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ORIGINAL ARTICLE

Adverse effects of anticholinergic activity on cognitive functions in Alzheimer's disease

Kimiko KONISHI,[1–3] Koji HORI,[2–4] Hiroyuki UCHIDA,[4] Koichiro WATANABE,[4] Itaru TOMINAGA,[5] Masaki KIMURA,[3] Makoto HOSOYAMADA,[3] Toshiaki SHIBASAKI,[3] Akira KATAOKA[6] and Mitsugu HACHISU[7]

[1]Tokyo Metropolitan Tobu Medical Center for Persons with Developmental/Multiple Disabilities, Tokyo, [3]Department of Pharmacotherapy, Faculty of Pharmacy, Keio University, Tokyo, [4]Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, [2]Department of Psychiatry, Showa University Northern Yokohama Hospital, Kanagawa, and [5]Department of Psychiatry, National Shimofusa Hospital, Chiba, Japan, [6]Department of Internal Medicine, Kyoyoka Kagamido Hospital, Chiba Japan, [7]Department of Clinical Psychopharmacy, School of Pharmaceutical Sciences, Showa University, Tokyo

Correspondence: Associate Professor Koji Hori MD PhD, Department of Psychiatry, Showa University Northern Yokohama Hospital, 35-1 Chigasakichuo, Tsuzukiku, Yokohama-City, Kanagawa 224-8503, Japan. Email: kojihori@showa-university-fujigaoka.gr.jp

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Abstract

Background: Elderly patients with Alzheimer's disease (AD) take more medicines, other than those for anti-dementia agents, than healthy people and are sensitive to anticholinergic medications. There are only a few reports, however, on the relationship between cognitive function and anticholinergic activity in AD patients, which is caused by taking prescribed medication.

Methods: We measured serum anticholinergic activity (SAA) in 76 AD patients referred to a Psychogeriatric Unit and separated them into SAA positive group ($n = 26$, SAA (+) group) and SAA negative group ($n = 50$, SAA (–) group). The difference in demographic data and cognitive functions were compared between the two groups.

Results and Conclusions: The total scores of the Mini-Mental State Examination (MMSE), the score of MMSE domain of registration and recall were significantly lower ($P < 0.05$) and the Functional Assessment Staging (FAST) score, the number of different kinds of prescribed psychotropic medications (the number of prescribed psychotropic medications) were significantly higher ($P < 0.05$) in the SAA (+) group than in the SAA (–). These results suggest that a higher number of psychotropic medications prescribed leads to a tendency for SAA to be positive and that anticholinergic activity accelerates Alzheimer's pathology and decreases cognitive function, especially memory in AD patients. We should more prudently prescribe psychotropic medications to AD patients, because the prescribed psychotropic medications are one of the important causes of decline in cognitive function of AD patients by way of anticholinergic activity.

INTRODUCTION

Since Tune and Coyle developed the radioreceptor assay method to evaluate serum anticholinergic activity (SAA),[1] SAA has been measured in patients taking medication; especially psychotropic medications, and SAA has been thought to be a cumulative effect of multiple medications and also their metabolites.[2] Elderly patients, especially those with Alzheimer's disease (AD), tend to take more medication than healthy people[3,4] and SAA was thought to be found in some elderly people taking medication.[5] Furthermore, demented patients with lowering central cholinergic activity have more sensitivity to anticholinergic agents than subjects with normal cognition.[6,7] Therefore, some patients with AD show positive SAA even at the first visit at a psychogeriatric hospital, before treatment and anticholinergic activity can influence cognitive functions and disease severity. There are only a few reports, however, on the relationship between cognitive functions and SAA in AD patients at the first visit to a psychogeriatric hospital. Therefore, we examined SAA in AD patients at the first visit to our

hospital, National Shimofusa Hospital (Chiba, Japan), and evaluated the relationships between SAA and cognitive functions.

Patients and methods

Seventy-six patients with AD who regularly visited the National Shimofusa Hospital from 1 May 2003 to 31 March 2005 because of behavioral symptoms (psychiatric symptoms) were enrolled in the present study. All subjects met the diagnostic criteria for probable AD developed by a working group of the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association.[8] The patients diagnosed with other psychiatric disorders before the onset of dementia, such as drug abuse, and those with cerebral hemorrhage or infarction were excluded from the study. We also excluded patients with an active physical illness.

