General Anesthesia

Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough

[L'administration iv de lidocaïne et d'éphédrine, mais non de propofol, supprime la toux causée par le fentanyl]

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Purpose: The aim of this study was to evaluate the effectiveness of lidocaine, propofol and ephedrine in suppressing fentanyl-induced cough.

Methods: One hundred and eighteen patients were randomly assigned into four groups and the following medications were given intravenously: patients in Group I (n = 31) received normal saline 2 mL, Group II (n = 29) received lidocaine 2 mg·kg^{-1}, Group III (n = 30) received propofol 0.6 mg·kg^{-1} and Group IV (n = 28) received ephedrine 5 mg. At one minute after the study medication, fentanyl 2.5 μg·kg^{-1} was given intravenously within two seconds. The occurrence of cough and vital sign profiles were recorded within two minutes after fentanyl bolus by an anesthesiologist blinded to study design.

Results: Sixty-five percent of patients in the placebo group had cough, whereas the frequency was significantly decreased in Groups II (14%) and IV (21%). Although a numerically lower frequency of cough was noted in Group III (37%), it was not statistically different from that of the placebo group. SpO_2 decreased significantly in patients of Group III compared to placebo; one patient experienced hypoxemia necessitating mask ventilation. Patients in Group III showed a decrease in heart rate and systolic blood pressure (2 beats·min^{-1} and 8 mmHg *vs* baseline). Patients in Group IV showed an increase in both measurements (5 beats·min^{-1} and 8 mmHg *vs* baseline). No truncal rigidity was observed throughout the study.

Conclusions: Intravenous lidocaine 2 mg·kg^{-1} or ephedrine 5 mg, but not propofol 0.6 mg·kg^{-1}, was effective in preventing fentanyl-induced cough. The results provide a convenient method to decrease fentanyl-induced cough.

Objectif : *Évaluer l'efficacité de la lidocaïne, du propofol et de l'éphédrine dans la suppression de la toux induite par le fentanyl.*

Méthode : *Cent dix-huit patients ont été répartis au hasard en quatre groupes et ont reçu : Groupe I (n = 31), 2 mL de solution saline ; Groupe II (n = 29), 2 mg·kg^{-1} de lidocaïne ; Groupe III (n = 30), 0,6 mg·kg^{-1} de propofol et Groupe IV (n = 28), 5 mg d'éphédrine. À une minute après la médication expérimentale, 2,5 μg·kg^{-1} de fentanyl iv ont été administrés en moins de deux secondes. L'occurrence de toux et les profils des signes vitaux ont été enregistrés par un anesthésiologiste impartial pendant les deux minutes qui ont suivi l'administration de bolus de fentanyl.*

Résultats : *Soixante-cinq pour cent des patients du groupe placebo ont eu de la toux, tandis que la fréquence a significativement diminué dans les Groupes II (14 %) et IV (21 %). Même si une fréquence de toux numériquement plus basse a été notée dans le Groupe III, elle n'était pas statistiquement différente de celle du groupe placebo. La SpO_2 a diminué significativement chez les patients du Groupe III comparé au groupe placebo ; un patient a présenté de l'hypoxémie nécessitant une ventilation au masque. Les patients du Groupe III ont subi une baisse de la fréquence cardiaque et de la tension artérielle systolique (2 battements·min^{-1} et 8 mmHg vs les mesures de base). Ceux du Groupe IV ont présenté une augmentation de ces deux paramètres (5 battements·min^{-1} et 8 mmHg vs les mesures de base). Aucune rigidité tronculaire n'a été observée pendant l'étude.*

Conclusion : *L'administration iv de 2 mg·kg^{-1} de lidocaïne ou de 5 mg d'éphédrine, mais non de 0,6 mg·kg^{-1} de propofol, a été efficace pour prévenir la toux induite par le fentanyl. Les résultats offrent une méthode pratique de diminuer la toux induite par le fentanyl.*

