[0005]

Patent Document 1: JP 05-031523 B

Patent Document 2: JP 3758164 B

Patent Document 3: WO 2020/091036

Non-Patent Literature

[0006]

Non-Patent Document 1: Pharmaceutical Research, Vol. 22, No. 1, 11-23, 2005

Summary of Invention

Technical Problem

[0007]

Generally, with respect to therapeutic agents for an oxidative stress disease, the same agent may have different conditions under which the agent can effectively exert its effect depending on the administration method of the agent. In addition, an oral formulation of edaravone is still under development, and conditions under which the same effect as that of the injection can be exerted has not been elucidated.

[0008]

Thus, an object of the present ~~invention~~disclosure is to provide a pharmaceutical composition containing edaravone as an active ingredient for oral administration and equivalent administration.

Solution to Problem

[0009]

A pharmaceutical composition according to an ~~embodiment~~ aspect of the present ~~invention~~ disclosure is characterized by containing edaravone as an active ingredient, the pharmaceutical composition being administered to a subject orally or intragastrically with any one first time interval selected from the group consisting of 1) to 3) below:

1) in a case where the subject has consumed a high-fat meal, 8 hours or longer after the consumption;

2) in a case where the subject has consumed a standard meal, 4 hours or longer after the consumption; and

3) in a case where the subject has consumed a light meal, 2 hours or longer after the consumption.

[0010]

A method of administering an edaravone-containing pharmaceutical composition according to an ~~embodiment~~ example of the present ~~invention~~disclosure is characterized by administering a pharmaceutical composition containing edaravone as an active ingredient to a subject orally or intragastrically with any one first time interval selected from the group consisting of 1) to 3) below:

1) in a case where the subject has consumed a high-fat meal, 8 hours or longer after the consumption;

2) in a case where the subject has consumed a standard meal, 4 hours or longer after the

consumption; and

3) in a case where the subject has consumed a light meal, 2 hours or longer after the consumption.

[0010a] In another aspect, there is provided the use of an edaravone-containing pharmaceutical composition which contains edaravone as an active ingredient, in the manufacture of a medicament, wherein the pharmaceutical composition is to be administered to a subject orally or intragastrically with any one first time interval selected from the group consisting of 1) to 3):

1) in a case where the subject has consumed a high-fat meal, 8 hours or longer after the consumption;

2) in a case where the subject has consumed a standard meal, 4 hours or longer after the consumption; and

3) in a case where the subject has consumed a light meal, 2 hours or longer after the consumption.

[0011]

The present inventors have found the present ~~invention~~ disclosure through the circumstances described below. These descriptions, however, do not particularly limit the present ~~invention~~disclosure.

[0012]

Food-drug interactions can have a significant effect on safety and efficacy of drugs. For

example, administration of a drug together with a meal may increase systemic absorption of the drug and change pharmacokinetics, and may result in improvement in efficacy and increase in the incidence of side effects. Alternatively, administration of a drug together with a meal may reduce systemic absorption of the drug and reduce efficacy.

[0013]

On the other hand, Wu et al. reported, for drugs exhibiting high solubility and high permeability and classified as BCS Class 1, meal consumption has little effect on pharmacokinetics, such as bioavailability, when the drugs are administered orally (Non-Patent Document 1).

[0014]

The present inventors found that a volume of water required for dissolving 1 g of edaravone is 500 mL (Drug Interview Form of Radicut (Revised in June 2017 (Revision 20)), which

means a volume of water required for dissolving 105 mg of edaravone is calculated as 52.5 mL, and thus edaravone is classified as a high solubility compound. In addition, the present inventors also determined that edaravone is classified as a high permeability compound from the results of a membrane permeability test using Caco-2 cells shown in Example 3 described below. Thus, edaravone is regarded as a BCS Class 1 drug with high solubility and high permeability in the report of Wu et al. These findings led to a presumption that edaravone is a compound whose pharmacokinetics are not affected by meal consumption.

