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Case Report

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Trihexyphenidyl Reduces Flashbacks in Patients with Posttraumatic Stress Disorder (PTSD)

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Abstract

Aim: This paper aims to develop a new therapy for reducing flashbacks in the posttraumatic stress disorder (PTSD).

Method: Previous studies have proved the potentiality of anticholinergic in reducing flashbacks in PTSD. This report describes the effects of the central anticholinergic drug trihexyphenidyl, which penetrates the blood–brain barrier (BBB) among 7 patients suffering from PTSD flashbacks.

Results: Drug effects were assessed using psychological tests, including a self-evaluation score, the IES-R (Impact of Events Scale-Revised), and CAPS (Clinician-administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders-IV [DSM-IV]).The mean of the self-evaluation score improved from 100 to 17.14 after the treatment, and the mean IES-R score improved to 25.57 from 70.42. The CAPS mean frequency (F) and intensity (I) of B-1(unwanted memories) improved from 3.42 to0.71and 3.42 to 0.57, respectively, after treatment. The mean F and I of B-2 (unpleasant dreams) improved from 1.85 to 0.42and 2.00 to 0.28, respectively. The mean of F and I of B-3 (flashbacks, etc.) improved from 3.71 to 0.85 and 3.28 to 0.85, respectively. Complete remission was achieved in 3 of 7 cases (48%), and partial remission was achieved for the remaining 4 (52%). Therefore, at least some remission was achieved in all patients in this study.

Conclusion: The central anticholinergic drug trihexyphenidyl is a novel and successful medical therapy in reducing flashbacks in subjects suffering from PTSD. This result suggests that the origin of flashbacks in PTSD is closely related to abnormal excitement of memory-related circuits comprised of the acetylcholine-based basal forebrain, amygdala, and hippocampus.

Keywords: Reliability; Validity; Trauma; PTSD; Substance use disorders, Treatment outcomes

Introduction

Several authors have discussed the potential applications of β-blockers, cortiso, opioids, and D-cycloserine, which affect the memory system, as new therapeutic and preventive methods to treat posttraumatic stress disorder (PTSD) [1-4]. Although flashbacks (FBs) are common among many patients with PTSD, no effective treatment for FBs in PTSD has been identified. Researchers have encountered a patient (Patient 1) showing improvement using scopolamine butylbromide (SB), a peripheral anticholinergic drug that does not cross the blood–brain barrier, (BBB) still managed to reduce FB. This report describes the mechanisms underlying FBs in PTSD and the effects of TP as a central anticholinergic drug. Three patients have participated in this study and four patients that were not described but were included in the data analysis were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V, Clinician-Administered PTSD scale for DSM-IV (CAPS) [5], and Impact of Event Scale-Revised (IES-R-J) [6].

Cases and Methods

Informed consent for drug administration was obtained from all patients. This study was approved by the Ethical Committee of the Medical Corporation Warakukai. Since this is a case report of psychiatric disease, all personal data were processed to maintain patient anonymity.

Patient 1 was a female in her 20s with PTSD and depressive disorder. Her father was an alcoholic, her mother had an anxiety disorder, and her older brother had schizophrenia and was being treated on an outpatient basis in another hospital. On a summer night when she was in the first year of high school, her father suddenly entered her room, held her down, and sexually abused her. The sexual abuse by her father caused considerable psychological trauma. She became emotionally unstable, developed depression, insomnia, and nightmares, remembered traumatic scenes, and began to have FBs. She visited the psychiatric department of a university hospital and was diagnosed with and treated for PTSD. However, following only slight improvement, she visited various psychiatric hospitals and clinics before visiting our clinic. She had been diagnosed with schizophrenia in another clinic and treated with haloperidol (8 mg). This may have been because the previous physician considered her FBs to be auditory hallucinations. Although the administration dose was almost maximal, her symptoms did not improve. She visited our clinic in X-5 with symptoms of drug-induced Parkinsonism. A close examination suggested that the symptoms were not due to schizophrenia but were PTSD associated Flash Backs. Therefore, haloperidol (8 mg) was discontinued, and selective serotonin reuptake inhibitor (SSRI) fluvoxamine (75 mg/day) and trihexyphenidyl (TP, 6 mg/day) were administered. After 2 weeks, her drug-induced Parkinsonism improved, and TP administration was discontinued. At the time, we did not notice any effects of TP on PTSD-associated Flash Backs, but her condition was relatively stable for 2 weeks when TP was administered. However, her symptoms were aggravated 2 weeks after the discontinuation of TP, and various PTSD symptoms recurred. Her unstable condition persisted despite the administration of various drugs, including antidepressant, a mood-stabilizer, tranquilizers, and atypical antipsychotic. She developed abdominal pain and diarrhea in X-4 and received drip infusion containing scopolamine butylbromide (SB) and antibiotic at the outpatient ward of another hospital. Her Flash Backs completely disappeared approximately 20 minutes after the drip infusion was initiated. She visited our clinic5 days later and requested a subcutaneous SB injection (10 mg) once a week thereafter. The oral administration of SB (10-mg tablet) 3 times daily was also continued for 5 weeks. The antidepressant, atypical antipsychotic, and mood-

