(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 April 2009 (09.04.2009)

PCT

(10) International Publication Number
WO 2009/045985 A1

(51) International Patent Classification:
A01N 43/42 (2006.01) *A61K 31/44* (2006.01)

(21) International Application Number:
PCT/US2008/078229

(22) International Filing Date:
30 September 2008 (30.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/976,652 1 October 2007 (01.10.2007) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

WO 2009/045985 A1

(54) **Title:** TREATMENT OF DRUG-INDUCED NAUSEA WITH OPIOID ANTAGONISTS

(57) **Abstract:** The invention provides methods of relieving side effects associated with administration of a chloride channel activator by co-administration with an opioid antagonist. The invention also provides methods of enhancing the effect of the chloride channel activators in treating the gastrointestinal disorder, such as constipation, while attenuating adverse side effects, such as nausea and emesis.

TREATMENT OF DRUG-INDUCED NAUSEA WITH OPIOID ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 60/976,652 filed on October 1, 2007 which is incorporated herein by reference in its entirety

FIELD OF INVENTION

The invention relates to methods of treating drug-induced gastrointestinal side effects such as nausea while enhancing treatment of constipation.

BACKGROUND

Many therapeutic drugs produce adverse gastrointestinal side effects, such as nausea and emesis. For example, many clinically useful narcotic analgesics, such as morphine and related opiates, meperidine, methadone and the like, which are given to ease pain, also produce nausea and emesis. Additionally, drugs commonly used for the treatment gastrointestinal disorders, such as constipation, inflammatory bowel disease, irritable bowel syndrome and post-operative bowel dysfunction, are often associated with the development of nausea and emesis. Such side effects often limit the usefulness of the drug and may even render the drug unacceptable for use.

While numerous antinausea and antiemetic compositions exist, these compositions often produce their own undesired patient side-effects. The result is often that the patient is put in the position of choosing between the condition she or he seeks to alleviate and the side effect of the therapy.

BRIEF DESCRIPTION OF THE INVENTION

The inventor has discovered effective antinausea and antiemetic formulations which have few side effects and permit use of therapeutic agents to effectively treat a condition or illness. In accordance with the invention, methods are provided for relieving gastrointestinal side effects, such as nausea and emesis, associated with the administration of certain drugs, specifically ion channel modulators, especially chloride channel activators, for the treatment of, e.g., constipation. An illustrated

embodiment of the invention provides methods of relieving, e.g., alleviating, inhibiting, attenuating, or reducing, nausea, including that associated with constipation treatment, by administering opioid antagonists, including, but not limited to, those that are peripherally restricted antagonists.

In another embodiment, the invention provides methods of treating gastrointestinal disorders by co-administering a chloride channel activator and an opioid antagonist. Such co-administered treatments may enhance laxation as well as treat nausea and other side effects. Thus, synergy of the co-administered chloride channel activator and the opioid antagonist is contemplated as another aspect of the invention.

Chloride channel activators useful for the treatment of gastrointestinal disorders include type 2 chloride channel activators, such as lubiprostone. In an illustrated embodiment, nausea induced by treatment of gastrointestinal disorders with lubiprostone is alleviated by administering an opioid antagonist, such as the peripheral opioid antagonist methylnaltrexone.

Suitable chloride channel activators include prostaglandin derivatives. For example, one class suitably is derivatives and analogs of prostaglandin E1 (PGE_1), e.g., derivatives that are bicyclic fatty acids. Lubiprostone is a PGE_1 metabolite analog and is a chloride channel activator of particular value for the treatments of constipation.

Suitable opioid antagonists generally include heterocyclic amine compounds that belong to several different classes of compounds. For example, one class is suitably tertiary derivatives of morphinan, and in particular, tertiary derivatives of noroxymorphone. In one embodiment, the tertiary derivative of noroxymorphone is, e.g., naloxone or naltrexone.

In important embodiments, the opioid antagonist is a peripheral opioid antagonist. Suitable peripheral opioid antagonists are generally heterocyclic amine compounds that may belong to several different classes of compounds. For example, one class is suitably quaternary derivatives of morphinan, and in particular, quaternary derivatives of noroxymorphone. In one embodiment, the quaternary derivative of noroxymorphone is, e.g., N-methylnaltrexone (or simply methylnaltrexone), N-methylnaloxone, N-methylnalorphine, N-diallylnormorphine, N-

allyllevallorphan, or N-methylnalmefene. Another class is N-substituted piperidines. In one embodiment, the N-piperidine is a piperidine-N-alkylcarbonylate, such as, e.g., alvimopan. Yet another class of compounds which may be of value in the methods of the present invention is quaternary derivatives of benzomorphans. Another class of compounds suitable for the methods of the invention is normorphinan derivatives. In one embodiment, the normorphinan derivative is a 6-carboxy-normorphinan derivative.

In some embodiments of the invention, the opioid antagonist may be a μ-opioid antagonist. In other embodiments, the opioid antagonist may be a κ-opioid antagonist. The invention also encompasses administration of more than one opioid antagonist, including combinations of μ-antagonists, combinations of κ-antagonists, and combinations of μ- and κ-antagonists, for example, a combination of methylnaltrexone and alvimopan, or a combination of naltrexone and methylnaltrexone.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention may be better understood and appreciated by reference to the detailed description of specific embodiments presented herein in conjunction with the accompanying drawings of which:

FIG. 1 is a graph demonstrating dose-dependent effects of pretreatment with methylnaltrexone (MNTX) on kaolin intake induced by lubiprostone (LBP).

DETAILED DESCRIPTION

The invention provides methods of relieving, e.g., alleviating, inhibiting, attenuating, or reducing, gastrointestinal side effects, such as nausea and emesis, associated with the administration of certain drugs, specifically ion channel modulators, especially chloride channel activators, for the treatment of, e.g., constipation.

Before explaining at least one embodiment of the invention, it is to be understood that the invention is not limited in its application to the details set forth in the following description as exemplified by the Examples. Such description and Examples are not intended to limit the scope of the invention as set forth in the appended claims. The invention is capable of other embodiments or of being

practiced or carried out in various ways. While the following detailed description describes the invention through reference to embodiments utilizing lubiprostone and effective derivatives thereof as the drug, it should be understood that other ion channel modulators, other chloride channel activators, or other anti-constipation agents where nausea is an adverse side effect, may also be suitable for use in accordance with the principles of the invention.

