Title: CYCLOOXYGENASE-2 INHIBITORS FOR APPETITE SUPPRESSION

Abstract: Methods and compositions for reducing or controlling appetite using cyclooxygenase-2 inhibitors are disclosed.
CYCLOOXYGENASE-2 INHIBITORS FOR APPETITE SUPPRESSION

Field of the Invention

[001] The present invention relates to methods of reducing or controlling appetite using cyclooxygenase-2 inhibitors.

Background of the Invention

[002] Obesity has become a significant health problem in many western countries. Pharmacological intervention is often necessary or desirable, although the side effects of most appetite suppressants and anti-obesity medications have provided less than ideal therapy. Pharmacological intervention with amphetamines and related stimulants (e.g. phentermine) is associated with a high incidence of abuse and, even when abuse is not a problem, the sympathomimetics often precipitate unacceptable side effects, such as hypertension, tachycardia, palpitation, CNS stimulation, tremor, restlessness and insomnia.

[003] Cyclooxygenase-2 inhibitors have recently emerged as highly effective agents for the treatment of inflammation. Moreover, cyclooxygenase-2 inhibitors appear to be accompanied by fewer of the undesirable side effects of earlier antiinflammatories. There have been no reports of the effect of cyclooxygenase-2 inhibitors on appetite.

Summary of the Invention

[004] It has now been discovered that cyclooxygenase-2 inhibitors provide effective treatment for obesity, exhibiting appetite suppressing effects at doses that are safe and well tolerated.
The present invention relates to methods for controlling appetite and inducing weight loss. The methods comprise administering to a mammal, particularly a human, an amount of a cyclooxygenase-2 inhibitor sufficient to reduce appetite and to induce weight loss.

The invention also relates to pharmaceutical compositions for suppressing appetite and thereby treating obesity. The compositions include a cyclooxygenase-2 inhibitor and one or more additional obesity treating drugs. The additional obesity treating drug may be sibutramine, an SSRI or a lipase inhibitor, such as orlistat.

In a further aspect, the invention relates to a kit comprising (a) a cyclooxygenase-2 inhibitor; and (b) instructions for administration for appetite suppression or weight loss. The kit may additionally contain (c) a second obesity treating drug chosen from the group consisting of sibutramine, an SSRI and a lipase inhibitor.

Detailed Description of the Invention

The present invention relates to a method for suppressing appetite administering a cyclooxygenase-2 inhibitor. Preferred cyclooxygenase-2 inhibitors are those that are selective for cyclooxygenase-2 over cyclooxygenase-1. Cyclooxygenase-2 selective inhibitors are preferred because fewer side-effects would be expected, but any compound that had potency comparable to that of piroxicam in inhibiting cyclooxygenase-2 would be effective in suppressing appetite. Preferred cyclooxygenase-2 inhibitors include rofecoxib, meloxicam, celecoxib, etoricoxib, lumiracoxib, valdecoxib, diclofenac, sulindac, etodolac, ketoralac, ketoprofen and piroxicam, although the invention is not restricted to these or other known cyclooxygenase-2 inhibitors. Selective cyclooxygenase-2 inhibitors, such as rofecoxib (VIOXX\textsuperscript{TM}), celecoxib (CELEBREX\textsuperscript{TM}), etoricoxib
(ARCOXIA™), lumiracoxib (PREXIGET™) and valdecoxib (BEXTRA™) are most preferred.

[009] The cyclooxygenase-2 inhibitors of the invention may be administered in a single dosage form together with another anti-obesity drug. The other anti-obesity drug is preferably sibutramine, an SSRI or a lipase inhibitor, such as orlistat. Selective serotonin reuptake inhibitors (SSRI's) are a subclass of drugs that inhibit the neuronal reuptake of monoamines (e.g. serotonin, norepinephrine and dopamine). The most widely known SSRI's are nefazodone, fluoxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, and sertraline. Other SSRI's may be found in US patent 5,788,986, the disclosure of which is incorporated herein by reference.