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REFLEX cough is often observed after an *iv* bolus of fentanyl during induction. The incidence of fentanyl-induced cough varies from 28 to 46% according to previous reports.[1–4] The tussive effect of fentanyl is usually transient and self-limited for most patients. Yet this phenomenon may be undesirable in patients with some co-existing diseases including increased intracranial pressure, open eye injury, dissecting aortic aneurysm, pneumothorax or reactive airway disease. Recently Tweed and Dakin even reported that an episode of explosive coughing after *iv* fentanyl in a seven-year-old boy led to multiple conjunctival and periorbital petechiae.[5]

Several pharmacological measures have been studied to mitigate this adverse effect with varying success. One study showed that premedication with morphine given one hour before induction is effective.[2] Another study demonstrated that the inhalation of terbutaline, a selective $ß_2$-adrenergic bronchodilator, could effectively suppress this reflex.[3] More recently Agarwal *et al.*[4] reported that aerosol inhalation of salbutamol, beclomethasone or sodium chromoglycate 15 min prior to entering the operating room could also reduce the incidence of cough. However, these methods can be inconvenient, so their clinical acceptance is somewhat limited. We conducted the present study in an attempt to find other drugs that could effectively attenuate fentanyl-induced cough while being convenient in clinical practice. We selected lidocaine, propofol and ephedrine, which are all readily available in the operation room. Both lidocaine and propofol have been shown to reduce airway reactiveness.[6,7] With its ß-adrenergic agonism, ephedrine has a bronchodilating effect and may be effective in suppressing the cough reflex. We investigated the effectiveness and adverse events of the three drugs in a randomized, prospective study.

Methods

After obtaining approval from the Institutional Review Board of our hospital and informed consents from the patients, 118 adult patients of ASA physical status class I or II were enrolled in the study. All patients were scheduled for elective surgical procedures, and their ages were between 18 and 65 yr. Exclusion criteria included history of asthma, chronic cough, smoking, upper respiratory tract infection in the previous two weeks, or medication with angiotensin-converting enzyme inhibitors. No premedication was allowed. Patients were randomly assigned into four groups. The table of random digits was used for randomization according to the four possible combinations which were obtained from the last two digits of the random number by odd or even number (i.e., odd + odd, odd + even, even + odd, or even + even). Each combination was assigned to one group in a random manner. All patients were monitored with a continuous electrocardiogram, pulse oximeter and noninvasive blood pressure measurement throughout the study. After establishing a freely running *iv* line, subjects were left undisturbed for one minute. Then, patients were given the following medications intravenously: Group I received 2 mL saline as placebo; Group II received lidocaine 2 $mg \cdot kg^{-1}$; Group III received propofol 0.6 $mg \cdot kg^{-1}$ and Group IV received ephedrine 5 mg.

At one minute after the aforementioned treatment in each group, fentanyl 2.5 $\mu g \cdot kg^{-1}$ was rapidly administered through the peripheral *iv* line within two seconds. The occurrence and intensity of cough within two minutes after the fentanyl injection were recorded since the cough generally happens within this period of time. The intensity of cough was arbitrarily graded as the following: no cough (grade zero), cough less than three seconds (grade one) and cough more than three seconds (grade two). A resident who was blind to group assignment recorded the cough intensity.

Blood pressure and heart rate were recorded before the administration of each drug and after the injection of fentanyl. The oxygen saturation was closely observed and when SpO_2 dropped below 90%, manually assisted mask ventilation with oxygen was to be applied immediately. The SpO_2 before the administration of the test drugs and the lowest reading after the administration of fentanyl were recorded for comparison. The occurrence of other side effects possibly related to drug treatment such as truncal rigidity, dizziness, injection pain, arrhythmia, nausea or vomiting, was also recorded.

