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(71) Applicant
Shionogi Seiyaku Kabushiki Kaisha (Japan),
12-3 Chome Dosho-machi, Higashi-ku, Osaka, Japan

(72) Inventors
Junichiro Mifune,
Hideo Yamada,
Noboru Nagafuji

(74) Agent and/or Address for Service
Boult, Wade & Tennant,
27 Furnival Street, London EC4A 1PQ

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GB 1392674
Martindale "The Extra Pharmacopoeia", 28th Edition, pub. December 1982, The Pharmaceutical Press see pages 8 to 9.

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A5B
C2C

# (54) Oral dobutamine preparation

(57) Pharmaceutical compositions for treating cardiac disease comprise dobutamine, (4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]-amino]ethyl]pyrocatechol), or an acid addition salt thereof, in a form adapted for oral administration.

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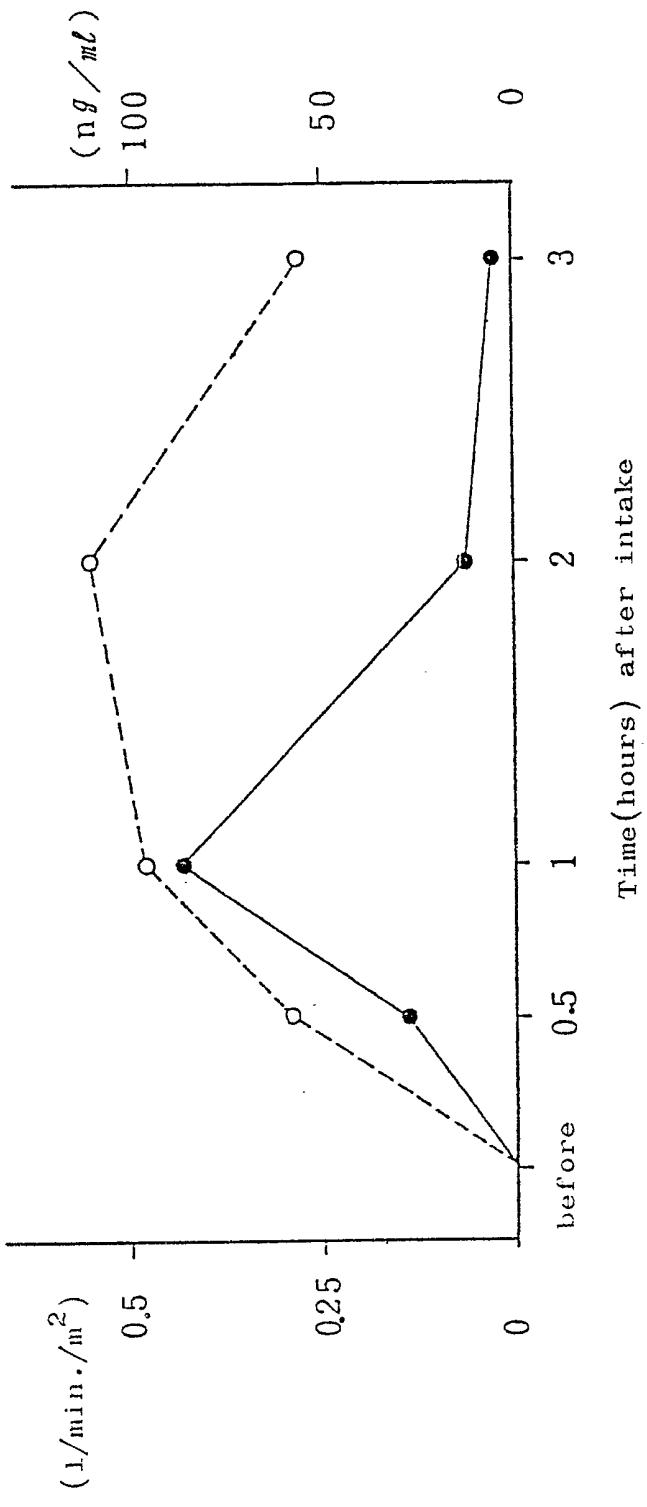



Figure 1.

Figure 2.

