Intravenous lidocaine 0.5 mg·kg^{-1} effectively suppresses fentanyl-induced cough

[L'administration iv de 0,5 mg·kg^{-1} de lidocaïne supprime efficacement la toux induite par le fentanyl]

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Purpose: To evaluate the minimal dose of lidocaine required for suppression of fentanyl-induced cough.

Methods: 320 ASA I and II patients, non-smokers of both sexes scheduled for elective surgery between the ages of 18 to 60 yr were randomly allocated into four equal groups. The patients were assigned to receive lidocaine 0.5 mg·kg^{-1} (Group I), 1.0 mg·kg^{-1}(Group II), 1.5 mg·kg^{-1} (Group III) or placebo (Group IV) over five seconds, one minute prior to the administration of fentanyl 3 μg·kg^{-1} in a randomized and double-blind fashion. Any episode of cough was classified as coughing and graded as mild (1–2) moderate (3–4) or severe (5 or more). The data were analyzed by test of proportion.

Results: Eleven, 12, 11 and 28 patients (13.75%, 15%, 13.75% and 35%) had cough in Groups I, II, III and IV respectively ($P < 0.05$ Groups I, II, III *vs* IV). There was no significant difference in the incidence and severity of cough among the lidocaine pretreated groups ($P > 0.05$).

Conclusion: The results of our study suggest that *iv* lidocaine 0.5 mg·kg^{-1} is the minimal dose required to suppress fentanyl-induced cough when administered one minute prior to fentanyl. Any further increase in the lidocaine dose does not reduce the incidence or severity of fentanyl-induced cough.

Objectif : *Évaluer la dose minimale de lidocaïne requise pour supprimer la toux induite par le fentanyl.*

Méthode : *Notre étude comportait 320 patients d'état physique ASA I et II, non-fumeurs des deux sexes, âgés de 18 à 60 ans et répartis en quatre groupes égaux avant une intervention chirurgicale réglée. De la lidocaïne, 0,5 mg·kg^{-1} (groupe I), 1,0 mg·kg^{-1} (groupe II), 1,5 mg·kg^{-1} (groupe III) ou un placebo (groupe IV) ont été administrés pendant cinq secondes, une minute avant 3 μg·kg^{-1} de fentanyl selon un mode randomisé et à double insu. Les épisodes de toux ont été classifiés et gradués : léger (1–2), modéré (3–4) ou sévère (5 ou plus). Les données ont été analysées par le test de proportion.*

Résultats : *Onze, 12, 11 et 28 patients (13,75 %, 15 %, 13,75 % et 35 %) des groupes I, II, III et IV ont respectivement eu de la toux ($P < 0,05$ groupes I, II, III vs IV). Chez les patients prétraités à la lidocaïne, l'incidence et la sévérité de la toux ont été comparables ($P > 0,05$).*

Conclusion : *Nos résultats indiquent que l'administration iv de 0,5 mg·kg^{-1} de lidocaïne est la dose minimale requise pour supprimer la toux induite par le fentanyl quand elle est administrée une minute avant le fentanyl. Toute dose plus élevée ne réduit pas l'incidence ou la sévérité de la toux induite par le fentanyl.*

OPIOIDS are used to allay anxiety and to decrease pain associated with surgery. Fentanyl is commonly used as a pre-induction adjunct because of its quick onset, short duration of action, intense analgesia, cardiovascular stability, and low histamine release, but a pre-induction bolus dose of fentanyl elicits cough.[1] Fentanyl-induced cough is common but has not been viewed as a serious anesthetic problem.[2] In a clinical trial, 46% of patients coughed after receiving 7 μg·kg^{-1} fentanyl through a central venous catheter and nearly 28% of patients coughed after a 1.5 μg·kg^{-1} *iv* dose of fentanyl injected through a peripheral cannula.[3,4] A fentanyl-induced cough is not always brief and benign, it may be explosive at times, and may require immediate intervention. It can be associated with an undesir-

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Accepted for publication August 5, 2004.

