Japanese Journal of Comprehensive Rehabilitation Science (2010)

Case Report

Use of Yi-Gan San (TJ-54) in patients with motor aphasia who refuse to participate in rehabilitation

Shinsuke Sato, MD,[1] Kyota Bunno, MD[2]

[1]Department of Rehabilitation Medicine, Sato Memorial Hospital, Katsuta-gun, Okayama, Japan
(present; Department of Rehabilitation Medicine, Showa University Fujigaoka Hospital, Yokohama, Kanagawa, Japan)
[2]Department of Rehabilitation Medicine, Sato Memorial Hospital, Katsuta-gun, Okayama, Japan
(present; Department of Rehabilitation Medicine, Kawasaki Medical School Hospital, Kurashiki, Okayama, Japan)

ABSTRACT

Sato S, Bunno K. Use of Yi-Gan San (TJ-54) in patients with motor aphasia who refuse to participate in rehabilitation. Jpn J Compr Rehabil Sci 2010; 7-10.

Since aphasic patients have difficulty communicating, they often have emotional lability, which can make clinical management difficult and may even lead to the patients' refusal to participate in rehabilitation programs.

Yi-Gan San (YGS) has recently been shown to improve behavioral and psychological symptoms of dementia (BPSD) associated with Alzheimer's dementia. Recently, 3 patients with motor aphasia were treated with YGS to stabilize psychiatric symptoms, and this treatment helped the patients, who initially refused to undergo rehabilitation, adapt to rehabilitation therapy. Within 1 to 2 weeks of starting the treatment with YGS, there was a marked improvement in the patients' emotional lability. Since the patients showed improvement within a short period, we think that the serotonin 5-HT_{1A} receptor partial agonist action of YGS is the main factor responsible for these pharmacologic effects.

In patients with impaired communication ability, such as those with motor aphasia, YGS may be effective and worthwhile as a supplemental therapy for secondary psychiatric symptoms such as emotional lability.

Correspondence: Shinsuke Sato, MD
Department of Rehabilitation Medicine, Sato Memorial Hospital, 45, Kurotsuchi, Shouou-cho, Katsuta-gun, Okayama 708-6688, Japan (present; Department of Rehabilitation Medicine, Showa University Fujigaoka Hospital, 1-30, Fujigaoka, Aoba-ku, Yokohama, Kanagawa 227-8501, Japan)
E-mail: shinne73@hotmail.com
Accepted: October 7, 2010
No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Key words: Yi-Gan San, aphasia, rehabilitation, Chinese herbal remedy, stroke

Introduction

Aphasic patients have difficulty communicating; therefore, they are often irritable and agitated, which can make clinical management difficult. When these patients are transferred from an acute hospital to a convalescent rehabilitation ward, they may even refuse to participate in rehabilitation programs. Psychotropic drugs have been used for treating patients with severe psychiatric symptoms, but because of their adverse reactions, such as the extrapyramidal symptoms caused by occupation of dopamine D2 receptors [1], these drugs can actually hinder rehabilitation therapy in many patients. Therefore, it would be fortunate if a Kampo medicine (Chinese herbal remedy) that does not show adverse effects on motor function could be used to improve these symptoms. However, some of the mechanisms of action of Kampo medicines are still unclear, and indications for rehabilitation therapy have seldom been reported.

Yi-Gan San (YGS: Tsumura & Co., Tokyo, Japan) is a Kampo medicine developed by Xue Kai in the year 1555 and comprises 7 types of herbs (Atractylodis lanceae rhizoma, Poria, Cnidii rhizoma, Uncariae uncis cum ramulus, Angelicae radix, Bupleuri radix, and Glycyrrhizae radix). YGS is effective for the treatment of neurosis, insomnia, childhood nighttime crying, and childhood nervousness [2]. Recently, YGS has also been shown to improve behavioral and psychological symptoms of dementia (BPSD), such as delusions, wandering, and violence, as well as activities of daily living (ADL) in patients with advanced Alzheimer's dementia and Lewy Body dementia [3-6]. Therefore, this drug has been attracting attention in the context of a rapidly ageing society.

In this study, we have reported the findings for 3 patients with motor aphasia who initially refused rehabilitation and adapted to rehabilitation therapy

after receiving YGS for stabilizing their psychiatric symptoms.

Methods

Subjects

Of the inpatients in our convalescent rehabilitation ward during 2008, 3 patients, who had right hemiplegia and motor aphasia because of a stroke and refused to participate in rehabilitation and could not adapt to training, were included in this study.

