METHOD AND PREPARATIONS FOR RELIEVING PAIN AND PRODUCING ANALGESIA

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References Cited


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ABSTRACT

A method of treating a host for inducing relief of pain or anesthesia which comprises administering histamine, its salts, or an agent inducing histamine release, and a dispersing agent such as hyaluronidase, at the place of the painful area or at the place indicated for acupuncture for the painful site.

9 Claims, No Drawings
METHOD AND PREPARATIONS FOR RELIEVING PAIN AND PRODUCING ANALGESIA

BACKGROUND OF THE INVENTION

1. Field of the Invention:
   This invention relates to a method and preparations for relieving pain and producing analgesia.

2. Description of the Prior Art:
   A great deal of research has been performed on the effect of histamine and related compounds, both in vivo and in vitro. The literature on this subject is so vast and conflicting that it is simply not practical to set forth any meaningful discussion on the subject. For example, Rosenthal et al. have reported in Am. J. Physiol. 155, 186-90 (1948) that painful sensations are produced by the injection of histamine and in the Proc. Soc. Ecptl. Biol. Med. 74, 167-70 (1950) that histamine introduced into the superficial layers of human skin causes an immediate as well as latent painful sensation. Jacob et al., Am. Inst. Pasteur 81, 128-92 (1951), have reported that histamine diHCl given to rats subcutaneously or intraperitoneally for 6 to 30 days decreased their sensitivity to thermal induced pain, but which returned after cessation of treatment.

Similarly a great deal of research has been performed with spreading agents such as the hyaluronidase enzyme. Hyaluronidase has been used alone and in combination with various drugs. The use of hyaluronidase and histamine has also been studied. For example, it has been reported by Seelich et al., Nature 168, 1125 (1951), that histamine does not neutralize heparin inhibition of hyaluronidase, and by Mathies et al., in Zeits. expetl. Med. 133, 32-37 (1960), that the inhibitory action of phenylbutazone against hyaluronidase could be blocked by the simultaneous administration of an antihistaminic agent. A vast amount of additional publications exist, both with respect to histamine and hyaluronidase, none of which, to applicant's knowledge, disclose or teach the invention disclosed and claimed herein.

SUMMARY OF THE INVENTION

It has been found that administering histamine, its salts, compounds inducing histamine release, and dispersing agent such as hyaluronidase, or derivatives of histamine, having substantially the same pharmacological activity of histamine, directly to the painful area or at the sites indicated for acupuncture for that painful area, will relieve the pain and produce analgesia at the painful area.

The term, histamine, is used herein in its generic sense, to include histamine, its non-toxic salts, compounds which induce histamine release in the body and histamine derivatives which produce a similar pharmacological activity within the body.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Histamine, its non-toxic salts, compounds inducing histamine release, and histamine derivatives having a similar pharmacological activity in the body are well known and their properties and pharmacological action well documented in the literature. All such compounds are operable so long as they are capable of depositing directly or indirectly a sufficient amount of histamine in combination with hyaluronidase to induce analgesia or relief of pain. The main object is to impart by injection to the painful area or at the acupuncture sites histamine or a related compound having the same pharmacological action as histamine in combination with hyaluronidase. Whether this is accomplished by use of histamine itself or its non-toxic salts, or in any other manner, is not material and is to be considered within the present invention.

The dispersing or spreading factor can be a hyaluronidase of different origins, for example, from honey-bee venom, snake venom, etc. 2-N-acetylglucosaminidase has been found to be most efficient. These dispersing agents or factors and the methods by which they may be obtained are well known in the art.

The pain relieving or analgesic compositions of this invention can be prepared for injection by placing the histamine compound and hyaluronidase in a suitable medium, such as water, saline solution, isotonic solution, etc., with proper sterilization, as will be apparent to those skilled in the art.

The histamine compound and the hyaluronidase can be separately injected into the painful area or the acupuncture site for that painful area, but it is, of course, more convenient to combine the histamine compound and the hyaluronidase in a convenient solution.

The concentration of the hyaluronidase enzyme, because of its variable activity, depending upon its source and other well known factors, is given in units as set by the National Formulary. The unit concentration is given on each package as units NF (TR) per volume of weight.

The amount of histamine and/or hyaluronidase that can be injected will depend upon the particular patient being treated, the extent of the painful area, and the degree of pain. A sufficient amount of the histamine compound and the hyaluronidase should, of course, be injected to overcome the pain as will be apparent to any physician.

With respect to the histamine compound, the minimum amount has so far been determined to be about 0.01 mg., and with respect to the hyaluronidase about 10 units NF (TR). [hereinafter referred to as units or units per ml.]. Lower amounts could be used if conditions so indicate.