Further, no admission is made that any reference, including any patent or patent document, cited in this specification constitutes prior art. In particular, it will be understood that, unless otherwise stated, reference to any document herein does not constitute an admission that any of these documents form part of the common general knowledge in the art in the United States or in any other country. Any discussion of the references states what their authors assert, and the applicant reserves the right to challenge the accuracy and pertinency of any of the documents cited herein.

Throughout this disclosure, various aspects of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity, and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, as will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof, as well as all integral and fractional numerical values within that range. As only one example, a range of 20% to 40% can be broken down into ranges of 20% to 32.5% and 32.5% to 40%, 20% to 27.5% and 27.5% to 40%, etc. For further example, if a polymer is stated as having 7 to 300 linked monomers, it is intended that values such as 7 to 25, 8 to 30, 9 to 90, or 50 to 300, as well as individual numbers within that range, for example 25, 50, and 300, are expressly enumerated in this specification. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third, and upper third, etc. Further, as will also be understood by one skilled in the art, all language such as "up to," "at least," "greater than," "less than," "more than" and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. In the same manner,

all ratios disclosed herein also include all subratios falling within the broader ratio. These are only examples of what is specifically intended. Further, the phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably.

Further, the use of "comprising," "including," "having," and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items, e.g., that other steps and ingredients that do not affect the final result can be added. This term encompasses the terms "consisting of" and "consisting essentially of." The use of "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

Unless otherwise defined, all scientific and technical terms are used herein according to conventional usage and have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. However, as used herein, the following definitions may be useful in aiding the skilled practitioner in understanding the invention:

"Subject" refers to mammals, e.g., humans, mice, dogs, cats.

"Alkyl" refers to a univalent aliphatic hydrocarbon group which is saturated and which may be straight, branched, or cyclic having from 1 to about 10 carbon atoms in the chain, and all combinations and subcombinations of chains therein. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

"Lower alkyl" refers to an alkyl group having 1 to about 6 carbon atoms.

"Alkenyl" refers to a univalent aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having from 2 to about 10 carbon atoms in the chain, and all combinations and subcombinations of chains therein. Exemplary alkenyl groups include, but are not limited to, vinyl, propenyl, butynyl, pentenyl, hexenyl, and heptnyl.

"Alkynyl" refers to a univalent aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having from 2 to about 10 carbon atoms in the chain, and combinations and subcombinations of chains therein. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl.

"Alkylene" refers to a divalent aliphatic hydrocarbon group having from 1 to about 6 carbon atoms, and all combinations and subcombinations of chains therein. The alkylene group may be straight, branched, or cyclic. There may be optionally inserted along the alkylene group one or more oxygen, sulfur, or optionally substituted nitrogen atoms, wherein the nitrogen substituent is an alkyl group as described previously.

"Alkenylene" refers to a divalent alkylene group containing at least one carbon-carbon double bond, which may be straight, branched, or cyclic. Exemplary alkenylene groups include, but are not limited to, ethenylene (–CH=CH–) and propenylene (–CH=CHCH$_2$–).

"Cycloalkyl" refers to a saturated monocyclic or bicyclic hydrocarbon ring having from about 3 to about 10 carbons, and all combinations and subcombinations of rings therein. The cycloalkyl group may be optionally substituted with one or more cycloalkyl-group substituents. Exemplary cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

"Acyl" means an alkyl-CO group wherein alkyl is as previously described. Exemplary acyl groups include, but are not limited to, acetyl, propanoyl, 2-methylpropanoyl, butanoyl, and palmitoyl.

"Aryl" refers to an aromatic carbocyclic radical containing from about 6 to about 10 carbons, and all combinations and subcombinations of rings therein. The aryl group may be optionally substituted with one or two or more aryl group substituents. Exemplary aryl groups include, but are not limited to, phenyl and naphthyl.

"Aryl-substituted alkyl" refers to a linear alkyl group, preferably a lower alkyl group, substituted at a terminal carbon with an optionally substituted aryl group,

preferably an optionally substituted phenyl ring. Exemplary aryl-substituted alkyl groups include, for example, phenylmethyl, phenylethyl, and 3(4-methylphenyl)propyl.

"Heterocyclic" refers to a monocyclic or multicyclic ring system carbocyclic radical containing from about 4 to about 10 members, and all combinations and subcombinations of rings therein, wherein one or more of the members of the ring is an element other than carbon, for example, nitrogen, oxygen, or sulfur. The heterocyclic group may be aromatic or nonaromatic. Exemplary heterocyclic groups include, for example, pyrrole and piperidine groups.

"Halo" refers to fluoro, chloro, bromo, or iodo.

"Peripheral," in reference to opioid antagonists, designates opioid antagonists that act primarily on physiological systems and components external to the central nervous system. In other words, they exhibit reduced or substantially no central nervous system (CNS) activity. For example, they do not readily cross the blood-brain barrier in an amount effective to inhibit the central effects of opioids, i.e., they do not effectively inhibit the analgesic effects of opioids when administered peripherally, that is, they do not reduce the analgesic effect of the opioids. The peripheral opioid antagonist compounds employed in the methods of the invention suitably exhibit less than about 5-15% of their pharmacological activity in the CNS, with about 0% (i.e., no) CNS activity, being most suitable. The non-centrally acting characteristic of a peripheral opioid antagonist is often related to charge, polarity, and/or size of the molecule or species. For example, peripherally-acting quaternary amine opioid antagonists as described herein are positively charged while the central-acting tertiary amine opioid antagonists are neutral molecules. The peripheral opioid antagonists useful in the present invention are typically mu and/or kappa opioid antagonists.

The phrases “pharmaceutically acceptable” or “pharmacologically acceptable” are meant to refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a subject such as a human. The opioid antagonists in accordance with the invention may be formulated as a free base, neutral or in a salt form. A “pharmaceutically acceptable salt” refers to a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts are non-toxic conventional salts and quaternary ammonium salts of the compounds in accordance with the invention that have properties acceptable for therapeutic use. Such salts

may be prepared, e.g., from inorganic or organic bases or acids. For example, acid addition salts may include acetate, ascorbate, benzoate, bisulfate, chloride, citrate, lactate, maleate, oxalate, sulfonate, tartrate and the like. Base salts may include alkali metal salts such as potassium and sodium salts, alkaline earth metals such as calcium and magnesium salts and ammonium salts with organic bases such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides, as well as long chain halides, and dialkyl or diamyl sulfates. Unless the context clearly indicates to the contrary, terms such as “compounds of the invention”, “a compound of the invention” or “compounds in accordance with the invention” and the like, as used herein, are intended to include the chemically feasible pharmaceutically acceptable salts of the referenced compounds. Additional information on suitable pharmaceutically acceptable salts can be found in Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams and Wilkens, Philadelphia, PA, which is incorporated herein by reference.