[0015]

Nevertheless, consumption of a meal prior to administration was found to affect the pharmacokinetics of edaravone as shown in Examples described below. Thus, as a result of further diligent research, the present inventors newly found that not only the presence or absence of a meal but also the type of meal can cause a difference in effects on the pharmacokinetics of edaravone, and further found that a suitable administration timing depends on each type of meal, and completed the present ~~invention~~disclosure.

Advantageous Effects ~~of Invention~~

[0016]

An ~~embodiment~~example of the present ~~invention~~ disclosure can optimize, for each type of meal, a first time interval after a meal to administration and thus, for example, can avoid effects of a meal on pharmacokinetics such as bioavailability in both oral administration and intragastric administration of edaravone. Thus, the pharmaceutical composition according to an

~~embodiment~~ example of the present ~~invention~~ disclosure can exhibit an excellent therapeutic effect on oxidative stress diseases as a formulation for oral administration (hereinafter also referred to as an "oral formulation") or a formulation for intragastric administration (hereinafter also referred to as an "intragastric formulation") similarly to an injection administered intravenously which is the administration method known in the art. In addition, the pharmaceutical composition according to an ~~embodiment~~ example of the present ~~invention~~ disclosure can be administered orally or intragastrically and thus can further reduce the burden on patients and caregivers.

Brief Description of Drawings

[0017]

FIG. 1 shows spaghetti plots comparing the Cmax after administration of edaravone oral formulation between a fasted group, a group administered 8 hours after high-fat meal consumption, a group administered 4 hours after standard meal consumption, and a group administered 2 hours after light meal consumption. The circles with solid lines represent individual values, and the crosses with dotted lines represent mean values.

FIG. 2 shows spaghetti plots comparing the $AUC_{0\text{-}1h}$ and $AUC_{1h\text{-}\infty}$ after oral administration of an edaravone oral formulation between a high-fat meal group consuming a high-fat meal 1 hour after the administration and a fasted group administered under fasted conditions. The circles with solid lines represent individual values, and the crosses with dotted lines represent mean values.

FIG. 3 shows a box plot (study #9) and individual plots (studies #5, #6, and #9) for the

Claims

[Claim 1]

A pharmaceutical composition containing edaravone as an active ingredient, the pharmaceutical composition being administered to a subject orally or intragastrically with any one first time interval selected from the group consisting of 1) to 3):

1) in a case where the subject has consumed a high-fat meal, 8 hours or longer after the consumption;

2) in a case where the subject has consumed a standard meal, 4 hours or longer after the consumption; and

3) in a case where the subject has consumed a light meal, 2 hours or longer after the consumption.

[Claim 2]

The pharmaceutical composition according to claim 1, wherein a second time interval from edaravone administration to next meal consumption is 30 minutes or longer.

[Claim 3]

The pharmaceutical composition according to claim 1 or 2, wherein the second time interval from edaravone administration to next meal consumption is 1 hour or longer.

[Claim 4]

The pharmaceutical composition according to any one of claims 1 to 3, which is for oral administration.

[Claim 5]

The pharmaceutical composition according to any one of claims 1 to 3, which is for intragastric administration.

[Claim 6]

The pharmaceutical composition according to any one of claims 1 to 5, wherein the intragastric administration is administration via a tube.

[Claim 7]

The pharmaceutical composition according to claim 6, wherein the tube is a percutaneous endoscopic gastrostomy tube (PEG tube).

[Claim 8]

The pharmaceutical composition according to claim 6, wherein the tube is a nasopharyngeal gastric tube (NG tube).

[Claim 9]

The pharmaceutical composition according to any one of claims 1 to 8, which is for treating an oxidative stress disease.

[Claim 10]

The pharmaceutical composition according to claim 9, wherein the oxidative stress disease is any one of diseases selected from the group consisting of amyotrophic lateral sclerosis, Parkinson's disease, spinocerebellar degeneration, muscular dystrophy, Alzheimer's disease, cerebral infarction, multiple sclerosis, systemic scleroderma, and stomatitis.

