PHARMACEUTICAL PRODUCTS PROVIDING ENHANCED ANALGESIA

The present invention relates to analgesic compositions comprising capsaicin or a capsaicin analog combined with a drug selected from the class of non-steroidal anti-inflammatory, antipyretic and analgesic compounds. These compositions, when administered to humans or lower animals, provide a synergistic analgesic effect while minimizing undesirable side effects and toxicity.

Capsaicin and its derivatives appear to produce an analgesic effect through a mechanism largely unrelated to that of the other two categories of analgesics, opioids (narcotics) and non-steroidal analgesics (aspirin-like drugs). Since both capsaicin and the non-steroidals produce an analgesic effect, although apparently through different mechanisms, it might be expected that their combined effect would be at best additive. However, tests have shown that the analgesic effect of the combination is not merely the sum of the effects of each component, but rather an unexpected, greatly enhanced synergistic effect. Furthermore, the undesirable side effects of the two categories of analgesics are not closely related and the addition of the second analgesic does not appear to potentiate the side effects of the first. It is therefore possible to combine the two analgesics in such a dosage as to provide greatly enhanced analgesia with no enhancement of side effects. Depending on the dosages employed, the capsaicin may either potentiate the degree of analgesia beyond that obtainable using the non-steroidal alone, or it may induce analgesia at dosages where no analgesic effect is obtained from either component alone.

BACKGROUND OF THE INVENTION

Traditionally, analgesics have fallen into two broad categories. Simple, non-narcotic analgesics, such as aspirin, which appear to work by inhibition of prostaglandin synthetase, are effective against pain of integumental origin such as headache and muscle aches, but are often ineffective in controlling deeper, more intense pain. Furthermore, they may cause undesirable side effects even at therapeutic dosages. The most common of these side effects is a propensity to induce dyspepsia and gastrointestinal bleeding. At higher dosages, the salicylates may have toxic effects on the central nervous system consisting of stimulation (including convulsions) followed by depression. Headache, dizziness, mental confusion, hearing difficulties and hyperventilation may also occur. Gastrointestinal symptoms may include epigastric distress, nausea and vomiting. The narcotic analgesics appear to work through interaction with the endorphin/enkephalin receptor system of the central nervous system and are useful in controlling pain which is too intense to be controlled by the weaker, non-narcotic analgesics. However, centrally-acting narcotic analgesics have several serious undesirable side effects, including the development of physical dependence and tolerance, sedation, respiratory depression, hypotension, increase in cerebrospinal fluid pressure, nausea, vomiting and constipation. In some patients, particularly the chronically ill, the narcotic side effects make it impossible to administer dosages sufficient to adequately control pain over the required time period.

This invention combines capsaicin or a capsaicin analog with a drug from the class of non-narcotic, non-steroidal anti-inflammatory, antipyretic and analgesic compounds (often referred to as an "aspirin-like" drug, since

the prototypical compound is aspirin), producing a synergistic increase in analgesia without a corresponding increase in side effects. The degree of analgesia produced by this combination has been found in some cases to be equivalent to that formerly obtainable only through the use of narcotics. Thus, the claimed combination makes it possible to control pain which is too severe to be adequately controlled by the non-steroidals alone, while avoiding the serious side effects and addiction potential inherent in the use of opioids.

It has been recently discovered that capsaicin, a natural product of certain species of the genus Capsicium, induces analgesia. Analgesic activity of capsaicin has been discussed in the chemical and medical literature, including Yaksh, et al, Science, 206, pp 481-483 (1979); Jancso, et al, Naunyn-Schmiedeberg's Arch. Pharmacol., Vol. 311, pp 285-288 and Holzer et al, Eur. J. Pharm. Vol. 58, pp 511-514 (1979). U.S. Patent 4,238,505, Nelson, issued December 9, 1980, discloses 3-hydroxyacetanilide for use in producing analgesia in animals. Other references disclosing capsaicin analogs are listed herein below.

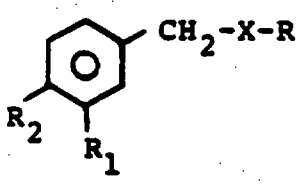
However, none of these references suggest in any way the desirability of concurrent administration of capsaicin or a capsaicin derivative with a non-steroidal. Further, the art suggests that it is extremely difficult to predict when a synergistic effect will be obtained from the concurrent administration of two pharmaceutical compounds which take effect through different mechanisms.

Although there are many patents which disclose analgesic and anti-inflammatory compositions containing a combination of two or more mechanistically unrelated analgesic and/or anti-inflammatory compounds, none of these compounds has a structure at all similar to that of capsaicin. See U.S. Patent 4,404,210, Schmidt, issued September 13, 1983; U.S. Patent 4,083,981, Yamamoto, issued April 11, 1978; U.S. Patent 4,315,936, Capetola et al, issued February 16, 1982; U.S. Patent 4,379,789, Capetola et al, issued April 12, 1983; and U.S. Patent 4,275,059, Flora, et al, issued June 23, 1981.

