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(54) **ALLEVIATION OF PAIN IN OSTEOARTHRITIS BY MEANS OF INTRA-ARTICULAR IMPLANTATION OF PERFLUORODECALIN.**

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(57) **ABSTRACT**

Methods of alleviating pain by the intra-articular application of perfluorodecalin are disclosed.

ALLEVIATION OF PAIN IN OSTEOARTHRITIS BY MEANS OF INTRA-ARTICULAR IMPLANTATION OF PERFLUORODECALIN.

FIELD OF INVENTION

[0001] This invention is related to the alleviation of pain in osteochondral lesions by means of intra-articular implantation of perfluorodecalin, a fully fluorinated fluorocarbon. The main objective of the invention is to introduce the new medical use of perfluorodecalin for the alleviation of pain when injected into joints wherein perfluorodecalin provides a lubrication and viscoelastic function that allows smooth movement of joints without appreciable pain.

BACKGROUND OF THE INVENTION

[0002] Osteoarthritis (OA) is characterized by several pathological events, including a progressive erosion of the articular cartilage (particularly the weight bearing areas of the joint), synovial inflammation, which may contribute to disease progression, and changes in the lubricating properties of the synovial fluid (SF). Pharmacologic therapy for osteoarthritis is presently only palliative and is based on the use of analgesic or anti-inflammatory agents. Simple analgesics, however, do not provide enough of an effect to satisfy the needs of many OA patients, and anti-inflammatory drugs that are currently available do not have favorable risk-to-benefit ratio in typical patients with OA. Recently, a well known Cox-2 inhibitor, Vioxx® was recalled from the market for its deleterious effects on heart.

[0003] Controlled clinical trials, which include placebo groups, suggest that there is little to be gained over joint aspiration alone, or even over a simple needle prick. Glucocorticoids may however offer a small additional symptom benefit over one or two weeks. Intra-articular radiotherapy probably confers little benefit. Serious adverse effects are rare but local effects may occur in up to 10% of patients treated with viscosupplements.

[0004] A need remains, therefore, for therapies that will be analgesic, appropriately anti-inflammatory when necessary, and that may favorably alter the natural history of the disease. In knees with osteoarthritis, normal joint fluid, called synovial fluid, becomes thinner and loses its elasticity and viscosity. The diseased synovial fluid cannot provide "cushioning" in the knee joint. Without this cushioning, the cartilage in the knee joint may be more likely to wear down over time. This deterioration along with the loss of cushioning can contribute to pain and stiffness in the knee. Knee osteoarthritis is a common but often difficult problem to manage in primary care. Traditional non-surgical management, consisting of lifestyle modification, physical therapy and pharmacologic therapy (e.g., analgesics, anti-inflammatory medications), is often ineffective or leaves residual symptoms. Viscosupplementation is a newly available option for patients with symptomatic knee osteoarthritis that involves a series of intra-articular injections of hyaluronic acid, among other products.

[0005] Viscosupplementation is a newer medical concept that has as its therapeutic goal the restoration of rheological homeostasis in pathological structures such as osteoarthritic joints. When the normal viscoelasticity of a solid tissue compartment or the elastoviscosity of a liquid tissue compartment is decreased under pathological conditions, normal function and regenerative processes are impaired. By introducing viscosupplementation devices, the normal rheological state of such compartments is restored or augmented. These devices stay in the tissue compartment for various periods of time, depending on the nature of the viscosupplements and the pathophysiology of the tissue compartment. Viscosupplementation therapy is based on the concept of replenishing a normal physiological component of synovial fluid and cartilaginous tissue. Viscosupplementation therapy can restore the elastic and viscous properties of synovial fluid and thus recreate the intra-articular joint homeostasis that is disrupted in the degenerative joint. Clinical experience and studies of the hyaluronic acid products, hyaluronan and hylan G-F 20, seem to indicate beneficial effects with minimal adverse reactions in a significant number of patients. There are various products on the market for viscosupplementation; these include hyaluronan preparations of relatively low molecular weight (Hyalgan® and ARTZ®), a hyaluron preparation of intermediate molecular weight, but still lower molecular weight than that of the hyaluron in normal healthy synovial fluid (Orthovisc®), and a cross-linked hyaluron (a hylan) of high molecular weight (Synvisc®).

