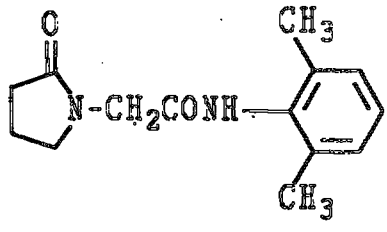
REPLACED SHEETS SG
☑ Description : paged ...1.... to paged ...18.....
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AGENT FOR IMPROVING DEMENTIA

FIELD OF THE INVENTION

This invention relates to an agent for improving dementia which contains N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl) acetamide (hereinafter, referred to as compound A) represented by the following formula (I):



(I)

or a salt thereof as an active ingredient.

BACKGROUND OF THE INVENTION

In developed countries including Japan, United States and European countries, the number of patients with dementia has been rapidly increasing with the sudden increase in aged population. Since there is no effective therapeutics for this disease, it is a serious social problem to treat and attend on these patients. Under these circumstances, a number of drugs have been examined in order to develop an effective remedy for dementia. However, no drug which is clinically usable therefor has been found out hitherto.

On the other hand, it is known that compound A is effective in prolonging the survival time upon a decrease

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in blood oxygen level and in relieving failure of memory due to cerebropathy, as described in JP-B-62-5404 (the term "JP-B" as used herein means an "examined Japanese patent publication") (corresponding to U.S. Patent 4,341,790). However, there has been never reported that the compound A is clinically usable for improving the symptoms of dementia.

SUMMARY OF THE INVENTION

The present inventors have found out that the administration of the compound A to patients with dementia such as Alzheimer type dementia or cerebrovascular dementia causes excellent effects of improving the symptoms of these types of diseases, which had never been expected from the conventional therapeutics, thus completing the present invention.

The present invention relates to an agent for improving dementia which contains compound A or a salt thereof as an active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

Demetia relating to the present invention can be mainly classified into Alzheimer type dementia and cerebrovascular demetia. Alzheimer type dementia may be classified into senile dementia and Alzheimer type disease. It is expected that compound A exerts excellent effects on these diseases.

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The compound A may be administered either orally or parenterally (for example, intravenously) in a dose of from 60 to 900 mg/day per adult (in the case of oral administration). Examples of preparations containing compound A include tablets, capsules, pills, emulsions, suspensions, fine subtilaes and injection. These preparations may be formulated by a known pharmaceutical techniques with the use of common additives (for example, fillers, binders (hydroxypropylcellulose, etc.), ingredient (lactose, cornstarch, etc.).

The compound A has a high safety. When orally administered to male and female mice, it showed acute toxicities (LD_{50}) of 2,005 mg/kg and 1,940 mg/kg, respectively. Thus it has been clinically confirmed that compound A is highly safe.

The compound A is highly effective in improving a decline in mental functions such as disorientation (place, time), which are the major symptoms of dementia, as well as general side symptoms such as decreased spontaneity, emotional disturbances, contact disturbances, abnormal behaviors, disturbances in activity of daily living and motivation. Accordingly, the compound A is a very excellent agent for improving dementia.

The present invention is further explained in detail hereinafter by the following Examples, but the

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present invention is not limited to these examples.

EXAMPLE 1

300 mg/day of compound A was orally administered for 8 to 12 weeks to 5 patients (excepting cerebrovascular dementia based on Hachinski cerebro-ischemic score) who showed encephalatrophy or ventricular enlargement in CT (computed tomography) or MRI (magnetic resonance image) and thus were diagnosed as Alzheimer type dementia based on clinical symptoms specified in DSM-III-R (Handbook for the Diagnosis of Mental Diseases prepared by U.S. Society of Psychopathy). Before the administration and 4 weeks, 8 weeks and 12 weeks thereafter, the dementia conditions of these patients were clinically evaluated by typical methods for evaluating dementia, namely, classification of severity by fast staging (hereinafter, referred to simply as Fast), criteria for evaluating cognitive functions (modified GBS), mini-mental state examination (hereinafter, referred to simply as MMS), Hasegawa's simplified dementia scale (hereinafter, referred to simply as HDS) and Crichton's criteria for evaluating behaviors. Based on the data thus obtained, the final global improvement rate (hereinafter, referred to simply as FGIR) and the overall safety rate (hereinafter, referred to simply as OSR) of each case were evaluated.