As used herein, the term “potency” is meant to refer to the ability or capacity of a chloride channel activator to relieve constipation, i.e., to induce laxation, in a subject suffering from constipation. Potency may also be expressed as the dose of a drug required to produce a specific effect of a given intensity.

As used herein, the term “side effect” is meant to refer to an effect other than the purpose or desired effect of a drug. Side effects may be beneficial or undesirable, i.e., adverse. In the instant case, undesirable effects often occur after the administration of a chloride channel activator such as lubiprostone. Such undesirable side effects include gastrointestinal side effects such as nausea, emesis, diarrhea, and abdominal distention and pain.

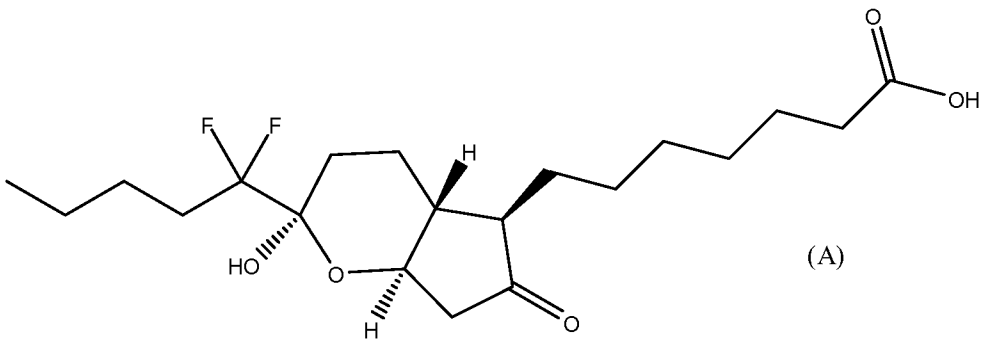
The terms “treating” or "treatment" used herein include any means of control of a medical condition such as prevention, care, relief of the condition, attenuation, alleviation, a reduction of the condition, and inhibition or arrest of progression of the pathological condition.

In the following description of the methods of the invention, process steps are carried out at room temperature and atmospheric pressure unless otherwise specified.

The invention relates to compositions and methods utilizing a combination of a chloride channel activator, for example, a type 2 chloride channel activator such a lubiprostone, and an opioid antagonist. Combinations of lubiprostone and an opioid antagonist, such as methylnaltrexone, unexpectedly treated the gastrointestinal side effects of lubiprostone, and may also have value in enhancing the anti-constipation (i.e., laxative) potency of lubiprostone.

The invention also provides methods of treating a gastrointestinal disorder which may include chronic idiopathic constipation, opioid-induced bowel dysfunction, opioid-induced constipation, postoperative ileus, irritable bowel syndrome, irritable bowel syndrome with constipation, gastrointestinal motility disorder, functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or colonic pseudo-obstruction, by co-administering a chloride channel activator and an opioid antagonist. The co-administered treatment may enhance laxation as well as treat side effects of the chloride channel activator such as nausea, and thus give rise to a synergy of the chloride channel activator and the opioid antagonist, when co-administered.

Chloride channel activators of particular interest in accordance with the present invention are prostaglandin E_1 (PGE_1) derivatives or metabolites. See, e.g., U.S. Patents 7,064,148, 6,982,283, and 7,253,295, each of which is hereby incorporated by reference. Of particular relevance is lubiprostone which is a PGE_1 metabolite analog. Lubiprostone is a bicyclic fatty acid, shown in formula (A) below, which activates type 2 chloride channels in the lining of the small intestine. This leads to an increase in intestinal fluid secretion and improves the passage of stool. The result is the alleviation of the symptoms due to constipation including abdominal discomfort and pain, and bloating. Currently lubiprostone is approved for marketing in the United States for the indications chronic idiopathic constipation and irritable bowel syndrome with constipation. Lubiprostone, however, has undesirable side effects which include nausea and emesis as well as abdominal distention and pain, diarrhea, headache and sinusitis.



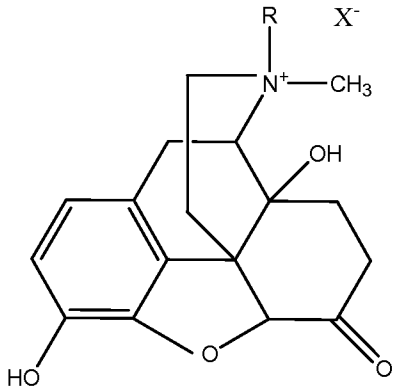
(A)

The opioid antagonists in accordance with the present invention include both centrally and peripherally acting opioid antagonists. It is contemplated that those antagonists of particular value are suitably the peripherally restricted opioid antagonists. Especially suitable may be a μ opioid antagonist, especially a peripheral μ opioid antagonist.

Opioid antagonists form a class of compounds that can vary in structure while maintaining their peripherally restrictive properties. These compounds include tertiary and quaternary morphinans, in particular noroxymorphone derivatives, N-substituted piperidines, and in particular, piperidine-N-alkylcarboxylates, tertiary and quaternary benzomorphans, and normorphinan derivatives, in particular 6-carboxy-normorphinan derivatives. Peripherally restricted antagonists, while varied in structure, are typically charged, polar, and/or of high molecular weight, each of which impedes their crossing the blood-brain barrier.

Examples of opioid antagonists that cross the blood-brain barrier and are centrally (and peripherally) active, include, e.g., naloxone, naltrexone (each of which is commercially available from Baxter Pharmaceutical Products, Inc.), and nalmefene (available, e.g., from DuPont Pharma). These may have value in treating nausea, such as drug-induced nausea, as well as other adverse effects in patients being treated for constipation.