[0010] The term "treating" when used in connection with these disorders means amelioration or prevention and includes the prophylactic administration of cyclooxygenase-2 inhibitors to substantially suppress the appetite and diminish the seriousness of the overweight condition. The term "cyclooxygenase-2 inhibitor" refers to compounds that exhibit IC₅₀'s below 10⁻⁶M in the standard test described by Wong et al. [Inflamm. Res 46, 51 (1997)]. Selective cyclooxygenase-2 inhibitors are preferred. Selective in this sense refers to compounds in which the difference between the IC₅₀ in inhibiting cyclooxygenase-1 and cyclooxygenase-2 is at least 10-fold. The term SSRI refers to compounds that exhibit a lower IC₅₀ in the serotonin assay described by Perovics and Müller [Arzneim. Forsch. / Drug Res. 45 : 1145-1148 (1995)] than in the dopamine assay described by Janowsky et al. [J. Neurochem. 46, 1272-1276 (1986)] and the norepinephrine assay described by Perovics and Müller, op.cit.

[0011] The magnitude of a prophylactic or therapeutic dose of cyclooxygenase-2 inhibitor will vary with the pharmacodynamics and intrinsic activity of the cyclooxygenase-2 inhibitor and the route of administration. The dose, and perhaps
the dose frequency, will also vary according to the age, body weight and response of the individual patient. In general, the total daily appetite-suppressant doses of cyclooxygenase-2 inhibitors are similar to the doses used to treat inflammation, ranging from about 10 mg per day to about 1000mg per day, depending on the potency of the particular cyclooxygenase-2 inhibitor. For those cyclooxygenase-2 inhibitors with a potency similar to rofecoxib, the dose is preferably about 10mg per day to about 50 mg per day, in single or divided doses. For those with a cyclooxygenase-2 inhibitory potency similar to celecoxib, the dose is preferably about 50 mg per day to about 400 mg per day, in single or divided doses. The choice of a dose is within the skill of the artisan. The regimen is not restricted, but it will generally be found advantageous to administer the cyclooxygenase inhibitor in the morning, so that its effects will persist through the waking hours. Therapy may be short-term, focusing on attaining a certain weight, or long-term, to generally suppress appetite. Further, it is noted that the clinician or treating physician knows how and when to interrupt, adjust or terminate therapy in conjunction with individual patient’s response.

[0012] Any suitable route of administration may be employed. For example, oral, rectal, transdermal, intranasal, and parenteral (including subcutaneous, intramuscular, and intravenous) routes may be employed, although the oral route is by far the most preferred. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules and patches. The pharmaceutical compositions employed in the present invention comprise a cyclooxygenase-2 inhibitor as active ingredient, and a pharmaceutically acceptable carrier and, optionally, other therapeutic ingredients, as described above. The term “cyclooxygenase-2 inhibitor” refers to neutral, acidic and basic cyclooxygenase-2 inhibitors as well as salts of acidic and basic compounds prepared from pharmaceutically acceptable non-toxic bases and acids.
[0013] Compositions suitable for oral, rectal, and parenteral administration are encompassed by the present invention. A preferred route of administration is oral. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy. Preferred unit dosage formulations are those containing an effective dose, or an appropriate fraction thereof, of the active ingredients.

[0014] The compositions of the present invention also include a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms, depending on the forms preparation desired for administration, for example, oral or parenteral (including intravenous). In preparing the composition for oral dosage form, any of the usual pharmaceutical media may be employed, such as, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents in the case of oral liquid preparation, including suspension, elixirs and solutions. Carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents may be used in the case of oral solid preparations such as powders, capsules and caplets, with the solid oral preparation being preferred over the liquid preparations. Preferred solid oral preparations are tablets or capsules, because of their ease of administration. If desired, tablets may be coated by a standard aqueous or nonaqueous techniques. Oral and parenteral sustained release dosage forms may also be used. The term “pharmaceutically acceptable carrier for oral therapy” refers to solids or liquids that exhibit no oral toxicity in the amounts given and that are not so bitter or sour or otherwise offensive that the patient population would decline to ingest them. Pharmaceutically acceptable carriers for oral therapy include all of the materials commonly employed in formulating commercially available drugs for oral therapy.

[0015] Oral syrups, as well as other oral liquid formulations, are well known to those skilled in the art, and general methods for preparing them are found in any
standard pharmacy school textbook, for example Remington: The Science and Practice of Pharmacy. Chapter 86 of the 19th edition of Remington entitled "Solutions, Emulsions, Suspensions and Extracts" describes in complete detail the preparation of syrups (pages 1503-1505) and other oral liquids. Similarly, sustained release formulation is well known in the art, and Chapter 94 of the same reference, entitled "Sustained-Release Drug Delivery Systems," describes the more common types of oral and parenteral sustained-release dosage forms (pages 1660-1675.) The relevant disclosure, Chapters 84 and 96, is incorporated herein by reference. Because they reduce peak plasma concentrations, as compared to conventional oral dosage forms, controlled release dosage forms are particularly useful for providing therapeutic plasma concentrations while avoiding the side effects associated with high peak plasma concentrations that occur with conventional dosage forms.