Thus, based on the art, one could not have predicted that the combination of capsaicin or a capsaicin analog with a non-steroidal would result in a synergistic increase in analgesia.

SUMMARY OF THE INVENTION

It has now been found that combinations of a capsaicinoid analgesic of the general formula



wherein R_1 is OH or OCH_3, R_2 is OH or $O(CO)R_3$, R_3 is selected from C_1-C_4 alkyl, phenyl and methyl, X is $-\overset{O}{\overset{\|}{C}}-$, $NHCO$, $NHCNH$, $NH\overset{S}{\overset{\|}{C}}NH$, $\overset{O}{\overset{\|}{C}}NH$, or $NHS(=O)=O$, and R is a C_5-C_{11} alkyl, C_5-C_{11} trans alkenyl, C_5-C_{23} cis alkenyl, C_{11}-C_{23} alkynyl, C_{11}-C_{23} alkadienyl, or C_{11}-C_{23} methylene substituted alkane, with a non-narcotic non-steroidal antiinflammatory, antipyretic and analgesic compound at weight ratios of capsaicinoid to non-steroidal from 20:1 to 1:20, and preferably from about 10:1 to 1:10, together with a pharmaceutically-acceptable carrier provide unexpectedly enhanced analgesic activity in humans and lower animals without a corresponding increase in undesirable side effects.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

By the term "comprising" as used herein is meant that various other inert ingredients, compatible drugs and medicaments, and steps can be employed in the compositions and methods of the present invention as long as the critical capsaicinoid/non-steroidal combination is present in the compositions and is used in the manner disclosed. The term "comprising" thus encompasses and includes the more restrictive terms "consisting essentially of" and "consisting of" which characterize the use of the compositions and methods disclosed herein.

By "compatible" herein is meant that the components of the composition are capable of being commingled without interacting in a manner which would substantially decrease the analgesic efficacy of the total composition under ordinary use situations.

All percentages and ratios herein are by weight unless otherwise specified.

Compositions

The compositions of the present invention comprise a safe and effective amount of:

(a) capsaicin or a capsaicin analog,

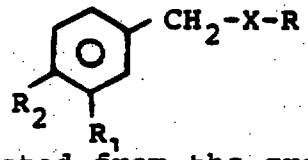
(b) a compound selected from the group of non-steroidal anti-inflammatory, antipyretic and analgesic drugs, and their pharmaceutically-acceptable salts; and

(c) a pharmaceutically-acceptable carrier.

A safe and effective amount of the composition is that amount which provides analgesia, thereby alleviating or preventing the pain being treated at a reasonable benefit/risk ratio, as is intended with any medical treatment. Obviously, the amount of the composition used will

vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the method of administration, and the specific formulation and carrier employed.

By the term "capsaicin or a capsaicin analog" or "capsaicinoid" is meant a compound of the general formula



wherein R_1 is selected from the group consisting of OH and OCH_3, R_2 is selected from the group consisting of OH and $O\overset{O}{\overset{\|}{C}}R_3$, R_3 is selected from the group consisting of a C_1-C_4 alkyl, phenyl and methyl, X is selected from the group consisting of $-NH\overset{O}{\overset{\|}{C}}-$, $-NH\overset{O}{\overset{\|}{C}}O-$, $-\overset{O}{\overset{\|}{C}}NH-$, $NH\overset{O}{\overset{\|}{C}}NH$, $NH\overset{S}{\overset{\|}{C}}NH$, $NHS(=O)(=O)$, and R is selected from the group consisting of a C_5-C_{11} alkyl, C_5-C_{11} <u>trans</u> alkenyl, C_5-C_{23} <u>cis</u> alkenyl, C_{11}-C_{23} alkynyl, C_{11}-C_{23} alkadienyl and C_{11}-C_{23} methylene substituted alkane.

Preferred compounds include those wherein both R_1 and R_2 are OH and X is $\overset{O}{\overset{\|}{C}}NH$ or $NH\overset{O}{\overset{\|}{C}}$; and those wherein R_1 is OCH_3, R_2 is OH or R_3CO and X is $\overset{O}{\overset{\|}{C}}NH$, $NH\overset{O}{\overset{\|}{C}}$ or $NH\overset{S}{\overset{\|}{C}}NH$.

