

The Anxiolytic Effects of the 5-Hydroxytryptamine-1A Agonist Tansospirone Before Otolaryngologic Surgery

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We studied 160 ASA I or II patients undergoing elective otolaryngologic surgery in order to compare the anxiolytic effects of a novel 5-hydroxytryptamine-1A agonist, tansospirone, with diazepam. To monitor preoperative anxiety, the following variables were used: systolic and diastolic arterial pressure, heart rate, and the state anxiety score yielded by the Spielberger State-Trait Anxiety Inventory. We performed pretreatment evaluation on the day before surgery and posttreatment examination immediately after entry into the operating room. In a double-blinded, randomized design, four groups of 40 patients each received one of the following

oral medications 90 min before entry into the operating room: 1) tansospirone 10 mg (T10 group); 2) tansospirone 30 mg (T30 group); 3) diazepam 10 mg (D group); or 4) placebo (P group). After premedication, the State-Trait Anxiety Inventory state anxiety decreased in the T10 ($P < 0.02$), T30 ($P < 0.02$), and D groups ($P < 0.001$), but it increased in the P group ($P < 0.001$). Tansospirone, 10 and 30 mg, safely reduced preoperative anxiety to a similar extent as oral diazepam 10 mg in patients undergoing elective otolaryngologic surgery.

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The main purpose of premedication is to relieve anxiety before surgery (1). Diazepam is frequently used because it can be given by oral administration, thus eliminating the need for injection (1). However, benzodiazepines such as diazepam, even if given orally, impair respiratory (1,2) and psychomotor (1) functions. 5-hydroxytryptamine (5-HT)-1A receptor-related anxiolytics are devoid of the aforementioned adverse effects (3–5). Tansospirone, a partial agonist of the 5-HT_{1A} receptor, has recently become available in oral tablet form for clinical use in Japan. However, no data have been published regarding the safety and effectiveness of 5-HT_{1A} receptor-related anxiolytics as premedicant drugs.

This study was designed to compare tansospirone with diazepam for safety and efficacy when both are used for anxiolysis in patients scheduled for elective otolaryngologic surgery. Preoperative anxiety was measured by using cardiovascular variables (systolic arterial blood pressure [SAP], diastolic arterial blood

pressure [DAP], and heart rate [HR]) and the standard Spielberger State-Trait Anxiety Inventory (STAI) (6).

Methods

The protocol was approved by the Ethics Committee of Gifu University School of Medicine. Written informed consent was obtained from 160 consecutive inpatients, aged 18–64 yr, ASA physical status I or II, all scheduled for otolaryngologic surgery. Exclusion criteria were malignancy, coexisting central nervous system disease, a variety of neurotic disorders (including use of centrally-acting medications, including benzodiazepines and 5-HT_{1A} receptor-related anxiolytics), inability to read or speak Japanese, and behavioral impairment.

Patients were divided, by using a randomized double-blinded design, into four groups of 40 patients each. Together with oral famotidine 20 mg, subjects received tansospirone 10 mg (T10 group), tansospirone 30 mg (T30 group), diazepam 10 mg (D group), or placebo (P group) 90 min before entry into the operating room. Pretreatment evaluation was performed on the eve of surgery, a time reported to provide a level representation of the anxiety occurring immediately before surgery (7). Posttreatment evaluation was performed in the operating room immediately after arrival.

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Table 1. Patients' Demographic Data in T10, T30, D, and P Groups

Group	Age (yr)	Male/female	Height (cm)	Weight (kg)	STAI-trait	Planned surgical procedure: tympanoplasty/tonsillectomy/laryngomicrosurgery/miscellaneous
T10	43.7 ± 12.7	17:23	159.0 ± 8.0	57.9 ± 9.4	40.5 ± 11.4	15:12:8:5
T30	44.4 ± 15.5	20:20	160.9 ± 9.8	57.0 ± 13.9	38.3 ± 10.3	15:12:9:4
D	41.5 ± 16.8	23:17	163.0 ± 7.9	60.2 ± 12.1	39.4 ± 10.2	12:15:9:4
P	42.6 ± 17.1	22:18	162.8 ± 8.7	60.5 ± 9.5	40.4 ± 10.1	13:13:10:4

STAI-trait-trait anxiety score yielded by the Japanese form of the standard Spielberger State-Trait Anxiety Inventory; T10 = tandospirone 30 mg; T30 = tandospirone 30 mg; D = diazepam 10 mg; P = placebo.