Interventions

YGS (2.5 g) was orally administered 2 to 3 times daily, and psychiatric symptoms and ADL were evaluated.

Evaluation method

For evaluation of neuropsychiatric symptoms, the nursing home version of the Neuropsychiatric Inventory (NPI-NH), which was first reported by Wood et al. in 2000, was used. The reliability of the Japanese version has already been demonstrated [7]. Evaluation was based on a structured interview, with the daily caregiver of the institutionalized patient serving as the information source. The total score was the product of the frequency (0-4) and severity (0-3) of the following 12 neuropsychiatric symptoms: delusions, hallucinations, agitation, dysphoria, apathy, anxiety, euphoria, disinhibition, irritability/lability, aberrant behavior, nighttime behavior, and appetite change. Items that could not be evaluated because of aphasia were excluded and assigned a score of zero. ADL was assessed using the Functional Independent Measure (FIM).

Patient 1 (a 73-year-old man)

History of present illness

The patient had extensive thrombosis involving the left middle cerebral artery territory and was treated conservatively. On day 58, the patient was transferred to our convalescent rehabilitation ward.

Findings of initial examinations

The patient could barely repeat words, and he had difficulty in making himself understood even when he was only uttering words. Understanding of simple instructions and conversation using phrases was occasionally possible. His understanding of situations was relatively good, and he was occasionally able to obey orders, such as an order to stand. The patient did not show apraxia. The Brunnstrom stages were as follows: right upper extremity, III; right hand, II; and right lower extremity, III. Sensation was markedly decreased. The FIM score was 22 points (motor, 14; cognition, 8). The patient appeared to be anxious about not being able to converse. He was often frustrated and refused to undergo rehabilitation. His mood fluctuated, and the amount of care required varied greatly. The patient's NPI score was 13 points (agitation, 6; disinhibition, 1; irritability, 6). At that time, his "Sho" (a symptom in Kampo medicine) was "Jitsu" (robust, strong resistance).

Course after admission

About 2 weeks after the transfer, the patient's mood fluctuations increased further, and he experienced recurring episodes of depression and agitation. He refused to undergo rehabilitation therapy about two-thirds of the times when he was asked to. The NPI score increased to 26 (agitation, 12; dysphoria, 2; disinhibition, 3; irritability, 6; nighttime behavior, 3). On day 32 after the transfer, YGS administration at a dose of 7.5 g/day was started. From day 38, he showed greater cooperation with the rehabilitation program. His anger diminished, and he became calmer. This improvement continued and the agitation abated; therefore, the YGS dose was decreased to 5.0 g/day from day 46. Subsequently, however, the patient started refusing to undergo rehabilitation and became less cooperative with care personnel, which necessitated an increase in the amount of care required. On day 63, the YGS dose was again increased to 7.5 g/day. By day 70, the patient became calmer, and he smoothly adapted to rehabilitation and care. His psychiatric symptoms subsided; the FIM score was 34 points (motor, 25; cognition, 9), and the NPI score improved to 0 points. On day 146, the patient was transferred to long-term care on YGS 7.5 g/day.

Patients 2 and 3 received the same treatment. Patient 2 (a 52-year-old woman) began to smile 5 days after YGS administration was started, and from day 9, she started willingly participating in rehabilitation, including transfer training and walking between parallel bars on the ward. The patient's NPI score improved from 50 to 11 points. Patient 3 (a 76-year-old man) was able to begin walking training between parallel bars on day 8 after starting YGS, and subsequently, his resistance to rehabilitation decreased. By day 16, he had almost fully adapted to rehabilitation. His NPI score improved from 24 to 8 points.

The detailed clinical courses of patients 1 to 3 are shown in Table 1.

Discussion

YGS has been reported to cause an improvement in symptoms of agitation/aggression and frustration/irritability together with an improvement in BPSD [3,4,8]. We think that the same mechanism of action was involved in the 3 cases reported in this study.