Preferred R groups include C_7-C_{10} alkyls and <u>trans</u> alkenyls, and C_{16}-C_{21} <u>cis</u> alkenyls and alkadienyls. The preferred moieties within these groups include C_8H_{17}, C_9H_{17} and $C_{17}H_{33}$. Especially preferred compounds include those wherein R_1 is OCH_3, R_2 is OH and X is NH(CO); those wherein R_1 is OCH_3, R_2 is $R_3(CO)O$, X is NH(CO) and R is C_7-C_{10} alkyl or C_7-C_{10} <u>trans</u> alkenyl; and those wherein R_1 is OCH_3, R_2 is OH, X is NH(CS)NH and R is C_{16}-C_{21} alkadienyl.

Preferred capsaicin analogs include N-vanillyl-alkadienamides, N-vanillyl-alkanedienyls, and N-vanillyl-cis-monounsaturated alkenamides. A particularly preferred capsaicinoid is N-vanillyl-9E-octadecenamide (N-vanillyloleamide).

Preferred capsaicin analogs and methods for their preparation are described in the following Patents and Patent Applications:

Capsaicin (8-methyl-N-vanillyl-6E-nonenamide) and "synthetic" capsaicin (N-vanillylnonanamide) are disclosed as analgesics in U.S. Patent 4,313,958, LaHann, issued February 2, 1982. European Patent Application 0089710, LaHann, et al, published September 28, 1983, describes hydroxyphenylacetamides with analgesic and anti-irritant activity. Similarly, analgesic and anti-irritant activity is disclosed for N-vanillylsulfonamides in European Patent Application 0068591, Buckwalter, et al, published January 5, 1983; N-vanillylureas in European Patent Application 0068590, Buckwalter, et al, published January 5, 1983; N-vanillylcarbamates in European Patent Application 0068592, Buckwalter, et al, published January 5, 1983; N-[(substituted phenyl)methyl] alkynyl-amides in U.S. Patent 4,532,139 Janusz, et al, filed July 14, 1983; methylene substituted-N-[(substituted phenyl)methyl]-alkanamides in U.S. Patent 4,544668, Janusz, et al, filed July 14, 1983; N[(substituted phenyl)methyl]-cis-monounsaturated alkenamides in U.S. Patent 4,493,848 LaHann, et al, filed July 14, 1983; and N-[(substituted phenyl)methyl]-diunsaturated amides in U.S. Patent 4,544,669 LaHann, et al, filed July 14, 1983.

By "non-steroidal anti-inflammatory, antipyretic and analgesic drugs", or "non-steroidal", is meant a heterogeneous group of compounds, often chemically un-

related (although most of them are organic acids) which share certain therapeutic actions and side effects. Their therapeutic activity appears to depend to a large extent upon the inhibition of prostaglandin biosynthesis. Their primary use is to provide symptomatic relief from pain and inflammation associated with certain diseases, particularly musculoskeletal disorders such as rheumatoid arthritis and osteoarthritis. These compounds are often referred to as "aspirin-like drugs", since the prototypical compound is aspirin. The pharmacological properties and therapeutic uses of the compounds included within this classification are described in detail in Goodman and Gilman, "Analgesic-Antipyretics and Anti-Inflammatory Agents; Drugs Employed in the Treatment of Gout", The Pharmacological Basis of Therapeutics, 6th Ed., Ch. 29 (1980); Verbeeck et al, "Clinical Pharmacokinetics of Non-steroidal Anti-inflammatory Drugs", Clinical Pharmakinetics 8, pp 297-331 (1983), and Scherrer and Whitehouse, Antiinflammatory Agents Chemistry & Pharmacology, Vol. 1, Academic Press, New York (1974);

Specific classes of non-steroidals useful in the present invention are disclosed in detail in the following U.S. Patents:

U.S. Patent 4,275,059, Flora, et al, issued June 23, 1983, discloses salicylic acid, its pharmaceutically-acceptable salts, and its pharmaceutically-acceptable esters and derivatives; U.S. Patent 4,264,582, Flora, et al, issued April 28, 1981, discloses p-(isobutylphenyl) acetic acid compounds, including the parent acid (ibufenac) and its salts and esters, and derivatives thereof; U.S. Patent 4,282,214, Flora, et al, issued August 4, 1981, discloses various phenylacetic acid derivatives, their pharmaceutically-acceptable salts, and their

pharmaceutically-acceptable esters; U.S. Patent 4,216,212, Flora, et al, issued August 5, 1980, discloses pyrazolidine compounds, their pharmaceutically-acceptable salts, and their pharmaceutically-acceptable esters; U.S. Patent 4,269,828, Flora, et al, issued May 26, 1981, discloses indole compounds, their pharmaceutically-acceptable salts, and their pharmaceutically-acceptable esters.

