J Anesth (2007) 21:131–135
DOI 10.1007/s00540-006-0490-x

Journal of
Anesthesia

Identification of independent predictors for intravenous thiopental-induced yawning

Tsutomu Oshima[1], Hirofumi Utsunomiya[2], Yoshiko Kasuya[3], Junko Sugimoto[1], Kazuo Maruyama[2], and Shuji Dohi[1]

[1] Department of Anesthesiology, Gifu University School of Medicine, Gifu 501-1194, Japan
[2] Department of Anesthesiology, Mie University School of Medicine, Tsu 514-8507, Japan
[3] Division of Anesthesia, Gifu Red Cross Hospital, Gifu 502-8511, Japan

Abstract
Purpose. To explore risk factors for the yawning response induced by the intravenous administration of thiopental during the induction of general anesthesia.
Methods. We analyzed data from a cohort of 1322 patients who underwent elective surgery under general anesthesia plus intravenous thiopental. The data collected were: (a) the patients' demographic findings (age, sex, height, weight, cigarette smoking, hypertension, and presence of cerebral lesion), and (b) anesthesia-related findings (the kind of preanesthetic medication, i.e., atropine, epidural lidocaine, priming dose of vecuronium, fentanyl, and the dose of intravenous thiopental). An association between an individual variable in the evaluation model and the likelihood of thiopental-induced yawning behavior was characterized by means of the odds ratio. Multiple logistic regression was used to examine the independent contribution of each candidate variable, while controlling for all variables.
Results. After the intravenous administration of thiopental, 461 patients exhibited a yawning response. The probability of this response was decreased by the prior use of intravenous fentanyl, by female sex, and by premedication with clonidine, but the probability was unaffected by premedication with hydroxyzine, by the prior use of atropine, or by the presence of hypertension or a cerebral lesion.
Conclusion. Thiopental-induced yawning may be suppressed by female sex, prior use of intravenous fentanyl, and premedication with clonidine. These findings may allow insights into the physiologic and pharmacological aspects of yawning in humans, thereby leading to the development methods to prevent thiopental-induced yawning.

Key words Yawning · Intravenous induction · Thiopental

Address correspondence to: T. Oshima, Department of Anesthesiology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
Received: September 8, 2006 / Accepted: December 6, 2006

Introduction

Yawning—which is characterized by gaping accompanied by a long inspiration, followed by a shorter expiration—resembles classical reflexes in that, once initiated, the specific pattern of motor output with associated inspiration and expiration proceeds to completion with only a minimal influence from sensory feedback [1]. Yawning can also be accompanied by changes in autonomic function, such as lacrimation and penile erection [2–4]. Furthermore, yawning has been established as a phenomenon that promotes arousal [5].

One of the most frequently encountered clinical situations in which yawning occurs is with the intravenous induction of general anesthesia using thiopental or propofol [6,7]. The yawning response can be observed within 1 min after the intravenous injection of thiopental or propofol, with an occurrence rate of over 50% [6,7]. We have recently demonstrated that the yawning response elicited during intravenous induction using thiopental or propofol is associated with a transient arousal shift during continuing loss of consciousness [7]. Therefore, the prevention of the yawning response during intravenous induction may contribute to a reduction in the likelihood of arousal, especially during the induction of general anesthesia. In the present study, we carried out an epidemiological investigation of the probability of thiopental-induced yawning, as a preliminary study to explore the physiologic and pharmacological aspects of yawning in humans, with the aim of leading to the development of methods to prevent thiopental-induced yawning.

Patients, materials, and methods

Institutional Review Board (IRB) approval was obtained for the study. The population consisted of 1322 consenting patients referred for elective surgery under

general anesthesia, with intravenous induction using thiopental, at Gifu University Hospital, Mie University Hospital, or Gifu Red Cross Hospital from January to December 2002. This study was a secondary historical cohort analysis of data obtained from a database maintained by three of the authors (T.O., H.U., and Y.K.)