We evaluated educational level, age at onset of dementia, age at the time of test, severity of dementia, the number of different kinds of prescribed psychotropic medications taken (the number of prescribed psychotropic medications) and prescribed non-psychotropic medications taken (the number of prescribed non-psychotropic medications). We also evaluated the severity of dementia with the Functional Assessment Staging (FAST)[9] and cognitive function with Mini-Mental State Examination (MMSE).[10] All clinical data were collected and evaluated at the first visit to our hospital (at study entry).

Blood samples were collected at study entry to evaluate SAA. They were clotted at room temperature, centrifuged at 3000 rpm for 15 min and obtained serums were stored at –80°C until the assay. To avoid the diurnal changes of SAA, the blood samples were collected approximately at the same time at 1000–1200 hours. SAA was assayed according to the protocol of Tune and Coyle[1] by means of receptor-binding assay at Pana Pharm Laboratory Co. Ltd, Kumamoto, Japan, without providing patients' information. This assay was based on the fact that the potent muscarinic receptor antagonist [^{3}H]-radiolabeled-quinuclidinyl benzilate ([^{3}H]-QNB) binds specifically and avidly to muscarinic receptors. In each assay run, a standard curve for displacement was carried out using the serum of young, healthy volunteers who had been prescribed no medicines. Various concentrations of atropine were added to this serum. The level of SAA was expressed as atropine equivalents, nanomoles of atropine equivalents per milliliter serum (nmol), according to the [^{3}H]-QNB counts in the patient's serum.

We compared the patients' demographic data and MMSE score (total scores of MMSE and the scores of each item) between the SAA positive (SAA (+)) group and SAA negative (the SAA (–)) group. The statistical analysis was carried out with a Student's *t*-test using the statistical software package SPSS-J (Statview Inc, Tokyo, Japan) version 12.0, and $P < 0.05$ was accepted as statistically significant.

We obtained informed consent from all study subjects or their proxies before carrying out the study. The present study was approved by the Ethical Committee of the National Shimofusa Hospital.

RESULTS

The relationship between atropine concentration (the amount of atropine in standard solution: nmol) and [^{3}H]-QNB counts (radiolabeled tritiated quinuclidinyl benzilate counts: disintegration per minute (dpm)) are liner when added atorpines were from 1.95nmol to 25nmol. Therefore, when the level of SAA was over 1.95 nmol, this patient belonged to SAA (+). Among the 76 AD patients enrolled in the present study, 26 patients were SAA (+) and 50 patients were SAA (–). The mean SAA value in the SAA (+) group was 4.14 ± 2.70 nmol.

Table 1 shows the demographic data of the SAA (+) and the SAA (–) groups. There were no significant

Table 1 Demographic data of the serum anticholinergic activity positive and the serum anticholinergic activity negative groups

	SAA (+)	SAA (–)	*P*-value
No. patients (male/female)	26 (12/14)	50 (20/30)	0.7867
Educational level in years	9.96 (3.84)	10.26 (4.00)	0.7553
Age at dementia onset	75.3 (8.3)	73.4 (7.9)	0.3323
Test age	78.9 (7.2)	77.9 (7.1)	0.5460
FAST stage score	5.46 (1.21)*	4.78 (0.98)	0.0096
No. psychotropic medications	1.3 (2.0)*	0.5 (1.1)	0.0234
No. non-psychotropic medications	1.8 (2.9)	1.0 (1.8)	0.1456

*$P < 0.05$. Data are given as mean (SD) except for number of patients.
Number of psychotropic medications is the number of different kinds of prescribed psychotropic medications taken; number of non-psychotropic medications is the number of different kinds of prescribed non-psychotropic medications taken.
FAST, Functional Assessment Staging; SAA, serum anticholinergic activity; SAA (+) group, SAA positive group; SAA (–) group, SAA negative group.

Table 2 Cognitive domains of the Mini-Mental State Examination of the serum anticholinergic activity positive and the serum anticholinergic activity negative groups

MMSE item (full scores)	SAA (+)	SAA (–)	*P*-value
Total MMSE (30)	8.89 (8.40)	13.16 (8.27)*	0.0367
Orientation: time (5)	0.81 (1.30)	1.48 (1.56)	0.0630
Orientation: place (5)	1.42 (1.82)	2.14 (1.70)	0.0928
Registration (3)	1.62 (1.47)	2.30 (1.20)*	0.0323
Attention/calculation (5)	0.77 (1.14)	1.28 (1.75)	0.1829
Recall (3)	0.00 (0.00)	0.34 (0.77)*	0.0282
Naming (2)	1.15 (1.01)	1.48 (0.86)	0.1444
Repeat (1)	0.42 (0.50)	0.58 (0.50)	0.1986
Listen and obey (3)	1.50 (1.48)	2.14 (1.29)	0.0551
Write and obey (1)	0.46 (0.51)	0.54 (0.50)	0.5226
Write sentence (1)	0.42 (0.50)	0.44 (0.50)	0.8895
Praxis (1)	0.31 (0.47)	0.44 (0.50)	0.2689