Specifically preferred non-steroidals may be roughly divided into four general classifications. The salicylates include compounds such as acetylsalicylic acid (aspirin), salicylic acid, sodium salicylate, diflunisal, and methyl salicylate. The salicylate-like anti-inflammatory agents include compounds such as phenylbutazone, indomethacin, zomapirac acid, sulindac, fluproquazone, and mefenamic acid. The arylalkanoic acids include ibuprofen, naproxen, ketoprofen, fenoprofen, suprofen, flurbiprofen, benoxaprofen, pirprofen, and carprofen. The salicylate-like analgesic-antipyretics include acetaminophen and phenacetin. In some cases, the non-steroidals may be mixed with each other or with other drugs such as caffeine. Two popular analgesic combinations are aspirin, phenacetin and caffeine (APC) and aspirin, phenacetin and acetaminophen. Non-steroidals most preferred for use in the capsaicinoid-non-steroidal combination include acetylsalicylic acid (aspirin), ibuprofen, acetaminophen, diflunisal, naproxen, fenoprofen, and mefenamic acid. A specifically preferred combination is APC.

Weight ratios of capsaicinoid to non-steroidal useful in the present invention range from 20:1 to 1:20, with the preferred ratio ranging from about 10:1 to about 1:10. The optimum weight ratio is dependent primarily upon the relative strength of the particular capsaicinoid and non-steroidal used, and the type of severity of the pain being treated. As a repre-

sentative example, preferred weight ratios of capsaicinoid:acetylsalicylic acid (aspirin) may range from about 3:1 to about 1:3; preferred weight ratios of capsaicinoid:diflunisal may range from about 3:1 to about 1:3; preferred weight ratios of capsaicinoid:acetaminophen may range from about 3:1 to about 1:3; and preferred weight ratios of capsaicinoid:ibuprofen may range from about 5:1 to about 1:5. The preferred weight ratio for the preferred combination of N-vanillyl-9E-octadecenmaide and aspirin is about 2:1.

By "pharmaceutically acceptable salts" is meant those salts of the above disclosed acids which are toxicologically safe for topical or oral administration. These include the sodium, calcium, potassium, magnesium, ammonium, lysine, and arginine salts.

By "pharmaceutically acceptable carrier" is meant a solid or liquid filler, diluent or encapsultaing substance which may be safely used in systemic or topical administration. Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well-known in the art, may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. The amount of the carrier employed in conjunction with the capsaicinoid/opioid combination is sufficient to provide a practical quantity of material per unit dose of analgesic.

Pharmaceutically-acceptable carriers for systemic administration, that may be incorporated into the compositions of this invention, include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Specific pharmaceutically-acceptable carriers are described in the

following U.S. Patent Applications:

U.S. Patent No. 4,401,663, Buckwalter, et al, issued August 30, 1983; European Patent Applications 089710, LaHann, et al, published September 28, 1983; and European Patent Application 0068592, Buckwalter, et al, published January 5, 1983. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, aqueous ethanol, sesame oil, corn oil, and combinations thereof.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents. Preferred carriers for oral administration include ethyl oleate, methyl cellulose, gelatin, propylene glycol, cottonseed oil, sesame oil, peanut oil, corn oil, soybean oil, oil and water emulsions, and self-emulsifying oils either as free-flowing liquids or encapsulated in soft gelatin capsules. Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms, which may be used in formulating oral dosage forms containing monoalkenamides, are described in U.S. Patent 3,903,297. Robert, issued September 2, 1975,

Techniques and compositions for making solid oral dosage

forms are described in Marshall, "Solid Oral Dosage Forms", Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979).

Specific systemic and topical formulations useful in this invention are described in the following U.S. Patent Applications, relating to specific capsaicin analogs and methods of treatment:

U.S. Patent No. 4,401,663, Buckwalter, et al, issued August 30, 1983; and European Patent Application 0089710; LaHann, et al, published September 28, 1983; European Patent Application 0068590, Buckwalter, et al, published January 5, 1983; and European Patent Application 0068592, Buckwalter, et al, published January 5, 1983. Topical vehicles, useful herein, are disclosed in the following U.S. Patent Applications:

"Improved Penetrating Topical Pharmaceutical Compositions Combining 1-dodecylazacycloheptan-2-one", USP 4,557,934 filed June 21, 1983; "Penetrating Topical Pharmaceutical Compositions Containing N-(1-hydroxyethyl)-pyrrolidone", USP 4,537,776, Cooper, filed June 21, 1983; and "Compounds Useful for Producing Analgesia", USP 4,493,848 LaHann and Buckwalter, filed July 14, 1983.

The composition herein will preferably be administered orally.

