Department of Pharmacy[1], Nursing Department[2], Department of Psychiatric Neurology, Ogaki Municipal Hospital[3], Laboratory of Drug Informatics, Gifu Pharmaceutical University[4], Gifu, Japan

Intervention of dementia support team pharmacists and its effects for the proper use of rivastigmine

K. Mori[1], M. Yoshida[2], K. Tomita[3], M. Nakamura[4], T. Yoshimura[1]

Received April 17, 2021, accepted May 21, 2021

**Corresponding author: Koki Mori, Department of Pharmacy, Ogaki Municipal Hospital, 4-86 Minaminokawa-cho, Ogaki-shi, Gifu 503-8502, Japan*
forest_kouki @yahoo.co.jp

Pharmazie 76: 334-337 (2021) *doi: 10.1691/ph.2021.1534*

Pharmacist participation in the medical team is expected in dementia care. We investigated the use of rivastigmine, the intervention of pharmacists for its proper use, and its effects. The number of prescription proposals from the dementia care team pharmacist to the doctor was 87, and the number of acceptances was 57. The content of the proposal was 31/52 for additions/changes (number of acceptances/number of proposals), 21/28 for dose increase, 3/4 for discontinuation of administration, 2/2 for usage changes, and 1/1 for others. In increasing the dose, the number of patients who increased the maintenance dose to 18 mg was significantly higher in the group with the intervention of the pharmacist in the dementia care team than in the group without the intervention (3/12 cases vs. 0/24 cases, $p = 0.031$). The dose of the brought-in drug also significantly increased with pharmacist intervention compared with that in the non-intervention group (7/12 cases vs. 1/24 cases, $p < 0.001$). The pharmacists of the dementia care team often intervened in the proper use of rivastigmine, which was found to be effective when increasing the dose. Thus, we believe that the active participation of pharmacists is necessary in dementia medication.

1. Introduction

It has been reported that 15% of people aged 65 years and over have dementia in Japan (Ninomiya et al. 2020). The prevalence of the disease increases with age; therefore, it is necessary to expand medical care, welfare, and community support for those with dementia. Patients with dementia often show behavioral and psychological symptoms (BPSD) due to changes in their living environment associated with hospitalization. Since BPSD is a burden on patients and the medical staff (Cerejeira et al. 2012; Matsumoto et al. 2007), intervention by the medical care team is necessary.

The Ogaki Municipal Hospital has set up a dementia support team (DST), which conducts rounds with allied health professions. Pharmacists, physiotherapists, occupational therapists, speech therapists, and nutritionists, among others, are part of this team. The participation of pharmacists in the treatment of dementia has been reported in other institutions as well (Gustafsson et al. 2017; Pfister et al. 2017). We believe that the pharmacist intervention in DST is of great importance in optimizing drug treatment.

Four types of drug treatments (donepezil, galantamine, rivastigmine, and memantine) can be used for patients with Alzheimer's disease (AD), and all of them are effective (di Santo et al. 2013). Among them, rivastigmine is formulated as a patch which can be administered to patients who cannot take it orally. It has few side effects (Nakamura et al. 2011) and an appetite-promoting impact (Oh et al. 2015). Additionally, it is hydrolyzed by esterase and not metabolized by cytochrome P450 (CYP) (Khoury et al. 2018), and it is a highly versatile drug with little need to change the dose according to the conditions. Rivastigmine can be expected to affect cognitive function (Nakamura et al. 2011) and appetite (Oh et al. 2015) when the dose is increased gradually, up to 18 mg. However, the administration of 9 mg is not significantly different from that of a placebo (Nakamura et al. 2011). In clinical practice, there are many cases in which the dose of rivastigmine has not been increased to 18 mg (Kröger et al. 2010), and intervention for its proper use is required.

This study investigates the intervention content of a pharmacist who participates in DST (DST pharmacist), and its effect on AD patients who used rivastigmine.

2. Investigations and results

2.1. Suggestions by DST pharmacists for patients using rivastigmine

Table 1 shows the suggestions made by pharmacists related to rivastigmine in the DST round. The total number of proposals was 87, and the number of acceptances was 58 (acceptance rate 66.7%). For each item, the additions and changes were 31/52 cases (59.6%) (accepted cases/proposed cases), the dose increase was 21/28 cases (75.0%), and the administration discontinuation was 3/4 cases (75.0%). The usage change was 2/2 cases (100.0%), and the others were 1/1 case (100.0%). The specific contents of the proposal are as follows: Regarding additions and changes, 43 cases were added to untreated cases with a diagnosis of AD, 5 cases were the resumption of brought-in drugs, and 4 cases were switched from other anti-dementia drugs because oral administration became impossible.

