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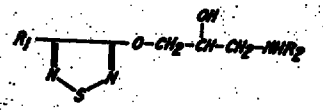
(54) ANTIHYPERTENSIVE COMPOSITIONS

(71) We, MERCK & CO INC, a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Hydralazine is an effective antihypertensive agent when used in combination with other drugs in the treatment of patients with moderate to severe, essential or renal hypertension. The primary effect is on diastolic blood pressure as a result of arteriolar vasodilatation thereby reducing peripheral vascular resistance. The pressor effect of angiotensin and norepinephrine are believed to be partially blocked by hydralazine. Hydralazine should not be used as the sole therapy of even mild to moderately severe disease since it is rarely completely effective and side effects are frequently troublesome when no other therapy is used. The side effects of headache, palpitations and tachycardia occur usually during initial therapy and frequently disappear to some extent as therapy is continued. The effect of direct-acting peripheral vasodilators in hypertension, typified by hydralazine, is limited by reflex increases in cardiac output.

This invention is concerned with pharmaceutical compositions containing hydralazine. The present invention is based on the discovery that co-administration of hydralazine with certain substituted 1,2,5-thiadiazoloxypropanolamines, which are β -adrenergic blocking agents, potentiates the antihypertensive action of hydralazine and prolongs its duration, so that it is possible in most instanced to use lower dosages of hydralazine at wider intervals to effect the same degree of antihypertension. The co-administration of these agents also minimizes the emergence of certain side effects induced by the hydralazine, specifically palpitations and tachycardia. This salutary effect is induced by a reduction in cardiac output.

The β-adrenergic blocking agents and its optically active isomers used in the compositions of this invention are represented by Formula I below:



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(including its optically active isomers) or are pharmaceutically acceptable salts thereof. In the formula, R_1 is hydrogen; halogen such as chlorine, bromine or fluorine; alkyl such as methyl, ethyl, propyl or *t*-butyl; alkenyl such as vinyl, allyl or methallyl; alkylthioalkyl, alkoxyalkyl, phenylthioalkyl, phenoxyalkyl, substituted phenoxyalkyl or phenylthioalkyl, in which the alkylthio and alkoxy radicals include methylthio, ethylthio, propylthio, methoxy, ethoxy and propoxy, the alkyl residues include methyl and ethyl and the substituents on the phenyl residues are halogen such as chlorine, bromine or fluorine, hydroxy, alkyl such as methyl, ethyl or propyl and/or alkoxy such as methoxy, ethoxy or propoxy, carbamoyl, alkylcarbamoyl, e.g. methyl carbamoyl, ethyl carbamoyl, isopropyl carbamoyl, or butyl carbamoyl; cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy or pentoxy; phenyl or substituted phenyl in which the substituent(s) is/are halo-

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gen such as chlorine or fluorine, C_{1-3} alkyl or C_{1-3} alkoxy, aralkyl or substituted aralkyl in which the substituent(s) is/are in the aryl residue and are halogen such as chlorine, fluorine or bromine, C_{1-3} alkyl, and/or C_{1-3} alkoxy; aziridinyl; azetidinyl; pyrrolidinyl; piperidinyl; hexahydro-azepino; morpholino; piperidino, thiazolidinyl; *p*-thiazinyl; or piperazinyl; and R_2 is alkyl, preferably having from 3 to 6 carbons such as isopropyl, *tert*-butyl or 2,2-dimethyl-propyl; alkenyl such as allyl, vinyl or methallyl; C_{2-6} alkynyl, such as propynyl, butynyl or propargyl; substituted alkyl in which the substituent(s) is/are hydroxy or halogen such as chlorine or bromine; carboxy; alkoxy; alkylthio, preferably C_{1-4} alkylthio; di-(C_{1-3} alkyl) amino; pyrrolidinyl; piperazinyl; morpholino; thiazolidinyl or thiazinyl.

Preferably R_1 is a hydrogen or halogen atom or an alkyl, alkoxy, morpholino or piperidino radical, R_2 is alkyl and the weight ratio of β-adrenergic blocking agent to hydralazine ranges from 1:1 to 1:10.