The maximum dosage of the preferred capsaicin analogue vanillyloleamide (VO) which would normally be administered orally to an average adult without unacceptable side effects is about 2000 mg (35.4 mg/kg). The minimum effective dosage is about 50 mg (0.85 mg/kg). The maximum dosage of a non-steroidal which can be administered to the average adult is also about 2000 mg (35.4 mg/kg). Thus, the maximum allowable dosage of the combination will be about 2000 mg (35.4 mg/kg). It should be noted that a sub-effective dosage of one compound may effectively potentiate the other compound; therefore, less-than-minimum dosages of each component may be utilized in some cases. Thus, when dealing with safe and effective dosage levels of the present compositions, it is more appropriate to speak of safe and effective dosages of the combination rather than of the individual components.

The compositions and combinations of this invention can be used to treat and prevent pain and inflammation associated with certain diseases, particularly muscular-skeletal disorders, and to provide analgesia in various disorders at the deeper structures, muscles, tendons, bursa and joints associated with disease and trauma, and in various other conditions in which capsaicinoids and/or non-steroidals have heretofore been used to alleviate pain and discomfort.

The compositions of the instant invention are normally administered either topically or orally.

The following non-limiting Examples illustrate the compositions of the present invention.

EXAMPLE I

An analgesic composition for oral administration was made using the following ingredients:

N-Vanillyl-9E-octadecenamide	120 mg
Aspirin	60 mg
Methylcellulose	30 mg
Saline	6.0 ml

The composition was prepared by dissolving the methylcellulose in the saline to yield a 0.5% solution, after which the solid aspirin and N-vanillyl-9-octadecenamide were added and uniformly suspended in the solution by exposure to sonication. Male mice weighing approximately 25 g were orally dosed with a volume of this suspension sufficient to deliver 200 mg/kg of the octadecenamide and 100 mg/kg of the aspirin. Identical groups of mice were dosed orally with similarly prepared formulations which lacked either the aspirin, the octadecenamide, or both. Analgesic activity was demonstrated using the phenylquinone writhing test.

EXAMPLE II

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9E-octadecenamide	120 mg
Ibuprofen	30 mg
Methylcellulose	30 mg
Saline	6.0 ml

The methylcellulose suspending agent was dissolved in the saline to yield a 0.5% solution, to which the two drugs were added. A homogeneous suspension was achieved by the aid of sonication. Male mice weighing approximately 25 g were dosed by gavage with 250 mg/kg of the mixture. Analgesic activity was demonstrated using the phenylquinone writhing test.

EXAMPLE III

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9E-octadecenamide	120 mg
Ibuprofen	30 mg
Ethyl oleate	6.0 ml

The two analgesic agents were suspended in the ethyl oleate with the aid of sonication, and analgesic activity was demonstrated using the phenylquinone writhing test.

EXAMPLE IV

An analgesic composition for oral administration is made using the following ingredients:

N-vanillyl-9E-octadecenamide	100 g
Acetylsalicylic acid	100 g
Ethyl oleate	300 g

The composition is made by simple dissolution of the octadecenamide in the ethyl oleate, followed by suspension of the finely divided acetylsalicylic acid in the resulting solution by vigorous mechanical blending under an inert atmosphere of argon or dry nitrogen. The creamy suspension is then loaded into soft gelatin capsules to deliver 325 mg acetylsalicylic acid and 325 mg N-vanillyl-9-octadecenamide per capsule. One such capsule is administered orally to a 60 kg human, producing analgesia.

Substantially similar results are produced when the octadecenamide is replaced, in whole or in part, by capsaicin; N-vanillyl-9Z-octadecenamide; N-vanillyl-9E-octadecenamide; N-[(4-acetoxy-3-methoxyphenyl)methyl]-9Z-octadecenamide; N-vanillyl-(Z,Z)-9,12-octadecadienamide; N-vanillyl-(E,E)-9,12-octadecadienamide; N-[(4-acetoxy-3-methoxyphenyl)methyl]-(E,E)-9,12-octadecadienamide;

N-vanillyl-(E,E)-10,13-nonadecadienamide; N-vanillyl-9-octadecyanamide; 9-methylene-N-[(4-acetoxy-3-methoxyphenyl)-methyl]octadecanamide; 4-acetoxy-3-methoxy-benzyl nonamide, or octyl 3,4-dihydroxyphenylacetamide.

Substantially similar results are also obtained when the acetylsalicylic acid is replaced, in whole or in part, by the sodium, calcium, or lysine salts of aspirin, ibuprofen, diflunisal, naproxen, mefenamic acid, fenoprofen, indomethacin, ketoprofen, suprofen, perprofen, carprofen, or an aspirin-phenacetin-caffeine combination (APC).

EXAMPLE V

A composition for oral administration is made with the following components:

	Bulk	Individual Tablet
N-vanillyl-9,12-octadecadienamide	140 g	350 mg
Ibuprofen	35 g	90 mg
Starch	12 g	30 mg
Magnesium stearate	2 g	5 mg
Microcrystalline cellulose	40 g	100 mg
Colloidal silicon dioxide	1 g	2.5 mg
Povidone	5 g	12.5 mg

The above ingredients are admixed in bulk and formed into compressed tablets, using tabletting methods known in the art, each containing 590 mg of the mixture. One such tablet is administered orally to a 60 kg human, producing analgesia.