[0006] The exact mechanism of action of these products is unclear, although increasing the viscoelasticity of the synovial fluid appears to play a role. The exact indications for viscosupplementation are still evolving, but it currently can be considered for use in patients who have significant residual symptoms despite traditional non-pharmacologic and pharmacologic treatments. In addition, patients who are intolerant of traditional treatments (e.g., gastrointestinal problems related to anti-inflammatory medications) can be considered for these treatments.

[0007] It has been proven that the change of the intra-articular fluids produces a blockage of the nociceptors of subsynovial and capsular tissues and that, in addition to the mechanical factors of the osteochondral pathology, the fluids exert a relevant influence with their lubricating properties. Thus the change in viscosity of these fluids acts favorably on the painful osteochondral symptoms when sodium hyaluronate is instilled.

[0008] Present invention reveals another alternative in the management of pain in the knee or other body joints through the intra-articular application of perfluorodecalin based on the principles of viscoelastic properties of perfluorodecalin wherein implanting an artificial matrix that provides instant lubrication and expansion of local cavity relieves pain.

SUMMARY OF THE INVENTION

[0009] This invention was developed to solve the problem related to the treatment of severe pain in osteoarthritis due to lack of lubrication. This invention introduces a method to achieve alleviation of pain through the intra-articular implantation of an artificial matrix in patients with grade I or II osteoarthritis in any joint of the human body. The product consists essentially of perfluorodecalin, sterilized by autoclaving and by injecting 0.5-2 mL in the target joint, with or without other analgesics or anesthetics and with or without other pharmaceutical adjuvants.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The product is applied by conventional intra-articular means with prior asepsis and antisepsis of the region.

The preferred method for this invention's pain alleviation is the intra-articular application of perfluorodecalin either as pure liquid or in a suitable pharmaceutical dosage form such as a gel wherein the total amount of perfluorodecalin injected consists of a dose of approximately 1.5 mL of the formulation, when dealing with a large joint, or 0.50 mL for a small joint. The treatment can be applied repeatedly and periodically for an indefinite period of time without any side effects. On an average, the relief of pain lasts for at one week as perfluorodecalin is gradually removed from the injection site and eliminated from the body through the reticuloendothelial system (RES).

[0011] Perfluorodecalin is liquid fully fluorinated polycyclic compound which is chemically stable to acids and alkalis. It is also thermally stable up to 720° K. It is easily autoclaved at 121° C. It is insoluble in water and in traditional organic solvents; it is unlimited in mixing with other fluorocarbonic fluids. Approximately 45 mL of oxygen will dissolve in 100 mL of a perfluorocarbon liquid. Carbon dioxide is approximately 2.5 times more soluble than is oxygen. It is incombustible, non-explosive and non-toxic. It is available in three purified forms: CAS 306-94-5, which is a mixture of cisand transforms, the CAS 60433-11-6, which is cis form and CAS 60433-12-7, which is transform. The product used in this invention is a mixture of cis and trans form.

[0012] The safety of perfluorodecalin to humans is established as a perfluorodecalin formulation (emulsion) under the brand name of Fluosol® (Alpha Therapeutics) has been approved Under Section 505 of the Act Administered by the Center for Biologics Evaluation (N860909, Dec. 26, 1989) for direct intravenous administration to humans. Side effects to this formulation (Fluosol®) were observed in some patients due to complement activation caused by the Pluronic® surfactant used in Fluosol®. Several newer forms of dosage forms are available or under development utilizing perfluorocarbons for human administration for its oxygen carrying capacity. Examples include Oxygent™ (perfluorooctyl bromide), Oxyflour® (Supercytes®), based on perfluorodichoroctane ($C_8F_{16}C_{12}$) with triglyceride and egg yolk lecithin. Acute single dose animal toxicity studies for these products have indicated a LD_{50} of 55 g/Kg body weight.

[0013] Perfluorodeclain is readily removed from the body through reticuloendothelial system (RES) and has high in vivo stability, and produces no known pharmacologic response in humans or animals.