Representative compounds used in the compositions of this invention are:

3 - chloro - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy)-1,2,5-thiadiazole

(+) - 3 - chloro - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

(−) - 3 - chloro - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

3 - bromo - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy)-1,2,5-thiadiazole

(+) - 3 - bromo - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

(−) - 3 - bromo - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

3 - (4 - hydroxypiperidino) - 4 - (3 - *t*-butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole

3 - morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate

(+) - 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate

(−) - 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate

3 - morpholino - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

3 - N - *t* - butylcarbamoyl - 4 - (3 - *t*-butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole

(+) - 3 - N - *t* - butylcarbamoyl - 4 - (3-*t* - butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole hydrochloride

(−) - 3 - N - *t* - butylcarbamoyl - 4 - (3 - *t*-butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrochloride

3 - N - isopropylcarbamoyl - 4 - (3 - isopropylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole

(+) - 3 - N - isopropylcarbamoyl - 4 - (3-isopropylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole hydrochloride

(−) - 3 - N - isopropylcarbamoyl - 4 - (3-isopropylamono - 2 - hydroxypropoxy)-1,2,5-thiadiazole hydrochloride

3 - morpholino - 4 - (3 - t - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole benzoate

3 - chloro - 4 - (3 - isopropylamino - 2-hydroxypropoxy)-1,2,5-thiadiazole

3 - bromo - 4 - (3 - isopropylamino - 2-hydroxypropoxy)-1,2,5-thiadiazole

(+) - 3 - chloro - 4 - (3 - isopropylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

3 - methyl - 4 - (3 - butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole

3 - ethoxy - 4 - (3 - butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole

In practical methods of using the compositions of the present invention, the compounds are administered orally at doses ranging at ratios from 1:1 to 1:10 (β-adrenergic blocking agent to hydralazine) by weight of the composition. The β-adrenergic blocking agent is administered at quantities ranging from 0.03 mg./kg. to 0.15 mg./kg. of body weight. Hydralazine is administered at quantities ranging from 0.03 mg./kg. to 1.5 mg./kg. of body weight. Of particular preference is the combination of 0.07 mg./kg. to 0.1 mg./kg. of body weight of the β-adrenergic blocking agent and 0.7 mg./kg. to 1.0 mg./kg. of body weight of hydralazine. The composition is administered for varying periods of treatment as required. The β-adrenergic blocking agent is administered at quantities ranging from 2 mg. to 10 mg. Hydralazine is administered at quantities from 2 mg. to 100 mg. Of particular preference is the administration of the composition which contains 5 mg. of the β-adrenergic blocking agent 3 - morpholino - 4 - (3 - t. - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole, advantageously the hydrogen maleate salt or the sinister isomer thereof, and 50 mg. of hydralazine four times a day. The formulations included herein are effective in the treatment of hypertensive conditions in patients.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the severity of the disease undergoing therapy.

Representative examples of the pharmaceutically acceptable salts of the blocking agents are the hydrochlorides, hydrobromides, phosphates, sulfates, oxalates, lactates, malates,

maleates, formates, acetates, succinates, tartrates salicylates, citrates, phenylacetates, benzoates and *p*-toluenesulfonates, as well as salts that provide relatively insoluble products that afford a slow release of the active material, for example a 1,1′ - methylene - bis - (2-hydroxy-3-naphthoate).

The β-adrenergic blocking agents are known from Belgian Patent Number 733390, which also disclosed processes for their preparation.

The following examples illustrate the preparation of the various compositions of the invention.

TABLE I

Ingredients	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
3-morpholino-4-(3-*t*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole	10	10	10	5	5	5
Hydralazine	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
Total (mg./tablet)	280	280	280	200	200	200

3 - morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole, hydralazine, part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

When other β-adrenergic blocking agents such as 3 - chloro - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3-(4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - piperazino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - piperidino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - N - isopropylcarbamoyl - 4 - (3-*t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole, 3 - N - isopropylcarbamoyl - 4-(3 - isopropylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole, 3 - methyl - 4 - (3 - t-butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole, 3 - ethoxy - 4 - (3 - t - butylamino - 2 - hydroxy - propoxy) - 1,2,5 - thiadiazole or representative salt thereof is substituted for 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, there is obtained the corresponding composition.