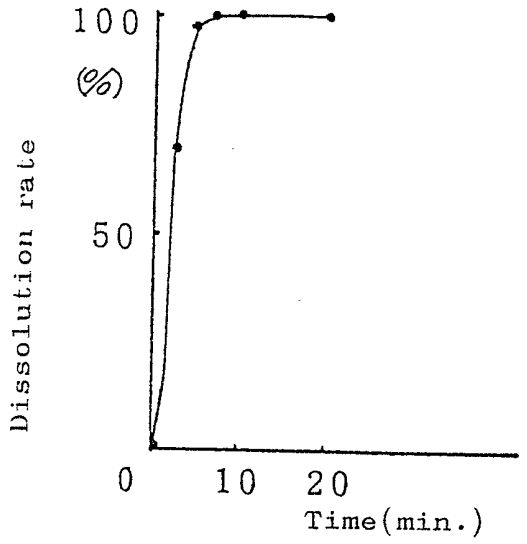



Figure 3.

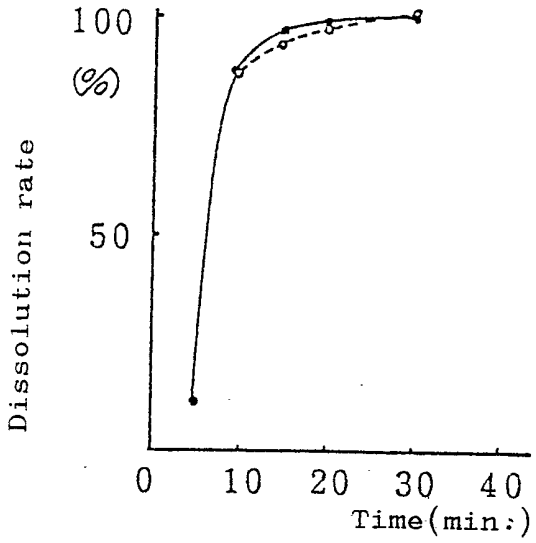
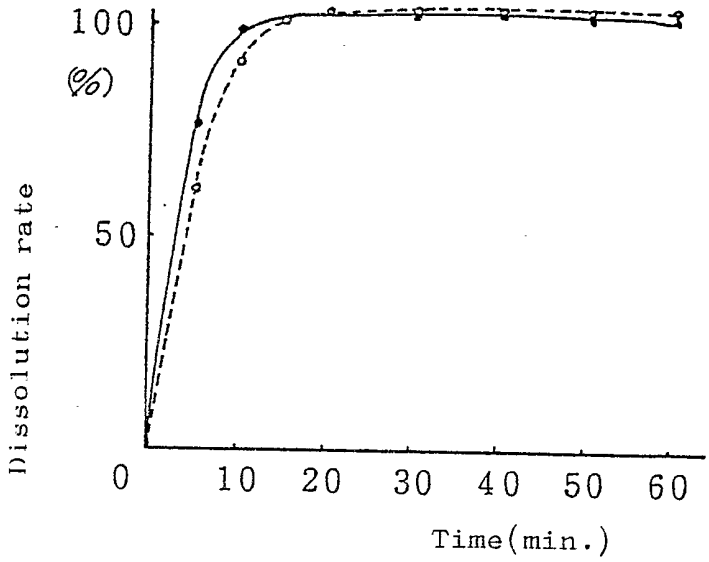



Figure 4.



SPECIFICATION

**Oral dobutamine preparation**

The present invention belongs to the field of pharmaceutical or veterinary preparations and provides new oral preparations of dobutamine (4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]pyrocatechol) or acid addition salts thereof.

The catecholamines include epinephirine, norepinephirine, isoproterenol, dopamine, and dobutamine, from which an appropriate one is selected according to the character of their actions. The main role of the present agents is to increase myocardial contractility upon heart failure. Epinephirine and norepinephirine among the abovementioned catecholamines should not be applied in the treatment of heart failure, as a rule. The reason why epinephirine should not be applied in the treatment of heart failure though it has potent cardiac action is that it increases the myocardial oxygen consumption simultaneously with the cardiac action, which causes an increase of myocardial working-load without improvement. Isoproterenol [Protanol® (brand name of Nikken Chemicals Co., Ltd.), Sooner® (Kaken Yakukako Co., Ltd.)], which is an inotropic agent too, should also not be administered, as a rule, in the treatment of heart failure caused by an acute myocardial infarction because it greatly accelerates the sinus rate simultaneously [Mashime et al, Rinshoyakuri & Yakubutsuryohogaku (Clinical Pharmacology & Pharmacotherapy), 298 (1980) published by Riko Gakusha in Japan].

On the basis of the above reasons, norepinephirine, dopamine or dobutamine have been recently used for improvement of contractility upon heart failure, nevertheless, it has been believed that each of them is inefficacious when administered orally. The reason for this misleading belief is based on the following.