Table 1 shows the results of FGIR and OSR, while

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Table 2 shows the number of improved or worsened patients for each symptom. Tables 3 and 4 show each a patient showing improvement in FGIR.

Table 1

Evaluation	No. of Case	I	II	III	IV	V	VI
FGIR	5		2		2		1
OSR	5	5					

[FGIR] I: remarkably improved.
II: improved.
III: slightly improved.
IV: unchanged.
V: slightly aggravated.
VI: aggravated.

[OSR] I: no safety problems.
II: negligible safety problems existed.
III: safety problems existed.
IV: significant safety problems existed.

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Table 2

Improved or Worsened Item (symptom)

	No. of Case	Improved	Worsened
Decreased spontaneity	5	2	0
Emotional disturbance	5	2	1
Contact disturbance	5	2	0
Decline in mental function	5	2	0
Abnormal behaviors	5	1	1
Disturbance in activity of daily living	5	1	1

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Table 3

List of Alzheimer type dementia symptoms

Sex/Age	Dose/Time	Complication/ Suffering Period/CT/MRI	Pretreatment/ Combined Drug	FAST/Hachinski Cerebro-ischemic Score/MMS/ Hasegawa's Scale	FGIR/OSR
Female/80	300 mg/12 weeks	iron-deficiency anemia/ 2 years/encephalatrophy: slight, and ventricular enlargement: moderate	no/no	5/1/(11)/13.0	improved/ no safety problem

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Table 3 (cont'd)

	Evaluation of Cognitive Function						
	Improvement			Severity			
	4 week	8 week	12 week	(pre	4 week	8 week	12 week)
FAST				(5	4	4	4)
**							
Orientation:							
space	III	III	III	(2	1	1	1)
time	III	III	III	(4	3	3	3)
Memory:							
private information before outbreak	IV	IV	IV	(3	3	3	3)
private information after outbreak	IV	IV	IV	(3	3	3	3)
Motivation:							
endogenous motivation	III	II	II	(3	2	1	1)
exogenous motivation	III	III	III	(3	2	2	2)
Consideration:							
suitability of judgement	III	III	III	(2	1	1	1)
development of conversation	IV	IV	IV	(3	3	3	3)
Emotion:							
variation of emotional expression	IV	IV	IV	(1	1	1	1)
self-suppression of emotional expression	III	III	III	(2	1	1	1)
Communication:							
precision of speaking	III	III	III	(3	2	2	2)
rationality of speaking	IV	IV	IV	(1	1	1	1)

	Pre		4 week		8 week		12 week
MMS	11	→	14	→	15	→	16
HDS	13.0	→	14.5	→	15.5	→	17.5

**: Degree of disorientation II: improved. III: slightly improved. IV: unchanged.

Table 3 (cont'd)

Crichton's Criteria for Behavior (modified) No.*	Change Pre		12 Weeks	Side Effect/ Abnormal Clinical Data	Comment
1.	1	→	1	no/no	Getting to be able to handle a gas water heater.
2.	3	→	2		
3.	2	→	2		Making purchases with a memo note, as previously, but never purchasing any unnecessary goods.
4.	3	→	2		
5.	2	→	1		Frankly stating her opinion. → Sometimes boycotting the test (refusing writing sentences in MM, "I'm weak in writing").
6.	2	→	2		
7.	2	→	1		The medicine of the invention was administered from the first examination, after confirming her husband that she had been in the same conditions for past 2 to 4 weeks. Although no change was shown in HDS or MMS score, IADL suggested obvious improvement. Improvement in these points can be hardly evaluated by the methods employed here.
8.	1	→	1		
9.	1	→	1		
10.	2	→	1		
11.	1	→	1		

*: 1: walking. 2: orientation. 3: conversation. 4: interpersonal contact. 5: unrest. 6: changing clothes. 7: eating. 8: incontinence. 9: sleeping. 10: objective mood. 11: subjective mood.