TABLE II

Ingredients	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
(–)-3-morpholino-4-(3-*t*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate	10	10	10	5	5	5
Hydralazine	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
Total (mg./tablet)	280	280	280	200	200	200

(—) - 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, hydralazine, part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry-milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

When other optically active β-adrenergic blocking agents such as (—) - 3 - chloro - 4-(3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (—)-3-(4-hydroxypiperidino) - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (—) 3 - piperidino) - 4 - (3-t - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate, (—)-3-N-t-butylcarbamoyl - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (—) - 3 - methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (—) - 3 - ethoxy - 4-(3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride or (—)-3-chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole is substituted for -3 - morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, there is obtained the corresponding composition.

TABLE III

Ingredients	Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
(+)-3-morpholino-4-(3-*t*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate	10	10	10	5	5	5
Hydralazine	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
Total (mg./tablet)	280	280	280	200	200	200

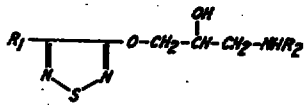
(+) - morpholino - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, hydralazine, part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry-milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

When other optically active β-adrenergic blocking agents such as (+) - 3 - chloro - 4-(3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-(4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - piperidino-4 - (3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-morpholino - 4 - (3 - *t* - butylamino - 2-hydroxpropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - N - *t* - butylcarbamoyl-4 - (3 - t - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - ethoxy - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, or (+) - 3 - chloro - 4 - (3 - *t*-butylamino - 2 - hydroxybutoxy) - 1,2,5 - thiadiazole hydrochloride is substituted for (+)-3 - morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, there is obtained the corresponding composition.

Other oral forms of administration such as capsules and aqueous suspensions or solutions are within the scope of this invention and may be prepared using known techniques.

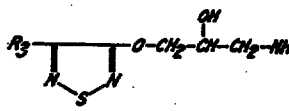
WHAT WE CLAIM IS:—

1. A composition comprising hydralazine or a pharmaceutically acceptable salt thereof and a β-adrenergic blocking agent of the formula:



(including its optically active isomers) or a pharmaceutically acceptable salt thereof, where R_1 is a hydrogen or halogen atom or an alkyl, alkenyl, carbamoyl, alkylcarbamoyl, cycloalkyl, alkoxy, phenyl, aralkyl, alkylthioalkyl, alkoxyalkyl, phenylthioalkyl, phenoxyalkyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, hexahydroazepino, morpholino, piperidino, thiazolidinyl, *p*-thiazinyl or piperazinyl radical, a substituted phenyl or aralkyl radical in which the substituent(s) is or are on the benzene ring and is or are halogen, C_{1-3} alkyl and/or C_{1-3} alkoxy; or a substituted phenylthioalkyl or phenoxyalkyl radical in which the substituent(s) is or are on the phenyl ring and is or are halogen, hydroxy, alkyl and/or alkoxy; and R_2 is an alkyl, alkenyl substituted alkyl in which the substituent(s) is or are hydroxy or halogen, alkynyl, carboxy, alkoxy, alkylthio, di(C_{1-3} alkyl)amino, pyrrolidinyl, piperazinyl, morpholino, thiazolidinyl or thiazinyl radical.

2. A composition as claimed in Claim 1 in which the β-adrenergic blocking agent has the formula:



where R_3 is a hydrogen or halogen atom or an alkyl, alkoxy, morpholino or piperidino radical and R_4 is alkyl; and in which the weight ratio of β-adrenergic blocking agent to hydralazine ranges from 1:1 to 1:10.

3. A composition as claimed in Claim 2 in which R_3 is morpholino, R_4 is *t*-butyl and the combining ratio is 1:10 by weight.

4. A composition as claimed in Claim 3 in which the β-adrenergic blocking agent is 3-morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate.

5. A composition as claimed in Claim 4 in which the 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate is in the (−) isomeric form.

6. A composition as claimed in Claim 4 in which the 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate is in the (+) isomeric form.

7. A composition as claimed in any one of Claims 3—6 in unit dosage form containing 5 mg. of the β-adrenergic blocking agent and 50 mg. of the hydralazine per unit dose.

8. A composition as claimed in any one of Claims 1—7 in the form of a tablet.

9. A composition as claimed in any one of Claims 1—7 in the form of a capsule.

10. A composition as claimed in any one of Claims 1—7 in the form of an aqueous suspension or solution.

11. A method for preparing a composition for potentiating the antihypertensive action of hydralazine by combining with it, for co-administration, a β-adrenergic blocking agent having the formula set forth in claim 1.