[0014] Perfluorodecalin is used widely in the field of ophthalmic surgery as a tool for maneuvering intraocular tissues and as a short- or medium-term vitreous substitute. The very high density of perfluorocarbons has made them of great interest to eye surgeons. The detachment of the retina from the back of the eye is a serious medical condition potentially leading to blindness. However, reattachment is now possible by passing perfluorocarbon into the eye. The heavy perfluorocarbon excludes the vitreous fluid from behind the retinal tear, gently pressing the retina back into place. The tear is sealed with a laser, and the perfluorocarbon is removed a few weeks later. In in vivo experiments, several types of lesions in retinal tissue have been described in conjunction with long-term perfluorodecalin treatment and these are attributed to its physical rather any pharmacologic toxic effects.

[0015] Perfluorodecalin is also used for intravenous administration for its potential utility as non-aqueous suspending vehicles for long-term in vivo delivery of therapeutic proteins.

[0016] Studies demonstrate the marked cytoprotectant effects of oxygenated perfluorodecalin and Pluronic F-68, both alone and/or in combination, for plant cells recovered from cryostorage. Such options offer alternative post-thaw handling strategies to cells of those plant species, which, normally, respond poorly to conventional recovery procedures.

[0017] The use of oxygen at high pressure to promote wound healing is well known. The nearer to the body's surface the less blood flow there is, and so oxygen supply is correspondingly reduced. Putting a patient into a high-pressure chamber increases the oxygen concentration at the skin's surface, accelerating healing. Oxygenated perfluorocarbons also increase surface oxygen concentration, but without the need for an expensive pressure chamber. They are especially useful for scars, leg ulcers and radiation burns. (J D Whitney, *Heart and Lung,* 1989, 18, 466. General information about high-pressure oxygen in wound healing.)

[0018] The utility of perfluorodecalin in preventing formation of adhesions and in providing viscosupplementation comes from its unique physical properties. Use of perfluorodecalin is described in the treatment of surgical adhesions (U.S. Pat. No. 6,235,796) by Niazi. Following is a comparison of physical properties of perfluorodecalin with water.

	Density, g/mL	Vapor pressure at 37° C., mm Hg	Surface tension, dynes/cm	O_2 solubility, mL/L	CO_2 solubility, mL/L
Water	1.0	47	72	30	570
Perfluorodecalin	1.95	14	15	490	1400

[0019] The low surface tension of perfluorodecalin provides for a mechanism that allows it to spread rapidly and evenly throughout the aqueous environment, leaving a fine film between the layers of tissues, reducing inflammation and speeding the healing process and thus reducing adhesion and attrition. The large capacity of perfluorodecalin to contain oxygen further assists in faster healing of wounds. Our clinical test supplies were provided by F2 Chemicals Ltd, (Lancashire, UK).

[0020] Perfluorodecalin is manufactured by passing a hydrocarbon over a heated bed of cobalt trifluoride. During this aggressive process some fragmentation and rearrangement does occur, leading to a variety of impurities. A comprehensive purification process eliminates virtually all unsaturated and hydrogen-containing components. What

remains is a small number of other perfluorocarbons. These all have very similar boiling points, and other physical properties, to perfluorodecalin, and are likewise considered non-toxic. The clinical test product was non-pyrogenic and sterilized by autoclaving.

[0021] The main purpose of this invention is to create a new treatment for knee osteoarthritis that does not seem to be favorably responding to normal drug treatment and the patients may be required to undergo orthoscopic surgery. In knees with osteoarthritis, normal joint fluid, called synovial fluid, becomes thinner and loses its elasticity and viscosity. The diseased synovial fluid cannot provide "cushioning" in the knee joint. Without this cushioning, the cartilage in the knee joint may be more likely to wear down over time. This deterioration along with the loss of cushioning can contribute to pain and stiffness in the knee. Knee osteoarthritis is a common but often difficult problem to manage in primary care. Traditional non-surgical management, consisting of lifestyle modification, physical therapy and pharmacologic therapy (e.g., analgesics, anti-inflammatory medications), is often ineffective or leaves residual symptoms. Viscosupplementation is a newly available option for patients with symptomatic knee osteoarthritis that involves a series of intra-articular injections of hyaluronic acid, among other products.