First, it has been confirmed from studying the metabolic pathway of the well-known compounds epinephirine and norepinephirine that both are ineffective when administered orally because they are inactivated in the digestive organs and liver [Ito, Yakuri-gaku (Pharmacology), 225 (1976) published by Eikodo]. Secondly, there has been no idea that the oral use of both dopamine and dobutamine could be effective, because they are metabolized in the same mechanism as the prior art catecholamines and are also metabolized with a short half-life, i.e. within a few minutes by intravenous infusion.

The present invention relates to a pharmaceutical or veterinary intropic preparation for oral administration, which comprises dobutamine (4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]pyrocatechol). The dobutamine may be in the form of an acid addition salt thereof. Moreover, when administered orally to an adult usually at a single dosage of 50 mg or more, preferably of 100 mg or more and more preferably within a range of about 200 mg to about 400 mg of the active substance as dobutamine, the preparation exhibits the same degree of inotropic action as injection preparations do.

*Figure 1* shows a dobutamine plasma-level curve and a curve of the changes in the cardiac index when dobutamine hydrochloride is orally administered, wherein the ordinate indicates the dobutamine plasma-level (ng/ml) or changes in the cardiac index (1/min/$m^2$), and the abscissa the time (hours) after the administration; and the curve of the solid line indicates the DBX plasma-levels and that of the dotted line the changes in the cardiac index.

*Figures 2, 3* and *4* show the dissolution rate in first and second fluids (defined in Japanese Pharmacopoeia Xth edition) tested on the respective preparations described in Examples 1, 2 or 3, wherein the ordinate indicates the dissolution rate (%) and the abscissa the time (minutes); and the curve of the solid or the dotted line indicates the dissolution property in the first or the second fluid, respectively.

Dobutamine hydrochloride, which was recently developed as a dopamine analogous agent is on the market only for injective use as an intravenous drip [Dobutrex® for injection; brand name of Eli Lilly Co., Ltd.]. It produces least peripheral vasoconstriction with its potent inotropic action, and in comparison with other catecholamines it has lesser adverse reactions such as acceleration of the sinus rate, arrhythmogenesis and the like; accordingly, it is an actually useful inotropic agent.

In the earliest stage of the screening test with animals, it was confirmed that the plasma half-life of free dobutamine (hereinafter referred to as DBX), which showed activity when administered intravenously, was very short, only 1 or 2 minutes, and the activity disappeared within a very short duration; this is the reason that the application has been limited to an intravenous drip infusion. Additionally, the DBX level in plasma could hardly be increased in oral administration to test-animals, so it was deduced that the oral administration of dobutamine was ineffective.

The present inventors found that even by oral administration, DBX in plasma reaches a sufficiently high level because the rate of metabolism of dobutamine becomes very slow at a high dosage; this is a surprising result. The present invention is based on these findings.

Recently, acute myocardial infarctions in Japan have had a tendency to increase in occurrence, but the highly efficient agents thus shown above have brought about a remarkable progress in the remedy of the disease at an acute stage and it becomes significant for patients to return to society.

How to return to society, which has been searched and attempted in many ways, is a recent important problem; rehabilitation and kinesitherapy for patients with myocardial infarction have been recognized to be an established system of acology. It has been studied by Nobutaka Doba in Clinica *10* (6), 496 (1983) how many disadvantages have been caused by the rest cure forced after recovery from the acute stage, and the early release from the rest cure and the earliest possible start of rehabilitation after recovery have been

required.

In the latest therapy, however, a catecholamine such as dobutamine has been continuously administered even after the cure from the acute stage in order to avoid occurrence of complicating disease until patients become free from the anxiety of reoccurrence of the disease. Additionally, the catecholamine always requires a continuous administration by means of intravenous drip infusion because of the shortness of its effective life. Therefore, the patients are forced to be on beds for a long period of time in order to keep the rest cure; therefore, it has been impossible for patients to leave their beds and begin rehabilitation at the early stage.

The preparations in this invention enable the patients to take dobutamine orally and to get up out of bed; on these clinical advantages it is quite effective with the patients thus mentioned above, and makes it possible to begin earlier rehabilitation and to leave hospital earlier. On the other hand, it can be given to outpatients for administration outside of hospital, so it is very useful for treatment of outpatients with refractory or chronic myocardial infarction and myocardial infarction accompanied with bradycardia as well as for prophylaxis of reoccurrence of the symptom.

As mentioned above, the present preparations have been developed so that patients with myocardial infarction can leave hospital and return to society and outpatients with refractory myocardial infarction can be treated outside of hospital.