As demographic findings, the database included details of each patient's age, sex, height, and weight. The other data collected concerned cigarette smoking, hypertension, and cerebral lesions (cerebral infarction and/or hemorrhage). As anesthesia-related findings, we recorded information concerning the kind of anxiolytic drug given as preanesthetic medication (benzodiazepines, clonidine, hydroxyzine, or no drug), prior administration of atropine, extradural catheterization and injection of lidocaine, priming dose of vecuronium, and prior intravenous administration of fentanyl, together with the dose of intravenously injected thiopental. An intravenous injection of thiopental was administered within a 5-s period, although the rate of administration of thiopental was not controlled. As the only clinical endpoint, one observer continuously assessed the occurrence of the yawning response (characterized by mouth-opening) during intravenous induction using thiopental.

Statistical analysis

To compare group data (demographic or anesthesia-related findings) between patient groups with and without a yawning response, categorical data were analyzed using either the Pearson χ^2 test (with Yates' correction) or Fisher's exact probability test, as appropriate. Continuous data were analyzed by means of one-way analysis of variance. In all tests, a value of $P < 0.05$ was considered statistically significant. On the other hand, the relative magnitudes of associations between individual variables (demographic or anesthesia-related findings) and the likelihood of a yawning response were compared using crude odds ratios (ORs). The precision of the estimated ORs was assessed by examining the 95% confidence intervals (CIs). The association between a given variable and the probability of the yawning response was considered significant when the CI did not include 1.0. The second step in the analysis involved the use of a multivariate logistic regression model containing all candidate variables to examine the independent contribution made by each variable, while controlling for all variables. This resulted in an adjusted OR and a calculated 95% CI. Value for group data are presented as means ± SD, numbers, or percentages. To evaluate the discrimination and calibration for the final model, the c-statistic and the Hosmer-Lemeshow goodness-of-fit χ^2, respectively, were calculated. Furthermore, to indicate the relative contribution to the final model, the likelihood χ^2 value for the predictors was presented. The statistics program used for the analysis was SPSS 11.5 J for Windows (SPSS Japan, Tokyo, Japan).

Results

Of the total 1322 patients, 461 exhibited a yawning response, characterized by opening of the mouth, after the intravenous injection of thiopental. As the principal findings obtained by our multivariate logistic regression analysis, prior use of intravenous fentanyl showed the best association with suppression of the response, followed by premedication with clonidine, and by female sex.

The demographic characteristics revealed that the group of patients showing the yawning response contained a lower percentage of cigarette smokers than the group not showing such a response (Table 1). Inspection of the anesthesia-related findings revealed that the yawning group also showed, by comparison with the nonyawning group, a significant difference in the type of premedication; namely, a higher percentage with prior use of atropine, a higher percentage with a priming dose of vecuronium, a lower percentage receiving prior intravenous fentanyl, and a lower dose of thiopental (Table 1).

Table 2 displays: (1) the numbers of patients found to have a demographic or anesthesia-related possible risk factor, as well as the percentage exhibiting the yawning response, (2) the crude ORs and 95% CIs, (3) the adjusted ORs (when adjusted for all variables in the model), and (4) the likelihood χ^2 value for each demographic and anesthesia-related possible risk factor. The results exhibited by the crude ORs were similar to those shown in Table 1. As facilitators of thiopental-induced yawning, our multivariate logistic regression analysis eliminated the absence of cigarette smoking, prior use of atropine, priming dose of vecuronium, and lower dose of thiopental among these promising candidate variables, and included male sex (Table 2; adjusted ORs). Overall, an absence of intravenous fentanyl, no use of clonidine as premedication, and male sex were found to be significant independent risk factors for the yawning response. Conversely, prior intravenous fentanyl, premedication with clonidine, and female sex were all associated with a decreased risk of the yawning response.