We conducted a pilot study using this protocol in 30 patients and observed that 22 patients had cough. We defined a significant suppressive effect as decreasing the incidence of cough to half of control. The smallest sample size required to detect such a difference was a total of 106 patients with an α value equaling 0.05 and a power of 0.8. One hundred and eighteen patients were enrolled in the present study. Results are expressed as mean ± standard deviation or mean (range). The frequency of cough in Groups II, III and IV was compared to that of the placebo group by Chi-square test or Fisher's exact test when appropriate with Bonferroni correction, as were other nominal data. One-way analysis of variance was used to compare the age, weight and height among the four groups. The differences between the vital sign profiles

TABLE I Demographic characteristics of the study population

Group	*I (n = 31)*	*II (n = 29)*	*III (n = 30)*	*IV (n = 28)*
Age (yr)	36.8 ± 14.1	44.0 ± 12.3	38.3 ± 11.7	39.2 ± 12.4
Weight (kg)	61.0 ± 10.9	57.1 ± 8.5	61.1 ± 9.0	59.4 ± 9.2
Height (cm)	161.9 ± 8.6	159.2 ± 5.9	160.7 ± 7.2	162.6 ± 7.8
Sex (F/M)	21/10	20/9	21/9	19/9
ASA class (I/II)	22/9	15/14	19/11	20/8

Values are expressed as mean ± standard deviation or number of cases. Group I = placebo; Group II = lidocaine; Group III = propofol; Group IV = ephedrine one minute before fentanyl injection. No significant difference between groups.

TABLE II Frequency and intensity of cough induced by fentanyl

Group	*Frequency (%)*	*Cough intensity scale*		
		0	*1*	*2*
I	20/31 (65%)	11/31	18/31	2/31
II	4/29 (14%)*	25/29	3/29	1/29
III	11/30 (37%)	19/30	9/30	2/30
IV	6/28 (21%)*	22/28	5/28	1/28

Group I = placebo; Group II = lidocaine; Group III = propofol; Group IV = ephedrine one minute before fentanyl injection. The intensity of cough = no cough (grade 0); cough less than three seconds (grade 1); cough more than three seconds (grade 2). Data are expressed as number of cases or percentage. *Indicates significant difference from Group I.

recorded before and after the treatment were compared by paired t test. The drop in SpO_2 was analyzed by Kruskal-Wallis test and subsequent Dunn test for post hoc comparisons against the placebo group. A P value less than 0.05 was considered to be statistically significant.

Results

The demographic data including age, weight, height, sex, ASA physical status and indications of surgery did not differ significantly among the four groups (Table I). In the placebo group 65% (20/31) of patients had cough, whereas the frequency was significantly decreased in Group II (4/29, 14%) and Group IV (6/28, 21%; $P < 0.001$ and $P = 0.002$, respectively; Table II). Although a numerically lower frequency of cough was noted in Group III (37%), it failed to show a statistically significant difference from that of the placebo group ($P = 0.055$). Incidentally, we found that there was an age-related incidence of fentanyl-induced cough. In the control group, 92% of patients (12/13) younger than 35 yr old, 54% of patients (7/13) between 36 and 50 yr old and only 20% of patients (1/5) older than 51 yr experienced cough, respectively ($P < 0.05$ by Chi-square test).

The baseline vital sign profiles were comparable among the four groups. The systolic blood pressure and heart rate readings did not differ significantly after treatment in Groups I and II, whereas a decrease in systolic blood pressure (about 8 mmHg) was observed in Group III and an increase (about 8 mmHg) was found in Group IV (both $P < 0.001$) after treatment (Table III). Similarly, a slight decrease in heart rate ($P < 0.05$) was found in Group III and an increase in heart rate was noted in the ephedrine group ($P < 0.001$). The patients in all four groups showed a decrease in SpO_2. On examining the extent of SpO_2 drop, we found that only the readings of Group III dropped significantly compared to placebo.

One patient in Group III suffered from hypoxemia ($SpO_2 < 90\%$) after the administration of fentanyl, necessitating manually assisted mask ventilation. Injection pain was most noticeable in the propofol group. Other adverse effects occurred rarely with no significant difference among the groups, as listed in Table IV. There was no cardiac arrhythmia or truncal rigidity in any of the patients throughout the study.

Discussion

We have shown that fentanyl, when administered through a peripheral venous line, provokes reflex cough in up to 65% of patients. The tussive effect induced by fentanyl can be suppressed by pretreatment with lidocaine 2 $mg \cdot kg^{-1}$ or ephedrine 5 mg given intravenously at one minute before fentanyl, but not by the administration of 0.6 $mg \cdot kg^{-1}$ propofol.

