Description

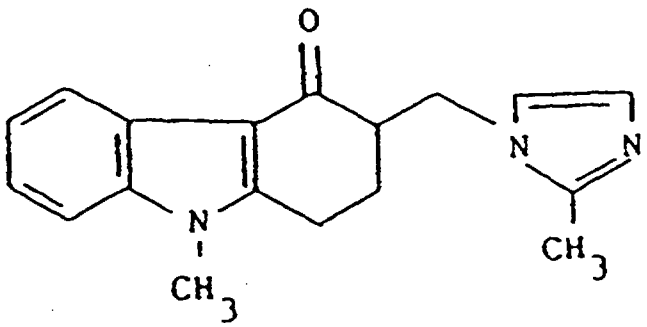
The present invention relates to the use of compounds in the manufacture of a medicament for use in the treatment of cytotoxic agent or radiation induced nausea and vomiting in mammals including humans, and to the use of compounds in the preparation of a medicament for the treatment of nausea and vomiting associated with cancer therapy.

Floreczyk et. al. (Cancer Treat. Rep. Vol. 66, 1982 p. 187-189) found that metoclopramide was effective in a ferret model of cisplatin induced emesis.

GB 2153821A describes a class of tetrahydrocarbazolones which are 5-HT M-receptor antagonists.

It has now been discovered that a compound from this class of compounds blocks the emetic response induced by cytotoxic agents such as cisplatin and also by radiation treatment. The compound is therefore of use in the treatment of nausea and vomiting associated with cancer therapy.

The invention therefore provides the use of a compound of formula (A):



(A)

which is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]4-carbazol-4-one, or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for use in the treatment of cytotoxic agent or radiation induced nausea and vomiting.

The pharmaceutically acceptable salts of the compound of the formula (A) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salt of the compound of the formula (A) is usually an acid addition salt with an acid such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic or acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

The compound of the formula (A) and its pharmaceutically acceptable salts may also form pharmaceutically acceptable solvates, such as hydrates, which are included whenever a compound of formula (A) is herein referred to.

The compound of the formula (A) may be prepared as described in the aforementioned U.K. patent application, or by analogous methods thereto.

Examples of cytotoxic agents include those routinely used in cancer chemotherapy, such as cisplatin, doxorubicin, cyclophosphamide, particularly cisplatin.

The administration of the compound of formula (A) or a pharmaceutically acceptable salt thereof may be by way of oral or parenteral administration.

An amount effective to treat the disorders hereinbefore described depends on the efficacy of the compound of formula (A), the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 100mg for example, 1 to 500mg, of the compound of formula (A), or a pharmaceutically acceptable salt thereof. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50mg/kg/day, more usually 0.002 to 25mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

It is preferred that the compound of formula (A) or a pharmaceutically acceptable salt thereof is administered in the form of a unit dose pharmaceutical composition in which is combined with a pharmaceutically acceptable carrier.

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

reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

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

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

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

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

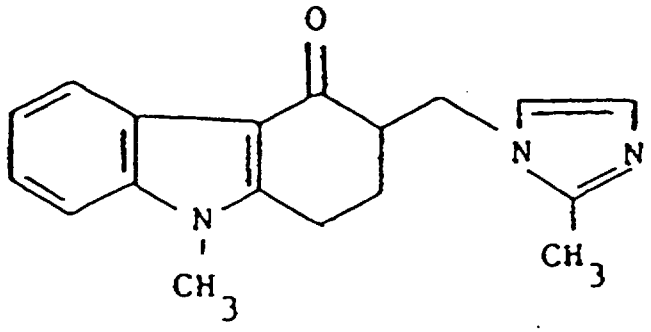
Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the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

The present invention further provides a pharmaceutical composition for use in the treatment of cytotoxic agent or radiation induced nausea and vomiting which comprises an effective amount of a compound of formula (A), or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

The following example illustrates the preparation of compound of formula (A) and the following pharmacological data illustrate the invention.

Example

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one



The title compound was prepared in accordance with the procedure described in Example 7 of GB 2153821A m.p. 229-230°C.