The maximum amount of the histamine compound that can be used will depend somewhat upon the patient and his tolerance to "flushes" due to histamine reaction. Generally, amounts up to 0.5 mg. can be tolerated.

The maximum amount of hyaluronidase that can be used will again depend upon the particular patient to be treated as well as the amount of histamine being injected. Investigation to date indicated that one would not require more than 50 units of hyaluronidase.

Thus, the preparations of this invention can be prepared in such a manner so that the patient can receive between about 0.01 mg. and 0.05 mg. of histamine and between about 10 and about 50 units of hyaluronidase. Experiments to date have shown that an injection of 0.02 mg. of histamine and 10 units of hyaluronidase is advantageous.

The solutions can be made up in varying concentrations and the total volume injected will, of course, depend upon the concentration of the solution. For example, if a solution is made up to contain 0.02 mg. of histamine per ml. and 10 units of hyaluronidase per ml., an injection of 1 ml. of this solution into the painful area or the acupuncture site should be sufficient.
The solutions can be injected into the painful area by any means sufficient to relieve the pain, such as, subcutaneously, or deeper into the tissues, perithecial, or even in the articulations, or in the sites used for acupuncture. Depending upon the area of pain, one injection may suffice or, if the painful area is larger, the composition or preparation may be injected into a plurality of places in the painful area, such as in Example 1, set forth below. Such a procedure is referred to herein as infiltration of the painful area. For example, in bursitis, at times, no burt can be located and in which case the entire painful area, the shoulder for example, may be infiltrated, injecting the total amount of desired histamine and hyaluronidase into the shoulder at a plurality of sites. In this case it may be, at times, desirable to have a more diluted solution, so that a larger area can be infiltrated and, at the same time, decrease the chance of any histamine reaction by the patient. Thus, the two main defects of the method, the missing of the painful spots and the "flushes" due to histaminic action, are controlled by this infiltration technique using more diluted solutions of histamine.

As previously mentioned the method of this invention can also be practiced by injecting the preparations at the acupuncture sites for the areas in which it is desired to relieve pain or produce analgesia. These sites are well known and are described for example, in Acupuncture Therapy, Current Chinese Practice, by T. Tan, Y.-C. Tan and Veith, Temple University Press, Philadelphia, 1973.

One advantage of this acupuncture technique is the fact that the results are not the function of the capacity of the individual to respond to the needle insertion with the liberation of histamine, and the use of this invention results in increased responses in the patient. Another advantage is the fact that the injection of the preparations, according to this invention, will affect the entire area or acupuncture site rather than just a single point, and the chances of having the necessary acupuncture site influenced is thus highly increased. The preparations of this invention can thus be used for the treatment of different conditions for which acupuncture is presently used, such as for the induction of anesthesia for surgical interventions.

It has also been noted that together with the suppression of the pain, the evolution of lesions also appears to be influenced.

In all cases where a patient is treated, as a precautionary measure, an antihistamine injection or adrenalin for injection was kept available in case of hypersensitivity to histamine. It is interesting to note, however, that in over 100 cases treated so far there was no need to use either the histaminic preparation or adrenalin, even in a case (Example 10) of the patient who had a history of severe histaminic reactions.

The following examples illustrate the practice of the invention:

**EXAMPLE 1**

A 60 year old male with severe pain and totally immobilized by a "frozen shoulder" due to bursitis. The condition had gotten progressively worse over the last two months and did not respond to various treatments. From a solution containing 0.2 mg. of histamine phosphate and 10 units of hyaluronidase per ml., 2 ml. divided in 4 injections were injected in the painful spots. The pain disappeared in less than 6 minutes, with recovery of movement. Seen after 2 weeks, the good effects were persistent.

**EXAMPLE 2**

A 58 year old female with severe arthritis pain in the coccygeal region for several months. The pain could not be controlled by various treatments. From a solution containing 0.05 mg. of histamine phosphate and 10 units of hyaluronidase per ml. - 1 ml. was injected in the painful area. The pain disappeared in 4 minutes and remained as such at an examination one month later.

**EXAMPLE 3**

A 50 year old male with pain due to a sciatica of the left leg, not responding to treatments for the last month. A total of 3 ml. of a preparation containing 0.05 mg. of histamine and 10 units of hyaluronidase per ml. was injected deep subcutaneously in 5 different painful spots. The pain disappeared and remained as such after 2 months.