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Table 4

List of Alzheimer type dementia symptoms

Sex/Age	Dose/Time	Complication/ Suffering Period/CT/MRI	Pretreatment/ Combined Drug	FAST/Hachinski Cerebro-ischemic Score/MMS/ Hasegawa's Scale	FGIR/OSR
Female/73	300 mg/9 weeks	hepatic function disorder/3 years/ encephalatrophy: slight, and ventricular enlargement: slight	Elen (Trade Mark, Indeloxazine Hydrochloride) (3T)/no	5/4/18/15.5	improved/ no safety problem

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Table 4 (cont'd)

	Evaluation of Cognitive Function						
	Improvement			Severity			
	4 week	8 week	12 week	(pre	4 week	8 week	12 week)
FAST				(5		5	)
**							
Orientation:							
space	IV	IV		(2	2	2	)
time	IV	IV		(4	4	4	)
Memory:							
private information before outbreak	IV	IV		(3	3	3	)
private information after outbreak	IV	IV		(3	3	3	)
Motivation:							
endogenous motivation	III	III		(3	2	2	)
exogenous motivation	II	II		(3	1	1	)
Consideration:							
suitability of judgement	IV	IV		(1	1	1	)
development of conversation	II	II		(3	1	1	)
Emotion:							
variation of emotional expression	III	III		(3	2	2	)
self-suppression of emotional expression	IV	IV		(2	2	2	)
Communication:							
precision of speaking	IV	IV		(2	2	2	)
rationality of speaking	IV	IV		(1	1	1	)

	Pre		8 week
MMS	18	→	21
HDS	15.5	→	18.5

**: Degree of disorientation II: improved. III: slightly improved. IV: unchanged.

Table 4 (cont'd)

No.*	Crichton's Criteria for Behavior (modified) Change Pre		12 Weeks	Side Effect/ Abnormal Clinical Data	Comment
1.	1	→	1	no/no	Beginning to give lessons in penmanship to grandchildren spontaneously (feeling tired before the administration).
2.	3	→	3		
3.	2	→	2		HDS and MMS show little change.
4.	2	→	1		Moderate improvement was observed even in a drug-rest period between 4 and 8 weeks.
5.	1	→	1		
6.	1	→	1		In this case, spontaneousness and positiveness were remarkably improved.
7.	1	→	1		
8.	1	→	1		No examination was made after 9 week. Having no contact with her family, it seems that the disorders in behaviors have never been worsened.
9.	1	→	1		
10.	2	→	1		
11.	2	→	1		

*: 1: walking. 2: orientation. 3: conversation. 4: interpersonal contact. 5: unrest. 6: changing clothes. 7: eating. 8: incontinence. 9: sleeping. 10: objective mood. 11: subjective mood.

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As the above Tables clearly show, compound A is effective in improving mental symptoms (for example, decreased spontaneity, emotional disturbances, contact disturbances, decline in mental functions, abnormal behaviors) of patients with Alzheimer type dementia. Evaluating the improvement effect on these symptoms, the overall improvement rate of compound A is 40% (2 (improvement case) per 5 all tried case). Also, as apparently from the Table 1, the mental symptoms of 2 cases per 5 cases were not worsened. Furthermore, any side effect was not observed for all tried patients.

Generally, a main characteristic points of patients with Alzheimer type dementia is just that the symptoms of this disease become worse and worse, and any medicines have never showed clinical effects to this disease.