Pharmacological Data

Inhibition of Chemotherapy Induced Nausea and Vomiting

Adult male ferrets (initial body weight 1.3-1.8kg) were individually housed, fed once daily (200g Chum Puppy Food plus 50g Lab Diet A) and were supplied with water ad libitum. Additionally, each animal was given ¼ pint of milk daily during an acclimatization period.

To facilitate intravenous administration of drugs, a chronic indwelling catheter was surgically implanted into the jugular vein using a modification of the technique described by Florczyk and Schurig, 1981 (Pharmacol. Biochem. Behav., 14, 255-257). Prior to surgery each animal was sedated with ketamine hydrochloride (40mg/animal intramuscularly) and anaesthetised with a halothane-N_2O-O_2 mixture. A four day recovery period was allowed before commencement of an experiment.

For each group of animals, a preliminary study was carried out to establish an intravenous dose level of cytotoxic agent(s) which would give a consistent and reproducible emetic response. The appropriate dose of example was administered intravenously twice to each animal; 30 minutes before and 30-45 minutes after dosing with cytotoxic agent(s). Running controls received vehicle and cytotoxic agent(s) only.

A single emetic response commenced when an animal assumed a characteristic posture with retching and was concluded when either vomitus was expelled or was present in the mouth as evidenced by a chewing movement. The total number of emetic responses was determined during the four hour period following administration of cytotoxic agent(s) and the number of animals completely protected from emesis determined for each treatment.

All solutions were prepared in water for injection. B.P. Cisplatin was prepared from vials of Neoplatin* for injection (Mead Johnson; dose volume of 3ml/kg). Doxorubicin (Adriamycin*); Farmitalia Carlo Erba Ltd. Cyclophosphamide (Endoxana*); W.B. Pharmaceuticals Ltd.

Results

At a treatment dose of 0.5mg/kg of test compound, 6mg/kg of doxorubicin and 80mg/kg of cyclophosphamide, the number of animals completely protected was 2/2 for the compound of the Example.

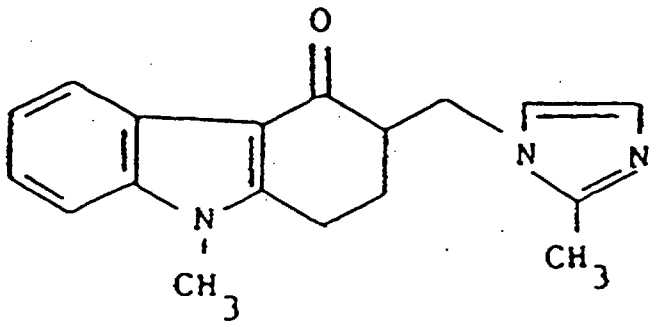
Claims

1. The use of a compound of formula (A):

* Trade Marks

Example

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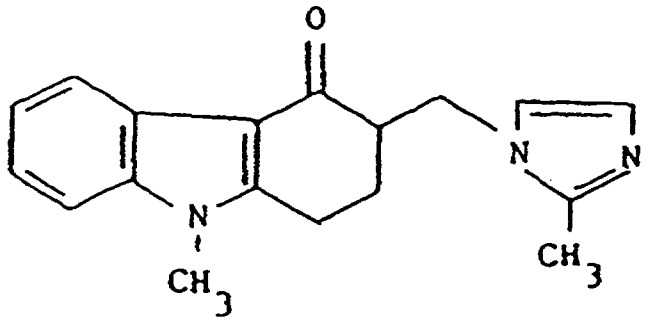
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* Trade Marks



(A)

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2. A use according to claim 1 wherein the medicament is for use in the treatment of cytotoxic agent induced nausea and vomiting.

3. A use according to claim 2 wherein the cytotoxic agent comprises cisplatin.

4. A use according to claim 2 wherein the cytotoxic agent comprises doxorubicin.

5. A use according to claim 2 wherein the cytotoxic agent comprises cyclophosphamide.

6. A use according to claim 2 wherein the cytotoxic agent is a combination of doxorubicin and cyclophosphamide.

7. A use according to any one of claims 2 to 6, wherein the medicament is for use in the treatment of nausea and vomiting induced by intravenously administered cytotoxic agent.

8. A use according to any one of claims 2 to 7, wherein the medicament is adapted for use before and after administration of the cytotoxic agent.