It has been proved on a main metabolic route of dobutamine that dobutamine is acted on by catechol-O-methyltransferase (hereinafter referred to as COMT) to be converted to 3-O-methyl-dobutamine (hereinafter referred to as MDBX), which is conjugated with glucuronic acid and excreted as the conjugated 3-O-methyldobutamine (hereinafter referred to as CMDBX). It is recognized that CMDBX is actually ineffective since its clinical activity is about 1/10 or less in comparison with that of free dobutamine.

Taking those findings into consideration, the present inventors searched to locate where dobutamine is absorbed in the body (as shown in Experiment 1) and concluded that dobutamine is absorbed mainly in the small intestine, slightly in the large intestine, but hardly in the stomach.

Dobutamine hydrochloride was administered as powder to rats in varying dosage and the rats were not fasted in some groups but fasted in others before the administration in order to elucidate how the DBX plasma level was affected by the conditions on administration (Experiment 2). It was revealed unexpectedly that the agent did not give an expected plasma-level of DBX in accordance with the dosage, and it might be needed for the present preparation to release the agent at high concentration in the small intestine as the main absorption site. As mentioned at the beginning of this specification, the inventors expected that the plasma-level of DBX reached a relatively high level since dobutamine was absorbed in the main absorption site at such a high rate that the metabolic path was saturated.

On the basis of the above conclusion and results from the fundamental experiments such as an acute toxicity test, the present inventors began the clinical trial with the catecholamine-dependent patients who seemed to need this preparation (Exp. 3). From this clinical trial it was confirmed that the preparation gave a sufficient DBX level in the plasma at an oral single dosage of 200 mg to 300 mg as dobutamine to show desired clinical actions such as increase of cardiac index, decrease of left ventricular filling pressure (pulmonary capillary wedge pressure) and the like.

It goes without saying that the amount to be administered as a single dose and a daily dose of dobutamine should be carefully determined in consideration of the conditions of the patients, since the single dose varies with the patient's age, body weight, conditions of food, state of liver function and other factors. In general, it has been found that the preparation of dobutamine should be orally administered at a dose of about 50 mg or more, preferably about 100 mg or more, and most preferably about 200 mg to about 400 mg as dobutamine 1-5 times a day.

The preparations of this invention are used in enforcing myocardial contractility, for example, for patients requiring rehabilitation after the treatment of myocardial infarction, or for treatment or prophylaxis of chronic heart failure. The preparations are suitable for patients whom it is difficult to take off intravenous infusion of the catecholamines, particularly dobutamine; patients with chronic heart failure not responding to cardiotonics such as digitalis or diuretics; and with heart failure accompanied by bradycardia, for example.

As mentioned above, it is quite necessary for patients to begin rehabilitation without delay after the recovery from myocardial infarction as well as to leave bed as early as possible. The present preparations make it possible for the patients to leave bed early under the stable conditions and to be out of hospital soon and return to their community. Since the preparations can be administered by the patients themselves outside the hospital, it is possible for the patients to receive treatment while making a normal living, particularly in treatment of refractory or chronic heart failures or in prophylaxis of the reoccurence of heart failures. As a result, both the mental and the physical sufferings of the patients caused by the long restraint in bed are reduced and their economic burden lightened.

Moreover, other emergency patients can receive the soonest treatment since hospitals can keep beds unoccupied; this is another advantage.

These preparations may also be administered through a stomach-tube to patients to whom injections can hardly be given and in an emergency case it can be administered even in a clinic which has no bed for inpatients. Furthermore, it gives no adverse-reactions in the injective site such as an injury or a pain on the inner wall of vein which is often caused by intravenous injection.

Also included within the invention are veterinary preparations containing dobutamine or an acid addition salt thereof for oral administration.

The preparations of the present invention are usually employed as powder, fine granules or tablets, or as readily soluble hard capsules which are filled with one of them. The preparations may comprise the active ingredient alone or a combination of the active ingredient with one or more diluents, excipients or carriers. They may be, if desired, used in any dosage form, for example, soft capsules prepared by suspension in oils or fats, or liquid preparations such as syrup, emulsion and suspension as long as their stability is not spoiled under the conditions of usual preservation.

In this invention, dobutamine is generally employed as acid addition salts thereof, especially dobutamine hydrochloride. The active ingredient may be in a form of powder of the compound itself or, if desired, powder admixed with one or more appropriate diluents, excipients or carriers, or granules prepared from the powder in a conventional manner or readily soluble hard capsules filled with the powder or granules.

The additives which can be employed as excipients include sugars, for example lactose, sucrose, glucose, D-mannitol, sorbitol, inositol and xylose; starches for example wheat starch, corn starch and dextrin; and crystalline cellulose. The excipients may be added to the active agent alone or as a mixture of them in a pharmaceutically suitable amount and then formulated. If desired, a suitable amount of fluidizing agent such as magnesium stearate, talc or Carplex® (brand name of Shionoi & Co. Ltd.), for example, may be added.