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stabilizing agents that had previously been used were discontinued. She continued to take sleeping pills (10 mg zolpidem), and her FBs improved. SB, a peripheral anticholinergic drug that was effective in reducing her FBs, was changed to TP, a central anticholinergic agent that more readily crosses the BBB, which was expected to be more effective. TP (2-mg tablet) was orally administered 3–4 times daily. Effects were observed approximately 1 hour after administration and continued for approximately 4–6 hours. The patient reported that TP was more effective than SB. IES-R and CAPS evaluations confirmed the improvements in FBs after TP administration. As shown in Table 1, her IES-R scores were 81 and 37 before and after TP administration, respectively. The CAPS score for the frequency of unwanted memories (B-1F) was 4 (daily or almost every day) before and 1 (once or twice a month) after administration, and the score for their intensity (B-1I) also improved from 4 (extreme) to 1 (mild). The CAPS score for the frequency of unpleasant dreams (B-2F) was 3 (several times a week) before the commencement of treatment is reduced to 0 (never) once the drugs are administred and the score for their intensity (B-2I) also improved from 3(severe) to 0(none). The score for the frequency of acting or feeling as if the traumatic event was recurring, which included a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes (B-3F), was 4(daily or almost every day) in the beginning was reduced to 1 (once or twice a month) after administration, while the score for its intensity (B-3I) also improved from 4(extreme) to 1(mild).

Patient 2 was a 40-year-old female with PTSD complicated by depressive and panic disorders. Her father died due to gastric cancer. Her mother ran a care-associated business. Her elder brother was healthy and is employed. The patient's younger sister had saved her from being hit by a car when she was 4 years old. Unfortunately, her sister was hit instead and died in front of her, was a reason for her trauma. The patient became very isolated in her third year of primary school, and she started to have mild FBs at the age of 13.She subsequently developed social withdrawal, self-harming behaviors, overeating, food refusal, nervousness, insomnia, excessive cautiousness, fright reactions, symptoms of panic disorder (sudden difficulty in breathing, palpations, and numbness of the hands and feet), and dissociative symptoms (presence of 2 or more distinct identities). She visited various hospitals and was treated with antidepressants, atypical antipsychotics, minor tranquilizers, and mood-stabilizing agents. She visited our clinic in X-9 for the treatment of PTSD. Her condition deteriorated in May, and she relived the tragic accident and heard a voice screaming for help at 15:00, the time when the tragic accident occurred. FBs occurred in rapid succession when her condition was severe. TP (2-mg tablet) was administered 3 times daily, and an additional tablet (2 mg) was given when FBs were severe. FBs began to decrease 1-1.5 hours after TP administration, and these effects continued for approximately 5–6 hours. Her self-evaluation score improved from 100 to 0 within 2 days following the initiation of TP. However, her score increased to approximately 50 on the third day due to stress. Other symptoms of PTSD also improved with the amelioration of FBs, and she gradually returned to work. She is currently being treated with an antidepressant (sertraline), a minor tranquilizer (clotiazepam), atypical antipsychotic (olanzapine), and sleeping pills (zolpidem). Her IES-R score improved from 63 to 40 and the CAPS score for B-1F improved from 3 (several times a week) to 2 (once or twice a week), while that of B-1I improved from 3(severe) to 1(mild). The CAPS score for B-2F improved from 3 (several times a week) to 2 (once or twice a week), while that for B-2I improved from 3 (severe) to 1 (mild). The CAPS scores for B-3F and B3I also improved from 4 (daily or almost every day) to 2 (once or twice a week) and from 3 (severe) to 2 (moderate), respectively.

