

(12) **UK Patent Application** (19) **GB** (11) **2 287 404** (13) **A**

(43) Date of A Publication **20.09.1995**

(21) Application No **9420055.7**

(22) Date of Filing **05.10.1994**

(30) Priority Data
(31) **08213327** (32) **15.03.1994** (33) **US**

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(51) INT CL⁶
A61K 45/06

(52) UK CL (Edition N)
**A5B BJA B170 B180 B32Y B327 B42Y B421 B43Y B433
B44Y B441 B45Y B453 B48Y B480 B481 B482 B483
B50Y B502 B52Y B523 B54Y B541 B55Y B551 B556
B56Y B566 B57Y B575 B576 B58Y B586 B60Y B606
B61Y B616 B64Y B646 B66Y B664
U1S S2416 S2417**

(56) Documents Cited
GB 2274777 A EP 0474561 A1

(58) Field of Search
**UK CL (Edition N) A5B BJA
INT CL⁶ A61K 45/06
ON LINE DATABASES: WPI, CLAIMS, CAS ONLINE,
EMBASE, MEDLINE, BIOSIS, JAPIO**

(54) **Antiinflammatory and analgesic compositions**

(57) Compositions for treating inflammatory diseases and pain comprise a substance P receptor antagonist and an antiinflammatory/analgesic compound. The substance P receptor antagonists include NK-1 antagonists within their scope. Typical antiinflammatories/analgesics are acetaminophen, aspirin, NSAID's, codiene, fentanyl, sufentanyl, morphine, ibuprofen, piroxicam, naproxen, sunlindac, ketorolac, or indomethacin. Administration may be oral, parenteral or topical.

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ANTI-INFLAMMATORY COMPOSITIONSBackground of the Invention

This invention relates to pharmaceutical compositions for the prevention and treatment of inflammatory diseases and pain, comprising substance P receptor antagonists, and to a method for such prevention and treatment.

10 The interactions of certain pathways with that of substance P has been described. For instance, Malmberg et al., Science, 257, 1276 (1992) refers to the action of nonsteroidal anti-inflammatory drugs (NSAIDs) by blocking the excessive sensitivity to pain (hyperalgesia) induced by the activation of substance P receptors. Dougherty et al., Pain, 47, 85 (1991) describes potentiation and prolongation of N-methyl-D-
15 aspartic acid (NMDA) responses by substance P based on recordings from spinothalamic neurons.

Substance P receptor antagonists, which include NK-1 antagonists, are known to be of value in the treatment of inflammatory diseases and pain and are disclosed in U.S. Patent No. 5,162,339 and other publications.

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Summary of the Invention

This invention relates to a pharmaceutical composition for the prevention or treatment of pain or inflammatory diseases which comprises a substance P receptor antagonist and an anti-inflammatory or analgesic agent.

The invention also relates to a method for prevention or treatment of pain or
25 inflammatory diseases by administering to a patient in need of such prevention or treatment an effective amount of a substance P receptor antagonist and an anti-inflammatory or analgesic agent.

In a preferred embodiment of the invention said anti-inflammatory or analgesic agent is selected from the group consisting of an opiate agonist, a lipoxygenase
30 inhibitor, a cyclooxygenase inhibitor, an NMDA antagonist, an inhibitor of nitric oxide and an inhibitor of the synthesis of nitric oxide.

Detailed Description of the Invention

The invention makes use of substance P receptor antagonists. Examples of such compounds include those described in U.S. Patents 5,162,339 and 5,232,929, WO
35 92/06079, 92/15585, 93/0330 and 93/06099, and European Patent Publication 533 280, which are all incorporated herein by reference.

The invention further makes use of anti-inflammatory and analgesic agents, not including substance P receptor antagonists. Examples of analgesic and anti-inflammatory agents include those listed in the Physician's Desk Reference (1993) under the headings: analgesics and anti-inflammatory agents. Also included are anti-inflammatory compounds that work by inhibiting the production of inflammatory mediators, e.g, corticosteroids.

More specifically, the anti-inflammatory or analgesic agents of use in the invention include but are not limited to acetaminophen, aspirin, NSAIDs, and narcotics such as codeine, fentanyl, sufentanyl, and morphine. Specific anti-inflammatory agents include ibuprofen, Feldene® (piroxicam), Naprosyn® (naproxen), ketorolac tromethamine, indomethacin, Clinoril® (sulindac), etc.

The invention includes combinations of substance P antagonists and two or more anti-inflammatory agents or an anti-inflammatory and an analgesic agent.

The invention is for the prevention and treatment of inflammatory diseases including arthritis, psoriasis, asthma and inflammatory bowel disease, and acute and chronic pain, such as postoperative pain, cancer-related pain, neuropathic pain syndromes and fibromyalgia.

The pharmaceutical composition of the invention may be administered by the oral, parenteral or topical routes. In general, these compositions are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the subject being treated and the individual's response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The anti-inflammatory or analgesic agent present in the compositions of the invention may be administered in conventional amounts of about 5 to about 1000 mg

per day, or in below conventional amounts of 10 to 50% of the conventional amounts may be used.

The compositions of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes
5 previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the compositions of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels,
10 pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compositions of the invention are present in such dosage forms at concentration levels
15 ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch, preferably
20 corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols.
25 When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

30 For parenteral administration, solutions of the composition of the invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection

purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

5 Additionally, it is also possible to administer the compositions of the invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

10 The activity of the compositions of the present invention may be determined by the standard carrageenin-induced rat foot edema test, C.A. Winter *et al.*, Proceedings of the Society for Experimental Biology and Medicine, Vol. 111, p. 544 (1962). Other methods include but are not limited to the formalin paw test, acetic acid writhing test, and models testing adjuvant-induced arthritis.

CLAIMS

1. A pharmaceutical composition for the prevention or treatment of pain or inflammatory diseases which comprises a substance P receptor antagonist and an anti-inflammatory or analgesic agent.
- 5 2. A composition according to claim 1 wherein said anti-inflammatory or analgesic agent is selected from the group consisting of an opiate agonist, a lipoxygenase inhibitor, a cyclooxygenase inhibitor and an NMDA antagonist.
3. A composition according to claim 1 wherein said anti-inflammatory agent is an inhibitor of nitric oxide or its synthesis.
- 10 4. A composition according to claim 1 wherein said anti-inflammatory agent is acetaminophen, aspirin, ibuprofen, piroxicam, naproxen, or indomethacin.
5. A method for the prevention or treatment of pain or inflammatory diseases which comprises administering to a patient in need of such prevention or treatment an effective amount of a substance P receptor antagonist and an anti-
15 inflammatory agent.

Relevant Technical Fields

- (i) UK Cl (Ed.N) A5B (BJA)
- (ii) Int Cl (Ed.6) A61K 45/06

Search Examiner
M R WENDT

Date of completion of Search
12 JANUARY 1995

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: WPI, CLAIMS, CAS ONLINE, EMBASE, MEDLINE, BIOSIS, JAPIO

Documents considered relevant following a search in respect of Claims :-
1-4

Categories of documents

- X:** Document indicating lack of novelty or of inventive step.
- Y:** Document indicating lack of inventive step if combined with one or more other documents of the same category.
- A:** Document indicating technological background and/or state of the art.
- P:** Document published on or after the declared priority date but before the filing date of the present application.
- E:** Patent document published on or after, but with priority date earlier than, the filing date of the present application.
- &:** Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
P,X	GB 2274777 A (RHONE-POULENC) see Example. Page 64 lines 1-18	1
X	EP 0474561 A1 (SANOFI) see Claims 9, 10 on page 48 and page 13 lines 18-21	1

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).