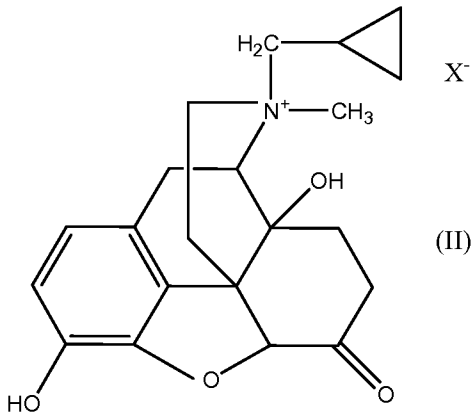
A peripheral opioid antagonist useful for the present invention may be a compound which is a quaternary morphinan derivative, and in particular, a quaternary noroxymorphone of formula (I):



(I)

wherein R is alkyl, alkenyl, alkynyl, aryl, cycloalkyl-substituted alkyl, or arylsubstituted alkyl, and X^- is the anion, for example, a chloride, bromide, iodide, or methylsulfate anion. The noroxymorphone derivatives of formula (I) can be prepared, for example, according to the procedure in U.S. Patent No. 4,176,186, which is incorporated herein by reference; see also, U.S. Patent Nos. 4,719,215; 4,861,781; 5,102,887; 5,972,954; and 6,274,591; U.S. Patent Application Nos. 2002/0028825 and 2003/0022909; and PCT publication Nos. WO 99/22737 and WO 98/25613, all of which are hereby incorporated by reference.

A compound of formula (I) of particular value is N-methylnaltrexone (or simply methylnaltrexone), wherein R is cyclopropylmethyl as represented in formula (II):



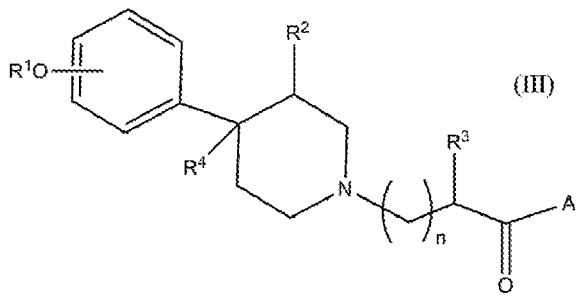
(II)

wherein X^- is as described above. Methylnaltrexone is a quaternary derivative of the opioid antagonist naltrexone. Methylnaltrexone exists as a salt, and "methylnaltrexone" or "MNTX", as used herein, therefore embraces salts. "Methylnaltrexone" or "MNTX" specifically includes, but is not limited to, bromide salts, chloride salts, iodide salts, carbonate salts, and sulfate salts of methylnaltrexone. In the literature, names used for the bromide salt of MNTX for

example, include: methylnaltrexone bromide; N-methylnaltrexone bromide; naltrexone methobromide; naltrexone methyl bromide; SC-37359; MRZ-2663-BR; and N-cyclopropylmethylnoroxy-morphine-methobromide.

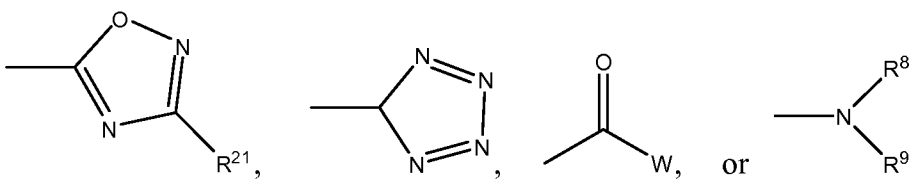
Methylnaltrexone is commercially available from, e.g., Mallinckrodt Pharmaceuticals, St. Louis, Mo. Methylnaltrexone is provided as a white crystalline powder, freely soluble in water, typically as the bromide salt. The compound as provided is 99.4% pure by reverse phase HPLC, and contains less than 0.011% unquaternized naltrexone by the same method. Methylnaltrexone can be prepared as a sterile solution at a concentration of, e.g., about 5 mg/mL.

Other suitable peripheral opioid antagonists may include N-substituted piperidines, and in particular, piperidine-N-alkylcarboxylates as represented by formula (III):



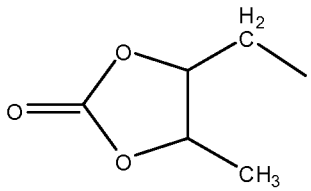
(III)

wherein R^1 is hydrogen or alkyl; R^2 is hydrogen, alkyl, or alkenyl; R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl; R^4 is hydrogen, alkyl, or alkenyl; A is OR^5 or NR^6R^7; wherein R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl; R^6 is hydrogen or alkyl; R^7 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl, or alkylene-substituted B or together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring selected from pyrrole and piperidine; B is



wherein R^8 is hydrogen or alkyl; R^9 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl or together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring selected from pyrrole and piperidine; W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkenyl, or aryl-substituted alkyl; R^{11} is hydrogen or alkyl; R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, or alkylene-substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring selected from pyrrole and piperidine;

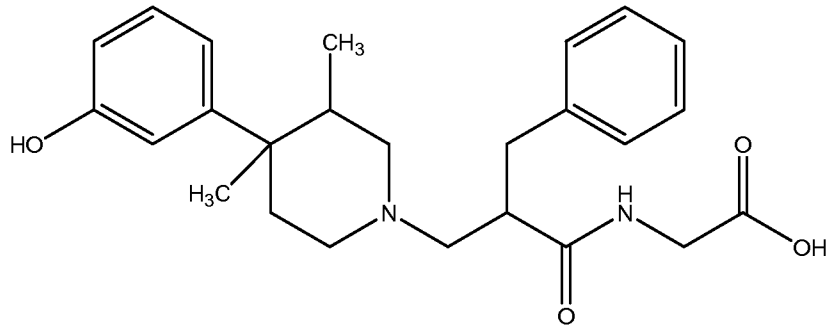
E is



alkylene-substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$; wherein R^{13} is alkyl-substituted alkylene; R^{14} is alkyl; D is OR^{15} or $NR^{16}R^{17}$; wherein R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl substituted alkyl, or aryl-substituted alkyl; R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl substituted alkyl, or cycloalkenyl-substituted alkyl; R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring selected from the group consisting of pyrrole or piperidine;

Y is OR^{18} or $NR^{19}R^{20}$; wherein R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl; R^{19} is hydrogen or alkyl; R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkylsubstituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring selected from pyrrole and piperidine; R^{21} is hydrogen or alkyl; and n is 0 to 4.

Particular piperidine-N-alkylcarbonylates which may be of value are N-alkylamino-3,4,4 substituted piperidines, such as alvimopan represented below as formula (IV):

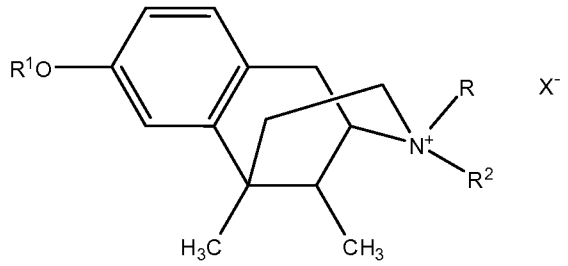


(IV)

Suitable N-substituted piperidines may be prepared as disclosed in U.S. Patent Nos. 5,270,328; 6,451,806; 6,469,030, all of which are hereby incorporated by reference. Alvimopan is available from Adolor Corp., Exton, PA. Such compounds have moderately high molecular weights, a zwitterion form, and a polarity, any of which may prevent penetration of the blood-brain barrier.