*$P < 0.05$. Data are given as mean (SD) except for number of patients.
MMSE, Mini-Mental State Examination; SAA, serum anticholinergic activity; SAA (+) group, SAA positive group; SAA (–) group, SAA negative group.

differences in sex distribution, educational level, age at onset of dementia and age at the time of test between the SAA (+) group and the SAA (–) group. However, the FAST score, and the number of psychotropic medications were higher in the SAA (+) group than those in the SAA (–) group ($P < 0.05$).

Table 2 shows the cognitive domains of MMSE of the SAA (+) and the SAA (–) groups. The total score of MMSE and each score of MMSE domain of registration and recall were significantly lower ($P < 0.05$) in the SAA (+) group than those in the SAA (–) group.

DISCUSSION

In the present study, SAA was detected in 26/76 AD patients (34.2 %), even at study entry when we had not prescribed psychiatric medication yet. However, Mulsant *et al.* reported that SAA was detectable in 180/201 subjects (89.6%).[5] We found that approximately one-third of AD patients were SAA (+) at study entry; Tune *et al.* reported that SAA at 7.5 nmol and higher concentrations in postoperative non-demented patients was associated with a higher risk of delirium.[11] In contrast, Tune and Coyle commented that SAA at 3.5 nmol and higher concentration was of benefit to schizophrenic patients in order to avoid extrapyramidal side-effects.[1] In the present study, the mean value of SAA was 4.14 nmol in SAA (+) AD patients. This was lower than the value that causes delirium in postoperative non-demented patients and somewhat higher than the value that causes clinical effects in schizophrenic patients reported by Tune and Coyle.[1] It is quite probable, however, that even low values of SAA could have an affect on certain cognitive symptoms for AD patients, though not affect cognition in non-demented patients.[6,7]

At study entry, there were no significant differences in sex distribution, educational level, age at onset of dementia, and age between the SAA (+) group and the SAA (–) group, whereas the number of prescribed psychotropic medications was significantly higher ($P < 0.05$) in the SAA (+) group than the SAA (–) group. Anticholinergic activity in the serum is caused by the cumulatively prescribed medications, even though each medication has no or not prominent anticholinergic activity.[2] Therefore, the more medications that are prescribed, the more likely it is that there is a tendency for SAA to be positive. Some of the patients, who showed behavioral and psychiatric symptoms, enrolled in the present study had been prescribed psychotropic medications and showed positive SAA even at study entry. Furthermore, psychotropic medications have prominent anticholinergic activity and are known to cause cognitive dysfunctions.[12,13] Accordingly, the more non-psychotropic medications we prescribed, the more the SAA tended to be positive because many non-psychotropic medications, for example, those for cardiac disorders, urinary tract disorders and gastrointestinal disorders, have prominent anticholinergic properties.[2] However, in regard to non-psychotropic medications, because patients with severe physical illness were not referred, there was no significant difference in the number of non-psychotropic medications between the SAA (+) group and the SAA (–) group. We considered, however, that if a higher number of non-psychotropic medications were prescribed, more SAA would tend to be positive, as with psychotropic medications. Of course, the prescribed medications were not the only cause of anticholinergic burden. For example, Flacker *et al.* commented that the SAA might reflect a non-specific stress response to illness in elderly people.[14] In fact, some of AD patients who were not prescribed psychotropic medications showed positive SAA. However, prescribed medicines, especially psychotropic medicines, were one of the main origins of positive SAA in AD patients.

