% to 16%. The alcohol is added to hold the gliadin in solution and to lower specific gravity.

Good results have been obtained with solutions prepared as follows: (1) monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol 10 grams, wheat gliadin 0.06 gram, absolute ethyl alcohol 16 cubic centimeters and distilled water in sufficient quantity to make 100 cubic centimeters. The doses to be applied averages about 2 cubic centimeters of this solution; (2) monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol 5 grams, wheat gliadin 0.03 gram, absolute ethyl alcohol 10 cubic centimeters and distilled water in sufficient quantity to make 100 cubic centimeters.

Instead of the monohydrochloride one may use the free base, although we prefer to use the monohydrochloride.

The ingredients of the solution are preferably combined in the following manner.

The monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol is dissolved in 20 cubic centimeters of distilled water. The alcohol is converted into a 75% alcohol solution by the addition of sufficient distilled water. The gliadin is then dissolved in the alcohol solution and then the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol solution is added and thoroughly mixed. A sufficient quantity of distilled

water is finally added to make 100 cubic centimeters.

We have also obtained good results by adding cereal mucilages to the spinal anæsthetic solution as we have found that cereal mucilages prepared from cereals containing gliadin, or their flours, by boiling in water contain sufficient gliadin suspended or adsorbed by the starch to prevent dissemination of the spinal anæsthetic solution when injected into the spinal fluid. The mucilage may be conveniently prepared by placing 15 to 20 grams of wheat flour in a gauze bag and then suspending the bag containing the wheat flour in 200 cubic centimeters of boiling distilled water for a period of three hours.

The addition of 3 cubic centimeters to 6 cubic centimeters of the clear supernatant mucilage to replace half of the gliadin or the addition of 5 cubic centimeters to 10 cubic centimeters of the clear supernatant mucilage instead of the gliadin included in the above example has been found sufficient for each 100 cubic centimeters of the spinal anæsthetic solution. We have also found that when cereal mucilage is employed instead of the gliadin the alcohol may be omitted.

In order to prevent infection of the spinal fluid it is essential that the spinal anæsthetic solutions be sterile. We have found that sterility may be insured by filling glass ampules of the desired volume with the freshly prepared solution, then promptly sealing off the ampules with the aid of a blow-pipe and then submerging the ampules in boiling water for 15 to 30 minutes on three successive days or autoclaving them in a live steam sterilizer for 20 minutes at 15 pounds steam pressure. This procedure has been found most practical because it prevents any loss by evaporation and also any accidental contamination after sterilization.

We have thoroughly tested these spinal anæsthetic solutions for sterility and stability. Relatively old ampules thereof have shown no change in color and have retained their full anæsthetic potency. By our improvements, we are able to produce ready-to-use spinal anæsthetic solutions which are far superior to the spinal anæsthetic solutions heretofore employed and which do not mix with the spinal fluid when employed clinically until the spinal anæsthetic agent has been absorbed, thereby regulating the time, extent and intensity of anæsthesia.

While we have described our improvements in great detail and with respect to preferred forms thereof, we do not desire to be limited to such details or forms since many modifications and changes may be made and the invention embodied in widely different forms without departing from the spirit or scope of the invention in its broader aspects. Hence we desire to cover all modifications and forms

coming within the scope or language of any one or more of the appended claims.

We claim:

1. A new composition of matter comprising
5 a spinal anæsthetic agent and a gluelike adhesive substance which is insoluble in the spinal fluid.
2. A new composition of matter comprising a spinal anæsthetic agent and gliadin.
- 10 3. A new composition of matter comprising a salt of para-amino-benzoyl-diethyl-amino-ethanol and a gluelike adhesive substance which is insoluble in the spinal fluid.
4. A new composition of matter comprising
15 the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol and gliadin.
5. A new composition of matter consisting of 5% to 10% of the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol,
20 0.03% to 0.06% of gliadin and 10% to 16% of ethyl alcohol, the residue being distilled water.
6. As a new composition of matter a solution of 10 grams of the monohydrochloride of
25 para-amino-benzoyl-diethyl-amino-ethanol and 0.06 gram of wheat gliadin in a mixture of 16 cubic centimeters of ethyl alcohol and distilled water in sufficient quantity to make 100 cubic centimeters.
- 30 7. A new composition of matter comprising a spinal anæsthetic agent and wheat flour mucilage.
8. A new composition of matter comprising the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol and wheat flour
35 mucilage.
9. A new composition of matter consisting of 5% to 10% of the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol,
40 5% to 10% of wheat flour mucilage and 10% to 16% of ethyl alcohol, the residue being distilled water.

In testimony whereof, we affix our signatures.

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