It should be kept in mind that since the acid addition salts of dobutamine, particularly dobutamine hydrochloride readily turn to brown by interaction with water in formulation into, for example, fine granules, granules and tablets, it is appropriate to formulate it by means of dry granulation, dry compressing or other dry formulation method.

In the formulation, it is also appropriate to add excipients, for example those mentioned above; disintegrators; for example carboxymethylcellulose potassium (CMC-Ca) or carboxymethyl starch sodium (CMS-Na); lubricants such as, e.g. magnesium stearate, potassium stearate or talc; and binders such as methylcellulose (MC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), potato starch or gelatine, for example, each in a proper amount in order to prepare fine granules, granules, tablets or other formulations.

The present invention is explained in more detail by the following Experiments and Examples, but the scope of this invention is not limited by those Examples.

*Experiment 1*

In order to determine the absorption site in gastrointestional tract for dobutamine, rats [Jcl: SD-strain male rats (body weight: 200-250 g), 3-4 rats per group] were anesthetized with urethan. Both ends of the stomach, small intestine or large intestine in the respective group were ligatured, into which a previously prepared isotonic solution of dobutamine hydrochloride (containing 5 mg/ml of dobutamine hydrochloride) was administered at a dose of 40 mg/kg.

Data shown in each Table are the average values obtained from 3-4 rats tested.

*(Method for quantitative analysis)*

a) *DBX remaining in the gastrointestinal tract*:

The digestive organs of rats were taken out, from which DBX was extracted twice with 20 ml of methanol. The extract was appropriately diluted with methanol, and the DBX was quantitatively analyzed by means of HPLC (High Performance Liquid Chromatography). The conditions of HPLC employed are shown below.

| | |
|---|---|
| Column | : Nucleosil$_{10}C_{18}$ (4mm × 300mm) (Chemco Co., Ltd.) |
| Mobile phase | : Methanol : PIC® $B_7$ (Waters Associates) =50 : 50 |
| Flow rate | : 1.3 ml/min. |

The objective compound was detected at 278 nm with an ultraviolet absorption detector.

b) *Plasma-levels of DBX and MDBX*

Concentrations of DBX were determined as follows: to a mixture of about 30 mg of activated alumina and a sample (1 ml) of the plasma was added 5 ml of purified water and the mixture centrifugally separated; the supernatant was removed. The alumina was washed with additional 5 ml of purified water, eluted thrice with 1 ml of a mixture of methanol/acetic acid (11:3) to give DBX as an eluate. The eluate was evaporated, and the residue dissolved into 200$\mu\ell$ of the mobile phase for HPLC and applied to HPLC.

The concentration of MDBX was determined as follows: a sample (1 ml) of the plasma was adsorbed on a column of SEPPAK® $C_{18}$ (made by Waters Associates), the column washed twice with 5 ml of purified water and eluted with 5 ml of methanol, and the methanol was removed by evaporation. The residue was measured in the same manner as in the above. The conditions of HPLC employed are shown below:

| | |
|---|---|
| Column | : Nucleosil$_{10}C_{18}$ (4mm × 300mm) |
| Mobile phase | : tetrahydrofuran : acetonitrile : 0.1M potassium dihydrogenphosphate buffer (pH 3.0, EDTA 250 mg/l) = 2 : 14.5 : 83.5 |
| Flow rate | : 1.5 ml/min. |

The active fraction was detected by voltammetry (charged voltage : 800 mV).

c) *Plasma-level of CMDBX*:

To 0.5 ml of the plasma was added 0.3 ml of conc. hydrochloric acid and the mixture allowed to stand at 100°C for 2 hours for hydrolysis and then adjusted at pH 10 with addition of 0.5 ml of 6N sodium hydroxide and then 2 ml of 1M borate buffer (pH 10.0). Dichloromethane (6 ml) was added and the mixture shaken for 15 minutes in order to extract the active component into the dichloromethane layer. After centrifugal separation, 5 ml of the organic layer is collected and evaporated, and the residue dissolved in 200$\mu\ell$ of the mobile phase mentioned below and applied to HPLC. The conditions of HPLC employed are as follows:

| | |
|---|---|
| Column | : Nucleosil$_{10}C_{18}$ |
| Mobile phase | : tetrahydrofuran : PIC $B_4$ = 11 : 89 |
| Flow rate | : 1.5 ml/min. |

The eluate was detected at 278 nm by an ultraviolet absorption detector.