**EXAMPLE 4**

A 38 year old female with lower abdominal pains due to an inflammation of both ovaries, lasting for months. (Three) 3 ml. of a solution containing 0.04 mg. per ml. of histamine phosphate and 10 units of hyaluronidase per ml. were injected subcutaneously in the right side painful area. The pain disappeared in 5 minutes and did not reappear. The pain in the left side was not influenced and was treated 4 days later with the same dose. The patient remained without pain for at least 6 weeks.

**EXAMPLE 5**

A 70 year old female with pains in the left knee, and unable to localize the pain otherwise than the entire anterior area of the knee. A subcutaneous infiltration of this region with 10 ml. of a solution containing 0.01 mg. per ml. of histamine phosphate and 10 units of hyaluronidase per ml. was followed by the disappearance and without recurrence of the pain after 12 days.

**EXAMPLE 6**

A 62 year old female with severe pain in the left sacroiliac articulation, persisting for months. A subcutaneous injection of 0.5 ml. of a solution containing 0.2 mg. per ml. of histamine and 10 units of hyaluronidase per ml. at the painful area did not completely suppress the pain after 15 minutes. A same amount of the solution injected deep into the articulation fully controlled the pain, with the effect still persisting after 3 weeks.

**EXAMPLE 7**

A 50 year old male with a cancer of the spine, at the 10–12 D and 1 D for which a decompression intervention was performed. The patient had very severe pain, on both sides of the lesion, only insufficiently controlled by opiates. From a solution containing 0.2 mg. of histamine phosphate per ml. and 10 units of hyaluronidase per ml., several injections totalling 1.5 ml. were made only at the right side of the spine. The pain disappeared after 6 minutes and still did not reappear after one week, while the pain persisted unchanged in the left side of the spine. The same injection in left side had the same good effect.

**EXAMPLE 8**

A 40 year old male with severe backache. The pain-
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A 3 year old male with pains in the elbow after playing tennis. The pain persisted for weeks, in spite of treatment. A local infiltration of 7.5 ml. of a solution containing 0.02 mg. per ml. of histamine and 20 units of hyaluronidase per ml. was injected locally. The pain disappeared in 5 minutes. The patient did not have any flushing sensation.

EXAMPLE 10

A 30 year old male with a very painful shoulder of osteoarthritic nature. An infiltration of the entire painful area, with 20 ml. of a solution containing 0.1 mg. of histamine per ml. and 10 units of hyaluronidase was made. The pain was controlled in less than 10 minutes. The patient remained without pain 6 weeks after the infiltration. The patient, who had a severe histaminic reaction because of a prior use of histamine for a gastric test, with headache, itching and vision troubles did not have any adverse reaction after treatment.

As can be seen from the above examples, abdominal pain from ovary inflammation and gallbladder colic were controlled by deep subcutaneous injections in the painful areas. Even cancer pains responded well to the injections. Good results were obtained for different neuralgias, such as sciatica, tic douloureux, post Zoster neuralgia, with injections made "locus dolendi" (painful spots). The effects were good also in fractures and especially in residual pains after trauma. In general, with only very few exemptions, the results in more than 100 cases treated are exceptionally good, with not only the pain immediately controlled and with functional recovery, but with the results lasting for a long period of time, weeks or even months after the injections. The pain entirely disappears in less than about 15 minutes in most cases. In some cases the pain was felt after one or two days, but in these cases the pain was felt in areas other than those injected. No local numbness was noted.

1. A method of relieving pain or producing analgesia in a host which comprises injecting a solution of histamine, or its non-toxic salts, and a hyaluronidase at the painful area or at the acupuncture sites for the area in which it is desired to relieve pain or produce analgesia.
2. The method of claim 1, wherein the preparation is infiltrated at the painful area.
3. The method of claim 1 in which the histamine and hyaluronidase are injected admixture.
4. A method of claim 1, wherein the hyaluronidase is z-N-Acetylglucosaminidase hyaluronidase.
5. The method of claim 1, wherein the solution contains from about 0.01 to about 0.5 mgs. of histamine per ml.
6. The method of claim 5, wherein the solution contains from about 10 to about 50 NF (TR) units of hyaluronidase.
7. Preparations for use in relieving pain or for producing analgesia which comprise a sterile solution of histamine or its non-toxic salts, and a hyaluronidase containing between about 0.01 mg. to about 0.5 mg. histamine per ml and between about 10 to about 50 NF (TR) units of the hyaluronidase.
8. The preparation of claim 7 wherein the ingredients are combined with a non-toxic liquid carrier.
9. A preparation of claim 8, wherein the carrier is water, saline solution or an isotonic solution.

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