Fentanyl-induced cough is commonly observed during the induction of anesthesia. In the study by Bohrer *et al.*,[1] 46% of the patients coughed after receiving 7 $\mu g \cdot kg^{-1}$ fentanyl through a central venous catheter. Another study by Lui *et al.*[3] showed that 43% of patients coughed after receiving 5 $\mu g \cdot kg^{-1}$ fentanyl injected through a peripheral venous line. Phua *et al.*[2] found that fentanyl 1.5 $\mu g \cdot kg^{-1}$ given through a peripheral venous line elicited cough in 28% of the patients and a similar incidence of cough was observed by Agarwal *et al.*[4] following 2 $\mu g \cdot kg^{-1}$ *iv* fentanyl through the same route over a period of five seconds. The discrepancy in the incidence of cough among these studies could be explained by different doses and routes of administration. In the present study, we chose a dose of fentanyl which is lower than those used in previous reports because this dose (2.5 $\mu g \cdot kg^{-1}$) is closer to that commonly administered in daily practice. It is noteworthy that the incidence of cough is still high, even at this dose. The reason why

TABLE III Changes in vital signs after treatment in each group

	Systolic blood pressure (mmHg)		*Heart rate (beats·min^{-1})*		*SpO_2 (%)*		*Drop in SpO_2 (%)*
Group	Before	After	Before	After	Before	Lowest	
I	133.2 ± 20.6	130.8 ± 21.7	82.7 ± 14.9	83.4 ± 15.8	98.5 (98–100)	97.7 (92–100)	0.8 (0–4)
II	135.3 ± 17.3	137.3 ± 22.4	84.4 ± 10.8	87.6 ± 14.4	98.6 (97–100)	97.8 (93–100)	0.9 (0–6)
III	130.7 ± 18.0	122.3 ± 14.3*	78.9 ± 9.2	76.8 ± 9.9*	98.7 (97–100)	94.7 (88–99)*	3.9 (0–11)†
IV	125.0 ± 15.1	133.1 ± 16.1*	77.3 ± 12.9	82.1 ± 13.1*	98.6 (97–100)	98.0 (93–100)	0.6 (0–3)

Group I = placebo; Group II = lidocaine; Group III = propofol; Group IV = ephedrine one minute before fentanyl injection. Data are expressed as mean ± standard deviation or mean (range). *Denotes a significant difference compared with the value before treatment in each group. †Indicates a significant difference compared with placebo.

TABLE IV Adverse effects

Group	*Injection pain*	*Nausea/ vomiting*	*Dizziness*	*Arrhythmia*
I (n = 31)	0	0	0	0
II (n = 29)	1	1	1	0
III (n = 30)	25*	0	2	0
IV (n = 28)	0	0	0	0

Group I = placebo; Group II = lidocaine; Group III = propofol; Group IV = ephedrine one minute before fentanyl injection. Data are expressed as number of cases. *Indicates $P < 0.05$ in comparison with Group I.

we observed such a high incidence of cough with a relatively low dose of fentanyl is uncertain. We propose two explanations for this phenomenon. First, we injected the bolus of fentanyl rapidly (in less than two seconds) as compared with five seconds in the study of Lui *et al.*[3] and Agarwal *et al.*[4] Nonetheless, we do not recommend that fentanyl should be administered with such rapidity as a clinical routine. Second, we noticed that the incidence of cough appears to be higher in younger patients. Hence the difference in the incidence of fentanyl-induced cough could be, in part, age-related. In the report by Bohrer *et al.*,[1] the average age of the control group was over 60 yr old. The possible age-related incidence of fentanyl-induced cough may be attributed to the different activity of underlying mechanisms, for example, heightened irritant receptor activity in the younger population.

