Oral tandospirone and clonidine provide similar relief of preoperative anxiety

[L'administration orale de tandospirone ou de clonidine fournit un soulagement similaire de l'anxiété préopératoire]

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Purpose: To compare oral tandospirone with oral clonidine in terms of preoperative anxiolysis.

Methods: Preoperative anxiety was measured using the Spielberger state-trait anxiety inventory (STAI-state). Pretreatment evaluation was performed on the day before surgery and post-treatment examination immediately after entry into the operating room. In a double-blind, randomized design, three groups of 40 patients received one of the following oral medications 90 min before entry into the operating room: 1) tandospirone 10 mg (T group); 2) clonidine 3 $\mu g \cdot kg^{-1}$ (C group); or 3) placebo (P group).

Results: Following premedication, the STAI-state decreased in the T group ($P < 0.05$) while exhibiting no significant changes in the C group. As far as the changes in the STAI-state were concerned, however, the P-group was different from each of the other groups ($P < 0.05$ *vs* T group and *vs* C group).

Conclusion: Oral tandospirone was equivalent to oral clonidine in terms of reduction in preoperative anxiety.

Objectif : *Comparer la tandospirone et la clonidine orales dans l'anxiolyse préopératoire.*

Méthode : *L'anxiété préopératoire a été mesurée à l'aide d'un questionnaire sur l'anxiété chronique et réactionnelle de Spielberger (State-Trait Anxiety Inventory, STAI-state). L'évaluation prétraitement a été réalisée le jour avant l'opération et l'examen post-traitement, immédiatement après l'entrée en salle d'opération. L'étude randomisée et à double insu comportait 40 patients qui ont reçu l'une des médications orales suivantes 90 min avant d'entrer dans la salle d'opération : 1) 10 mg de tandospirone (groupe T) ; 2) 3 $\mu g \cdot kg^{-1}$ de clonidine (groupe C) ou 3) un placebo (groupe P).*

Résultats : *Après la prémédication, le STAI-state a baissé dans le groupe T ($P < 0,05$) et n'affichait aucun changement significatif dans le groupe C. Concernant les changements du STAI-state, le groupe P différait de chacun des autres groupes ($P < 0,05$ vs T et C).*

Conclusion : *L'administration orale de tandospirone ou de clonidine a été équivalente pour réduire l'anxiété préopératoire.*

PREOPERATIVE anxiolysis and sedation are the main objectives of premedication, and both involve a number of possible mechanisms of action implicating central gamma-aminobutyric acid and adrenergic receptors. We have recently demonstrated that oral administration of tandospirone, a partial agonist of the 5-hydroxytryptamine-1A ($5\text{-}HT_{1A}$) receptor, reduces preoperative anxiety to the same extent as oral diazepam[1] and exerts antiemetic effects postoperatively.[2] On the other hand, clonidine, an α_2-adrenergic receptor agonist, has been used as a premedicant because of its central nervous system (CNS)-mediated responses including anxiolysis, sedation, attenuation of pain perception, and anesthetic sparing effects.[3,4] However, there are no data available regarding the anxiolysis of oral tandospirone compared with oral clonidine before surgery.

The present study was designed to compare oral tandospirone with oral clonidine when both are used as preanesthetic drugs in patients scheduled for elective otolaryngologic surgery. Preoperative anxiety was measured using the standard Spielberger state-trait anxiety inventory (STAI). We hypothesized that tandospirone would be equivalent to clonidine for the relief of preoperative anxiety.

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TABLE Demographic characteristics, baseline STAI-trait and surgical procedures

	Age	*Male/female*	*Height*	*Weight*	*STAI-trait*	*Planned surgical procedure Tympanosplasty/tonsillectomy/ laryngomicrosurgery/miscellaneous*
T-group	44.4 ± 11.9	18/22	159.1 ± 8.6	57.6 ± 9.5	39.5 ± 11.0	13/11/9/7
C-group	41.2 ± 14.0	20/20	163.6 ± 9.0	61.2 ± 9.7	39.7 ± 11.2	12/14/7/7
P-group	40.9 ± 15.5	23/17	162.9 ± 10.2	62.1 ± 12.8	40.8 ± 9.0	13/14/6/7

STAI-trait: trait anxiety score measured by the Japanese form of the standard Spielberger state-trait anxiety inventory.

Patients and methods

The protocol was approved by the Ethics Committee of the Gifu University School of Medicine. Written informed consent was obtained from 120 consecutive inpatients, aged 18 to 64 yr, ASA physical status I or II, scheduled for otolaryngologic surgery. Exclusion criteria were malignancy, coexisting CNS disease, a variety of neurotic disorders, use of centrally acting medications including tandospirone and clonidine, inability to read or speak Japanese, and behavioural impairment.