For the final logistic regression model with all of the independent valuables, the c-statistic was 0.799, and the Hosmer-Lemeshow goodness of fit χ^2 value was 6.66 with 8 degrees of freedom. The observed significance

Table 1. Demographic characteristics and anesthesia-related findings in patients with and without yawning

Demographic characteristics and anesthesia-related findings	Patients with yawning (n = 461)	Patients without yawning (n = 861)	P value
Age (years)	52.8 ± 20.8	51.3 ± 20.0	0.217
Male / Female	234/227	392/469	0.073
Height (cm)	156.7 ± 14.1	157.5 ± 12.3	0.299
Weight (Kg)	55.7 ± 14.0	55.3 ± 12.9	0.571
Cigarette smokers (%)	27.8	33.6	0.035
Hypertension (%)	25.4	23.2	0.381
Premedication (no anxiolytics / benzodiazepines / clonidine / hydroxyzine)	103/215/18/125	106/422/166/167	<0.001
Use of atropine (%)	28.0	19.7	0.001
Epidural injection of lidocaine (%)	40.3	42.6	0.447
Vecuronium (%)	30.4	6.7	<0.001
Intravenous fentanyl (%)	3.0	51.6	<0.001
Thiopental dose per weight (mg·kg^{-1})	3.8 ± 1.0	4.0 ± 1.0	<0.001

Table 2. Associations between possible risk factors and yawning

Possible risk factors	n (1322 total)	Yawning (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Likelihood χ^2 (degree of freedom)
Age (years)			1.0 (1.0–1.0)	1.0 (1.0–1.0)	2.0 (1)
Sex					
Female	696	32.6	0.81 (0.65–1.0)	0.69 (0.52–0.93)	5.9 (1)
Male	626	37.4			
Cigarette smoking					
Present	417	30.7	0.76 (0.59–0.98)	0.73 (0.52–1.0)	3.7 (1)
Absent	905	36.8			
Hypertension					
Present	317	36.9	1.1 (0.86–1.5)	1.1 (0.77–1.5)	0.21 (1)
Absent	1005	34.2			
Cerebral lesion					
Present	76	32.9	0.91 (0.56–1.5)	0.59 (0.33–1.0)	3.4 (1)
Absent	1246	35.0			
Premedication					
Clonidine	184	9.8	0.11 (0.064–0.20)	0.24 (0.13–0.46)	22.8 (3)
Hydroxyzine	292	42.8	0.77 (0.54–1.1)	0.39 (0.10–1.5)	
Bezodiazepine	637	33.8	0.52 (0.38–0.72)	0.71 (0.48–1.0)	
No anxiolytics	209	49.3			
Atropine					
Present	299	43.1	1.6 (1.2–2.1)	2.4 (0.65–9.1)	1.8 (1)
Absent	1023	32.5			
Epidural lidocaine					
Present	553	33.6	0.91 (0.72–1.1)	1.1 (0.85–1.5)	0.69 (1)
Absent	769	35.8			
Vecuronium					
Present	293	10.6	0.17 (0.11–0.24)	0.81 (0.48–1.4)	0.58 (1)
Absent	1029	41.8			
Fentanyl					
Present	458	3.1	0.029 (0.017–0.051)	0.038 (0.021–0.069)	222.1 (1)
Absent	864	51.7			
Thiopental dose			0.73 (0.65–0.82)	0.91 (0.79–1.1)	1.5 (1)

level for this χ^2 value was 0.574. Therefore, we do not reject the null hypothesis that there is no difference between the observed and predicted values. This model appears to fit the data reasonably well.

Discussion

Our analysis of adjusted ORs demonstrated that the probability of the yawning response elicited by intravenous thiopental was decreased by the prior use of intravenously injected fentanyl, by premedication

with clonidine, and by female sex (Table 2, adjusted ORs).

These results differ in some respects from those shown in Table 1 and in the crude ORs in Table 2, which suggests that the predisposing factors additionally include the absence of cigarette smoking, the prior administration of atropine, a priming dose of vecuronium, the absence of intravenous fentanyl, and a lower dose of intravenous thiopental, while excluding male sex. This study is a secondary historical cohort analysis of data obtained from our database. Our use of a multiple logistic regression model provided an adjusted OR with 95% CI, allowing us to assess the independent contribution of each variable, while controlling for all variables. As predisposing factors for thiopental-induced yawning, this method excluded the absence of cigarette smoking, the prior administration of atropine, a priming dose of vecuronium, and a lower dose of intravenous thiopental, while also including male sex (Table 2, adjusted ORs).