YGS has a serotonin 5-HT_{1A} receptor partial agonist action [9]; this action has been attributed to geissoschizine methyl ether, one of the ingredients of

Table 1. Characteristics and clinical courses in the 3 cases

	Patient 1 73-year-old man	Patient 2 52-year-old woman	Patient 3 76-year-old man
Disease	Cerebral infarction (extensive infarction of left MCA)	Left putamen hemorrhage (after open hematoma evacuation)	Cerebral infarction (stenosis at origin of the left internal carotid artery)
Past medical history	Hypertension, diabetes	Hypertension, diabetes	Hypertension, diabetes, hyperlipidemia, angina pectoris
Brunnstrom stage: Right upper extremity-hands-lower extremity	III-II-III	II-II-II	II-II-II
"Sho" (symptom in Kampo medicine)	"Jitsu" (Robust, strong resistance)	Moderate	"Jitsu" (Robust, strong resistance)
NPI score (at start of administration)	26 (agitation, 12; dysphoria, 2; disinhibition, 3; irritability, 6; nighttime behavior, 3)	50 (hallucinations, 8; agitation, 12; dysphoria, 9; anxiety, 3; irritability, 8; aberrant behavior, 8; appetite change, 2)	24 (agitation, 12; apathy, 3; disinhibition, 1; irritability, 8)
NPI score (at discharge)	0	11 (hallucinations, 1; agitation, 4; dysphoria, 1; anxiety, 1; irritability, 1; aberrant behavior, 3)	8 (agitation, 3; apathy, 2; irritability, 3)
FIM score (at start of administration)	22 points (motor, 14; cognition, 8)	27 points (motor, 22; cognition, 5)	22 points (motor, 17; cognition, 5)
FIM score (at discharge)	34 points (motor, 25; cognition, 9)	49 points (motor, 39; cognition, 10)	29 points (motor, 19; cognition, 10)
Effects of YGS	Smooth adaptation to rehabilitation starting on day 7. The patient's anger subsided and he became calmer.	Started to smile on day 5. Began to adapt to rehabilitation on day 9.	First able to perform walking training on day 8. Completely adapted to rehabilitation by day 16.

the constituent herb Uncariae uncis cum ramulus [10,11]. 5-HT_{1A} receptors are related to emotional activation [12] and show inhibitory effects on agitation and irritability via the anxiolytic effects caused by the partial agonist action [13,14]. YGS stimulation of 5-HT_{1A} receptors also induces desensitization (downregulation) of 5-HT_{2A} receptor proteins in the prefrontal region [15-17], but an interval of 2-4 weeks between the start of dosing and the onset of this effect can be expected. In our patients, early effects were seen in 1-2 weeks, which suggested that the main factor was a partial agonist action on 5-HT_{1A} receptors.

YGS also has an effect on the neuroexcitatory glutamic acid nervous system in the brain [18,19] and exerts neuroprotective effects against beta amyloid-induced cytotoxicity [2]. These neuropharmacological actions contribute to the sedative effects of YGS, but the complete mechanism of action has not been fully elucidated. Further research on this issue is anticipated. At present, it seems appropriate to limit the use of YGS to reducing symptoms such as anger and agitation that develop secondary to a communication disorder.

Patient 1 experienced drowsiness for about 2 days after starting YGS treatment, but this condition rapidly improved; therefore, a causal relationship could not be established. YGS has been reported to prolong sleep time, particularly non-REM sleep [20], and it may have a beneficial effect on sleep structure [5]. When using YGS, caution should be taken to prevent nighttime staggering caused by hypersomnolence.

The introduction of Oriental medical methods such as Kampo medicine and acupuncture in rehabilitation is a rational and worthwhile approach; these methods

can be used to improve psychiatric symptoms as well as physical function. However, these effects have not yet been adequately investigated. Proper use of this medicine in conjunction with psychotropics should be evaluated in a larger number of patients. Long-term administration is an issue for further investigation.

Conclusion

In patients with communication disorders such as motor aphasia, secondary psychiatric symptoms such as emotional lability can occur and may be difficult to treat. In these patients, YGS may be effective and worthwhile as supplemental therapy.