A randomization list was computer generated, and identical pills containing each drug, according to the list, were prepared by personnel who were not involved in this study. One hundred and twenty patients were divided, using a randomized double-blind design, into three groups of 40 patients each. Together with oral famotidine 20 mg, subjects received oral tandospirone 10 mg (T group), clonidine 3 $\mu g \cdot kg^{-1}$ (C 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 representative of the anxiety occurring immediately preoperatively. Post-treatment evaluation was performed upon arrival in the operating room.

Pre- and post-treatment measurements consisted of the state anxiety score measured by the Japanese form of STAI (STAI-state). In addition, the pretreatment evaluation incorporated the trait anxiety score given by the Japanese form of STAI (STAI-trait). The STAI is a standardized psychomotor test composed of 40 questions that subjects answer using a four-point scale. The sum of 20 responses gives STAI-trait, which is directly proportional to baseline tendencies towards anxiety independent of the subject current situation. The remaining 20 questions yield STAI-state, which increases proportionally to situational anxiety level.

To compare data among the T, C, and P groups, categorical data were analyzed using the Pearson Chi-square tests with Yates correction or Fisher exact probability test, as appropriate. Continuous data were analyzed by means of Bonferroni multiple comparison tests after a one-way analysis of variance. In each premedication group, a comparison between post- and pretreatment values was performed using a paired t test. In all tests, a value of $P < 0.05$ was considered statistically different. Data are presented as the mean ± standard deviation, unless otherwise indicated. Power analysis was performed to determine the number of patients in the study on the basis of the assumptions that 1) the change in STAI-state after premedication in the P-group and in either the T or C group would be 4 ± 10 and -3 ± 10, respectively, as in our recent study;[1] 2) this difference was considered as clinically significant; and 3) $\alpha = 0.05$ and $1\text{-}\beta = 0.8$. On the basis of these assumptions, at least 32 patients per group were required.

Results

There were no significant differences among the T, C, and P groups in terms of age, sex, height, weight, STAI-trait, or planned surgical procedures (Table), or in the baseline values obtained prior to premedication for STAI-state (Figure 1).

When post-treatment values were compared with pretreatment values, STAI-state decreased in the T- ($P < 0.05$), but increased in the P-group ($P < 0.05$), and remained unchanged in the C-group (Figure 1). As far as changes in STAI-state were concerned, the P-group was significantly different from each of the other groups ($P < 0.05$ *vs* T-group and *vs* C-group) with no significant difference between the T and C groups (Figure 2).

Discussion

The principal finding of our study is that the anxiolytic effect of oral tandospirone was equivalent to that of oral clonidine as measured by the STAI-state. The STAI-state was decreased by oral tandospirone, increased in the placebo group and remained unchanged with oral clonidine. Nevertheless, no dif-

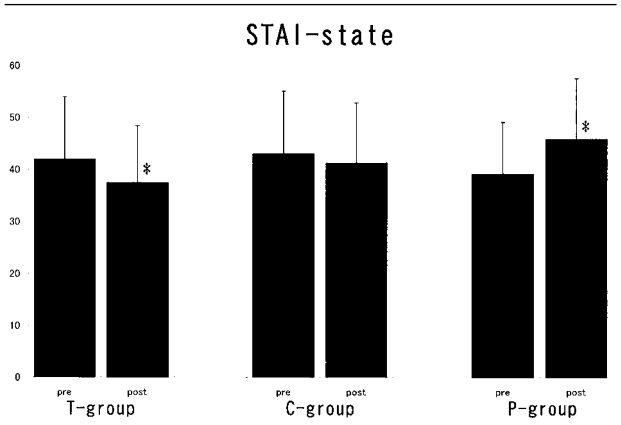

FIGURE 1 State anxiety scores measured by the Spielberger state-trait anxiety inventory (STAI-state) in T, C, and P groups. *$P < 0.05$ compared with pretreatment STAI-state.