Pre- and posttreatment measurements consisted of the following: noninvasively measured SAP and DAP, electrocardiogram-derived HR, and the state anxiety score yielded by the Japanese form of the STAI (STAI-state) (6). In addition, the pretreatment evaluation incorporated the trait anxiety score given by the Japanese form of the STAI (STAI-trait) (6). The STAI is a standardized psychomotor test composed of 40 questions that subjects answer by using a four-point scale. The sum of 20 responses gives STAI-trait, which is directly proportional to baseline tendencies toward anxiety, independent of the subject's current situation. The remaining 20 questions yield STAI-state, which increases proportionally with the situational anxiety level. The safety of tandospirone was examined by monitoring undesirable adverse effects, such as dizziness and headache, that the subject claimed up to the time of the induction of general anesthesia in all patients who participated.

To compare the group data among the T30, T10, D, and P groups, categorical data were analyzed with Pearson χ^2 tests with Yates' correction, and continuous data were analyzed by means of the Scheffé multiple comparison tests after a one-way analysis of variance. In each premedication group, a comparison between post- and pretreatment values was performed with a paired *t*-test. In all tests, $P < 0.05$ was considered statistically different. Group data are presented as mean ± SD, unless otherwise indicated.

Results

There were no significant differences among the T10, T30, D, and P groups in terms of age, sex, height, weight, STAI-trait, or planned surgical procedures (Table 1) or in the baseline values obtained before premedication for STAI-state (Table 2), SAP, DAP, or HR (Table 3).

When posttreatment values were compared with pretreatment values, STAI-state (Table 2), SAP, and DAP (Table 3) showed a statistically significant change in one or more groups. After premedication, the STAI-state decreased in the T10 ($P < 0.02$), T30 ($P < 0.02$), and D ($P < 0.001$) groups but increased in the

Table 2. State Anxiety Scores Yielded by the Spielberger State-Trait Anxiety Inventory in T10, T30, D, and P Groups

Group	Pretreatment	Posttreatment	Difference
T10	41.8 ± 12.1	37.3 ± 11.3*	-4.5 ± 11.2†
T30	42.6 ± 12.1	39.2 ± 11.0*	-3.3 ± 8.5†
D	40.3 ± 13.5	35.8 ± 11.6‡	-4.5 ± 6.7†
P	38.2 ± 9.4	43.8 ± 10.1‡	5.6 ± 7.6

T10 = tandospirone 10 mg; T30 = tandospirone 30 mg; D = diazepam; P = placebo.

* $P < 0.02$ compared with pretreatment value in the same group; † $P < 0.001$ compared with placebo; ‡ $P < 0.001$ compared with pretreatment value in the same group.

P group ($P < 0.001$). As far as the changes in STAI-state were concerned, the P group from each of the other three groups was significantly different ($P < 0.001$) from each of the other three groups. There was an increase in SAP in the P group ($P < 0.003$) and a decrease in DAP in the D group ($P < 0.03$). However, overall there were no differences among the four groups in terms of the changes in SAP and DAP after premedication (Table 3). Furthermore, there were no significant differences among the four groups with respect to adverse effects such as dizziness and headache.

Discussion

In patients undergoing elective otolaryngologic surgery, both of the tandospirone doses (10 and 30 mg orally) reduced preoperative anxiety to the same extent as oral diazepam 10 mg. This finding suggests that tandospirone can be substituted for diazepam as an oral premedicant drug for the relief of preoperative anxiety.

Tandospirone is a new addition to the azapirone class of anxiolytics, which may be useful for the long-term treatment of anxiety and depressive neuroses (5). The optimal dosage is 30 mg tandospirone in three divided doses daily as the initial regimen (8), and to achieve a therapeutic action requires several weeks of administration (5). In this study, from which patients with neurotic disorders were excluded, acute anxiety developed with both tandospirone 10- and 30-mg

Table 3. Hemodynamic Variables in T10, T30, D, and P Groups

Group	Pretreatment			Posttreatment			Difference		
	SAP	DAP	HR	SAP	DAP	HR	SAP	DAP	HR
T10	119.3 ± 12.1	73.5 ± 12.8	71.9 ± 10.8	122.6 ± 18.4	70.1 ± 10.4	68.3 ± 10.0	3.3 ± 15.9	-3.4 ± 10.8	-3.6 ± 13.5
T30	126.1 ± 17.6	77.0 ± 11.6	75.5 ± 13.1	130.0 ± 16.5	73.2 ± 11.6	74.1 ± 10.9	3.9 ± 14.7	-3.8 ± 9.7	-1.4 ± 13.9
D	121.9 ± 17.3	74.2 ± 10.2	75.2 ± 9.5	120.7 ± 18.0	69.2 ± 11.6*	71.4 ± 11.9	-1.2 ± 15.5	-5.0 ± 13.6	-3.9 ± 13.1
P	123.0 ± 22.9	76.0 ± 13.6	71.3 ± 11.9	133.4 ± 20.7†	72.4 ± 13.7	70.9 ± 14.3	10.7 ± 19.1	-3.6 ± 14.2	-0.4 ± 11.8

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate; T10 = tandospirone 10 mg; T30 = tandospirone 30 mg; D = diazepam 10 mg; P = placebo.