9. A use according to claim 1, wherein the medicament is for use in the treatment of radiation induced nausea and vomiting.

10. A use according to any one of claims 2 to 9 wherein the medicament is adapted for parenteral administration.

11. A use according to any one of claims 2 to 9 wherein the medicament is adapted for intravenous administration.

12. A use according to claim 11 wherein the medicament is adapted for use at a dosage level of from 0.5 to 35 mg per unit dose.

13. A use according to claim 12 wherein the medicament is adapted for use at a dosage level of from 1 to 35 mg per unit dose.

14. A use according to any one of claims 1 to 6, or claim 9, wherein the medicament is adapted for oral administration.

15. A use according to any one of claims 1 to 5, 9, 10, or 11 wherein the medicament is adapted for use at a dosage level of from 0.5 to 100 mg per unit dose.

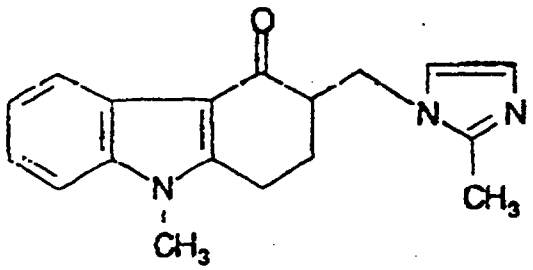
16. A use according to any one of claims 1 to 5, 9, 10 or 11 wherein the medicament is adapted for use at a dosage level of from 1 to 500 mg per unit dose.

17. The use of a compound of formula (A) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of nausea and vomiting associated with can-

cer therapy.

Patentansprüche

1. Verwendung einer Verbindung der Formel (A):



(A)

nämlich 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]4-carbazol-4-on, oder einem pharmazeutisch verträglichen Salz davon zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von durch ein zytotoxisches Mittel oder durch Bestrahlung hervorgerufener Übelkeit und Erbrechen.

2. Verwendung gemäß Anspruch 1, wobei das Arzneimittel zur Behandlung von durch ein zytotoxisches Mittel hervorgerufener Übelkeit und Erbrechen verwendet wird.

3. Verwendung gemäß Anspruch 2, wobei das zytotoxische Mittel Cisplatin umfaßt.

4. Verwendung gemäß Anspruch 2, wobei das zytotoxische Mittel Doxorubicin umfaßt.

5. Verwendung gemäß Anspruch 2, wobei das zytotoxische Mittel cyclophosphamid umfaßt.

6. Verwendung gemäß Anspruch 2, wobei das zytotoxische Mittel eine Kombination aus Doxorubicin und Cyclophosphamid ist.

7. Verwendung gemäß einem der Ansprüche 2-6, wobei das Arzneimittel zur Behandlung von durch ein intravenös verabreichtes zytotoxisches Mittel hervorgerufener Übelkeit und Erbrechen verwendet wird.

8. Verwendung gemäß einem der Ansprüche 2-7, wobei das Arzneimittel zur Verwendung vor oder nach Verabreichung des zytotoxischen Mittels angepaßt ist.

9. Verwendung gemäß Anspruch 1, wobei das Arzneimittel zur Behandlung von durch Bestrahlung hervorgerufener übelkeit und Erbrechen verwendet wird.

10. Verwendung gemäß einem der Ansprüche 2-9, wobei das Arzneimittel für die parenterale Verabreichung angepaßt ist.

11. Verwendung gemäß einem der Ansprüche 2-9, wobei das Arzneimittel für die intravenöse Verabreichung angepaßt ist.

12. Verwendung gemäß Anspruch 11, wobei das Arzneimittel zur Verwendung bei einer Dosierung von 0,5 bis 35 mg pro Dosiseinheit angepaßt ist.

13. Verwendung gemäß Anspruch 12, wobei das Arzneimittel zur Verwendung bei einer Dosierung von 1 bis 35 mg pro Dosiseinheit angepaßt ist.

14. Verwerdung gemäß einem der Ansprüche 1-6 oder Anspruch 9, wobei das Arzneimittel zur oralen Verabreichung angepaßt ist.