Although various kinds of drugs, such as adrenocorticotropic hormone-melanocyte stimulating hormone (ACTH-MSH) peptides, cholinomimetic drugs (physostigmine, pilocarpine, and others), dopamine D_2 receptor agonists, oxytocin, *N*-methyl-D-aspartae (NMDA), and nitric oxide donors, have been demonstrated to induce yawning behavior in animals [1,3–5,8], no drugs other than apomorphine, as a D_2 receptor agonist, have been previously shown to elicit yawning in humans [9]. For this reason, we cannot reach a conclusion about how the numerous hypotheses regarding the physiologic and pharmacological aspects of yawning that have arisen as a result of animal experiments are related to humans [1,3–5,8]. To allow insights into the physiologic and pharmacological aspects of yawning in humans, the present findings need to be compared with previous data accumulated from both clinical observations [9] and from studies of conventional experimental yawning models in animals [1,3–5,8].

Firstly, an inhibitory effect of intravenous fentanyl on the yawning response is consistent with experimental data previously obtained in rats. For example, morphine, a traditional opioid peptide, has been reported to prevent the yawning response in conscious rats [10,11], while naloxone, an opioid receptor antagonist, reportedly increases the yawning response [11]. Further, yawning is one of the commonest signs of opiate-withdrawal syndrome in opiate addicts. Secondly, the suppressive effect of premedication with clonidine on the yawning response may be attributable to a reduction in central sympathetic outflow mediated by the stimulation of presynaptic alpha$_2$-adrenoceptors, although, admittedly, some previous findings are controversial, especially regarding the role of the alpha$_1$- and alpha$_2$-adrenoceptor subtypes in the expression of yawning [12–14]. Interestingly, we have recently demonstrated that thiopental-induced yawning is related to a transient arousal shift during progressive loss of consciousness [7]. Clonidine is likely to prevent a transient arousal shift during ongoing loss of consciousness by virtue of its anesthetic-sparing effects [15]. However, these hypothetical mechanisms must await further investigations. Thirdly, the increased probability of the yawning response in male patients in the present study is consistent with the finding that yawning was found to be an androgen-dependent sexually dimorphic behavior, occurring in males more frequently than in females in adult rhesus monkeys [16,17].

In the present study, some apparently promising demographic and anesthesia-related factors were found to be unrelated to the probability of thiopental-induced yawning. Firstly, an inhibitory effect of premedication with hydroxyzine, a histamine 1 receptor antagonist, on the yawning response was excluded. This finding was contrary to previous experimental findings that the microinjection of histamine into the paraventricular nucleus evoked the yawning response in anesthetized rats [18] and that a histamine 1 receptor antagonist injected subcutaneously into conscious rats inhibited the apomorphine-induced yawning response [19]. Secondly, an effect of atropine on the yawning response was also excluded by our analysis. This finding is inconsistent with previous data obtained in animals, which showed that muscarinic receptor antagonists that cross the blood–brain barrier (atropine and scopolamine) prevented the yawning response in rats [10,20]. These inconsistencies may be explained by species differences and/or by the dose of either hydroxyzine or atropine used in this study being too low to have this effect. Lastly, effects of a cerebral lesion or existing hypertension on the yawning response were ruled out in this study. These results are inconsistent with the frequent occurrence of yawning associated with orthostatic hypotension [21], in which a sudden postural change from the supine to the upright position results in fainting in some subjects, and is explained as a failure to regulate the cerebral circulation. Further studies are needed to elucidate these unsolved problems.

The present findings suggest that a male patient may have a high risk of thiopental-induced yawning, and that the prior use of fentanyl combined with clonidine premedication may be recommended to prevent the yawning behavior and associated transient arousal shift [7] during the intravenous induction of general anesthesia using thiopental. However, further prospective, double-blinded, placebo-controlled trials are needed to confirm the effects of these plausible influencing factors on the yawning response, and it is hoped that such trials will lead to the establishment of the means by which this phenomenon can be prevented in the clinical setting.

Moreover, the question of whether these possible preventive methods could indeed reduce the likelihood of arousal during general anesthesia also awaits further investigation.