EXAMPLE VI

A composition for oral administration is made with the following ingredients:

N-vanillyl-9E-octadecenamide	225 g
Aspirin	125 g
Phenacetin	83 g

Caffeine	17 g
Mannitol	487 g
Acacia	29.3 g
Starch	48.1 g
Talc	15 g
Calcium stearate	2 g

The above ingredients are admixed in bulk and formed into tablets weighing 100 mg each using tabletting methods known in the art. Two such tablets are administered orally to a 70 kg human, producing analgesia.

EXAMPLE VII

A composition for transdermal topical delivery is made by admixing the following components:

N-vanillyl-9,12,15[E,E,E]-octadecatrienamide	4.0%
Ibuprofen	1.0%
Myristyl alcohol	1.0%
Propylene glycol	94.0%

Approximately 4.0 ml of the lotion is applied to an 80 sq. cm. portion of the skin of a 60 kg human, producing analgesia.

Effectiveness in Providing Analgesia

Phenylquinone Writhing Tests

The extent of analgesia obtained was determined using the phenylquinone writhing test model. Groups of eight male mice weighing between approximately 25 and 30g were dosed orally by gavage with the analgesic composition to be tested. Identical groups of mice were dosed with control compositions. Three hours after this initial administration, the mice were injected intraperitoneally with a 0.2% solution of phenylbenzoquinone in aqueous ethanol. The ability of the analgesic compositions tested to relieve the discomfort induced was measured by counting the number of abdominal contractions, or "writhes", occurring in each mouse during a 10 minute period be-

ginning 10 minutes after injection of the phenylbenzoquinone solution. The results are expressed as a percent of the "writhing" response observed in the vehicle control group.

EXAMPLE VIII

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9-octadecenamide	120 mg
Aspirin	60 mg
Methylcellulose	30 mg
Saline	6.0 ml

The composition was prepared by dissolving the methylcellulose in the saline to yield a 0.5% solution, after which the solid aspirin and N-vanillyl-9-octadecenamide were added and uniformly suspended in the solution by exposure to sonication.

Male mice weighing approximately 25 g were orally dosed with a volume of this suspension sufficient to deliver 200 mg/kg of the octadecenamide and 100 mg/kg of the aspirin. Identical groups of mice were dosed orally with similarly prepared formulations which lacked either the aspirin, the octadecenamide, or both. The mouse "writhing" method for assessing pain response described above was used. The data, summarized in the following table, were normalized based on the vehicle control taken as 100.

Treatment	% Writhing Response
Methylcellulose alone	100
Octadecenamide (200 mg/kg)	54
Aspirin (100 mg/kg)	78
Aspirin (100 mg/kg) + octadecenamide (200 mg/kg)	10

The response of the group given aspirin alone was not statistically distinguishable from that of the control group. The 90% inhibition of the writhing response

resulting from the combination treatment (aspirin plus octadecenamide) is greater than that expected from the sum of the aspirin treatment (22% inhibition) and octadecenamide treatment (45% inhibition) when given separately.

EXAMPLE IX

An analgesic combination for oral administration was prepared in a manner similar to that described for Example I, the only difference being the ratio of aspirin to N-vanillyl-9-octadecenamide:

N-vanillyl-9-octadecenamide	120 mg
Aspirin	120 mg
Methylcellulose	30 mg
Saline	6.0 ml

A solution was prepared as described in Example I. The analgesic activity of the combination was assessed in mice using the "writhing" method described above. The activity of the combination was contrasted with those of similar formulations lacking the aspiring component, the octadecenamide component or both:

Treatment	% Writhing Response
Methylcellulose alone	100
Aspirin (200 mg/kg)	15
Octadecenamide (200 mg/kg)	33
Aspirin (200 mg/kg + octadecenamide (200 mg/kg)	1.5

The analgesic efficacy obtained from the combination is significantly greater than that from either component alone.

EXAMPLE X

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9-octadecenamide	120 mg
Ibuprofen	30 mg
Methylcellulose	30 mg
Saline	6.0 ml

The methylcellulose suspending agent was dissolved in the saline to yield a 0.5% solution, to which the two drugs were added. A homogeneous suspension was achieved by the aid of sonication. The analgesic efficacy of this formulation was evaluated by dosing the mice by gavage with a sufficient dosage to provide 250 mg/kg of the mixture. The analgesic strength of the treatment was assessed using the "writhing" method described above. The efficacy of the combination was compared with that of similar formulations lacking the octadecenamide, the ibuprofen, or both.

