PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/195, A61P 1/14 — A1

(11) International Publication Number: **WO 00/50027**

(43) International Publication Date: 31 August 2000 (31.08.00)

(21) International Application Number: PCT/EP00/01103

(22) International Filing Date: 3 February 2000 (03.02.00)

(30) Priority Data:
99400440.6 23 February 1999 (23.02.99) EP

(71) Applicant *(for all designated States except US)*: WARNER–LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). DIOP, Laurent [FR/FR]; 38, rue de Villeras, Val d'Albian, F–91400 Saclay (FR).

(74) Agent: DURNING, Bernard; Warner–Lambert Company, Parke–Davis, Patent Department, 3–9, rue de la Loge – B.P. 100, F–94265 Fresnes Cedex (FR).

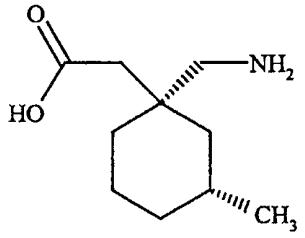
(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: GABAPENTIN DERIVATIVE FOR PREVENTING AND TREATING VISCERAL PAIN



(57) Abstract

[1S–(1α,3β)]–(1–aminomethyl–3–methyl–cyclohexyl)–acetic acid is useful to prevent and treat visceral pain.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

GABAPENTIN DERIVATIVE FOR PREVENTING AND TREATING VISCERAL PAIN

FIELD OF THE INVENTION

This invention relates to a method for preventing and for treating visceral pain, and gastrointestinal disorders such as functional bowel disorders (FBD) and inflammatory bowel diseases (IBD) through the use of effective amounts of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid.

BACKGROUND OF THE INVENTION

Gabapentin (1-(aminomethyl)cyclohexane acetic acid) is an antiepileptic drug, active in various animal models of epilepsy, and effective in decreasing the frequency of seizures in patients. Gabapentin, although a γ-aminobutyric acid (GABA) structural analogue, does not significantly bind to GABA receptors, but binds to the $\alpha_2\delta$ subunit of a calcium channel (Gee N.S. *et al.*(1996) J. Biological Chemistry **271**: 5768-5776), suggesting that modulation of voltage-dependent neuronal Ca^{2+} channels is important to the action of gabapentin. Also, a correlation has been shown between the affinity of ligands at the [^{3}H]gabapentin binding site and anticonvulsant activity (Taylor C. P. *et al.* (1993) Epilepsy Res. **14**: 11-15). Gabapentin *s.c.* has recently been shown to suppress TNBS-induced colonic hypersensitivity in a model of chronic allodynia (Diop L. *et al.* (1998) Soc. Neurosci. Abstr.: **24**: 639).

International patent application WO 97/33858 describes substituted derivatives of gabapentin, including [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, which bind to the $\alpha_2\delta$ subunit of a calcium channel, and are useful in the treatment of epilepsy and related central nervous system (CNS) disorders.

Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD).

These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, and the irritable bowel syndrome (IBS), and – for IBD, Crohn's disease, ileitis, and ulcerative colitis, and that all regularly produce visceral pain. It has been shown recently in these pathologies, in particular the irritable bowel syndrome and dyspepsia, that the visceral pain threshold is decreased, indicating a visceral hypersensitivity.

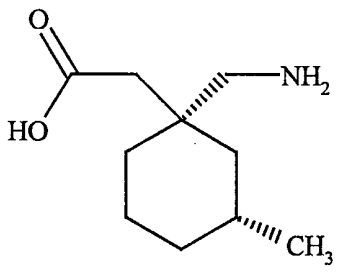
Few drugs are known to act selectively upon GI disorder-associated hypersensitivity (Farthing M.J. (1998) Drugs **56**:11-21).

Available treatments of pain fall into two categories: 1) nonsteroidal anti-inflammatory drugs, used to treat mild pain, but whose therapeutic use is limited by GI adverse effects (gastric erosion, peptic ulcer formation, inflammation of the duodenum and colon); 2) morphine and related opioids, used to treat moderate to severe pain but whose therapeutic use is limited by undesirable side effects including constipation, respiratory depression, tolerance, and abuse potential.