(Result)

TABLE 1

Remains (%) of dobutamine in each site 30 min. after the administration and the plasma-levels (ng/ml)

| *Site* | *Remains (%) of dobutamine in each site* | *Plasma-levels (ng/ml)* *DBX* | *MDBX* | *CMDBX* |
|---|---|---|---|---|
| Stomach | 86.7 | 25.2 | 14.1 | 119 |
| Small intestin | 43.7 | 3113.9 | 412.2 | 2349 |
| Large intestin | 61.7 | 1531.6 | 278.3 | 1007 |

(Conclusion)

On the basis of the above data, it was confirmed that dobutamine was absorbed best in the small intestine, well in the large intestine, but unsatisfactorily in the stomach.

*Experiment 2*

Measurement of the DBX, MDBX, or CMDBX plasma-levels at several doses.

In this experiment, dobutamine hydrochloride (powder) was administered to rats according to the following manner.

About 30 mg of talc was packed into a polyethylene-tube at the end so as to be 1 mm thickness and then powdery dobutamine hydrochloride placed onto the talc layer. The end of the tube was attached to the top of an stomach-tube and the drug was administered with 0.5 ml of purified water to a test site of gastrointestinal tract.

1) Dobutamine hydrochloride was orally administered to rats with fasting at a dose of 8 mg/kg and the plasma-levels were measured according to the manner as shown in Experiment 1-b) or c) (Table 2).

TABLE 2

| *Time after the administration (hours)* | *Plasma levels (ng/ml)* *DBX* | *MDBX* | *CMDBX* |
|---|---|---|---|
| 0.25 | N.D.[1)] | 23.3 | 897 |
| 0.50 | N.D. | 12.3 | 1178 |
| 1.00 | N.D. | 10.3 | 1010 |
| 3.00 | N.D. | 0.7 | 381 |

1) N.D.: The active ingredient could be detected but not quantitatively because of the extremely low level.

2) Dobutamine hydrochloride was administered to unfasted rats at a dose of 60 mg/kg and the plasma-levels were determined in the same manner as in the above paragraph 1) (Table 3).

TABLE 3

| *Time after the administration (hours)* | *Plasma levels (ng/ml) DBX* | *MDBX* | *CMDBX* |
|---|---|---|---|
| 0.25 | 154.0 | 107.7 | 1536 |
| 0.50 | 70.4 | 37.4 | 1835 |
| 1.00 | 13.2 | 11.9 | 2466 |
| 3.00 | 5.8 | 13.2 | 2112 |

3) Dobutamine hydrochloride was administered to rats with fasting at a dose of 60 mg/kg and the plasma-levels were determined in the same manner as in the above paragraph 1) (Table 4).

TABLE 4

| *Time after the administration (hours)* | *Plasma levels (ng/ml) DBX* | *MDBX* | *CMDBX* |
|---|---|---|---|
| 0.25 | 234.4 | 78.1 | 798 |
| 0.50 | 152.2 | 138.1 | 2130 |
| 1.00 | 216.9 | 148.1 | 1931 |
| 3.00 | 34.1 | 23.9 | 1547 |

(Conclusion)

From the data shown in Table 3 and 4, it was confirmed that the DBX plasma-levels in unfasted rats were unxpectedly lower than those in fasted rats at the same dose. It was deduced that in this case dobutamine was diluted by food, and slowly transferred to the main absorption site, the small intestine, at a low concentration over a long period of time. On the other hand, if dobutamine is assumed to be an orally administrable agent which could give plasma-levels in accordance with the doses, the DBX plasma-levels in Table 2 might approximately meet to those proportionally calculated from the data in Table 4; but the data in Table were against expectations.

On the basis of those findings, it could be deduced that the present preparations do not give desirable DBX plasma-levels until they reach the main absorption site, the small intestine, at a reasonably high concentration.

*Experiment 3*

Dobutamine capsules (containing 100 mg of an active ingredient as dobutamine per capsule) for oral administration as described in Example 1 were prepared and administered to 9 patients with heart-failure.

Five men and 4 women aged 19-78 years, with a body surface area between 1.34 and 1.75 $m^2$ were employed, of which 4 are congestive heart-failures and 5 myocardial infarctions. The degree of the seriousness of them was classified according to the classification by NYHA (New York Heart Association) [K. Nanba et al, Junkanki-byo no chiryokeikaku (Guide for Treatment of Cardiovascular Disease), 84 (1969)].

The aforementioned capsules of dobutamine were orally administered to each patient with fasting at a single dose of 2-3 capsules (at 200-300 mg as dobutamine), the effects were hemodynamically observed at the prefixed time.