15. Verwendung gemäß einem der Ansprüche 1-5, 9, 10 oder 11, wobei das Arzneimittel zur Verwendung bei

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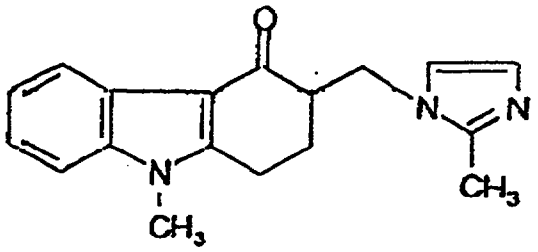
einer Dosierung von 0,5 bis 100 mg pro Dosiseinheit angepaßt ist.

16. Verwendung gemäß einem der Ansprüche 1-5, 9, 10 oder 11, wobei das Arzneimittel zur Verwendung bei einer Dosierung von 1 bis 500 mg pro Dosiseinheit angepaßt ist.

17. Verwendung der Verbindung der Formel (A) gemäß Anspruch 1 oder einem pharmazeutisch verträglichem Salz zur Herstellung eines Arzneimittels zur Behandlung von Übelkeit und Erbrechen, die mit der Krebstherapie verbunden sind.

Revendications

1. Utilisation d'un composé de formule (A) :



(A)

qui est le 1,2,3,9-tétrahydro-9-méthyl-3-[(2-méthyl-1H-imidazol-1-yl)méthyl]-4-carbazol-4-one, un sel pharmaceutiquement acceptable de celui-ci ; dans la fabrication d'un médicament pour l'utilisation dans le traitement des nausées et vomissements induits par un agent cytotoxique ou par des radiations.

2. Utilisation selon la revendication 1, dans laquelle le médicament est destiné au traitement des nausées et vomissements induits par un agent cytotoxique.

3. Utilisation selon la revendication 2, dans laquelle l'agent cytotoxique comprend du cisplatine.

4. Utilisation selon la revendication 2, dans laquelle l'agent cytotoxique comprend de la doxorubicine.

5. Utilisation suivant la revendication 2, dans laquelle l'agent cytotoxique comprend du cyclophosphamide.

6. Utilisation selon la revendication 2, dans laquelle l'agent cytotoxique est une combinaison de doxorubicine et de cyclophosphamide.

7. Utilisation selon l'une quelconque des revendications 2 à 6, dans laquelle le médicament est destiné au traitement des nausées et vomissements induits par l'agent cytotoxique administré par voie intra-veineuse.

8. Utilisation selon l'une quelconque des revendications 2 à 7, dans laquelle le médicament est adapté pour l'utilisation avant et après l'administration de l'agent cytotoxique.

9. Utilisation selon la revendication 1, dans laquelle le médicament est utilisé dans le traitement des nausées et vomissements induits par les radiations.

10. Utilisation selon l'une quelconque des revendications 2 à 9, dans laquelle le médicament est adapté pour l'administration parentérale.

11. Utilisation selon l'une quelconque des revendications 2 à 9, dans laquelle le médicament est adapté pour l'administration intra-veineuse.

12. Utilisation selon la revendication 11, dans laquelle le médicament est adapté pour l'utilisation à une dose comprise entre 0,5 et 35 mg par dose unitaire.

13. Utilisation selon la revendication 12, dans laquelle le médicament est adapté pour une utilisation à une

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dose comprise entre 1 et 35 mg par dose unitaire.

14. Utilisation selon l'une quelconque des revendications 1 à 6, ou selon la revendication 9, dans laquelle le médicament est adapté pour l'administration orale.

15. Utilisation selon l'une quelconque des revendications 1 à 5, 9, 10 ou 11, dans laquelle le médicament est adapté pour l'utilisation à une dose comprise entre 0,5 et 100 mg par dose unitaire.

16. Utilisation selon l'une quelconque des revendications 1 à 5, 9, 10 ou 11, dans laquelle le médicament est adapté pour l'utilisation à une dose comprise entre 1 à 500 mg par dose unitaire.

17. Utilisation d'un composé de formule (A) tel que défini dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, pour la fabrication d'un médicament utilisable dans le traitement des nausées et vomissements associés à la thérapie anti-cancéreuse.