Terbutaline inhalation suppresses fentanyl-induced coughing

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Purpose: To study the suppressive effect of inhalation of a selective β_2 -adrenergic bronchodilator terbutaline, and the effect of an intravenous anticholinergic, atropine, on fentanyl-induced coughing.

Methods: We studied 131 ASA class I patients, aged 16–45 yr, scheduled for elective surgery, randomized into four groups. Fifteen minutes before bolus fentanyl ($5 \mu\text{g} \cdot \text{kg}^{-1}$, iv), patients inhaled either normal saline (4 ml; Group 1, $n = 30$) or terbutaline (5 mg in 2 ml normal saline; Group 2, $n = 34$) via a jet nebulizer. After inhalation of normal saline, patients in Group 3 ($n = 32$) received sterile water iv instead of fentanyl. Patients in Group 4 ($n = 35$) were pretreated with atropine ($0.01 \text{ mg} \cdot \text{kg}^{-1}$, iv) 10 min before iv fentanyl bolus. The onset, frequency and intensity of cough were observed immediately by an anaesthetist blinded to the study.

Results: The cough frequency was higher in Groups 1 (43%) and 4 (46%) than in Groups 2 (3%) and 3 (0%) ($P < 0.05$). The onset time and intensity of cough showed no difference among groups. No trunco rigidity was observed in patients receiving fentanyl bolus iv. The blood pressure, heart rate, and peripheral oxygen saturation did not change in Groups 1, 2, and 3, while patients in Group 4 showed an increase in heart rate ($25.5 \pm 15.2\%$).

Conclusions: The inhalation of a selective β_2 -adrenergic bronchodilator, terbutaline, effectively inhibited fentanyl-induced cough, whereas atropine, an antimuscarinic vago-

lytic, had no efficacy. Our results suggest that bronchoconstriction may underlie the mechanism on fentanyl-induced cough.

Objectif: Étudier l'effet inhibiteur sur la toux induite par le fentanyl de l'inhalation d'un bronchodilatateur sélectif β_2 -adrénergique, la terbutaline et d'un anticholinergique intraveineux, l'atropine.

Méthodes: L'étude portait sur 131 patients ASA I, âgés de 16 à 45 ans, programmés pour une chirurgie non urgente et répartis aléatoirement entre quatre groupes. Quinze minutes avant l'administration d'un bolus de fentanyl ($5 \mu\text{g} \cdot \text{kg}^{-1}$, iv), les patients inhalaient soit du sol.phys. (4 ml; groupe 1, $n = 30$), soit de la terbutaline (5 ml dans 2 ml de sol.phys.; groupe 2, $n = 34$) par nébulisation. Après avoir inhalé du sol.phys., les patients du groupe 3 ($n = 32$) recevaient de l'eau stérile iv à la place du fentanyl. Les patients du groupe 4 ($n = 35$) étaient prétraités à l'atropine ($0,01 \text{ mg} \cdot \text{kg}^{-1}$, iv) 10 min avant le bolus de fentanyl iv. Le début, l'intensité et la fréquence de la toux étaient observés immédiatement par un anesthésiste neutre.

Résultats: La fréquence de la toux était plus élevée dans les groupes 1 (43%) et 4 (46%) que dans le groupe 2 (3%) et 3 (0%) ($P < 0,05$). Le moment du début et l'intensité de la toux ne différaient pas entre les groupes. On n'a pas observé de rigidité tronculaire chez les patients recevant le bolus de fentanyl iv. La pression artérielle, la fréquence cardiaque et la saturation périphérique en oxygène n'ont pas changé dans les groupes 1, 2 et 3, alors que dans le groupe 4, la fréquence cardiaque augmentait ($25,5 \pm 15,2\%$).

Conclusion: L'inhalation du bronchodilatateur β_2 -adrénergique, terbutaline, inhibe efficacement la toux induite par le fentanyl, alors que l'atropine, un vagolytique antimuscarinique n'a pas cet effet. Ces résultats suggèrent que la bronchoconstriction pourrait être à l'origine de la toux induite par le fentanyl.

Key words

ANALGESICS: fentanyl;

COUGH;

SYMPATHETIC NERVOUS SYSTEM: beta-adrenergic agonists, terbutaline;

PARASYMPATHETIC NERVOUS SYSTEM: atropine.

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Intravenous administration of fentanyl, $6\text{--}8 \mu\text{g} \cdot \text{kg}^{-1}$, has been used as a supplement to reduce the hyperdynamic response to tracheal intubation during anaesthetic induction.¹ However, it is commonly accompanied by cough on induction of anaesthesia.^{2,3} Bohrer *et al.*² suggested that this phenomenon may be due to stimulation, by fen-

tanyl, of pulmonary chemoreflex and J-receptors. Its mechanism, however, needs to be further elucidated. In the present study, we hypothesized that fentanyl may induce bronchoconstriction of the airways, which leads to coughing. The purpose of this study aimed to evaluate the effects of terbutaline, a selective β_2 -adrenergic bronchodilator, administered via a jet nebulizer, on the suppression of coughing evoked by fentanyl bolus *iv*. The participation of the vagal efferent in this phenomenon was also studied by pretreating patients with an anticholinergic, atropine *iv*.