There is a need for drugs that can alleviate visceral pain without undesirable side effects.

SUMMARY OF THE INVENTION

This invention provides a method for preventing and treating visceral pain and GI disorders comprising administering to a subject in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid (I)



(I)

or a pharmaceutically acceptable salt thereof.

This invention also concerns the use of a compound of Formula I for the preparation of a medicament useful for preventing or treating visceral pain and gastrointestinal disorders, in particular by the oral route.

DETAILED DESCRIPTION OF THE INVENTION

The compound used in the instant invention, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid (Formula I above), is described in international patent application WO 97/33858 which is incorporated herein by reference, and which more generally describes substituted derivatives of gabapentin, including [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid; such derivatives bind to the $\alpha_2\delta$ subunit of a calcium channel, and are useful in the treatment of epilepsy. In that application WO 97/33858, the compound utilized in the instant invention has been shown to have an affinity similar to that of gabapentin for the $\alpha_2\delta$ subunit derived from porcine brain tissue.

It has now been found that [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, although of similar activity or less active than gabapentin on somatic pain or epilepsy, is surprisingly ten-fold more effective than gabapentin on visceral pain.

This finding is at odds with the well recognized knowledge that, at every level of the nervous system, a close relationship prevails between somatic pain pathways and visceral pathways (Cross S.A. (1994) Mayo Clin Proc **69**: 375-83).

The compounds utilized in the present invention include solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the compound of Formula I.

Where it is appropriate to form a salt, the pharmaceutically acceptable salts include acetate, benzenesulfonate, benzoate, bitartrate, calcium acetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine,

hydrobromide, hydrochloride, hydrogencarbonate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate or hemi-succinate, sulfate or hemi-sulfate, tannate, tartrate or hemi-tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, ammonium, tetramethyl ammonium, calcium, lithium, magnesium, potassium, sodium, and zinc. (See also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, which is incorporated herein by reference.)

The term "patient" is intended to include a mammal, especially a human.

All that is required to practice the method of preventing and treating visceral pain and GI disorders FBD or IBD according to the present invention is to administer [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid in an amount that is effective to prevent or treat the damaged condition, i.e. to control visceral pain and/or FBD or IBD. The effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid to be utilized will generally be from about 1 to about 300 mg / kg of patient body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult patient of normal weight. Typical FBD conditions include gastro-esophageal reflux disease, dyspepsia, and IBS. Typical IBD conditions include ileitis, ulcerative colitis, and Crohn's disease.

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of visceral pain and GI disorders comprising the active component, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, of Formula I. Pharmaceutical compositions of the compound of the present invention –including one of its salts, are produced by formulating this active component in dosage unit form with at least one pharmaceutically acceptable carrier or excipient. For preparing pharmaceutical compositions from the compound used in this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. They preferably contain 5% to about 70% of [1S-(1α, 3β)]-

(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid. In such solid dosage forms, the active component is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinyl-pyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They can also be of such composition that they release the active component in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active component can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, and the like.

Suspensions, in addition to the active component, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compound of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature, and therefore melt in the rectum and release the active component.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable liquid carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), and suitable mixtures thereof.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. Some examples of dosage unit forms are tablets, capsules, pills, powders, suppositories, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses.

The percentage of the active component in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10 % in a solid composition and at least 2 % in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active component is present, for example, from 10 % to 90 % by weight.

Routes of administration of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or its salts are parenteral or, preferably, oral. For example, a useful oral dosage is between 20 and 800 mg, and a useful intravenous dose is between 5 and 50 mg. The dosage is within the dosing range used in treatment of visceral pain and GI disorders such as FBD or IBD, or as would be dictated by the needs of the patient as described by the physician.

A unit dosage form of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid to be used in this invention may also comprise other compounds useful in the therapy of visceral pain and GI disorders.

The advantages of using [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid in the instant invention include the selective activity of the compound on visceral pain, the relatively nontoxic nature of the compound, the ease of preparation, the fact that the compound is well tolerated, and the ease of *i.v.* and, in particular, oral administration of the drug.