Treatment	% Writhing Response
Methylcellulose alone	100
Ibuprofen (50 mg/kg)	114
Octadecenamide (200 mg/kg)	48
Octadecenamide (200 mg/kg) + ibuprofen (50 mg/kg)	2

In this case, the addition of an ineffective dose of ibuprofen to a moderately effective dose of octadecenamide resulted in a greatly potentiated analgesic effect.

EXAMPLE XI

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9-octadecenamide	120 mg
Ibuprofen	30 mg
Ethyl oleate	6.0 ml

The two analgesics were suspended in ethyl oleate with the aid of sonication, and evaluated for analgesic efficacy exactly as described in Example X.

Treatment	% Writhing Response
Ethyl oleate alone	100
Octadecenamide (200 mg/kg)	36
Ibuprofen (50 mg/kg)	154
Octadecenamide (200 mg/kg) + ibuprofen (50 mg/kg)	5

Although the response of the group receiving 50 mg/kg of ibuprofen alone did not vary significantly from that of the control group, the addition of this sub-effective amount of ibuprofen to the octadecenamide greatly potentiated its analgesic effect. Further, the combination of ibuprofen with the octadecenamide can provide anti-inflammatory/anti-arthritis efficacy lacking in N-vanillyl-9-octadecenamide and related capsaicin analogs.

EXAMPLE XII

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9E-octadecenamide	120 mg
3-(2',4'-diflurophenyl)-salicylic acid (diflunisal)	60 mg
Ethyl oleate	6.0 ml

The two analgesics were suspended in ethyl oleate with the aid of sonication and were evaluated for analgesic efficacy as described in Example X.

TREATMENT	% WRITHING RESPONSE
Ethyl oleate alone	100
Diflunisal (100 mg/kg)	121
Octadecenamide (200 mg/kg)	50
Diflunisal (100 mg/kg) + Octadecenamide (200 mg/kg)	15

In this case, the addition of an ineffective dose of diflunisal to a moderately effective dose of octadecenamide resulted in a greatly potentiated analgesic effect. Additionally, diflunisal provides anti-inflammatory activity not possessed by the octadecenamide alone.

EXAMPLE XIII

An analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9E-octadecenamide	75 mg
Acetaminophen	75 mg
Ethyl oleate/benzyl alcohol (98:2 vol/vol)	5 ml

The two analgesics were suspended in the ethyl oleate solution with the aid of sonication and were evaluated as in Example X.

TREATMENT	% WRITHING RESPONSE
Ethyl oleate solution alone	100
Acetaminophen (150 mg/kg)	127
Octadecenamide (150 mg/kg)	57
Acetaminaphen (150 mg/kg + octadecenamide (150 mg/kg)	17

In this case, the addition of an ineffective dose of acetaminophen to a marginally effective dose of octadecenamide resulted in a greatly potentiated analgesic effect.

EXAMPLE XIV

In order to determine the preferred capsaicinoid: non-steroidal ratios, an analgesic combination for oral administration was made using the following ingredients:

1:1 Octadecenamide:aspirin Combination

N-vanillyl-9E-octadecenamide	75 mg
Aspirin	75 mg
Ethyl oleate	10 ml

1:2 Octadecenamide:aspirin Combination

N-vanillyl-9E-octadecenamide	50 mg
Aspirin	100 mg
Ethyl oleate	10 ml

1:5 Octadecenamide:aspirin Combination

N-vanillyl-9E-octadecenamide	25 mg
Aspirin	125 mg
Ethyl oleate	10 ml

The two analgesics were suspended in ethyl oleate with the aid of sonication and were evaluated for analgesic efficacy as described in Example X.

TREATMENT	% WRITHING RESPONSE
Ethyl oleate alone	100
150 mg/kg aspirin	92
150 mg/kg Octadecenamide	43
150 mg/kg Octadecenamide:Aspirin (1:1)	48
150 mg/kg Octadecenamide:Aspirin (1:2)	28
150 mg/kg Octadeceaamide:Aspirin (1:5)	77

The responses of the ethyl oleate control group, the 1:5 combination group (25 mg/kg octadecenamide + 125 mg/kg aspirin) and the group receiving 150 mg/kg aspirin were not significantly different. The groups receiving the octadecenamide alone and the 1:1 combination (75 mg/kg aspirin + 75 mg/kg octadecenamide) displayed a moderate analgesic effect. The group receiving the 1:2 combination (50 mg/kg octadecenamide + 100 mg/kg aspirin) displayed an analgesic effect unexpectedly superior to that of any of the other groups.

Since the aspirin component of this combination provides an anti-inflammatory benefit not possessed by the octadecenamide or the other capsaidin analogs, and the octadecenamide provides greater analgesia than is obtainable using aspirin alone without many of the limitative side effects of aspirin, including gastrointestinal effects, the combination clearly provides benefits not attainable using either compound alone.