12. A method as claimed in claim 11 in which the β-blocking agent has the formula set forth in claim 2.

13. A composition as claimed in claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

14. A method as claimed in claim 11, substantially as hereinbefore described with reference to any one of the foregoing Examples.

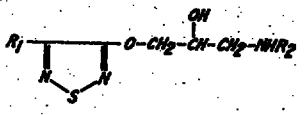
(+) - morpholino - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, hydralazine, part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry-milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

When other optically active β-adrenergic blocking agents such as (+) - 3 - chloro - 4-(3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-(4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - piperidino-4 - (3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-morpholino - 4 - (3 - *t* - butylamino - 2-hydroxpropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - N - *t* - butylcarbamoyl-4 - (3 - t - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride, (+) - 3-methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (+) - 3 - ethoxy - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, or (+) - 3 - chloro - 4 - (3 - *t*-butylamino - 2 - hydroxybutoxy) - 1,2,5 - thiadiazole hydrochloride is substituted for (+)-3 - morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, there is obtained the corresponding composition.

Other oral forms of administration such as capsules and aqueous suspensions or solutions are within the scope of this invention and may be prepared using known techniques.

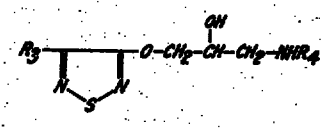
WHAT WE CLAIM IS:—

1. A composition comprising hydralazine or a pharmaceutically acceptable salt thereof and a β-adrenergic blocking agent of the formula:



(including its optically active isomers) or a pharmaceutically acceptable salt thereof, where R_1 is a hydrogen or halogen atom or an alkyl, alkenyl, carbamoyl, alkylcarbamoyl, cycloalkyl, alkoxy, phenyl, aralkyl, alkylthioalkyl, alkoxyalkyl, phenylthioalkyl, phenoxyalkyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, hexahydroazepino, morpholino, piperidino, thiazolidinyl, *p*-thiazinyl or piperazinyl radical, a substituted phenyl or aralkyl radical in which the substituent(s) is or are on the benzene ring and is or are halogen, C_{1-3} alkyl and/or C_{1-3} alkoxy; or a substituted phenylthioalkyl or phenoxyalkyl radical in which the substituent(s) is or are on the phenyl ring and is or are halogen, hydroxy, alkyl and/or alkoxy; and R_2 is an alkyl, alkenyl substituted alkyl in which the substituent(s) is or are hydroxy or halogen, alkynyl, carboxy, alkoxy, alkylthio, di(C_{1-3} alkyl)amino, pyrrolidinyl, piperazinyl, morprolino, thiazolidinyl or thiazinyl radical.

2. A composition as claimed in Claim 1 in which the β-adrenergic blocking agent has the formula:



where R_3 is a hydrogen or halogen atom or an alkyl, alkoxy, morpholino or piperidino radical and R_4 is alkyl; and in which the weight ratio of β-adrenergic blocking agent to hydralazine ranges from 1:1 to 1:10.

3. A composition as claimed in Claim 2 in which R_3 is morpholino, R_4 is *t*-butyl and the combining ratio is 1:10 by weight.

4. A composition as claimed in Claim 3 in which the β-adrenergic blocking agent is 3-morpholino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate.

5. A composition as claimed in Claim 4 in which the 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate is in the (−) isomeric form.

6. A composition as claimed in Claim 4 in which the 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate is in the (+) isomeric form.

7. A composition as claimed in any one of Claims 3—6 in unit dosage form containing 5 mg. of the β-adrenergic blocking agent and 50 mg. of the hydralazine per unit dose.

8. A composition as claimed in any one of Claims 1—7 in the form of a tablet.

9. A composition as claimed in any one of Claims 1—7 in the form of a capsule.

10. A composition as claimed in any one of Claims 1—7 in the form of an aqueous suspension or solution.

11. A method for preparing a composition for potentiating the antihypertensive action of hydralazine by combining with it, for co-administration, a β-adrenergic blocking agent having the formula set forth in claim 1.

12. A method as claimed in claim 11 in which the β-blocking agent has the formula set forth in claim 2.

13. A composition as claimed in claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

14. A method as claimed in claim 11, substantially as hereinbefore described with reference to any one of the foregoing Examples.

* C L M S *

(15)

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