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(54) Title: USE OF 5-HT4 MODULATORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF THE BLADDER DISEASES

(57) Abstract

A compound which acts as an antagonist at 5-HT_4 receptors is of potential use in the treatment of conditions associated with bladder hypersensitivity, such as urinary incontinence, which is often associated with irritable bowel syndrome (IBS) and a compound which acts as an agonist at 5-HT_4 receptors is of potential use in the treatment of conditions associated with a poorly functioning bladder, such as urinary bladder hypoactivity following prostectomy.

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Use of 5-HT4 modulators for the manufacture of a medicament for the treatment of the bladder diseases

This invention relates to treatment of conditions associated with bladder hypersensitivity, and conditions associated with a poorly functioning bladder.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that tropisetron (ICS 205-930), which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor and metoclopramide is an agonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

Metoclopramide has been shown to be effective in treating a poorly functioning bladder, (Scand. J. Urology and Nephrology, 13:79-82 (1979) but this has not been specifically linked to any known action of metoclopramide.

There are reports in the literature of 5-HT_4 receptors potentiating contractions in human bladder (Br. J. Pharmacol, 61, 115P) and inhibiting contractions in monkey bladder (2nd International Symposium on Serotonin, Houston, September 1992, page 86).

We have now discovered that a compound which acts as an antagonist at 5-HT_4 receptors is of potential use in the treatment of conditions associated with bladder hypersensitivity, such as urinary incontinence, which is often associated with irritable bowel syndrome (IBS) and a compound which acts as an agonist at 5-HT_4 receptors is of potential use in the treatment of conditions associated with a poorly functioning bladder, such as urinary bladder hypoactivity following prostectomy. When used herein the term '5-HT_4 modulator' is used to denote antagonists and agonists.

The invention therefore provides a method for the treatment and/or prophylaxis of conditions associated with bladder hypersensitivity and conditions associated with a poorly functioning bladder in mammals, including

humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT_4 modulator.

5-HT_4 modulators may be identified according to standard methods, such as those described hereinafter, and that described in Naunyn-Schmiedeberg's Arch Pharmacol. 342, 619-622.

Examples of 5-HT_4 receptor antagonists include ICS 205-930 (tropisetron - Sandoz), R 50 595 (Janssen), which is described in FR 76530 and Eur.J. Pharmacol., 181 119-125 (1990), and SDZ 205-557, which is described by K.H. Buchheit and R. Gamse in Naunyn-Schmiedeberg's Arch. Pharmacol., 343 (Suppl.), R101 (1991). DAU 6285 (Naunyn-Schmiedeberg's Arch. Pharmacol, 345; 264-269 (1992) and RS 23597-190 (Syntex - British Pharmacology Society Meeting, September 1992).

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 receptor antagonist activity and reports 5-HT_4 receptors are believed to be associated with conditions involving *inter alia* the urinary tract (e.g. urinary incontinence).

Examples of 5-HT_4 receptor agonists include cisapride, renzapride and zacopride.

In one aspect, the 5-HT_4 modulator is more potent at 5-HT_4 receptors than at 5-HT_3 receptors.

Preferably, the 5-HT_4 modulator is in substantially pure pharmaceutically acceptable form.

The administration of the 5-HT_4 modulator may be by way of oral, sublingual, transdermal or parenteral administration.

An amount effective to treat the disorder hereinbefore described depends on the usual factors such as the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the 5-HT_4 modulator. Unit doses will normally be administered once or more than once a day, for example 2, 3,

or 4 times a day, more usually 1 to 3 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.1 to 5 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

For oral or parenteral administration, it is greatly preferred that the 5-HT_4 modulator is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or

hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the 5-HT_4 modulator and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

The present invention also provides the use of a 5-HT_4 modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity. Such treatment and/or prophylaxis may be carried out as hereinbefore described.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT_4 modulator, and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

5-HT_4 modulator activity

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}Mn and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10-9M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 modulator are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP.

From this data, IC_{50} values are determined, being defined as the concentration of antagonist or agonist which reduces or increases the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist and a compound which increases the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor agonist.

2) **Rat oesophagus**

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

Claims

1. A method for the treatment and/or prophylaxis of conditions associated with bladder hypersensitivity and conditions associated with a poorly functioning bladder in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT_4 modulator.

2. The use of a 5-HT_4 modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity.

3. A pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT_4 modulator, and a pharmaceutically acceptable carrier.

4. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_4 modulator is a 5-HT_4 receptor antagonist.

5. A method, use or composition according to claim 4 for the treatment of urinary incontinence.

6. A method, use or composition according to claim 5 for the treatment of urinary incontinence associated with irritable bowel syndrome.

7. A method, use or composition according to claim 4, 5 or 6 wherein 5-HT_4 receptor antagonist is R 50 595, SDZ 205-557, DAU 6285, RS 23597-190 or a compound described in relation to EP-A-501322 (Glaxo Group Limited).

8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_4 modulator is a 5-HT_4 receptor agonist.

9. A method, use or composition according to claim 8 for the treatment of urinary bladder hypoactivity following prostectomy.

10. A method, use or composition according to claim 8 or 9 wherein 5-HT_4 receptor agonist is cisapride, renzapride or zacopride.

INTERNATIONAL SEARCH REPORT

PCT/GB 92/02376

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/40; A61K31/445; A61K31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	EP,A,0 501 322 (GLAXO GROUP LTD) 2 September 1992 cited in the application see page 5, line 18 - line 37; claims 1-16	1-7
P,X	EP,A,0 467 365 (E.R.SQUIBB & SONS, INC.) 22 January 1992 see page 2, line 49 - page 3, line 56	1-3,8-10
X	PARAPLEGIA vol. 26, no. 3, 1988, pages 162 - 164; M.ETIENNE ET AL.: 'Treatment with cisapride of the gastrointestinal and urological sequelae of spinal cord transection: case report' see conclusion see abstract	1-3,8-10

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 MARCH 1993	06.04.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	TZSCHOPPE D. A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	PARAPLEGIA vol. 26, no. 3, 1988, pages 159 - 161; G.H. DE GROOT ET AL.: 'Effects of cisapride on constipation due to neurological lesion' see discussion see abstract	1-3,8-10
X	ACTA BELG. MED. PHYS. vol. 12, no. 3, 1989, pages 81 - 88; P.HANSON ET AL.: 'Effet du cisapride sur les vessies neurologiques' see conclusions	1-3,8-10
P,X	DRUG. DEV. RES. vol. 27, no. 4, 1992, pages 361 - 375; WILLIAM D. STEERS ET AL.: 'Effects of serotonic agonists on micturation and sexual function in the rat' see abstract	1-3,8-10
A	DRUGS FUTURE vol. 16, no. 11, 1991, pages 1011 - 1026; M. TURCONI ET AL: 'Azabicycloalkyl benzimidazolones: Interaction with serotonergic 5-HT3 and 5-HT4 receptors and potential therapeutic implications' see the whole document	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9202376
SA 68535

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0501322	02-09-92	AU-A-	1209492	15-09-92
		WO-A-	9214727	03-09-92
EP-A-0467365	22-01-92	CA-A-	2044854	20-01-92
		JP-A-	4234328	24-08-92