Still other suitable peripheral opioid antagonist compounds may include quaternary benzomorphan compounds.

The quaternary benzomorphan compounds which may be employed in the methods of the present invention have the following formula (V):



(V)

wherein R^1 is hydrogen, acyl, or acetoxy; and R^2 is alkyl or alkenyl; R is alkyl, alkenyl, or alkynyl and X^- is an anion, for example, a chloride, bromide, iodide, or methylsulfate anion.

Specific quaternary derivatives of benzomorphan compounds that may be employed in the methods of the present invention include the following compounds of

formula (V): 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide; 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide; 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide; and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

Other quaternary benzomorphan compounds that may be employed in methods of the invention are described, for example, in U.S. Pat. No. 3,723,440, the entire disclosure of which is incorporated herein by reference.

Other peripheral opioid anatagonists may include 6-carboxy-normorphinan derivatives, particularly N-methy-C-normorphinan derivatives, as described in U.S. Application Serial No. 11/888,955, entitled “6-Carboxy-Normorphinan Derivatives, Synthesis and Uses Thereof,” hereby incorporated in its entirety herein by reference.

As described above, compounds of the invention may suitably exist and be formulated as pharmaceutically acceptable salts.

The compounds employed in methods of the invention may exist in prodrug form. As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug according to formulas (I) to (V) or other formulas or compounds employed in the methods of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds employed in the present methods may, if desired, be delivered in prodrug form. Thus, the present invention contemplates methods of delivering prodrugs. Prodrugs of the compounds employed in the present invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound.

Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, iso-

propyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

As noted, the compounds employed in the methods of the present invention may be prepared in a number of ways well known to those skilled in the art. All preparations disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram, or commercial pharmaceutical scale.

Compounds employed in methods of the inventions may contain one or more asymmetrically-substituted carbon atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. It is well known in the art how to prepare and isolate such optically active forms. For example, mixtures of stereoisomers may be separated by standard techniques including, but not limited to, resolution of racemic form, normal, reverse-phase, and chiral chromatography, preferential salt formation, recrystallization, and the like, or by chiral synthesis either from chiral starting materials or by deliberate synthesis of target chiral centers.

In some embodiments of the invention, the opioid antagonist may be a μ opioid antagonist. In other embodiments, the opioid antagonist may be a κ opioid antagonist. The invention also encompasses administration of more than one opioid antagonist, including combinations of μ antagonists, combinations of κ antagonists, and combinations of μ and κ antagonists, for example, a combination of methylnaltrexone and alvimopan.

The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, e.g., any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical (as by powder, ointment, drops, transdermal patch, or iontophoretic device), transdermal, sublingual, intramuscular, infusion, intravenous, pulmonary, intramuscular, intracavity, as an aerosol, aural (e.g., via eardrops), intranasal, inhalation, intraocular, or subcutaneous.

When administered, the compounds of the invention are given in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions or preparations. Such preparations may routinely contain salts, buffering agents, preservatives, and optionally other therapeutic ingredients.

When used in medicine, the salts should be pharmaceutically acceptable, but non- pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. As described above, such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluenesulfonic, tartaric, citric, methanesulfonic, formic, succinic, naphthalene-2--sulfonic, pamoic, 3-hydroxy-2-naphthalenecarboxylic, and benzene sulfonic. Suitable buffering agents include, but are not limited to, acetic acid and salts thereof (1-2% w/v); citric acid and salts thereof (1-3% w/v); boric acid and salts thereof (0.5-2.5% w/v); and phosphoric acid and salts thereof (0.8-2% w/v).

Suitable preservatives include, but are not limited to, benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v); and thimerosal (0.004-0.02% w/v).

For ease of administration, a pharmaceutical composition of the peripheral opioid antagonist may also contain one or more pharmaceutically acceptable excipients, such as lubricants, diluents, binders, carriers, and disintegrants. Other auxiliary agents may include, e.g., stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, coloring, flavoring, and/or aromatic active compounds.

A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material, or formulation auxiliary of any type. For example, suitable pharmaceutically acceptable carriers, diluents, solvents, or vehicles include, but are not limited to, water, salt (buffer) solutions, alcohols, gum arabic, mineral and vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, vegetable oils, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxyl methylcellulose, polyvinyl pyrrolidone, etc. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in

the case of dispersions and by the use of surfactants. Prevention of the action of microorganisms may be ensured by the inclusion of various antimicrobial, e.g., antibacterial and antifungal, agents such as paraben, chlorobutanol, phenol, sorbic acid and the like.

If a pharmaceutically acceptable solid carrier is used, the dosage form of the compounds suitable for use in methods of the invention may be tablets, capsules, powders, suppositories, or lozenges. If a liquid carrier is used, soft gelatin capsules, transdermal patches, aerosol sprays, topical cream, syrups or liquid suspensions, emulsions, or solutions may be the dosage form.

For parenteral application, particularly suitable are injectable, sterile solutions, preferably nonaqueous or aqueous solutions, as well as dispersions, suspensions, emulsions, or implants, including suppositories. Ampoules are often convenient unit dosages. Injectable depot-form may also be suitable and may be made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled.

For enteral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules such as soft gelatin capsules. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed.

As noted, other delivery systems may include time-release, delayed-release, or sustained-release delivery system. Such systems can avoid repeated administrations of the compounds of the invention, increasing convenience to the patient and the physician and maintain sustained plasma levels of compounds. Many types of controlled-release delivery systems are available and known to those of ordinary skill in the art. Sustained- or controlled-release compositions can be formulated, e.g., as liposomes or those wherein the active compound is protected with differentially degradable coatings, such as by microencapsulation, multiple coatings, etc. Thus, the opioid antagonists in accordance with the invention may be administered as an enterically coated tablet or capsule. In some embodiments, the opioid antagonist is administered by a slow infusion method or by a time-release or controlled-release method or as a lyophilized powder.