In conclusion, the probability of thiopental-induced yawning in patients was decreased by prior use of intravenous fentanyl, by premedication with clonidine, and by female sex, but was unaffected by premedication with hydroxyzine, by prior use of atropine, or by hypertension or cerebral infarction and/or hemorrhage.

Acknowledgments. This study was supported in part by Grant-in-Aid 17591624 from the Japan Society for the Promotion of Science.

References

1. Argiolas A, Melis MR (1998) The neuropharmacology of yawning. Eur J Pharmacol 343:1–16
2. Heusner AP (1946) Yawning and associated phenomena. Physiol Rev 26:156–168
3. Melis MR, Argiolas A, Gessa GL (1986) Oxytocin-induced penile erection and yawning: site of action in the brain. Brain Res 398: 259–265
4. Melis MR, Argiolas A, Gessa GL (1987) Apomorphine-induced penile erection and yawning: site of action in brain. Brain Res 415:98–104
5. Sato-Suzuki I, Kita I, Oguri M, Arita H (1998) Stereotyped yawning responses induced by electrical and chemical stimulation of paraventricular nucleus of the rat. J Neurophysiol 80:2765–2775
6. Kim DW, Kil HY, White PF (2002) Relationship between clinical endpoints for induction of anesthesia and bispectral index and effect-site concentration values. J Clin Anesth 14:241–245
7. Kasuya Y, Murakami T, Oshima T, Dohi S (2005) Does yawning represent a transient arousal-shift during intravenous induction of general anesthesia? Anesth Analg 101:382–384
8. Bertolini A, Gessa GL (1981) Behavioral effects of ACTH and MSH peptides. J Endocrinol Invest 4:241–251
9. Lal S, Tesfaye Y, Thavundayil JX, Thompson TR, Kiely ME, Nair NP, Grassino A, Dubrovsky B (1989) Apomorphine: clinical studies on erectile impotence and yawning. Prog Neuropsychopharmacol Biol Psychiatry 13:329–339
10. Ferrari W, Gessa GL, Vargiu L (1963) Behavioural effects induced by intra-cisternally injected ACTH and MSH. Ann N Y Acad Sci 104:330–345
11. Berendsen HHG, Gower AJ (1986) Opiate–androgen interaction in drug-induced yawning and penile erection in the rat. Neuroendocrinology 45:185–190
12. Poggioli R, Vergoni AV, Guarini S, Bertolini A (1984) Influence of clonidine on the ACTH-induced behavioral syndrome. Eur J Pharmacol 101:299–301
13. Kimura H, Yamada K, Nagashima M, Furukawa T (1996) Involvement of catecholamine receptor activities in modulating the incidence of yawning in rats. Pharmacol Biochem Behav 53: 1017–1021
14. Zarrindast MR, Fazli-Tabai S, Semnanian S, Fathollahi Y (1999) Influence of different adrenoceptor agonists and antagonists on physostigmine-induced yawning in rats. Pharmacol Biochem Behav 62:1–5
15. Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE (1997) Substitution of a mutant alpha2a-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 94:9950–9955
16. Serra G, Collu M, Serra A, Gessa GL (1984) Estrogens antagonize apomorphine-induced yawning in rats. Eur J Pharmacol 104: 383–386
17. Graves FC, Wallen K (2006) Androgen-induced yawning in rhesus monkey females is reversed with a nonsteroidal antiandrogen. Horm Behav 49:333–236
18. Seki Y, Sato-Suzuki I, Kita I, Oguri M, Arita H (2002) Yawning/cortical activation induced by microinjection of histamine into the paraventricular nucleus of the rat. Behav Brain Res 134:75–82
19. Gower AJ, Berendsen HHG, Broekkamp CL (1986) Antagonism of drug-induced yawning and penile erection in rats. Eur J Pharmacol 122:239–244
20. Urbá-Holmgren R, González RM, Holmgren B (1977) Is yawning a cholinergic response? Nature 267:261–262
21. Shvartz E (1996) Endurance fitness and orthostatic tolerance. Aviat Space Environ Med 67:935–939