[0022] There are various products on the market for viscosupplementation; these include hyaluronan preparations of relatively low molecular weight (Hyalgan® and ARTZ®), a hyaluronan preparation of intermediate molecular weight, but still lower molecular weight than that of the hyaluronan in normal healthy synovial fluid (Orthovisc®), and a cross-linked hyaluronan (a hylan) of high molecular weight (Synvisc®).

[0023] This invention discloses that administration of pefluorodecalin by intra-articular injection in a dose of about 0.75 to 2.25 mL once per week for per two weeks or longer, for as long as needed weeks yields similar effects as obtained by other products used for this purpose. Because of the fluid nature of the compound, the invention is also expected to act as a "shock absorber" to cushion the knee joint. There is also a need to develop a cheaper alternate to currently approved therapies by the US FDA. For example, Synvisc® therapy costs about $500 per knee for a series of three injections. Because of the nature of this product and the method of its manufacture, perfluorodecalin, can be made available to patients at a fraction of the cost currently incurred in such treatments. Also, the safety profile of perfluorodecalin is much more validated that any other compound currently used for this purpose.

[0024] The efficacy of treatment was determined by a validated clinical test method and side effects recorded. This was a single group, open-label study, including outpatients of both sexes, aged between 18 and 85 years, with symptomatic knee OA. All patients (25) underwent weekly intra-articular injections of perfluorodecalin for 5 consecutive weeks and were followed-up for 10 additional weeks. The safety and tolerability profile (primary end-point) was assessed by adverse event reporting. The secondary end-point was efficacy evaluated by changes in the Western Ontario and McMaster Universities (WOMAC) score vs. baseline. Patient and physician satisfaction were also recorded. Intra-articular perfluorodecalin was generally well tolerated. The most frequent adverse event was pain at the injection site (10% of the injections); no serious treatment-related adverse events were reported. The WOMAC score was significantly reduced within the first 2 weeks of treatment (from 5±2 to 3±2;, $p<0.001$), further decreased by the end of the injection series (week 6: 2±1.5; $p<0.001$) and maintained during the follow-up. The WOMAC subscores were also significantly reduced from week 4 for 'pain' and from week 6 for 'stiffness' and 'physical function'.

[0025] The functional result subsequent to the implantation of the product was very satisfactory for most of treated patients. The difference between the plain systemic drug management and the intra-articular application of perfluorodecalin is very evidently in favor of the latter. It must be considered that the plain intra-articular rheological change (viscosity, elasticity and plasticity) reduces the pain and stimulates a synovial response, changing the viscoelastic features of the fluid.

Conclusions

[0026] In the present study, intra-articular perfluorodecalin was well tolerated and safe in patients with symptomatic knee OA. Based on the sustained improvements in WOMAC score and subscores, a carry-over effect lasting for at least 3 weeks after the last injection are proposed. These results further confirm the evidence of efficacy and safety of intra-articular perfluorodecalin in the management of knee OA. The treatment of pain in osteochondral lesions using implantation with perfluorodecalin has proven to have a significantly favorable clinical response compared with the conventional treatment, particularly in those patients who have turned refractory to analgesics. The experts in the technique will recognize that the preferred modes may be altered or amended without straying away from the true spirit and scope of the invention as defined in the enclosed claims.

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REVIEW ARTICLES ON PERFLUORODECALIN

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What is claimed is:

1. A therapeutic method for the alleviation of pain caused by osteoarthritis, comprising the intra-articular implantation of perfluorodecalin in a pharmaceutically elegant dosage form.

2. The therapeutic method according to claim 1 for a joint selected from the group consisting of: knee, shoulder and sacroiliac.

3. The therapeutic method according to claim 1 for a joint selected from the group consisting of coxofemoral, ankle and elbow.

4. The therapeutic method according to claim 1 for a joint selected from the group consisting of interphalangeal and wrist.

5. The therapeutic method according to claim 1, wherein perfluorodecalin is combined with other pain relievers.

6. The therapeutic method according to claim 1, wherein perfluorodecalin is combined with anesthetic agents.

7. The therapeutic method according go claim 1, wherein perfluorodecalin is oxygenated prior to implantation.

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