For example, compounds in accordance with the invention may be combined with pharmaceutically acceptable sustained-release matrices, such as biodegradable polymers, to form therapeutic compositions. A sustained-release matrix, as used herein, is a matrix made of materials, usually polymers, which are degradable by enzymatic or acid-base hydrolysis or by dissolution. Once inserted into the body, the matrix is acted upon by enzymes and body fluids. A sustained-release matrix may be desirably chosen from biocompatible materials such as liposomes, polymer-based system such as polylactides (polylactic acid), polyglycolide (polymer of glycolic acid), polylactide co-glycolide (copolymers of lactic acid and glycolic acid), polyanhydrides, poly(ortho)esters, polysaccharides, polyamino acids, hyaluronic acid, collagen, chondroitin sulfate, polynucleotides, polyvinyl propylene, polyvinyl pyrrolidone, and silicone; nonpolymer systems such as carboxylic acids, fatty acids, phospholipids, amino acids, lipids such as sterols, hydrogel release systems; silastic systems; peptide-based systems; implants and the like. Specific examples include, but are not limited to: (a) an erosional system in which the polysaccharide is contained in a form within a matrix, found in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152 (herein incorporated by reference in their entireties), and (b) a diffusional system in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974, and 5,407,686 (herein incorporated by reference in their entireties). In addition, a pump-based hard-wired delivery system can be used, some of which are adapted for implantation. Suitable enteric coatings are described in PCT publication No. WO 98/25613 and U.S. Patent No. 6,274,591, both incorporated herein by reference.

Respecting MNTX specifically, aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted to between 3.0 and 3.5. Formulations that are stable to autoclaving and long term storage are described in U.S. Patent Application Serial No. 10/821811, published as 2004/0266806, entitled "Pharmaceutical Formulation," the disclosure of which is incorporated herein by reference. Formulations of methylnaltrexone with increased shelf-life are also described in International Patent Publication No. WO 2008/19115, entitled “Formulations for Parenteral Delivery of Compounds and Uses Thereof,” hereby incorporated by reference. Lyophilized formulations of methylnaltrexone are described in U.S. Patent Application Serial No. 11/899,724 and formulations comprising particles containing methylnaltrexone are described in U.S. Patent No. 6,419,959, which is incorporated herein by reference.

Formulations suitable for transdermal delivery of methylnaltrexone are described in International Patent Publication No. 2007/41544, hereby incorporated by reference.

In one embodiment, compounds in accordance with the invention are administered in a continuous dosing regimen of the compound to a subject, e.g., a regimen that maintains minimum plasma levels of the opioid antagonist, and preferably eliminates the spikes and troughs of a drug level with conventional regimens. Suitably, a continuous dose may be achieved by administering the compound to a subject on a daily basis using any of the delivery methods disclosed herein. In one embodiment, the continuous dose may be achieved using continuous infusion to the subject, or via a mechanism that facilitates the release of the compound over time, for example, a transdermal patch, or a sustained release formulation. Suitably, compounds of the invention are continuously released to the subject in amounts sufficient to maintain a concentration of the compound in the plasma of the subject effective to inhibit or reduce nausea induced by treatment with a chloride channel activator such as lubiprostone.

Compounds in accordance with the invention, whether provided alone or in combination with other therapeutic agents, are provided in an anti-nausea effective amount. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, one technique is to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

If desired, the effective daily dose may be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. As noted, those of

ordinary skill in the art can readily optimize effective doses and co-administration regimens (as described herein) as determined by good medical practice and the clinical condition of the individual patient.

Generally, oral doses of the opioid antagonists, particularly peripheral antagonists, will range from about 0.01 to about 80 mg/kg body weight per day. It is expected that oral doses in the range from 1 to 20 mg/kg body weight will yield the desired results. Generally, parenteral administration, including intravenous and subcutaneous administration, will range from about 0.001 to 5 mg/kg body weight. It is expected that doses ranging from 0.05 to 0.5 mg/kg body weight will yield the desired results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending on the mode of administration. For example, it is expected that the dosage for oral administration of the opioid antagonists in an enterically coated formulation would be from 10 to 30% of the non-coated oral dose. In the event that the response in a patient is insufficient with such doses, even higher doses (or effectively higher than 30% dosage by a different, more localized delivery route) may be employed to the extent that the patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds. Appropriate system levels can be determined by, for example, measurement of the patient's plasma level of the drug using routine HPLC methods known to those skilled in the art.

In illustrated embodiments of the invention, the opioid antagonists are co-administered with a chloride channel activator, e.g., lubiprostone. The term "co-administration" is meant to refer to a combination therapy by any administration route in which two or more agents are administered to a patient or subject. Co-administration of agents may also be referred to as combination therapy or combination treatment. The agents may be in the same dosage formulations or separate formulations. For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times. The agents may be administered simultaneously or sequentially (e.g., one agent may directly follow administration of the other or the agents may be given episodically, e.g., one can be given at one time followed by the other at a later time, e.g., within a week), as long as they are given in a manner sufficient to allow both agents to achieve effective concentrations in the body. The agents may also be

administered by different routes, e.g., one agent may be administered intravenously while a second agent is administered intramuscularly, intravenously, or orally. In other words, the co-administration of the opioid antagonist compound in accordance with the present invention with, e.g., lubiprostone is suitably considered a combined pharmaceutical preparation which contains an opioid antagonist and lubiprostone, the preparation being adapted for the administration of the peripheral opioid antagonist on a daily or intermittent basis, and the administration of lubiprostone on a daily or intermittent basis. Thus, the opioid antagonists may be administered prior to, concomitant with, or after administration of lubiprostone. Particularly suitable is administration of the opioid antagonist prior to administration of lubiprostone.

Co-administrable agents also may be formulated as an admixture, as, for example, in a single formulation or single tablet. These formulations may be parenteral or oral, such as the formulations described, e.g., in U.S. Patent Nos. 6,277,384; 6,261,599; 5,958,452 and PCT Publication No. WO 98/25613, each hereby incorporated by reference.

The present invention is further explained by the following examples, which should not be construed by way of limiting the scope of the present invention.

EXAMPLES

Example 1: Animal model for nausea

Rats react to emetic stimuli by altered feeding habits, manifested as increased consumption of non-nutritive substances such as kaolin (a type of clay), known as pica (Mitchell et al., 1976; Takeda et al., 1993; Takeda et al., 1995). We have quantified kaolin consumption as a measure of nausea in our experimental animals and observed that drug-induced pica consumption could be reduced by selected pharmacological agents (Aung et al., 2003; Aung et al., 2005).

Example 2: *In vivo* study

Adult male Wistar strain rats (Harlan Sprague Dawley, Indianapolis, IN) weighing between 150-300 g were used. All the animals were housed in standard isolation cages (45cm x 35cm x 25cm) in environmentally controlled conditions with a 12 hr light/12 hr dark cycle. Rats were allowed free access to water, standard

laboratory rat chow (Harlan-Teklad, Madison, WI), and kaolin (see below), placed in separated containers continuously available throughout the experiment.