Various hypotheses to explain the mechanism of fentanyl-induced cough have been proposed in the literature. Fentanyl is known to enhance vagal activity,[8,9] which could trigger cough and reflex bronchoconstriction. However, the involvement of a vagal-dependent pathway was not favoured in the previous studies because atropine, an antimuscarinic agent, failed to suppress cough.[2,3] Additionally, possible mechanisms of fentanyl-induced cough include a pulmonary chemoreflex mediated by vagal C-fibre receptors (also known as J-receptors) with its nonmyelinated afferent fibres,[1,10] direct stimulation of the vagal nucleus which augments the bronchomotor tone,[8,9] opioid-induced histamine release,[11,12] the release of neuropeptides after activation of prejunctional μ-opioid receptors by fentanyl and subsequent activation of presynaptic sensory C fibres,[13] and stimulation of the irritant receptors in upper pulmonary mucosa secondary to fentanyl-induced tracheal smooth muscle constriction or bronchoconstriction.[14] Sudden adduction of the vocal cords or supraglottic obstruction by soft tissue caused by opioid-induced muscle rigidity has also been proposed.[15] Despite a wide range of mechanistic studies, only *im* morphine, or inhalational treatments, including terbutaline, salbutamol, beclomethasone and sodium chromoglycate, were shown to attenuate the cough reflex.[2–4]

Although the bronchodilating effect of lidocaine has been questioned,[16] *iv* lidocaine was proved to be a suppressant of coughing during tracheal intubation.[17,18] Our results also clearly demonstrate that *iv* lidocaine can prevent fentanyl-induced cough. Nonetheless, relatively high plasma concentrations of lidocaine are required for suppression of coughing. Yukioka *et al.*[18] reported that a dose of 2 mg·kg^{-1}, with resultant plasma concentrations in excess of 4 μg·mL^{-1}, was more effective than the dose of 1 or 1.5 mg·kg^{-1} in suppressing cough during tracheal intubation in elderly patients. Accordingly we decided to use lidocaine at the dose of 2 mg·kg^{-1}. No serious complications possibly related to *iv* lidocaine were observed.

There were two reasons that prompted us to evaluate the effect of propofol on fentanyl-induced cough. Pizov *et al.* showed that the incidence of wheezing was significantly reduced in asthmatic patients receiving a propofol-based induction of anesthesia compared to a

barbiturate-based induction.[19] Cigarini *et al.* demonstrated that propofol was able to prevent fentanyl-induced bronchoconstriction in surgical patients.[7] Thus propofol could be a promising drug to suppress fentanyl-induced cough. However, we did not see significant cough suppression with 0.6 $mg \cdot kg^{-1}$ propofol in the present study. While this dose may be subtherapeutic, higher doses may not be well tolerated for this indication. A decrease in SpO_2 was identified in the propofol group. This was probably due to the synergistic, depressant effect of fentanyl and propofol on respiration. Therefore, we do not recommend the use of propofol to decrease fentanyl-induced cough.

Ephedrine has long been recognized as a bronchodilator due to its ß-adrenergic activity and is readily available in the operating room. Our study showed that *iv* ephedrine at the dose of 5 mg was indeed effective in suppressing fentanyl-induced cough. The adrenergic agonism of the drug might simply suppress cough by reversing the fentanyl-triggered bronchoconstriction. Even though the relationship between reflex bronchoconstriction and fentanyl-induced cough has been questioned recently,[20] ß-agonists were shown to suppress the cough reflex in different studies.[3,4] We chose to test the effect of ephedrine at a relatively low dose to avoid major hemodynamic changes. The mild cardiovascular stimulating effect of low dose ephedrine should be well tolerated in an otherwise healthy patient. Hence ephedrine remains a reasonable alternative to suppress fentanyl-induced cough, considering its convenience compared with inhalational agents. Although ephedrine may not have reached its peak effect before fentanyl was administered in our study, it still suppressed fentanyl-induced cough, indicating its rapid onset by *iv* administration. Nonetheless, additional studies are needed to define the optimal injection time of ephedrine for this indication.

In conclusion, our study demonstrates that pretreatment with lidocaine 2 $mg \cdot kg^{-1}$ or ephedrine 5 mg given intravenously at one minute before fentanyl are effective in preventing fentanyl-induced cough. On the other hand, propofol at the dose of 0.6 $mg \cdot kg^{-1}$ is ineffective for the suppression of this reflex. Our results suggest convenient alternatives to suppress fentanyl-induced cough in clinical practice.