Regarding the dose increase, there were 28 proposals to increase the dose according to the method of use. The administration was discontinued in 2 cases of worsening condition, 1 case of side effects (irritability), and 1 case of difficulty in continuing due to hospital transfer. There were two usage changes according to the compliance. In other cases, the dose increased in a short term, alerting to gastrointestinal symptoms.

2.2. Rivastigmine dose at admission

Figure 1 shows the current state of rivastigmine dose at admission. Of the 151 patients who received rivastigmine at admission, 75 were included, and 76 were low-dose for less than 4 weeks. The doses of the target patients were 4.5 mg in 7 patients (9.3%), 9 mg in 27 patients (36.0%), 13.5 mg in 6 patients (8.0%), and 18 mg in

Table 1: Suggestions by DST pharmacists for patients using rivastigmine

	Number of proposals	Number of accept	Acceptance rate
Total	87	58	66.7%
Items			
Addition/change	52	31	59.6%
Dose increase	28	21	75.0%
Administration discontinuation	4	3	75.0%
Usage change	2	2	100.0%
Others	1	1	100.0%

35 patients (46.7%) (Fig. 1). Of the 40 low-dose patients, 5 (12.5%) were confirmed by a doctor, and 8 (20.0%) were confirmed by a pharmacist.

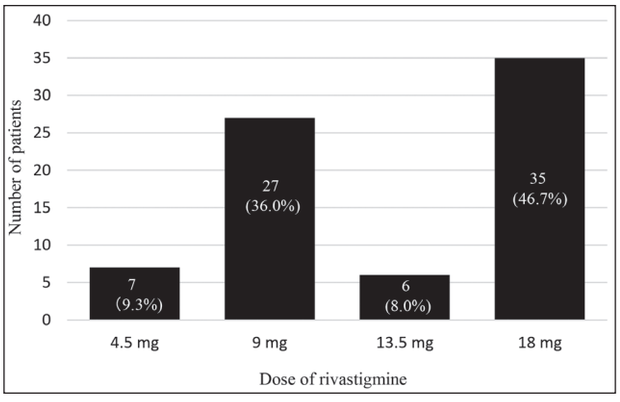

Fig. 1: The current state of rivastigmine dose at admission. Numbers in in the graph show: number of patients (rate %)

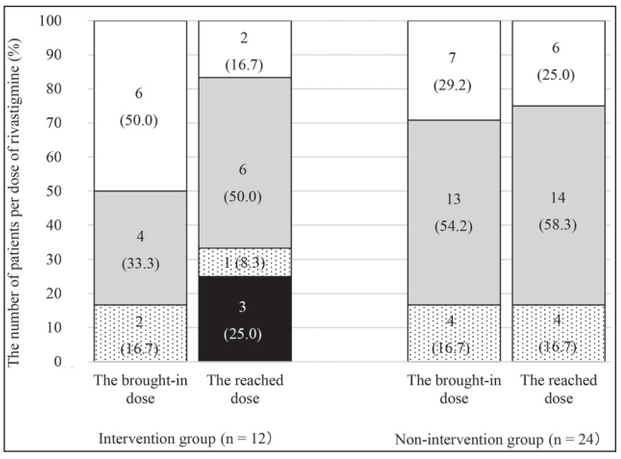

Fig. 2: The number of patients per brought-in dose and reached dose of rivastigmine. Numbers in in the graph show: number of patients (rate %)
18 mg 13.5 mg 9 mg 4.5 mg

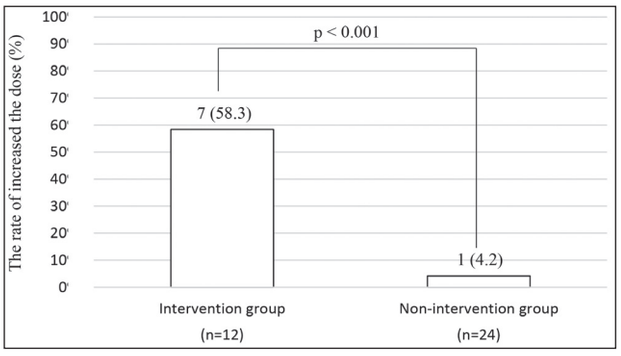

Fig. 3: The rate of increased the reached dose of rivastigmine form the brought dose. Numbers in in the graph show: number of patients (rate %)

2. 3. Effect of DST pharmacist intervention on rivastigmine dose increase

Table 2 presents the patient's background. There were 36 patients, 12 in the DST pharmacist intervention group and 24 in the non-intervention group. In terms of patient background, there was no significant difference between the intervention and non-intervention groups regarding age and sex. Moreover, no serious side effects of rivastigmine were observed in any of the patients.