Therefore, these clinical effect of compound A to Alzheimer type dementia, that is, the improvement effect on the symptoms, the suppresing effect on getting worse relating to the symptoms and the effect relating to the safety have never been expected from the clinical effect of convertional medicines for this disease.

EXAMPLE 2

150 to 450 mg/day of compound A was orally administered for 8 weeks to 145 patients with cerebro-

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vascular dementia who showed infarction or hemorrhagic lesions in CT (computed tomography) and scored less than 22 points in Hasegawa's simplified dementia scale (HDS) frequently employed in the simplified diagnosis for dementia. The clinical conditions of each patient were evaluated with HDS, which is frequently used for evaluating the effects of nootropic agents, before the initiation of the administration and 4 weeks and 8 weeks thereafter. Based on these data, the final global improvement rate (FGIR) and the overall safety rate (OSR) were determined.

Table 1 shows the results of FGIR and OSR, while Table 2 shows the improvement rate (%) for each symptom.

Table 1

	No. of Case	I	II	III	IV	V	DP	
FGIR	145	7	37	57	33	5	6	72.7 [improvement rate (%)*]
OSR	145	134	8	3	0	-	0	97.9 [safety rate (%)**]

*: improvement rate = (I + II + III)/139 × 100

**: safety rate = (I + II)/145 × 100

[FGIR] I: remarkably improved. II: moderately improved.
III: slightly improved. IV: unchanged.
V: aggravated. DP: dropped out.

[OSR] I: no safety problem.
II: negligible safety problems existed.

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III: doubtful in safety.

IV: safety problems existed.

Table 2

Symptom	No. of Case	Improved (%)	Worsened (%)
Decreased spontaneity	138	59.4	0.0
Emotional disturbance	135	54.1	1.5
Contact disturbance	122	38.5	0.8
Decline in mental function	139	46.0	2.2
Abnormal behaviors	49	49.0	10.2

As the above Tables clearly show, compound A is effective in improving mental symptoms (for example, decreased spontaneity, emotional disturbances, contact disturbances, decline in mental functions, abnormal behaviors) of patients with cerebrovascular dementia. The overall improvement rate determined by generally evaluating these results in 72.7%, showing excellent effects.

In general, it is considered that the effects of medicinal treatments on cerebrovascular dementia are inferior to those on sequela of cerebrovascular disorders, namely, the preceding stage of the former. However, compound A achieves a high overall improvement rate (72.7%) for cerebrovascular dementia which is comparable to, or even exceeds, the overall improvement rate (about 70%) of conventional nootropic agent for the sequela of cerebrovascular disorders.

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Further, it is doubtful whether or not medicinal treatments are effective on the decline in mental function, i.e., the major symptom of dementia. The overall improvement rate of compound A on this symptom is 46% which is higher than those of pracebo (25%) and other nootropic agent (about 35%).

On the other hand, it has been confirmed that compound A is highly safe (OSR = 97.9%) and only fugitive side effects were observed in 4 cases (3%).

These results indicate that compound A is highly superior in the effects of improving cerebrovascular dementia to drugs conventionally employed therefor.

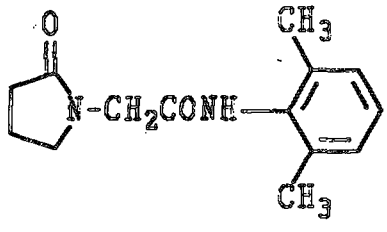
While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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WHAT IS CLAIMED IS:

1. An agent for improving dementia containing N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide represented by the formula (I):



(I)

or a salt thereof as an active ingredient.

2. An agent as claimed in claim 1, wherein dementia is Alzheimer's dementia.

3. An agent as claimed in claim 1, wherein dementia is celebrovascular dementia.

4. An agent for improving a decline in mental functions containing N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide.

5. An agent as claimed in claim 4, wherein decline in mental functions is a disorientation.

6. An agent for improving symptoms of dementia containing N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolodinyl)acetamide.

* C L M S *

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