Prior to the beginning of observation (Day 0), there was a 3-day adaptation period.

Kaolin was prepared based on the method previously described (Mitchell et al., 1976; Takeda et al., 1995). In brief, 99 g of pharmacological grade kaolin (or hydrated aluminum silicate; Fisher, Fair Lawn, NJ) was mixed with 1 g of acacia (Fisher), i.e., in a 99:1 ratio, with distilled water to form a thick paste. The paste was rolled on stainless steel tray and cut into pieces in the shape and size similar to regular rat chow pellets. The pellets were placed on steel trays, and completely dried at room temperature for 72 hr.

Rats received lubiprostone in the morning on 2 consecutive days (0 and 24 hrs) by oral gavage. Vehicle, naloxone, or methylnaltrexone (MNTX) pretreatments were administered intraperitoneally, 30 min prior to each lubiprostone administration. Rats were observed immediately and at hr 2 to ensure that animals were not distressed and were comfortable. The animals did not demonstrate any signs of adverse effects such as restlessness, respiratory distress, or diarrhea following test drug administrations.

During the experiment, kaolin and food pellets were weighed to the nearest 0.1 g and replaced in the containers every morning at the same time after collecting the remaining kaolin and food from the previous day. Kaolin and food intake was measured every 24 hr for 5 days. Data were expressed in mean ± standard error (S.E.). Area under the concentration curve (AUC) was calculated. Data were analyzed using a two-way analysis of variance (ANOVA) with group and time as the two factors. Statistical significance was considered at $P < 0.05$. The results are discussed below.

1. Effects of naloxone on lubiprostone-induced nausea

After 5.0 μg/kg lubiprostone administration, kaolin intake increased significantly compared to the vehicle group ($P < 0.01$), indicating that lubiprostone induces nausea. This kaolin intake increase was attenuated significantly by 30 μg/kg naloxone (a non-selective opioid antagonist) administration ($P < 0.01$).

2. Dose-dependent effects of methylnaltrexone on lubiprostone-induced nausea

The results of pretreatment with methylnaltrexone (MNTX) on kaolin intake induced by lubiprostone (LBP) in rats are shown in Figure 1. Increased kaolin intake induced by LBP was attenuated with MNTX in a dose-dependent manner ($P < 0.01$). In other words, MNTX reduced the lubiprostone-induced kaolin ingestion in a dose-dependent manner. For each group, n=7. MNTX (3.0 mg/kg plus vehicle) did not increase kaolin intake. In addition, the combination of lubiprostone and methylnaltrexone did not significantly affect food intake and body weight in these experimental animals.

The data demonstrated that methylnaltrexone significantly attenuated the lubiprostone-induced nausea. Methylnaltrexone, thus, may have a clinical value in decreasing lubiprostone-induced nausea when co-administered with lubiprostone.

3. Role of opioid antagonists in chronic idiopathic constipation

Data from previous investigations showed that naloxone may be effective in cases of idiopathic constipation (Kreek et al., 1983) and irritable bowel syndrome (Hawkes et al., 2002). A prior *in vitro* study of the inventors demonstrated that methylnaltrexone reversed morphine-induced inhibition of contraction elicited by electrical stimulation in isolated guinea-pig ileum and human small intestine (Yuan et al., 1995). An interesting observation in this study was that when methylnaltrexone alone was applied to the tissue bath, the force produced by muscle contraction was enhanced in a dose-related manner up to 27% compared to control level, suggesting an inhibitory modulation by endogenous opioids in these two species. The enhancement of muscle contraction in isolated human intestine is significantly greater than that in guinea-pig ileum tissue, indicating that endogenous opioid action in the regulation of human gastrointestinal motility may be stronger.

If a relative or absolute excess of endogenous opioids or an altered opioid receptor affinity contributes to hypomotility in chronic idiopathic constipation in certain gut dysfunction populations, opioid antagonists may have a therapeutic role. Compared to non-selective opioid antagonists which have undesirable central activities, methylnaltrexone acts peripherally on the gastrointestinal tract and may have potential as a prokinetic agent when endogenous opioids in the periphery

contribute to human pathology. In combination with lubiprostone, methylnaltrexone can not only attenuate lubiprostone-induced nausea, but may also enhance lubiprostone's effects on chronic constipation, i.e., the agent may work synergistically.

In summary, the invention provides methods for relieving drug-induced gastrointestinal side effects, such as nausea induced by an anti-constipation agent, e.g., lubiprostone-induced nausea, utilizing opioid antagonists, particularly, peripherally restricted opioid antagonists, such as methylnaltrexone. The opioid antagonist may enhance the anticonstipation effects of anticonstipation agents such as type 2 chloride channel activators, e.g., lubiprostone. In addition, type 2 chloride channel activators, e.g., lubiprostone, may enhance the effects of opioid antagonists in the treatment of gastrointestinal disorders, including but not limited to chronic idiopathic constipation, opioid-induced bowel dysfunction, opioid-induced constipation, postoperative ileus, irritable bowel syndrome, irritable bowel syndrome with constipation, gastrointestinal motility disorder, functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or colonic pseudo-obstruction.

All publications, patents, and patent applications are herein expressly incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated by reference. In case of conflict between the present disclosure and the incorporated patents, publications and references, the present disclosure should control.

The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

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CLAIMS

1. A method of reducing gastrointestinal side effects associated with treatment with a chloride channel activator, comprising administering to a patient suffering therefrom, in combination with the chloride channel activator, an amount of an opioid antagonist sufficient to reduce drug-induced gastrointestinal side effects.

2. The method of claim 1, wherein the side effect is nausea or emesis or both.

3. The method of claim 1, wherein the opioid antagonist is administered prior to administering the chloride channel activator.

4. The method of claim 1, wherein the chloride channel activator is lubiprostone.

5. The method of claim 1, wherein the opioid antagonist is naloxone.

6. The method of claim 1, wherein the opioid antagonist is a peripheral opioid antagonist.

7. The method of claim 6, wherein the peripheral opioid antagonist is methylnaltrexone.

8. The method of claim 6, wherein the peripheral opioid antagonist is a piperidine-N-alkylcarboxylate compound.

9. The method of claim 6, wherein the peripheral opioid antagonist is a quaternary morphinan compound.

10. The method of claim 9, wherein the quaternary morphinan compound comprises a quaternary salt of a compound selected from the group consisting N-methylnaltrexone, N-methylnaloxone, N-methylnalorphine, N-diallylnormorphine, N-allyllevallorphan, and N-methylnalmefene.