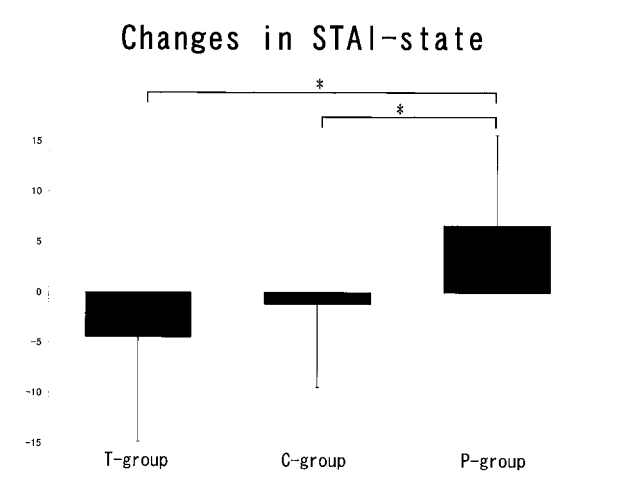

FIGURE 2 Changes in state anxiety scores measured by the Spielberger state-trait anxiety inventory (STAI-state) in T, C, and P groups. *$P < 0.05$ compared with the P group.

ferences were observed between oral tandospirone and oral clonidine. In terms of preoperative anxiolysis, we were unable to demonstrate the superiority of oral tandospirone to oral clonidine, but at least we could exclude the inferiority of oral tandospirone to oral clonidine.

Oral tandospirone and oral clonidine have different mechanisms of action. Tandospirone is considered to produce its anxiolytic effects by stimulating presynaptic 5-HT_{1A} receptors in the brainstem raphe nuclei. This results in attenuation of postsynaptic cell firing and subsequent inhibition of serotonergic neurotransmission in the limbic system.[5–7] On the other hand, the site of action of oral clonidine is probably the locus coeruleus, because infusion of α_2-adrenergic receptor agonists and antagonists into the locus coeruleus of rats can increase or decrease, respectively, activity in the Porsolt forced swim test, a widely accepted predictive model of the efficacy of antidepressant drugs.[8,9] The anxiolytic effects of tandospirone have been demonstrated to be separate from its sedative, anticonvulsant and muscle relaxant effects,[10,11] while clonidine is an α_2-adrenergic receptor agonist and its sedative properties have been well documented.[3] A similar functional duality has been demonstrated to exist in the modulation of depression in patients: serotonergic agents tend to improve mood, whereas noradrenergic agents tend to improve drive or motivation.[12] In the present study, however, we did not examine the sedative effects produced by each test drug. Further studies are needed in this area.

In conclusion, oral tandospirone is equivalent to oral clonidine in the relief of preoperative anxiety.

References

1 *Oshima T, Kasuya Y, Terazawa E, Nagase K, Saitoh Y, Dohi S.* The anxiolytic effects of 5-hydroxytryptamine-1A agonist tandospirone before otolaryngologic surgery. Anesth Analg 2001; 93: 1214–6.

2 *Oshima T, Kasuya Y, Okumura Y, Terazawa E, Dohi S.* Prevention of nausea and vomiting with tandospirone in adults after tympanoplasty. Anesth Analg 2002; 95: 1442–5.

3 *Lakhlani PP, MacMillan LB, Guo TZ, et al.* Substitution of a mutant α_{2}a-adrenergic receptor via "hit and run" gene targeting reveals the role of this subtype in sedative, analgesic, anesthetic sparing-responses in vivo. Proc Natl Acad Sci USA 1997; 94: 9950–5.

4 *Schramm NL, McDonald MP, Limbird LE.* The α_{2A}-adrenergic receptor plays a protective role in mouse behavioral model of depression and anxiety. J Neurosci 2001; 21: 4875–82.

5 *De Vry J.* 5-HT_{1A} receptor agonists: recent developments and controversial issues. Psychopharmacology 1995; 121: 1–26.

6 *Sommermeyer H, Schreiber R, Greuel JM, De Vry J, Glaser T.* Anxiolytic effects of the 5-HT_{1A} receptor agonist ipsapirone in the rat: neurobiological correlates. Eur J Pharmacol 1993; 240: 29–37.

7 *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.

8 *Simson PG, Weiss JM, Hoffman LJ, Ambrose MJ.* Reversal of behavioral depression by infusion of an alpha-2 adrenergic agonist into the locus coeruleus. Neuropharmacology 1986; 25: 385–9.

9 *Weiss JM, Simson PG, Hoffman LJ, Ambrose MJ, Cooper S, Webster A.* Infusion of adrenergic receptor agonists and antagonists into the locus coeruleus and ventricular system of the brain. Effects on swim-motivated and spontaneous motor activity. Neuropharmacology 1986; 25: 367–84.

10 *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.

11 *Unrug-Neervoort A, van Luijtelaar G, Coenen A.* Cognition and vigilance: differential effects of diazepam and buspirone on memory and psychomotor performance. Neuropsychobiology 1992; 26: 146–50.

12 *Healy D, McMonagle T.* The enhancement of social functioning as a therapeutic principle in the management of depression. J Psychopharmacol 1997; 11(Suppl.): S25–31.