The brought-in dose and the reached dose in the intervention group and in the non-intervention group are shown in Fig. 2. Three patients in the intervention group were able to reach 18 mg, but none in the non-intervention group managed to do so ($p = 0.031$). Moreover, the number of patients who were able to increase the reached dose compared to the brought-in dose was significantly higher in the intervention group (7/12 cases; 58.3%) than in the non-intervention group (1/24 cases; 4.2%) ($p < 0.001$) (Fig. 3).

3. Discussion

This study examined the intervention of DST pharmacists and its effects on the proper use of rivastigmine. Interventions for the appropriate prescription of rivastigmine by DST pharmacists ranged from addition/change of rivastigmine, dose increase, discontinuation of administration, and change of usage, depending on the patient's condition. It was shown that the maintenance dose of rivastigmine could be increased by the intervention of a DST pharmacist.

Most interventions by DST pharmacists were additions and resumptions. There are many cases in which treatment is not performed despite the diagnosis of AD (Hessmann et al. 2018). It is reported that pharmacist intervention in patients with dementia improves drug therapy (Hessmann et al. 2018; Nguyen et al. 2019); the results of this study are similar. We also proposed changing the patch to rivastigmine for patients who have difficulty taking it, and we were able to perform interventions considering the route of administration. There were many proposals for a dose increase, and the acceptance rate was higher than that for addition/resumption. This aspect was thought to be the result of interventions related to proper use. Other interventions were made according to the patient's condition, such as administration discontinuation, usage change, and side effect management. This intervention was considered because the pharmacist participated in the DST and fully understood the current situation.

In a survey of rivastigmine maintenance doses in hospitalized patients, 18 mg cases were 46.7%, which was less than half the total number. Patients who had received low doses for four weeks or more needed to increase the dose, but it was not done. It is presumed that this situation was due to factors such as prescriptions by non-specialists when hospitalized, changes in doctors, and difficulty in grasping symptoms and start dates. Furthermore, 12.5% of low-dose patients were confirmed by doctors, and 20% were confirmed by pharmacists. The fact that doctors and pharmacists were not aware of the need to increase the dose of rivastigmine is also considered to be a factor in low-dose administration.

As a result of the DST pharmacist intervention, the number of patients with a reached dose of 18 mg rivastigmine increased, and the carry-on dose could also be increased. With pharmacist intervention, it is possible to increase the dose by determining the prescription date of rivastigmine and proposing an appropriate schedule that enables the renewed dose. Since rivastigmine is

Table 2: Characteristics of patients in the study effect of DST pharmacist intervention

Characteristic	Intervention group (n=12)		Non-intervention group (n=24)		p value	
Age (yaers)	83	[79–89]	83	[80–87]	0.507	a)
Sex					0.238	b)
Mele	8	(66.7)	11	(45.8)		
Female	4	(33.3)	13	(54.2)		
Height (cm)	155.0	[149.0–160.0]	154.0	[145.6–158.0]	0.595	a)
Weight (kg)	49.0	[41.0–61.3]	44.4	[39.7–51.0]	0.660	a)
Body Mass Index (kg/m^2)	21.1	[16.0–24.2]	20	[18.4–21.2]	0.379	a)
The duration of the hospital stay						
Days of hospitalization	25.0	[17.3–42.5]	21.0	[10.8–30.0]	0.312	a)
Patients hospitalized for 4 weeks or more	5	(41.7)	7	(58.3)	0.479	b)
Severe side effects due to ribastigmin	0	(0.0)	0	(0.0)		
Concomitant medications						
Number of drugs	4	[1–6]	5	[3-7]	0.297	b)
Patients with 6 or more drugs	3	(25.0)	9	(37.5)	0.509	a)
Dietary intake						
Immediately after admission (%)	29.2	[0.0–62.4]	25	[0.0–55.6]	0.724	a)
Immediately before discharge (%)	54.1	[33.1–80.4]	64.1	[28.8–92.5]	0.802	a)

The number of patients (%) or median [interquartile range]

a) Mann-Whitney's U test, b) Fisher's exact test

effective when increased to 18 mg (Nakamura et al. 2011), we believe that the intervention of a DST pharmacist could actively contribute to the treatment of dementia. As our facility is an acute care hospital, few patients are hospitalized for four weeks or more. The median length of hospital stay was less than four weeks in both the intervention group (25 days) and the non-intervention group (21 days). However, utilizing the information on the medicines brought-in, such as the medicine notebook and the letter of introduction, the exact start date can be determined. The dose of rivastigmine can be increased even with a short hospital stay.