EXAMPLE XV

In order to determine the preferred dosages of the capsaicinoid/non-steroidal combination in the rat, a 2:1 octadecenamide:ibuprofen analgesic composition for oral administration was made using the following ingredients:

N-vanillyl-9E-octadeceanmide	100 mg
Ibuprofen	50 mg
Ethyl oleate/benzyl alcohol (98:2 vol/vol)	5 ml

The two analgesics were suspended in the ethyl oleate solution with the aid of sonication, and varying

dosages of the combination, as well as the individual components, were evaluated for analgesic efficacy as described in Example X.

TREATMENT	% WRITHING RESPONSE
Ethyl oleate solution alone	100
50 mg/kg ibuprofen	150
100 mg/kg octadecenamide	83
400 mg/kg octadecenamide	21
75 mg/kg 2:1 octadecenamide: ibuprofen combination	40
150 mg/kg 2:1 octadecenamide:	6
300 mg/kg 2:1 octadecenamide: ibuprofen combination	0.5

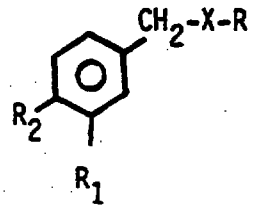
All three dosage levels of the combination produced a significant analgesic effect, although the 75 mg/kg dosage produced less analgesia than the other two dosages. Preferred dosage levels will depend on the severity of the pain to be treated, the relative severity of adverse side effects, and other factors within the judgment of the physician.

Although neither 50 mg/kg ibuprofen nor 100 mg/kg octadecenamide provided significant analgesia by themselves, the 150 mg/kg combination (100 mg/kg octadecenamide + 50 mg/kg ibuprofen) demonstrated an extremely strong analgesic effect. Furthermore, only 150 mg/kg of the 2:1 combination produced a greater analgesic effect than 400 mg/kg of octadecenamide alone, and only 75 mg/kg of the 2:1 combination (sub-effective amounts of both components) produced a greater analgesic effect than 100 mg/kg of octadecenamide alone. These results indicate a synergistic increase in analgesia when the two analgesics are combined.

CLAIMS

1. An analgesic composition characterized in that it comprises a safe and effective amount of:

(a) an analgesic capsaicinoid compound of the general formula.



wherein R_1 is selected from OH and OCH_3, R_2 is selected from OH and OCR_3, R_3 is selected from C_1-C_4 alkyl, phenyl and methyl, X is selected from

$-NHC-$, $-NHCO-$, $-CNH-$, $NHCNH$, $NHCNH$, and NHS, and R is selected from C_5-C_{11} alkyl, C_5-C_{11} trans alkenyl, C_5-C_{23} cis alkenyl, C_{11}-C_{23} alkynyl, C_{11}-C_{23} alkadienyl and C_{11}-C_{23} methylene substituted alkane;

(b) an analgesic selected from non-narcotic, non-steroidal anti-inflammatory, antipyretic and analgesic compounds and their pharmaceutically-acceptable salts; and

(c) a pharmaceutically-acceptable carrier;

wherein the weight ratio of (a):(b) is from 20:1 to 1:20.

2. A composition according to Claim 1, characterized in that R_1 and R_2 are both OH and X is CNH or NHC.

3. A composition according to Claim 1, characterized in that R_1 is OCH_3, R_2 is OH, and X is NHC.

4. A composition according to Claim 3, characterized in that R is a C_7-C_{10} alkyl or C_7-C_{10} trans alkenyl.

5. A composition according to Claim 3, characterized in that R is a C_{16}-C_{21} cis alkenyl or C_{16}-C_{21} alkadienyl.

6. A composition according to Claim 1, characterized in that R_1 is OCH_3, R_2 is R_3CO, X is NHC and R is a C_7-C_{10} alkyl or C_7-C_{10} trans alkenyl.

7. A composition according to Claim 1, characterized in that R_1 is OCH_3, R_2 is OH, X is $NHCNH$, and R is C_{16}-C_{21} alkadienyl.

8. A composition according to any of Claims 1-7, characterized in that the non-steroidal is selected from salicylates and their pharmaceutically-acceptable salts.

9. A composition according to any of Claims 1-7, characterized in that the non-sterioidal is selected from arylalkanoic acids and their pharmaceutically-acceptable salts.

10. A composition according to any of Claims 1-7, characterized in that the non-steroidal is selected from acetylsalicylic acid, diflunisal, ibuprofen, naproxen, and acetominophen.

11. A composition according to any of Claims 1 and 8-10, characterized in that the capsaicinoid is N-vanillyl-9-octadecenamide.

* C L M S *