[Claim 11]

The pharmaceutical composition according to claim 9 or 10, wherein the oxidative stress disease is amyotrophic lateral sclerosis.

[Claim 12]

The pharmaceutical composition according to any one of claims 1 to 11, wherein the first time interval is a time interval during an administration period of intermittent administration or daily administration.

[Claim 13]

The pharmaceutical composition according to any one of claims 1 to 12, wherein a dose per administration is from 90 to 120 mg of edaravone.

[Claim 14]

The pharmaceutical composition according to any one of claims 1 to 12, wherein a dose per administration is from 90 to 105 mg of edaravone.

[Claim 15]

The pharmaceutical composition according to any one of claims 1 to 14, wherein a daily administration frequency is once, and a dose per administration is 105 mg of edaravone.

[Claim 16]

Use of ~~A method of administering~~ an edaravone-containing pharmaceutical composition which contains edaravone as an active ingredient, in the manufacture of a medicament, wherein ~~the method comprising administering~~ the pharmaceutical composition is to be

administered to a subject orally or intragastrically with any one first time interval selected from the group consisting of 1) to 3):

1) in a case where the subject has consumed a high-fat meal, 8 hours or longer after the consumption;

2) in a case where the subject has consumed a standard meal, 4 hours or longer after the consumption; and

3) in a case where the subject has consumed a light meal, 2 hours or longer after the consumption.

[Claim 17]

The ~~method~~ use according to claim 16, wherein a second time interval from administration of the pharmaceutical composition to next meal consumption is 30 minutes or longer.

[Claim 18]

The ~~method~~ use according to claim 16 or 17, wherein the second time interval from administration of the pharmaceutical composition to next meal consumption is 1 hour or longer.

[Claim 19]

The ~~method~~ use according to any one of claims 16 to 18, wherein the pharmaceutical composition is to be administered orally.

[Claim 20]

The ~~method~~ use according to any one of claims 16 to 18, wherein the pharmaceutical

composition is to be administered intragastrically.

[Claim 21]

The ~~method~~use according to claim 20, wherein the intragastric administration is to be administration via a tube.

[Claim 22]

The ~~method~~ use according to claim 21, wherein the tube is a percutaneous endoscopic gastrostomy tube (PEG tube).

[Claim 23]

The ~~method~~ use according to claim 21, wherein the tube is a nasopharyngeal gastric tube (NG tube).

[Claim 24]

The ~~method~~use according to any one of claims 16 to 23, wherein the pharmaceutical composition is to be administered to treat an oxidative stress disease.

[Claim 25]

The ~~method~~ use according to claim 24, wherein the oxidative stress disease is any one of diseases selected from the group consisting of amyotrophic lateral sclerosis, Parkinson's disease, spinocerebellar degeneration, muscular dystrophy, Alzheimer's disease, cerebral infarction, multiple sclerosis, systemic scleroderma, and stomatitis.

[Claim 26]

The ~~method~~ use according to claim 24 or 25, wherein the oxidative stress disease is

amyotrophic lateral sclerosis.

[Claim 27]

The ~~method~~ use according to any one of claims 16 to 26, wherein

administration of the pharmaceutical composition includes intermittent administration or daily administration; and

the pharmaceutical composition is to be administered with the first time interval during an administration period of the intermittent administration or daily administration.

[Claim 28]

The ~~method~~ use according to any one of claims 16 to 27, wherein the pharmaceutical composition is to be administered at a dose per administration of ~~the pharmaceutical composition is~~ from 90 to 120 mg of edaravone.

[Claim 29]

The ~~method~~ use according to any one of claims 16 to 27, wherein the pharmaceutical composition is to be administered at a dose per administration of ~~the pharmaceutical composition is~~ from 90 to 105 mg of edaravone.

[Claim 30]

The ~~method~~ use according to any one of claims 16 to 29, wherein the pharmaceutical composition is to be administered at a daily administration frequency of ~~the pharmaceutical composition is~~ once, and a dose per administration of ~~the pharmaceutical composition is~~ 105 mg of edaravone.