Further, in the intervention group, many cases were confirmed in which the dose of the brought-in drug could be increased even if it did not reach 18 mg. In acute care hospitals with short hospital stays, the dose of rivastigmine cannot be increased to 18 mg and the patients is often discharged. However, increasing the dose will be the first step to reach 18 mg.

Regarding safety, no side effects that made it difficult to continue treatment with rivastigmine were confirmed in any of the patients. The side effects of rivastigmine are reported to occur in approximately 73% of cases. Although there are reports that gastrointestinal symptoms are dose-dependent (Farlow et al. 2013; Nguyen et al. 2019), most of the side effects are cutaneous symptoms, and gastrointestinal symptoms are less than 10% (Nakamura et al. 2011). Therefore, the incidence of side effects is not high, even if the dose is increased in patients who continue to receive rivastigmine. In Japan, products with modified base materials containing liquid paraffin are sold. Liquid paraffin may reduce skin disorders (Patzelt et al. 2012) and reduce the discontinuation rate. Therefore, this study considered that the dose could be increased without severe side effects. Additionally, there was no significant difference in food intake between those in the intervention group and in the non-intervention group. Consequently, there were no gastrointestinal symptoms such as loss of appetite due to increased dose, and the dose could be safely increased.

The first limitation of this study was that it was impossible to evaluate the therapeutic effect of increasing the dose of rivastigmine. It is necessary to assess the impact of nootropics using cognitive function tests, such as the Hasegawa Dementia Scale and the Mini-Mental State Examination (MMSE). However, this retrospective study could not be evaluated. Second, there were few patients who were hospitalized for four weeks or longer, and it is possible that the evaluation items have not been assessed correctly. As indicated earlier, it is necessary to administer the drug for four weeks or more to increase the dose. Finally, because this was a retrospective study of a small number of single institutions, similar results may not be obtained at other medical institutions. Therefore, we hope that prospective studies with an increased number of cases, such as multicenter joint studies, will be conducted in the future.

Even with short hospital stays in acute care hospitals, pharmacists in the dementia care team can contribute significantly to the proper use and introduction of rivastigmine. With the diversification of drug treatment, the significance of pharmacists in the medical care team is high, and we believe that their active participation in DST is also necessary.

4. Experimental

4.1. Subjects and methods

4.1.1. Suggestions by DST pharmacists for patients using rivastigmine

The number and content of proposals by DST pharmacists to patients indicated for rivastigmine from October 2018 to May 2020, and who used the medication, were tabulated. The content of the proposals was classified into "addition/change," "dose increase," "administration discontinuation," "usage change," and "others,"; the number of proposals, the number of acceptances, and the acceptance rate of each item were investigated. Furthermore, the reasons for intervention were examined for each of the five items.

4.1.2. Rivastigmine dose at admission

We retrospectively investigated the maintenance dose of inpatients who received rivastigmine between November 2015 and September 2018. For adults, rivastigmine is usually started at 4.5 mg or 9 mg once daily. As a general rule, the dose is increased every four weeks, and the maintenance dose is 18 mg once daily. Therefore, the latest dose of the target patient was investigated, and if 18 mg was prescribed, 18 mg was set as the maintenance dose. If the dose did not reach 18 mg and was administered at the same dose for longer than four weeks, it was used as the maintenance dose. For patients receiving doses less than 18 mg (low doses), the presence or absence of confirmation by doctors and pharmacists regarding the low-dose administration was investigated. The confirmation by the doctor was the presence or absence of the low-dose and side effects in the medical records, and the confirmation of the pharmacist was the presence or absence of the dose in the pharmacist record.

4.1.3. Effect of DST pharmacist intervention on rivastigmine dose increase

Patients admitted to Ogaki Municipal Hospital from October 2018 to May 2020, who continued to receive rivastigmine and underwent DST intervention, were included in the study. Patients who had received one DST pharmacist intervention were classified into the intervention group, while the other patients were placed in the non-intervention group. Patients who had already received 18 mg of rivastigmine were excluded. The final dose of rivastigmine administered during hospitalization (reached dose) was investigated as the primary endpoint. A comparison of the number of patients with a reached dose of 18 mg was done between the intervention group and the non-in-

tervention group. As a secondary endpoint, the dose of rivastigmine brought-in drug (brought-in dose) was investigated. The number of patients whose reached dose could be increased from the brought-in dose was compared between the two groups. The patient background included age, sex, height, weight, body mass index (BMI), and the duration of the hospital stay (days of hospitalization, number of patients hospitalized for four weeks or more). Further, severe side effects due to rivastigmine, concomitant medications (number of drugs, number of patients with six or more drugs), and dietary intake (immediately after admission, immediately before discharge) were retrospectively investigated using electronic medical records.