Methods

After institutional approval by our Human Investigation Committee, we studied 131 ASA physical status I patients, aged 16–45 yr, scheduled for elective surgical procedures. Informed consent was obtained before the study. Exclusion criteria included a history of asthma, chronic cough, upper respiratory tract infection in previous two weeks, smoking, or patients receiving angiotensin converting enzyme inhibitors. No premedication was given. Upon arrival in the operating room, a 20-gauge catheter was inserted into a dorsal vein of the hand. The blood pressure (BP), heart rate (HR) and pulse oximeter (SpO₂) were monitored throughout the study. Fifteen minutes before fentanyl bolus (5 $\mu\text{g} \cdot \text{kg}^{-1}$) *iv*, patients inhaled randomly either normal saline (4 ml; Group 1, $n = 30$) or terbutaline (Bricanyl, 2.5 $\text{mg} \cdot \text{ml}^{-1}$, Astra, Sweden; 5 mg freshly dissolved in 2 ml normal saline; Group 2, $n = 34$) via a jet nebulizer (Whisper Jet™ Nebulizer System, Marquest Medical Products, Inc. Englewood, CO, USA). The table of random digits was used for randomization.⁴ We used the last two digits of the table with odd and even numbers, resulting in four possible combinations (i.e., odd+odd, odd+even, even+odd, even+even). Each combination was thus assigned to each group in a random manner. Oxygen was delivered through the jet nebulizer at 8 $\text{L} \cdot \text{min}^{-1}$. Fentanyl was rapidly administered *iv* over 5 sec. After the inhalation of normal saline, patients in Group 3 ($n = 32$) received sterile water *iv* instead of fentanyl to exclude the tussive effect of its low osmolality (5 $\text{mOsm} \cdot \text{L}^{-1}$). Patients in Group 4 ($n = 35$) were pretreated with atropine (0.01 $\text{mg} \cdot \text{kg}^{-1}$, *iv*) 10 min before fentanyl bolus *iv*. Immediately after fentanyl administration, the onset, frequency and intensity of cough as well as truncal rigidity were assessed by an anaesthetist blinded to the study. The intensity of cough was graded as: no cough (grade 1), cough less than 5 sec (grade 2), and cough >5 sec (grade 3). The occurrence of truncal rigidity was registered if patients encountered impairment in ventilation with or without extremity stiffness after fentanyl bolus *iv*.

TABLE I Demographic data

Group	Age (yr)	Sex (M/F)	Weight (kg)
1 ($n = 30$)	36.6 $\pm$ 5.5	16/14	53.3 $\pm$ 5.5
2 ($n = 34$)	37.5 $\pm$ 4/2	16/18	52.6 $\pm$ 6.3
3 ($n = 3$)	32.5 $\pm$ 5.8	17/15	56.2 $\pm$ 4.8
4 ($n = 35$)	33.8 $\pm$ 5.9	16/19	58.0 $\pm$ 5.2

Values are mean $\pm$ SEM.

TABLE II Incidence and onset time of cough response induced by fentanyl

Group	Frequency (%)	Onset (sec)	Cough grade†		
			1	2	3
1	13/30 (43)	42 $\pm$ 8	0	8/13	5/13
2	1/34 (3)*	55	0	1/1	0
3	0/32 (0)*	–	0	0	0
4	16/35 (46)	45 $\pm$ 10	0	9/16	7/16

Values are mean $\pm$ SEM

* $P < 0.05$ vs Group 1 and Group 4 (Fisher's test).

†Cough intensity scale: 1 = no cough, 2 = cough < 5 sec, 3 = cough > 5 sec.

Results are expressed as mean $\pm$ SD. Fisher's exact test was used to compare the incidence of cough among groups. The demographic data, haemodynamic changes, and the intensity of cough were assessed by one-way ANOVA, followed by Scheffé's multiple comparison test for a posteriori comparisons. Results were considered statistically significant if $P < 0.05$.

Results

The demographic data did not differ among groups (Table I). The BP, HR, and SpO₂ showed no differences among Groups 1, 2, and 3, but patients in Group 4 showed an increase in HR (25.5 $\pm$ 15.2%) after atropine administration. After fentanyl bolus *iv*, patients in Group 1 (13/30, 43%) and 4 (14/35, 46%) coughed more than those in Group 2 (1/34, 3%) ($P < 0.05$, Table II). However, none coughed after *iv* sterile water (Group 3). Patients who coughed did not differ in onset. Coughing occurred within one minute after fentanyl bolus *iv*. The cough intensity showed no difference between Groups 1 and 4 (Table II). No truncal rigidity was observed in all patients receiving fentanyl bolus *iv*.