The total score of MMSE was lower and the FAST score was higher ($P < 0.05$) in the SAA (+) group than those in the SAA (–) group. Based on this result, we emphasize that the anticholinergic burden might

accelerate AD pathology and lead the patients to a more severe stage. Although these results of the relationship between SAA and the MMSE score in AD[5,7,15–18] have been inconclusive so far, many studies have suggested that there was a significant relationship between higher SAA and lower MMSE score. For example, Tollefson *et al.* reported that a negative relationship was seen between the SAA and the MMSE score in nursing home patients.[16] Chew *et al.* reported that there was a significant correlation between the SAA and the MMSE score even in moderately to severely demented patients.[18] On the contrary, a substantial number of studies reported that the total MMSE score is not influenced by SAA (+). For example, Rovner *et al.* showed that the MMSE score in the SAA below median group was not different from that in the SAA median and higher concentration group in nursing home patients.[15] Remillard also reported the similar results to those of Rovner *et al.* regarding the relationship between the total MMSE score and the value of SAA.[17] Thienhaus *et al.* also reported that patients evaluated by the global screening inventory of the MMSE did not show any lowering of cognitive change by anticholinergic agents.[7] In the present study, not only the total score of MMSE but also the score of registration and recall domains in MMSE were significantly lower ($P < 0.05$) in the SAA (+) group compared with those in the SAA (–) group. It was already reported that memory is sensitively disrupted by anticholinergic activity.[6,7] For example, Sunderland *et al.* reported that a low dose of scopolamine (0.25 mg) induced significant impairment in new learning and semantic knowledge in AD patients, but not in non-demented controls.[6] Thienhaus *et al.* also reported that when evaluated by not MMSE but tests of short-term memory, concentration, knowledge memory and intrusion error, the lowering of cognition by anticholinergic agents was shown.[7] Regretfully, to the best of our knowledge, there are no reports comparing the score of each item in the MMSE. However, the present study showed adequate results that the scores of memory functions (the score of registration and recall domains in MMSE) were significantly lower in the SAA (+) group compared with those in the SAA (–) group. Our data expressed a possibility that memory domains of the MMSE were more confidently vulnerable to anticholinergic burden in AD patients and that memory functions were more highly dependent on the cholinergic function than other cognitive domains of the MMSE.

From the present results, we should more prudently prescribe psychotropic medications to AD patients. The prescribed medicines were one of the important causes of worsening cognitive function in AD patients, especially memory domains. Moreover, a warning on prescription of antipsychotic agents to demented elderly patients is issued to increase mortality of the patients.[19] The impairments of cognitive functions were principally reversible,[20] however, it took a lot of time to recover and partially reverse these impairments, even though the prescribed medications were discontinued.[21] In the present study, the stage of dementia in the SAA (+) group was more severe than in the SAA (–) group, although there were no significant differences in age at onset of dementia and age at the time of the test between these two groups. Furthermore, Perry *et al.* reported that amyloid plaque densities were more than 2.5-fold higher in cases treated with antimuscarinic medications in the long term (more than 2 years) compared with untreated or treated in short-term (less than 2 years) cases with antimuscarinic medications.[22] Lu and Tune commented that chronic exposure to anticholinergic medications accelerated the clinical course AD.[23] From these results, we considered that anticholinergic activity not only directly worsens cognitive functions, especially memory domain in AD, but also exacerbates AD pathology through increasing amyloid plaques and that there would be the possibility that long-term exposure of anticholinergic medications caused irreversible changes in AD. Therefore, SAA should be examined in AD patients when they present at geriatric hospitals for treatment. It is a problem that there is no useful clinical yardstick for anticholinergic toxicity in the elderly, especially demented patients.[24] If we find SAA in AD patients, we should manage the use of psychotropic medications in these patients and select medications with less anticholinergic activity. In another paper, we reported that it is useful to evaluate SAA in AD patients to determine the anticholinergic toxicity and the level of cognitive function using SAA.[25]

The study was limited by small sample size without control subjects, cross-sectional or a longitudinal course of SAA. We focused attention only at study entry. Therefore, the temporal relationship of SAA, prescribed medications and cognitive functions (or severity of dementia) was not perfectly explicit and there is the possibility that psychiatrists tend to prescribe a higher number of psychotropic medications

for more severe stage AD patients than less severe counterparts because, generally speaking, the more severe the dementia becomes, the more severe the behavioral symptoms (psychiatric symptoms) are.[26–28] If so, we should more and more prudently prescribe psychotropic medications to AD patients, because previous reports commented that chronic exposure to anticholinergic medications accelerated the clinical course of AD.[23] Although the present study was limited in the scope of target and the MMSE might be too simple to identify precise cognitive impairment, the results showed that not only total scores of the MMSE but also the registration and recall domains score of the MMSE in the SAA (+) group were significantly lower than those in the SAA (–) group. Further investigations would be necessary to delineate more a precise relationship between SAA and cognitive performance in AD patients with longitudinal observations of large samples.

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