Patient 3 was a 30-year-old female with PTSD complicated by depression and anxiety disorders. Her father was violent and addicted to gambling. Her mother and father did not get along well and divorced when she was in the second year of high school. Her older brother was also emotionally unstable and sometimes violent toward her. She had diabetes mellitus and was being treated as an outpatient. A typhoon and earthquake hit the region where she lived in her second year of primary school. She witnessed many corpses and destroyed buildings. She was also physically abused by her mother and older brother in her primary and junior high school days, which resulted in a broken nose. These experiences were severely traumatic. The patient was attacked by a neighbor when she was 23 years old, which triggered a FB of her childhood trauma. FBs then occurred approximately once every 3 months. Although the severity of her condition varied, she continued her daily life. However, she underwent cardiac surgery at the age of 28, which led to repeated FBs. She visited our clinic in X-2with a depressive state, social withdrawal, anthropophobia, emotional instability, overeating, insomnia, nightmares of being chased, and dissociative symptoms (blurred sense of identity). Although various antidepressants, mood-stabilizing agents, sleeping pills, and atypical antipsychotics were administered, no improvement was observed in her condition. In March X, sodium valproate (600 mg/day), clotiazepam (15 mg/day), aripiprazole (9 mg/day), mirtazapine (30mg/day) and zolpidem (10 mg/day) were administered, and TP (2 mg, 3 times daily) was added to reduce FBs. The patient's self-evaluation score decreased from 100 to 50 after TP administration for 2 weeks and reduced further from 50 to 0 after 4 weeks of treatment. Her FBs have been completely eradicated. Although TP administration was discontinued in June X, no FBs occurred, indicating complete remission. Her social withdrawal and other PTSD symptoms have gradually improved, and she began to work as a part-timer. The above drugs, excluding sleeping pills, were discontinued, and her condition has remained stable. Her IES-R score improved from 58 to 26 and CAPS scores for B-1F and B-1I improved from 4 (daily or almost every day) to 0 (never) and from 4 (extreme) to 0 (none), respectively; those for B-2F and B-2I improved from 4 (daily or almost every day) to 0 (none) and from 4 (extreme) to 0 (none), respectively; and those for B-3F improved from 4 (daily or almost every day) to 0 (never) and from 4 (extreme) to 0 (none), respectively.

Analysis of PTSD patients with FBs

In addition to the three patients described in detail here, 4 other PTSD patients responded to TP. The effects of TP administration were analyzed in all 7 patients, and the results are summarized in Table 1.

The following scores were used for IES-R: Not at all=0, slightly=1, moderately=2, very much=3, and extremely=4. The mean score in the 7 patients was 70.42 before TP administration but improved to 25.57. CAPS scores were usedto evaluate symptoms. The mean scores for B-1F and B-1I (F=Frequency, I=intensity), B-2F and -2I, and B-3F and B-3I were calculated before and after TP administration. Improvements were observed in B-1F (3.42 $\Rightarrow$ 0.71), B-1I (3.42 $\Rightarrow$ 0.57), B-2F (1.85 $\Rightarrow$ 0.42), B-2I (2.00 $\Rightarrow$ 0.28), B-3F (3.71 $\Rightarrow$ 0.85), and B-3I (3.28 $\Rightarrow$ 0.85) after TP administration. Marked changes were observed in all 7 patients with PTSD, including a decrease inthe frequency of FBs.

Table 1: IES-R and CAPS scores

Patient	1	2	3	4	5	6	7	
IES-R								**Mean**
Before TP administration	81	63	58	52	68	86	64	70.42
After TP administration	37	40	26	21	29	0	18	25.57
CAPS								**Mean**
B-1F before TP administration	4	3	4	4	4	4	4	3.42
B-1F after TP administration	1	2	0	1	1	0	0	0.71
B-1I before TP administration	4	3	4	4	3	4	3	3.42
B-1I after TP administration	1	1	0	1	1	0	0	0.57
B-2F before TP administration	3	3	4	0	3	3	0	1.85
B-2F after TP administration	0	2	0	0	1	0	0	0.42
B-2I before TP administration	3	3	4	0	3	3	0	2.00
B-2I after TP administration	0	1	0	0	1	0	0	0.28
B-3F before TP administration	4	4	4	3	4	4	4	3.71
B-3F after TP administration	1	2	0	1	2	0	0	0.85
B-3I before TP administration	4	3	4	2	4	4	3	3.28
B-3I after TP administration	1	2	0	1	2	0	0	0.85

IES-R scoring: Not all=0, Slightly=1, Moderately=2, Very much=3, Extremely=4
CAPS scoring: Clinician-Administered PTSD Scale. B-1, B-2, B-3, F (Frequency), Never=0, Once or twice=1, Once or twice a week=2, Several times a week=3, Daily or almost every day=4. (Intensity) None=0, Mild=1, Moderate=2, Severe=3, Extreme=4

Discussion

No case reports have demonstrated the effectiveness of SB in reducing FBs. SB is a peripheral anticholinergic drug with a transfer rate of 0.11% across the rat BBB [7]. Therefore, SBs typically cannot reduce the occurrence of FBs. However, SB combined with sleeping pills for only 5 weeks ameliorated PTSD-associated FBs in Patient 1. These findings cannot be attributed to the placebo effect; therefore, we analyzed this response in terms of systems neurophysiology. Arita [8] reported that stimulation of the nucleus basalis of Meynert in the basal forebrain activated muscarinic receptors in astrocytes, resulting in an increase in local blood flow in the brain and alterations in BBB permeability [9,10]. Although this association has not yet been elucidated in detail, it is supposed that this possibility is thought about by the clinical case that a peripheral anticholinergic drug showed an effect in patient 1. Thus, we speculated that the nucleus basalis of Meynert and acetylcholinergic (ACh) signaling pathways in Patient 1's brain were abnormally stimulated, leading to the activation of muscarinic receptors in astrocytes, played an important role in BBB formation and alterations [11,12].