The effects after dobutamine intake are shown as an average value in each item obtained from 9 patients.

TABLE 5

| *Time after the administration (hours)* | *Before* | *0.5* | *1.0* | *2.0* | *3.0* | *4.0* |
|---|---|---|---|---|---|---|
| Cardiac index l/min/m$^2$ | 2.08 ±0.08 | 2.37 ±0.25 | 2.56 ±0.22 | 2.63 ±0.21 | 2.35 ±0.12 | 2.39 ±0.11 |
| Mean blood pressure mmHg | 82.3 ±4.8 | 80.7 ±7.0 | 86.2 ±4.4 | 81.4 ±4.5 | 79.6 ±5.3 | 81.7 ±5.4 |
| Diastolic pulmonary arterial pressure mmHg | 20.1 ±1.4 | 17.5 ±2.1 | 17.3 ±2.2 | 17.4 ±2.0 | 18.0 ±2.1 | 19.1 ±1.6 |
| Pulmonary capllary wedge pressure mmHg | 19.4 ±1.1 | 17.6 ±1.8 | 16.2 ±2.1 | 17.3 ±1.9 | 15.8 ±1.9 | 17.6 ±1.5 |
| Right atrial pressure mmHg | 7.8 ±1.1 | 6.9 ±1.2 | 6.1 ±1.2 | 6.5 ±1.3 | 6.8 ±1.3 | 7.4 ±1.3 |
| Heart rate /min | 77.0 ±5.4 | 85.1 ±7.2 | 86.9 ±5.0 | 88.1 ±5.7 | 88.1 ±7.3 | 83.3 ±8.5 |

DBX plasma-levels at the prefixed time on 6 patients whose plasma-levels could be measured are shown below. The procedures and conditions for measurement of plasma-levels were referred to the method described in Experiment 1-b).

TABLE 6

*DBX plasma levels (ng/ml)*

| *Time after the administration (hours)* | | *0.5* | *1.0* | *2.0* | *3.0* |
|---|---|---|---|---|---|
| Subject | 3 | 5.4 | 262.2 | 44.2 | 4.5 |
| | 4 | 0 | 80.2 | 5.7 | 2.0 |
| | 5 | 34.1 | 44.0 | 15.3 | 1.7 |
| | 6 | 9.6 | 3.9 | 0 | 0 |
| | 7 | 3.7 | 34.0 | 5.6 | 3.3 |
| | 9 | 29.6 | 97.4 | 2.4 | 8.1 |
| Mean | | 13.7±5.9 | 87.0±37.6 | 12.2±6.7 | 3.3±1.1 |

In oral administration at a dose of 200-300 mg of dobutamine, the mean increases of cardiac index after 1 hour and 2 hours were 0.48 L/min./m$^2$ and 0.55 L/min./m$^2$, respectively: the rate of increase at the time (2 hours after) when the maximal effects were seen, is 26.4%. As for the other hemodynamical effects, the mean increase in the heart-rate was 14.7%, the mean decrease in the left ventricular filling pressure (pulmonary capillary wedge pressure) 18.7%, and almost no changes in mean blood pressure were seen. The following Table 7 is a list showing clinical efficacy in each patient and the numbers given to the subjects are common to those in other Tables in these Experiments.

TABLE 7

| Subject | *2 Sex | Age | Body Surface Area ($m^2$) | Disease | Degree by NYHA | Dose of dobutamine | Clinical Efficacy | Adverse Reaction |
|---|---|---|---|---|---|---|---|---|
| *1 1 | M | 19 | 1.67 | Congestive heart failure | IV° | 250 mg | Good | |
| 2 | F | 70 | 1.34 | 〃 | III°-IV° | 200 mg | 〃 | |
| 3 | M | 50 | 1.60 | 〃 | III° | 300 mg | 〃 | |
| 4 | F | 55 | 1.45 | 〃 | III°-IV° | 200 mg | 〃 | |
| 5 | F | 75 | 1.43 | 〃 | IV° | 200 mg | 〃 | |
| 6 | M | 67 | 1.63 | 〃 | III° | 200 mg | 〃 | |
| 7 | F | 78 | 1.63 | 〃 | IV° | 200 mg | 〃 | |
| 8 | M | 75 | 1.56 | 〃 | IV° | 300 mg | 〃 | *3 |
| 9 | M | 66 | 1.75 | 〃 | IV° | 200 mg | 〃 | |

*1 Dobutamine was administered to the subject 1 at a dose of 3 capsules (one of which contains 50 mg of dobutamine)
*2 M: Male, F: Female
*3 Palpitations 2-3 hours after intake.