4.2. Statistical analysis

The differences in continuous data were compared using the Mann–Whitney U test, and differences in categorical data were compared using Fisher's exact test. In all statistical analyses, statistical significance was set at $p<0.05$. All statistical analyses were performed using the EZR commercial software. (Saitama Medical Center, Jichi Medicine University, http://www.jichi.ac.jp/saitamasct/SaitamaHP.files/statmedEN.-html),which is a graphical user interface for R (R Foundation for Statistical Computing, version 2.13.0).

4.3. Ethical considerations

This study was approved by the Institutional Review Board of Ogaki Municipal Hospital.

Conflicts of interest: None of the authors have a conflict of interest to declare.

References

Cerejeira J, Lagarto L, Mukaetova-Ladinska EB (2012) Behavioral and psychological symptoms of dementia. Frontiers Neurol 3: 1–21.

Di Santo SG, Prinelli F, Adorni F, Caltagirone C, Musicco M (2013) A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J Alzheimer's Dis 35: 349–361.

Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M (2013) A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. CNS Neurosci Ther 19: 745–752.

Gustafsson M, Sjölander M, Pfister B, Jonsson J, Schneede J, Lövheim H (2017) Pharmacist participation in hospital ward teams and hospital readmission rates among people with dementia: A randomized controlled trial. Eur J Clin Pharmacol 73: 827–835.

Hessmann P, Dodel R, Baum E, Müller MJ, Paschke G, Kis B, Zeidler J, Klora M, Reese J-P, Balzer-Geldsetzer M (2018) Use of antidementia drugs in German patients with Alzheimer's disease. Int Clin Psychopharmacol 33: 103–110.

Khoury R, Rajamanickam J, Grossberg GT (2018) An update on the safety of current therapies for Alzheimer's disease: Focus on rivastigmine. Ther Adv Drug Safety 9: 171–178.

Kröger E, van Marum R, Souverein P, Egberts T (2010) Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: A retrospective cohort study. Drugs Aging 27: 663–675.

Matsumoto N, Ikeda M, Fukuhara R, Shinagawa S, Ishikawa T, Mori T, Toyota Y, Matsumoto T, Adachi H, Hirono N, Tanabe H (2007) Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. Dementia Geriatr Cogn Disord 23: 219–224.

Nakamura Y, Imai Y, Shigeta M, Graf A, Shirahase T, Kim H, Fujii A, Mori J, Homma A (2011) A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. Dementia Geriatr Cognit Disord Extra 1: 163–179.

Nguyen TA, Gilmartin-Thomas J, Tan ECK, Kalisch-Ellett L, Eshetie T, Gillam M, Reeve E (2019) The impact of pharmacist interventions on quality use of medicines, quality of life, and health outcomes in people with dementia and/or cognitive impairment: A systematic review. J Alzheimer's Dis 71: 89–96.

Ninomiya T, Nakaji S, Maeda T, Yamada M, Mimura M, Nakashima K, Mori T, Takebayashi M, Ohara T, Hata J, Kokubo Y, Uchida K, Taki Y, Kumagai S, Yonemoto K, Yoshida H, Muto K, Momozawa Y, Akiyama M, Kubo M, Ikeda M, Kanba S, Kiyohara Y (2020) Study design and baseline characteristics of a population-based prospective cohort study of dementia in Japan: The Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD). Environ Health Prev Med 25: 64–75.

Oh Y-S, Kim J-S, Lee PH (2015) Effect of rivastigmine on behavioral and psychiatric symptoms of Parkinson's disease dementia. J Movement Disord 8: 98–102.

Patzelt A, Lademann J, Richter H, Darvin ME, Schanzer S, Thiede G, Sterry W, Vergou T, Hauser M (2012) In vivo investigations on the penetration of various oils and their influence on the skin barrier. Skin Res Technol 18: 364–369.

Pfister B, Jonsson J, Gustafsson M (2017) Drug-related problems and medication reviews among old people with dementia. BMC Pharmacol Toxicol 18: 52–62.