References

1. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000; 157: 514-20.
2. Tateno M, Ukai W, Ono T, Saito S, Hashimono E, Saito T. Neuroprotective effects of Yi-Gan San against beta amyloid-induced cytotoxicity on rat cortical neurons. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 1704-7.
3. Iwasaki K, Nakagawa ST, Maruyama M, Monma Y, Nemoto M, Tomita N, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. J Clin Psychiatry 2005; 66: 248-52.
4. Mizukami K, Asada T, Kinoshita T, Tanaka K, Sonohara K, Nakai R. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. Int J Neuropsychopharmacol 2008; 12: 191-9.
5. Shinno H, Inami Y, Inagaki T, Nakamura Y, Horiguchi J. Effect of Yi-Gan San on psychiatric symptoms and sleep structure at patients with behavioral and psychological symptoms of dementia. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 881-5.
6. Monji, A, Takita M, Samejima T, Takaishi T, Hashimoto K, Matsunaga H, et al. Effect of yokukansan on the behavioural and psychological symptoms of dementia in elderly patients with alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 308-11.
7. Shigenobu K, Hirono N, Tabushi K, Ikeda M. Validity and reliability of the Japanese version of the Neuropsychiatric Inventory- Nursing Home version (NPI-NH). Brain Nerve 2008; 60: 1463-9.
8. Hayashi Y, Ishida Y, Inoue T, Udagawa M, Takeuchi K, Yoshimuta H, et al. Treatment of behavioral and psychological symptoms of Alzheimer-type dementia with Yokukansan in clinical practice. Prog Neuropsychopharmacolo Biol Psychiatry 2010; 34: 541-5.
9. Terawaki K, Ikarashi Y, Sekiguchi K, Nakai Y, Kase Y. Partial agonistic effect of yokukansan on human recombinant serotonin 1A receptors expressed in the membranes of Chinese hamster ovary cells. J Ethnopharmacol 2010; 127: 306-12.
10. Kanatani H, Kohda H, Yamasaki K, Hotta I, Nakata Y, Segawa T, et al. The active principles of the branchlet and hook of Uncaria sinensis Oliv. examined with a 5-hydroxytryptaomine receptor binding assay. J Pharm Pharmacol 1985; 37: 401-4.
11. Pengsuparp T, Indra B, Nakagawasai O, Tadeno T, Mimaki Y, Sashida Y, et al. Pharmacological studies of geissoshizine methylether, isolated from uncaria sinensis oliv., in the central nervous system. Eur J Pharmacol 2001; 425: 211-8.
12. Lai MKP, Tsang SWY, Francis PT, Esiri MM, Keene J, Hope T, et al. Reduced serotonin 5-HT_{1A} receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. Brain Res 2003; 974: 82-7.
13. Cantillon M, Brunswick R, Molina D, Bahro M. Buspirone vs. haroperidol: a double-blind trial for agitation in a nursing home population with Alzheimer's disease. Am J Geriatric Psychiatry 1996; 4: 263-7.
14. Sato S, Mizukami K, Asada T. A preliminary open-label study of 5-HT_{1A} partial agonist tandospirone for behavioural and psychological symptoms associated with dementia. Int J Neuropsychopharmacol 2007; 10: 281-3.
15. Egashira N, Iwasaki K, Ishibashi A, Hayakawa K, Okuno R, Abe M, et al. Repeated administration of Yokukansan inhibits DOI-induced head-twitch response and decreases expression of 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptors in the prefrontal cortex. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 1516-20.
16. Carrasco GA, Kar LDVd, Jia C, Xu H, Chen Z, Chadda R, et al. Single exposure to a serotonin 1A receptor agonist, (+)8-hydroxy-2-(di-n-propylamino)-tetralin, produces a prolonged heterologous desensitization of serotonin 2A receptors in neuroendocrine neurons in vivo. J Pharmacol Exp Ther 2007; 320: 1078-86.
17. Kanno H, Sekiguchi K, Ymaguchi T, Terawaki K, Yuzurihara M, Kase Y, et al. Effect of yokukansan, a traditional Japanese medicine, on social and aggressive behavior of para-chloramphetamine-injected rats. J Pharm Pharmacol 2009; 61: 1249-56.
18. Takeda A, Itoh H, Tateno H, Yuzurihara M, Oku N. Suppressive effect of Yokukansan on excessive release of glutamate and aspartate in the hippocampus of zinc-deficient rats. Nutritional Neurosci 2008; 11: 41-6.
19. Kawakami Z, Kanno H, Ueki T, Terawaki K, Tabuchi M, Ikarashi Y. Neuroprotective effects of yokukansan, a traditional Japanese medicine, on glutamate-mediated excitotoxicity in cultured cells. Neuroscience 2008; 159: 1397-407.
20. Aizawa R, Kanbayashi T, Saito Y, Ogawa Y, Sugiyama T, Kitajima T, et al. Effects of Yoku-kan-san-ka-chimpi-hange on the sleep of normal healthy adult subjects. Psychiatry Clin Neurosci 2002; 56: 303-4.