* $P < 0.03$ compared with pretreatment DAP; † $P < 0.003$ compared with pretreatment SAP.

oral doses. Although an acute anxiolytic effect of tandospirone has been previously demonstrated in a number of animal studies (9–11), this is the first demonstration of its acute anxiolytic effects in humans.

In this study, adverse effects were monitored solely during the preoperative period. However, the acute anxiolysis produced by tandospirone should be separated from sedative, anticonvulsant, and muscle-relaxant effects after surgery, because these can be excluded during chronic administration of this drug (3–5). These findings suggest that tandospirone could be useful as an oral premedicant drug for relieving anxiety before day-case surgery. Although 10 mg orally administered tandospirone was as effective as 30 mg orally administered, the optimization of oral single-dose tandospirone for anxiolysis before day-case surgery will require further studies involving postoperative monitoring of adverse effects.

Within the central nervous system, 5-HT_{1A} receptors are located both presynaptically (predominantly on cell bodies of serotonergic neurons located in the raphe nuclei) and postsynaptically (predominantly in the limbic structures such as the hippocampus and septum) (5). Although the question of the relative contributions made by pre- and postsynaptic 5-HT_{1A} receptors to anxiolysis is controversial (5), the balance of evidence supports the involvement of presynaptic receptors in the mechanism underlying anxiolysis, at least upon acute administration of 5-HT_{1A}-receptor agonists (5,12,13).

In conclusion, in patients undergoing elective otolaryngologic surgery, both oral doses of tandospirone tested (10 and 30 mg) safely reduced preoperative anxiety to a similar extent as oral diazepam 10 mg. This finding implies that, for relieving anxiety before surgery, tandospirone can be substituted for diazepam as an oral premedicant drug.

References

- Lichter JL, Zacny JP. Psychological preparation and preoperative medication. In: Miller RD, ed. *Anesthesia*. 4th ed. New York: Churchill Livingstone, 1994:1015–43.
- Leiter JC, Knuth SL, Krol RC, Bartlet D Jr. The effects of diazepam on the genioglossal muscle activity in normal human subjects. *Am Rev Respir Dis* 1985;132:216–9.
- Rapoport DM, Greenberg HE, Goldring RM. Differing effects of the anxiolytic agents buspirone and diazepam on control of breathing. *Clin Pharmacol Ther* 1991;49:394–401.
- Unrug-Neervoort A, Van Luijtelar G, Coenen A. Cognition and vigilance: differential effects of diazepam and buspirone on memory and psychomotor performance. *Neuropsychobiology* 1992;26:146–50.
- De Vry J. 5-HT_{1A} receptor agonists: recent developments and controversial issues. *Psychopharmacology* 1995;121:1–26.
- Spielberger CD, Gorsich RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1970.
- Lichter JL, Johanson CE, Mhoon D, et al. Preoperative anxiety: does anxiety level the afternoon before surgery predict anxiety level just before surgery? *Anesthesiology* 1987;67:595–9.
- Murasaki M, Mori A, Endo S, et al. Late phase II study of a new anxiolytic, SM-3997 (tandospirone) on neurosis [in Japanese]. *Rinsho Hyoka* 1992;20:259–93.
- Kitaoka Y, Shibata K, Miyazaki A, et al. Involvement of the dorsal hippocampus in mediation of the antianxiety action of tandospirone, a 5-hydroxytryptamine_{1A} agonistic anxiolytic. *Neuropharmacology* 1991;30:475–80.
- Pollard GT, Nanry KP, Howard JL. Effects of tandospirone in three behavioral tests for anxiolytics. *Eur J Pharmacol* 1992;221:297–305.
- Shimizu H, Tatsuno T, Tanaka H. Serotonergic mechanisms in anxiolytic effects of tandospirone in the Vogel conflict test. *Jpn J Pharmacol* 1992;59:105–12.
- Sommermeier H, Schreiber R, Greuel JM, et al. Anxiolytic effects of the 5-HT_{1A} receptor agonist ipsapirone in the rat: neurobiological correlates. *Eur J Pharmacol* 1993;240:29–37.
- Jolas T, Schreiber R, Laporte AM, et al. Are postsynaptic 5-HT_{1A} receptors involved in the anxiolytic effects of 5-HT_{1A} receptor agonists and in their inhibitory effects on the firing of serotonergic neurons in the rat? *J Pharmacol Exp Ther* 1995;272:920–9.