Similarly, Nishijima et al. [13] stated that neuronal activity drives the localized BBB transport of serum insulin-like growth factor-1, which cannot actively diffuse across the BBB into the central nervous system. Experiments on rats showed abnormal excitement of the brain, leading to alteration in BBB permeability. SB is a peripheral anticholinergic drug that cannot cross the BBB, could still reduce FBs in Patient 1. This result suggests that FBs were induced by an abnormal excitation state in the brain, such as abnormal excitation of memory-related circuits (ACh-MC) which comprises the acetylcholine-based basal forebrain (the nucleus basalis of Meynert, medial septal nucleus, and Broca's diagonal band) and the amygdala-hippocampus. In particular, abnormal excitation of the nucleus basalis of Meynert may have stimulated muscarinic receptors on astrocytes, which induced BBB alterations that allowed SB to cross the BBB and exert inhibitory effects on the ACh-MC, reducing FBs. The case analysis of Patient 1 demonstrated the FB-reducing effects of anticholinergic drugs on FBs in PTSD. Zelikowsky et al. [14] stated that low doses of scopolamine may be a clinically promising adjunct to exposure therapy by making extinction more relapse-resistant, whereas higher doses of scopolamine severely disrupted extinction learning. However, as described above, BBB permeability in Patient 1 may have been increased by the abnormal excitation of ACh -MC, allowing low levels of SB to pass through BBB, entering the brain, and exert anticholinergic effects with the ultimate effect of reducing FBs. Lettfuss et al. [15] reported improvements in the development of behavioral sensitization of MDMA (3,4-methylenedioxy-N-methylamphetamine) following the administration of a muscarinic Ach receptor antagonist. An experimental study in rats by Mitsushima et al. [16] showed that fear memory formation required increased ACh release, and the synaptic delivery of AMPA receptors and hippocampus was mediated by this increase.

They identified molecules that mediate the formation of traumatic memories from the aforementioned studies, and announced that there could be a clue for treating PTSD and related disorders (website of Department of Physiology, Yokohama City University Graduate School of Medicine, November 2014). Mclay and Ho [17] demonstrated that acetylcholinesterase inhibitors could induce PTSD-like symptoms, indicating that anticholinergic drugs may inhibit abnormal ACh-MC excitation, ultimately reducing FBs. These findings on rats and humans provide indirect support for the hypothesis regarding PTSD pathogenesis and the mechanisms underlying the beneficial effects of TP. In the present study, TP was used to treat FBs in 7 patients with PTSD, and a reduction in FBs was observed in all of them, suggesting that ACh-MCs are closely involved in the mechanism underlying FBs. Other central anticholinergic drugs may also reduce FBs. This report evaluated a clinical response by the open label method. I would like to do a clinical evaluation by Randomized Controlled Trial (RCT) on-site at the small clinic but since it is impossible, it is hoped that a big medical institution can develop the further detailed study by RCT.

Conclusion

TP was used to treat FBs in 7patients with PTSD, and moderate to marked reductions in FBs were observed. A 2-mg TP tablet was administered 2-4 times daily or only when required based on the patient's condition. In many instances, a sufficient effect appeared and

was fast-acting with a "pill in the pocket" approach. Effects appeared approximately 1-1.5 hours after TP was administered and continued for approximately 5-6 hours. The duration of effects varied according to the symptoms. No side effects were observed in any of the patients. Complete remission was achieved in three (42.8%) out of 7 patients, with no FBs occurring even after the discontinuation of TP and improvements in other PTSD symptoms (e.g., re-experience other than FBs, avoidance, paralysis, hyperarousal, cognitive and mood abnormalities, dissociation symptoms, and physical symptoms). Aggravation was observed under stressful conditions among 4 other patients; however, FB severity was markedly reduced. TP has been proved relatively as a safe drug for 50 years. Other centrally acting anticholinergic drugs, such as biperiden-hydrochloride and profenamine-hydrochloride, may have similar effects. The FB-attenuating effects of TP as a central anticholinergic drug on FBs may confirm the close involvement of ACh nuclei in the basal forebrain and ACh-MC, consisting hippocampus and amygdala in PTSD pathogenesis. The case of Patient 1 provides insight into the underlying association between ACh pathways and BBB permeability.

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