Figure 1 shows DBX plasma-levels and the time-dependent changes in cardiac index. In this Figure, the curve of the solid line indicates the DBX plasma-level (ng/ml) and that of the dotted line increase in the cardiac index (l/min./$m^2$). In this connection, the increase in the cardiac index means the difference between the data before and after the administration shown in Table 5.

The plasma levels are shown as the average values of 6 patients and the changes in the cardiac index as those of 9. As seen from this Figure, dobutamine gave appropriate DBX plasma-levels on oral administration, which were accompanied by marked increase in the cardiac index over 3 hours. Particularly, 2 hours after the administration at which time maximal effects were observed, the hemodynamically desirable effects were recognized, that is, the cardiac index increased by 26.4% and the left ventricular filling pressure decreased by 18.7%. These results indicate that the preparations in the present invention are satisfactory in clinical efficacy.

*Example 1*
(Capsules)

Dobutamine hydrochloride (7.847 g) and 7.00 g of D-mannitol are well admixed and filled in hard-capsules No. 1 (total 70 capsules).

The preparation contains 112.1 mg of dobutamine hydrochloride, which corresponds to 100 mg of dobutamine, per capsule and showed a desirable dissolution property (Figure 2) in the dissolution test with the first fluid described in Japanese Pharmacopoeia Xth edition (hereinafter referred to as JPX).

The dissolution test was conducted at 100 r.p.m. according to the second method (the paddle method) using the same apparatus as defined therein. As the test medium 900 ml of the first or the second fluid as defined in the disintegration test of JPX was employed. The method was applied to all the dissolution tests in the following Examples.

*Example 2*
(Tablets)

A mixture of 2 g of dobutamine hydrochloride, 0.4 g of CMC-Ca and 0.02 g of magnesium stearate was formulated into tablets (121 mg/tablet) (ø7mm) by means of a direct compression method with a single punch machine (Kikusui Press No. 4 : Kikusui Seisaku-sho Ltd.)

The preparation containing 100 mg of dobutamine per tablet showed a desirable dissolution property (Figure 3) in both the first and the second fluid on the dissolution test.

*Example 3*
(Granules)

To a mixture of 2 g of dobutamine hydrochloride and 0.4 g of CMC-Ca was added 1.3 g of 10% HPC-SL and then kneaded in a mortar. The kneaded mixture was granulated by passing through a ø1.2 mm screen with

pressure and dried under aeration at 60°C for 3 hours in a tray dryer oven. The granules is shifted through a 14 mesh sieve and then through a 20 mesh one to remove fine powder, whereby 2 g of uniform granules in a range of 14-20 mesh particles are obtained.

Said granules, which contain 0.79 g of dobtamine hydrochloride per gram, showed a sufficient dissolution property in both the first and the second fluids in the dissolution test (Figure 4).

CLAIMS

1. A pharmaceutical or veterinary inotropic preparation for oral administration containing dobutamine as an active ingredient.
2. A preparation as claimed in claim 1 wherein the dobutamine is as an acid addition salt thereof.
3. A pharmaceutical preparation as claimed in claim 1 or claim 2, formulated for administration in a dosage of at least 50 mg of the active ingredient as dobutamine.
4. A preparation as claimed in claim 3, formulated for administration in a dosage of at least 100 mg of the active ingredient as dobutamine.
5. A preparation as claimed in claim 4, formulated for administration in a dosage of from about 200 mg to about 400 mg of the active ingredient as dobutamine.
6. A pharmaceutical preparation as claimed in claim 1 or claim 2 which is in unit dosage form, each unit containing at least 50 mg of the active ingredient as dobutamine.
7. A preparation as claimed in claim 6 wherein each unit contains at least 100 mg of the active ingredient as dobutamine.
8. A preparation as claimed in claim 7 wherein each unit contains from about 200 mg to about 400 mg of the active ingredient as dobutamine.
9. A preparation as claimed in any one of the preceding claims wherein the active ingredient is dobutamine hydrochloride.
10. A preparation as claimed in any one of the preceding claims which is in the form of powder, fine granules, granules, tablets, capsules or a liquid.
11. A pharmaceutical preparation as claimed in any one of the preceding claims which further comprises a pharmaceutically acceptable diluent, excipient or carrier, or a veterinary preparation as claimed in any one of claims 1, 2, 9 or 10 which further comprises a veterinarily acceptable diluent, carrier or excipient.
12. A preparation as claimed in claim 11 wherein the diluent, carrier or excipient is as exemplified hereinbefore.
13. A dobutamine preparation substantially as hereinbefore described in any one of the Examples.

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