11. The method of claim 1 wherein the opioid antagonist is a μ opioid antagonist.

12. The method of claim 1 wherein the opioid antagonist is a κ opioid antagonist.

13. The method of claim 1, wherein the opioid antagonist is a combination of a μ opioid antagonist and a κ opioid antagonist.

14. A method of treating an adverse gastrointestinal side effect associated with administration of lubiprostone to a human subject, comprising co-administering to the human subject an anti-constipation amount of lubiprostone and an amount of an opioid antagonist effective to treat the adverse side effect.

15. The method of claim 14, wherein the adverse side effect is nausea, emesis, diarrhea, abdominal distention and pain or a combination therapy.

16. The method of claim 15, wherein the adverse side effect is nausea or emesis or both.

17. The method of claim 14, wherein the opioid antagonist is a quaternary morphinan compound.

18. The method of claim 17, wherein the quaternary morphinan compound comprises a quaternary salt of a compound selected from the group consisting of N-methylnaltrexone, N-methylnaloxone, N-methylnalorphine, N-diallylnormorphine, N-allyllevallorphan, and N-methylnalmefene.

19. The method of claim 18, wherein the quaternary salt of a quaternary morphinan compound is N-methylnaltrexone.

20. A method of treating constipation in a human subject in need of such treatment, comprising co-administering an anti-constipation amount of lubiprostone and an amount of an opioid antagonist effective to enhance the anti-constipation effects of lubiprostone and/or attenuate the frequency and/or severity of lubiprostone-induced gastrointestinal side effects in the subject.

21. The method of claim 20, wherein the gastrointestinal side effect is nausea, emesis, diarrhea, abdominal distention and pain, or combinations thereof.

22. The method of claim 20, wherein the opioid antagonist is administered prior to administering the lubiprostone.

23. The method of claim 20, wherein the administration of the opioid antagonist is oral, sublingual, intramuscular, subcutaneous, intravenous, and transdermal.

24. The method of claim 23, wherein the administration is oral.

25. The method of claim 20, wherein the opioid antagonist is methylnaltrexone.

26. The method of claim 25, wherein the effective amount of methylnaltrexone is from about 0.001 mg/kg to about 80 mg/kg of body weight per day.

27. The method of claim 26, wherein the effective amount of methylnaltrexone is from about 0.05 mg/kg to about 50 mg/kg of body weight per day.

28. The method of claim 26, wherein the effective amount of methylnaltrexone is from about 1 mg/kg to about 20 mg/kg of body weight per day.

29. The method of claim 20, wherein the lubiprostone and methylnaltrexone synergistically treat the constipation.

30. A method of treating a gastrointestinal disorder, comprising co-adminstering a chloride channel activator and an opioid antagonist.

31. The method of claim 30, wherein the gastrointestinal disorder is chronic idiopathic constipation, opioid-induced bowel dysfunction, opioid-induced constipation, postoperative ileus, irritable bowel syndrome, irritable bowel syndrome with constipation, gastrointestinal motility disorder, functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or colonic pseudo-obstruction.

32. The method of claim 31, wherein the gastrointestinal disorder is idiopathic chronic constipation or irritable bowel syndrome with constipation.

33. A method of treating nausea following administration of an effective amount of an anti-constipation agent in a subject in need thereof, comprising co-administering an effective amount of an opioid antagonist.

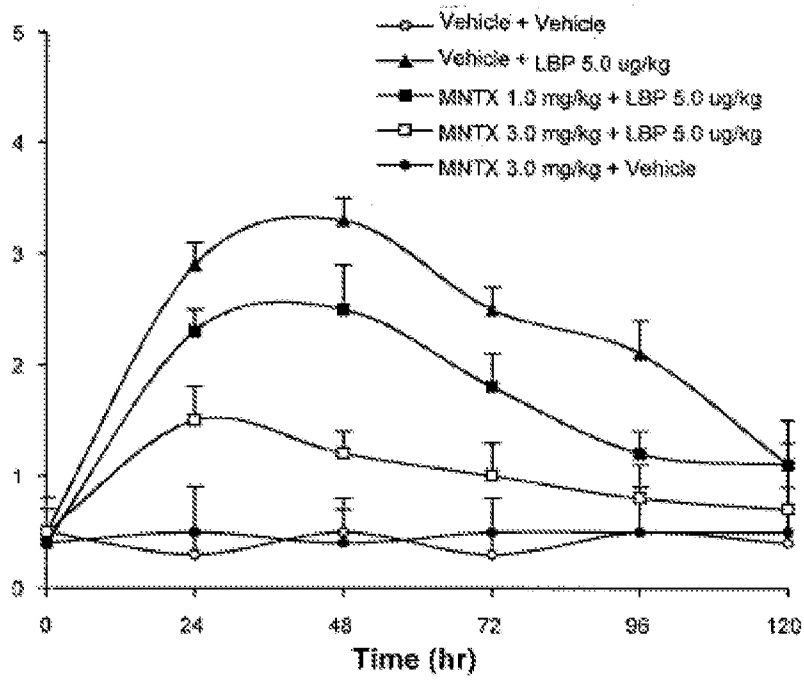
Vehicle + Vehicle
Vehicle + LBP 5.0 ug/kg
MNTX 1.0 mg/kg + LBP 5.0 ug/kg
MNTX 3.0 mg/kg + LBP 5.0 ug/kg
MNTX 3.0 mg/kg + Vehicle
5
4
3
2
1
0
0
24
48
72
96
120
Time (hr)

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/78229

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/42; A61K 31/44 (2008.04)
USPC - 514/282
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)
USPC- 514/282

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 424/449, 469-470; 514/44, 326, 465 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO, Dialog Classic
Search terms used: nausea; gastrointestinal; constipation; chloride; opioid; chloride channel activator; lubiprostone; piperidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2007/0010450 A1 (Currie et al.) 11 January 2007 (11.01.2007) para [0006], [0010]-[0012], [0198],[268]	1-7, 9-13 --- 8
X	US 2006/0094658 A1 (Currie et al.) 4 May 2006 (05.04.2006) para [0184], [0200], [0207], [0256], [0279], [305]-[306],[288]	14-33
Y	US 2006/0063792 A1 (Dolle et al.) 23 March 2006 (03.23.2006) para [0008]	8

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent but published on or after the international filing date
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"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
17 Dec 2008	24 DEC 2008

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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