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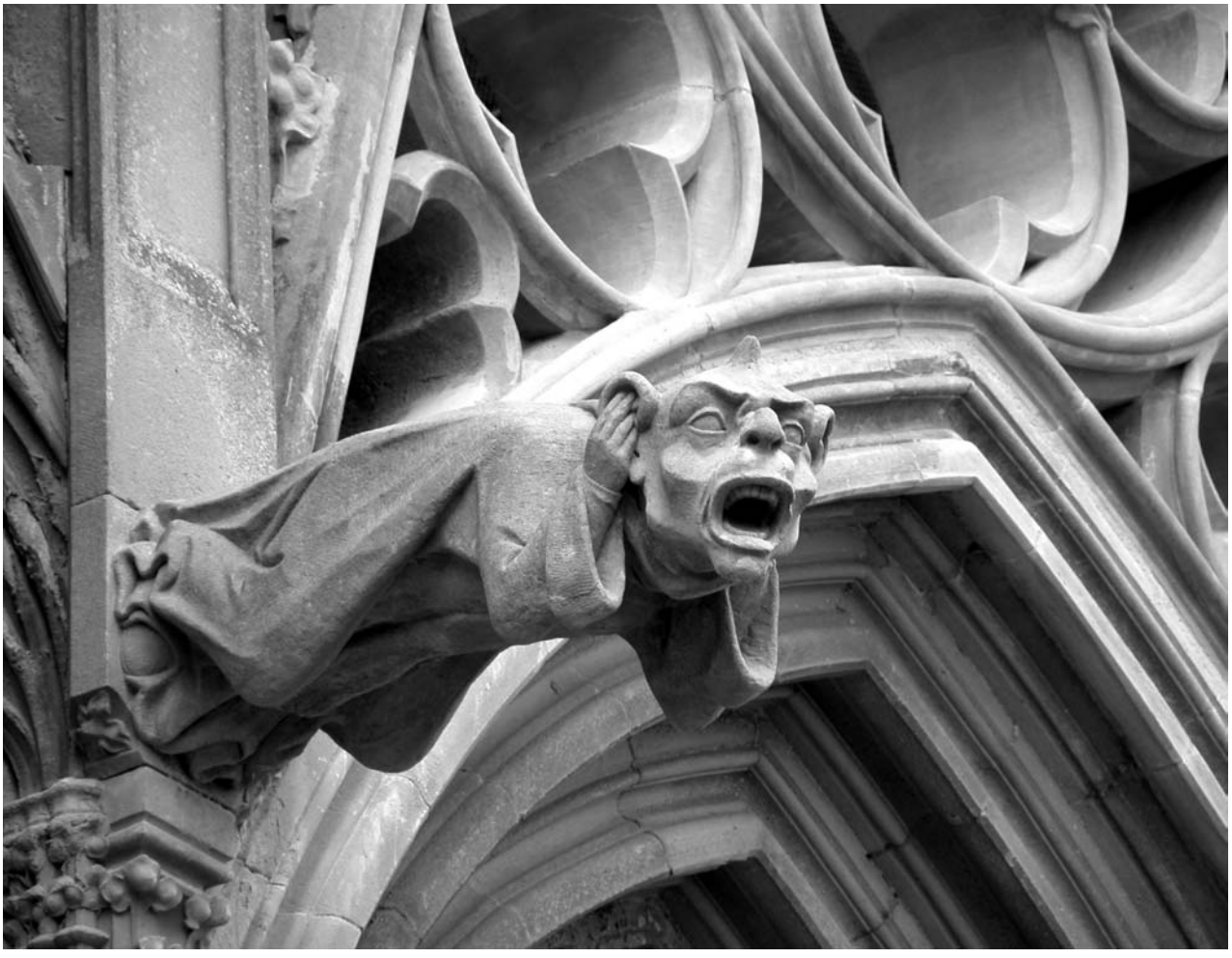

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