Pharmacological data

Initially, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic had proved of similar activity or less active than gabapentin in animal models of somatic pain and epilepsy. However, as regards visceral pain, the ability of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid to treat selectively GI disorders according to this invention has been established in two animal models of allodynia.

Somatic pain:

Carrageenin-induced hyperalgesia in rats: effect of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesymeter (Randall L.O. and Sellitto J.J. (1957) Arch. Int. Pharmacodyn. **4**: 409-419). Male Sprague Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 µl of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 h after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, or saline at 3.5 h after carrageenin, and nociceptive thresholds were examined at 4, 4.5, and 5 h post-carrageenin.

Results

Effect of gabapentin

Dose *p.o.* (mg/kg)	**Inhibition at 1 h (%)**	**Inhibition at 2 h (%)**
30	48	20

Effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid:

Dose *p.o.* (mg/kg)	**Inhibition at 1 h (%)**	**Inhibition at 2 h (%)**
30	68	34

Epilepsy:

Semicarbazide-induced tonic seizures in mice: effect of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid

Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is noted. Any mice not convulsing within 2 h after semicarbazide are considered protected and given a maximum latency score of 120 min.

At the same dose of 30 mg/kg *p.o.*, gabapentin protected 100% of the animals whereas [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid protected 40%.

Visceral pain:

In humans, GI disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. Two experimental models of visceral pain were used to evaluate the effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid *p.o.*: TNBS-induced colitis and septic shock-induced rectal allodynia in awake rats. In each model, the effect is compared with that of gabapentin *p.o.*

1°) TNBS-induced chronic visceral allodynia in rats: effect of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid

Injections of trinitrobenzene sulfonic acid (TNBS) into the wall of the rat colon have been found to induce chronic colitis. In this experimental model of colonic distension in awake rats, previous injection of TNBS into the proximal colon had lowered the visceral pain threshold.

Materials and methods

Male Sprague-Dawley rats weighing 340-400 g are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 5 % humidity, with light 8:00 am to 8:00 pm). At day 0, under anesthesia (ketamine 80 mg/kg *i.p.*; acepromazine 12 mg/kg *i.p.*), the injection of TNBS (50 mg/kg in ethanol 30 %), or saline (1.5 ml/kg) for control rats, is performed into the proximal colon wall (1 cm from the cecum). After the surgery, animals are individually housed in

polypropylene cages and kept in a regulated environment (20 °C, 50 % humidity, with light 8:00 a.m. to 8:00 p.m.) during 7 days. At day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus, and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. Oral administration of gabapentin or of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is performed 1 h before the colonic distension cycle: the balloon is progressively inflated by steps of 5 mm Hg (0.667 kPa), from 0 to 75 mm Hg, each step of inflation lasting 30 s. Each cycle of colonic distension is controlled by a standard barostat. The threshold (mm Hg) corresponds to the pressure which produced the first abdominal contraction, and the cycle of distension is then discontinued. The colonic threshold is determined after performance of four cycles of distension on the same animal.

Data is analyzed by comparing test compound-treated groups with a TNBS only-treated group and the control group. Mean and SEM are calculated for each group. The antiallodynic activity of each oral dose of the test compound is calculated as follows:

$$Activity = \frac{A - T}{C - T}$$

where A = mean threshold of the test compound-treated group,

T = mean threshold of the TNBS only-treated group,

C = mean threshold of the control group.

The results measured in the test compound-treated groups are expressed in % inhibition of the TNBS-induced decrease in the pain threshold.

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired *t*-test; differences were considered statistically significant at $p < 0.05$.