Example 1

Tablets

<table>
<thead>
<tr>
<th>Composition per tablet:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>rofecoxib</td>
<td>25 mg</td>
</tr>
<tr>
<td>croscarmellose</td>
<td>60 mg</td>
</tr>
<tr>
<td>colloidal silicon dioxide</td>
<td>8 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>1 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>190 mg</td>
</tr>
<tr>
<td>croscarmellose</td>
<td>15 mg</td>
</tr>
<tr>
<td>talc</td>
<td>10 mg</td>
</tr>
<tr>
<td>Total</td>
<td>534 mg</td>
</tr>
</tbody>
</table>

[0016] The rofecoxib and silicon dioxide are dry mixed, the first portion of croscarmellose is added and the mixture is further dry mixed. The magnesium stearate is added, dry mixed and the mixture is run through a roller compactor and mill. The resulting dry granulate is mixed with the remaining three ingredients and compressed into tablets.
Example 2

**Powder-filled Capsules**

<table>
<thead>
<tr>
<th>Composition per unit dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>celecoxib</td>
</tr>
<tr>
<td>lactose</td>
</tr>
<tr>
<td>corn starch</td>
</tr>
<tr>
<td>magnesium stearate</td>
</tr>
</tbody>
</table>

[0017] The celecoxib, lactose and cornstarch, in the proportions shown above, are blended until uniform and then the magnesium stearate is blended into the resulting powder, which is sieved and filled into suitably sized, two-piece, hard gelatin capsules using conventional machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing the capsule size to suit.
CLAIM

1. A method for suppressing appetite comprising administering to a patient an amount of a cyclooxygenase-2 inhibitor sufficient to reduce appetite.


3. A method for inducing weight loss comprising administering to a patient in need of weight loss an amount of a cyclooxygenase-2 inhibitor sufficient to induce weight loss.

4. A method according to any of claims 1 to 3 wherein said cyclooxygenase-2 inhibitor is chosen from the group consisting of rofecoxib, meloxicam, celecoxib, diclofenac, sulindac, etodolac, piroxicam, etoricoxib, lumiracoxib and valdecoxib.

5. A method according to any of claims 1 to 3 wherein said cyclooxygenase-2 inhibitor is a selective cyclooxygenase-2 inhibitor.

6. A method according to claim 5 wherein said selective cyclooxygenase-2 inhibitor is chosen from rofecoxib, celecoxib, etoricoxib, lumiracoxib and valdecoxib.

7. A method according to any of claims 1 to 3 additionally comprising administering a second obesity treating drug chosen from the group consisting of sibutramine, an SSRI and a lipase inhibitor.

8. A composition for suppressing appetite comprising:
   (a) an amount of a cyclooxygenase-2 inhibitor sufficient to reduce appetite and
   (b) a second obesity treating drug chosen from the group consisting of sibutramine,
an SSRI and a lipase inhibitor.

9. A composition according to claim 8 wherein:
(a) said cyclooxygenase-2 inhibitor is chosen from the group consisting of rofecoxib, meloxicam, celecoxib, diclofenac, sulindac, etodolac, piroxicam etoricoxib, lumiracoxib and valdecoxib; and
(b) said second obesity treating drug is chosen from the group consisting of sibutramine, orlistat and an SSRI.

10. A composition according to claim 9 wherein said second drug is chosen from the group consisting of sibutramine, orlistat, nefazodone, hydroxynefazodone, fluoxetine, norfluoxetine, venlafaxine, milnacipran, citalopram, desmethylcitalopram, fluvoxamine, paroxetine, sertraline and norsertraline.

11. A kit comprising (a) a cyclooxygenase-2 inhibitor; and (b) instructions for administration for appetite suppression or weight loss.

12. A kit according to claim 11 additionally comprising (c) a second obesity treating drug chosen from the group consisting of sibutramine, an SSRI and a lipase inhibitor.