Discussion

The inhalation of terbutaline, a selective β_2 -adrenergic bronchodilator, effectively suppressed fentanyl-induced cough, whereas atropine *iv* failed to blunt this reflex. Our results confirm our hypothesis that bronchocon-

striction may underlie the mechanism on coughing elicited by *iv* fentanyl.

In this study, 43% patients coughed after fentanyl, $5 \mu\text{g} \cdot \text{kg}^{-1}$ *iv*, administered through a peripheral venous line. This result is comparable to the findings of Bohrer² where fentanyl $7 \mu\text{g} \cdot \text{kg}^{-1}$, given through a central venous line, elicited cough in 45.9% patients. In that trial, only 2.7% patients coughed after receiving fentanyl through a peripheral venous line. However, the incidence is higher than observed by Phua,³ in which 28% patients coughed after receiving fentanyl. However, in that study, a lower dose of fentanyl, $1.5 \mu\text{g} \cdot \text{kg}^{-1}$, was given. The differences in the incidence of cough may be ascribed to the doses and routes of administration. It is not surprising that the onset of cough was longer in our study in which fentanyl was given via a peripheral venous line, than via a central vein.

Fentanyl has been shown to inhibit central sympathetic outflow activity and vagal efferents may be excited causing bradycardia and hypotension.⁵⁻⁷ In addition, activation of vagus nerves induces cough and reflex bronchoconstriction.^{8,9} Our results are consistent with Phua's study that fentanyl-induced cough is not mediated by vagal stimulation because an antimuscarinic agent, atropine, failed to block this reflex.³ We also considered that histamine release by fentanyl may initiate the cough reflex, either directly or via bronchoconstriction.^{10,11} This appears to be unlikely because, in contrast to morphine, fentanyl rarely causes histamine release in humans and human lung mast cells.^{12,13} Release of neuropeptides, by activation of presynaptic sensory C-fibres, can also induce bronchoconstriction and cough.^{14,15} It is possible that activation of prejunctional μ -opioid receptors by fentanyl may lead to bronchoconstriction and cough as a result of neuropeptide release. However, this is also unlikely as opioids have been shown to decrease the release of these mediators,¹⁵ and inhibit reflex bronchoconstriction and cough.¹⁶

Bohrer *et al.*² speculated that pulmonary C-fibre receptors, also known as J-receptors, with its nonmyelinated afferent fibres are most likely involved in the mediation of the pulmonary chemoreflex that leads to cough evoked by fentanyl. This suggestion was based on the finding that J-receptors are readily accessible via pulmonary circulation and are more sensitive to chemical irritants.^{17,18} However, studies in experimental animals showed that J-receptors stimulation did not induce cough, although mediating pulmonary chemoreflexes.¹⁹ Instead of triggering cough, activation of these receptors in cats inhibit the cough reflex from the larynx and tracheobronchial conduit.²⁰

In humans, fentanyl constricts tracheal smooth muscle,²¹ and hence the "irritant" receptors nearby may be

stimulated secondary to deformation of the tracheobronchial wall.² These receptors, when stimulated, can trigger the cough reflex via the vagal afferent pathway.²² Irritant receptors, also known as rapidly adapting or cough receptors, appear to be the more likely candidate for cough because they are highly concentrated in the walls of proximal tracheobronchial airways and found superficially within the mucosa.²³ The latter explains their ability to respond to weak chemical irritation that leads to coughing. In addition, intravenous injection of irritants such as histamine or prostaglandins can gain access to these receptors.¹⁹

Apart from producing bronchodilatation,²⁴ selective β_2 -adrenergic agonists such as terbutaline are also effective antitussive agents both in normal and in asthmatic subjects.^{25,26} When given as aerosols, terbutaline has a rapid onset (five minutes) and long duration of action (four to six hours).²⁷ Most studies suggest that aerosolization by jet nebulizer results in deposition of 10% of the drug in the lungs.²⁸ Accordingly, in our study, one tenth or 0.5 mg terbutaline can reach the tracheobronchial tree. This dose has been reported to be effective in causing bronchodilatation.²⁷ Cough is frequently related to bronchoconstriction, which may be alleviated by bronchodilators.²⁹ Given the observation that bronchoconstriction is the prime trigger of the cough reflex,³⁰ we speculate from our study that terbutaline aerosols, by means of their bronchodilatory effect, blunt the bronchoconstriction evoked by fentanyl. This bronchodilatation may, in turn, suppress the cough reflex. This notion is also supported by Yasuda's finding²¹ that droperidol, with its α -adrenergic blocking effect,³¹ inhibited tracheal smooth muscle constriction induced by fentanyl, suggesting adrenergic involvement. Although cough and reflex bronchoconstriction have been shown to be mediated by separate sensory receptors in the airways,^{32,33} it is unknown how bronchodilatation interacts concurrently with the cough reflex. Their interactions await further investigation.

In conclusion, pretreatment with an inhaled selective β_2 -adrenergic bronchodilator is an effective method of reducing cough evoked by fentanyl.

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