Results

Effect of gabapentin:

Dose *p.o.* (mg/kg)	Inhibition at 1 h (%)	Number of rats
100	14.7 ± 5.1 % *	7
300	48.6 ± 13.3 % **	8
500	64.9 ± 10.5 % ***	8
1000	75.2 ± 6.1 % ***	8

* : $p < 0.05$ ** : $p < 0.01$ *** : $p < 0.001$

The median effective dose (ED_{50}) of gabapentin is 321 mg/kg *p.o.*

Effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid:

Dose *p.o.* (mg/kg)	Inhibition at 1 h (%)	Number of rats
10	34.0 ± 9.7 % *	8
30	46.6 ± 8.4 % **	7
100	97.4 ± 22.4 % **	8

The ED_{50} of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is 22.9 mg/kg *p.o.*

By the subcutaneous (*s.c.*) route, gabapentin is known not to modify the colonic threshold in control conditions; by contrast, in the same conditions morphine (*s.c.*) increased the colonic threshold in both TNBS-treated animals and in controls, suggesting a different mechanism of action. (Diop L. *et al.* (1998) Soc. Neurosci. Abstr.: **24**: 639).

[1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid produced a potent antiallodynic activity in a model of visceral pain in rats, the compound being more than 10-fold more active than gabapentin in the same conditions. The respective ED_{50} values are 321 mg/kg *p.o.* for gabapentin and 23 mg/kg *p.o.* for [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid. Furthermore this effect does not involve an opiate mechanism.

2°) LPS-induced rectal hypersensitivity in rats

Intraperitoneal injection of bacterial lipo-polysaccharide (LPS) has been shown to induce rectal hyperalgesia in awake rats.

Materials and methods

Animals are surgically prepared for electromyography: rats are anaesthetized by intraperitoneal injection of acepromazine (0.6 mg/kg) and ketamine (120 mg/kg). Three groups of three electrodes are implanted in the abdominal external oblique musculature, just superior to the inguinal ligament. Electrodes are exteriorized on the back of the neck and protected by a glass tube attached to the skin. Animals are individually housed in polypropylene cages and kept in a temperature-controlled room (21°C). Food (UAR pellets, Epinay, France) and water are provided ad libitum.

Electromyographic recordings begin five days after surgery. The electrical activity of abdominal striated muscles is recorded with an electroencephalograph machine (Mini VIII Alvar, Paris, France) using a short time constant (0.03 s) to remove low-frequency signals (< 3 Hz) and a paper speed of 3.6 cm/min. Spike bursts are recorded as an index of abdominal contractions.

Distension procedure: Rats are placed in plastic tunnels (6 cm diameter x 25 cm long), where they cannot move, escape, or turn around, in order to prevent damage to the balloon. Animals are accustomed to this procedure for four days before rectal distension in order to minimize stress reactions during experiments. The balloon used for distension is an arterial embolectomy catheter (Fogarty, Edwards Laboratories Inc.). Rectal distension is performed by insertion of the balloon (2 mm diameter x 2 cm long) into the rectum, at 1 cm from the anus, and catheter is fixed at the base of the tail. It is inflated progressively with tepid water by steps of 0.4 ml, from 0 to 1.2 ml, each step of inflation lasting 5 min. To detect possible leakage, the volume of water introduced in the balloon is checked by complete removal with a syringe at the end of the distension period.

Experimental protocol: Rats are injected i.p. with LPS (1 mg/kg (*Escherichia coli*, serotype O111:B4) Sigma-Aldrich chemical Co., St Louis, MO.) or its vehicle, and rectal distension with concomitant electromyographic recording of abdominal contractions is performed 9 and 12 h after this administration. To determine the antinociceptive properties of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid in hyperalgesia conditions, gabapentin (10 and 30 mg/kg), [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid (3, 10 and 30 mg/kg) or the vehicle (NaCl 0.9 % 0.3 ml/rat) are administered per os 1 h before rectal distension but preceded (12 h) by injection of LPS (1 mg/kg i.p.).

Drugs: All compounds were dissolved in sterile NaCl (0.9 % isotonic saline) immediately before use.

Statistics: Statistical analysis of the number of abdominal contractions occurring during each period of rectal distension is performed by one-way ANOVA followed by parametric Student's unpaired t test.

Results

Effect of gabapentin: Gabapentin administered at 30 mg/kg p.o. significantly inhibits (85.3 %, $p < 0.001$) the number of abdominal contractions induced by rectal distension at 0.4 ml in LPS treated rats. At 10 mg/kg p.o., gabapentin does not produce a significant antihyperalgesic activity (24.9 %).

Effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid: After oral administration, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid (3, 10, 30 mg/kg p.o.) inhibits in a dose-related manner the number of abdominal contractions induced by rectal distension at 0.4 ml after LPS treatment. The ED 50 is of 3.81 mg/kg p.o.

In conclusion, these results show that gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid produce an antihyperalgesic activity on LPS-induced rectal hypersensitivity, a model of visceral pain in rats. [1S-(1α, 3β)]-(1-

aminomethyl-3-methyl-cyclohexyl)-acetic acid displays a more potent anti-hyperalgesic activity than gabapentin; the comparison of the active doses show that [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is about 5 times more potent than gabapentin in this model of visceral pain.

The foregoing data establish that [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is effective in preventing and treating visceral pain, in particular in GI disorders such as functional bowel disorders (FBD) and inflammatory bowel diseases (IBD). In addition, such efficacy of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is observed following oral administration of the compound.

Furthermore this compound, which had proved of similar or less active than gabapentin in animals models of somatic pain and epilepsy, is surprisingly 5 to 10 times more potent than gabapentin in models of visceral pain.

CLAIMS

What is claimed is:

1. A method for preventing visceral pain comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

2. A method for treating visceral pain comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

3. A method for preventing gastrointestinal disorders comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

4. A method for treating gastrointestinal disorders comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

5. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is characterized as functional bowel disorder or inflammatory bowel disease.

6. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is a functional bowel disorder.

7. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is gastro-esophageal reflux disease.

8. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is dyspepsia.

9. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is the irritable bowel syndrome.

10. A method according to Claim 3 or Claim 4 wherein the condition treated is selected from Crohn's disease, ileitis, and ulcerative colitis.

11. A method according to Claim 3 or Claim 4 wherein [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof is administered by the oral route.

12. The use of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful for preventing or treating visceral pain.

13. The use according to claim 12 wherein the medicament is a formulation for oral administration.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 00/01103

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P1/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 33858 A (WARNER LAMBERT CO ;HORWELL DAVID CHRISTOPHER (GB); BRYANS JUSTIN S) 18 September 1997 (1997-09-18) cited in the application page 1 -page 3 page 15, line 25 - line 30 page 17, line 1 - line 21 ---	1-13
Y	BRYANS ET AL.: "Identification of novel ligands for the Gabapentin binding site..." J.MED.CHEM., vol. 41, 1998, pages 1838-1845, XP002139354 see table 1, compound 19 --- -/—	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	27/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/01103

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 11680 A (GLAXO GROUP LTD ;BAYS DAVID EDMUND (GB); BOUNTRA CHARANJIT (GB)) 25 April 1996 (1996-04-25) page 1, line 24 - line 28 page 2, line 32 -page 3, line 17 ---	1-13
Y	DIOP ET AL.: "Gabapentin and S-(+)-Isobutylgaba inhibit ..." SOC.NEUROSCI.ABSTR., vol. 24, page 639 XP000909847 cited in the application the whole document ---	1-13
P,X	WO 99 08671 A (BUENO LIONEL ;CHOVET MARIA (FR); DIOP LAURENT (FR); LITTLE HILARY) 25 February 1999 (1999-02-25) page 1 -page 3; claims 1-11 -----	1-13

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/EP 00/01103

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733858 A	18-09-1997	AU 2051197 A	01-10-1997
		BG 102733 A	30-04-1999
		BR 9708200 A	27-07-1999
		CA 2244912 A	18-09-1997
		CZ 9802863 A	17-03-1999
		EP 0888286 A	07-01-1999
		NO 984205 A	14-09-1998
		PL 328816 A	15-02-1999
WO 9611680 A	25-04-1996	AU 3745895 A	06-05-1996
WO 9908671 A	25-02-1999	AU 8668598 A	08-03-1999
		AU 9293098 A	08-03-1999
		NO 20000786 A	17-02-2000
		WO 9908670 A	25-02-1999