Revision accepted November 8, 2004.

able increase in intracranial, intraocular and intra-abdominal pressures if left untreated.[1,2]

Intravenous lidocaine suppresses the cough reflex during endotracheal intubation, extubation, bronchography, bronchoscopy and laryngoscopy.[5–7] It has been found effective when given intravenously to suppress the cough reflex of endotracheal intubation and cough induced by manual displacement of the endotracheal tube and instillation of distilled water into the trachea in anesthetized patients.[8–10] In a placebo-controlled clinical study it has been demonstrated that lidocaine 1.5 $mg \cdot kg^{-1}$ decreased fentanyl-induced cough from 34.22% to 13.14% (absolute risk reduction was 21.08% and relative risk reduction was 62%) one minute prior to fentanyl administration.[11] We evaluated the minimal dose of lidocaine for suppression of fentanyl-induced cough in this randomized, prospective and placebo-controlled study.

Material and methods

The Institute's Ethics Committee approved the study and written informed consent was obtained from each participant. Three hundred and twenty patients of ASA physical status I and II of both sexes scheduled for elective surgery were recruited for the study. The exclusion criteria were: body weight exceeding 20% of the ideal body weight; those older than 60 yr or younger than 18 yr; impaired kidney or liver function; patients with a history of bronchial asthma and chronic obstructive pulmonary disease, patients having a history of smoking, a respiratory tract infection, hypertensive patients on angiotensin converting enzyme inhibitors and a history of hypersensitivity to local anesthetics.

All patients received a premedication with oral lorazepam 0.04 $mg \cdot kg^{-1}$ the evening before surgery and in the morning one hour prior to surgery. In the operating room venous access was established on the dorsum of the non-dominant hand and an electrocardiogram, noninvasive blood pressure and pulse oximeter were applied. Patients were randomly assigned into four groups using a computer generated table of random numbers to receive *iv* lidocaine 0.5 $mg \cdot kg^{-1}$ (Group I), 1.0 $mg \cdot kg^{-1}$ (Group II) or 1.5 $mg \cdot kg^{-1}$ (Group III) or placebo (Group IV) over five seconds one minute prior to the *iv* administration of fentanyl 3 $\mu g \cdot kg^{-1}$. Any episode of cough was classified as coughing. An observer, unaware of the type of medication given to the patients, recorded the number of episodes of coughing, if any. Severity of coughing was graded based on the number of episodes of cough (mild 1–2, moderate 3–4 and severe 5 or more).

Considering the incidence of coughing following peripherally administered *iv* fentanyl is 30%, and assuming a reduction of 20% (assumption based on the results of a previous clinical investigation)[11] at the 5% level of significance and 80% confidence of detecting a true difference following lidocaine treatment, a minimum of 79 patients was required in each group. After completion of the study, the treatment groups were decoded and the data were entered into the statistical software package SPSS 9.0 (Chicago, IL, USA). The demographic data were compared by one-way ANOVA and Chi-square test. Comparison between the groups was performed for overall incidence of cough by test of proportion (Z test) and severity of cough by Fisher Exact test. A P value < 0.05 was considered statistically significant.

Results

The demographic data were comparable for age, weight and gender (Table I). Eleven, 12 and 11 patients (13.75%, 15% and 13.75%) had cough in Groups I, II, and III respectively. Twenty-eight patients (35%) of Group IV had cough ($P < 0.05$; Table II). There was no significant difference in the severity of cough among the groups ($P > 0.05$; Table II).

Discussion

Our study demonstrates that pre-treatment with lidocaine in doses of 0.5 $mg \cdot kg^{-1}$, 1.0 $mg \cdot kg^{-1}$ and 1.5 $mg \cdot kg^{-1}$ one minute prior to fentanyl administration significantly decreases the incidence of cough compared to placebo but that there is no difference in the incidence of cough among the lidocaine pre-treated groups (Table II). The incidence of cough in the placebo group (IV) was 35%, higher than in previous reports (28%).[1,3] The higher incidence of fentanyl-induced cough in our study is probably because of a larger dose of fentanyl (3 $\mu g \cdot kg^{-1}$) compared to the studies by Agarwal *et al.* (2 $\mu g \cdot kg^{-1}$) and Phua *et al.* (1.5 $\mu g \cdot kg^{-1}$).[1,4] A 46% incidence of cough has been reported with 7 $\mu g \cdot kg^{-1}$ fentanyl administered through a central venous catheter over one second by Bohrer *et al.*, whereas the same incidence was reported by Lui *et al.* with 5 $\mu g \cdot kg^{-1}$ administered through a peripheral vein over five seconds.[3,12]

Intravenous lidocaine administration has been shown to suppress both mechanical and chemical induced airway reflexes, including the cough reflex.[5,6,8–10] The dose of lidocaine required for the effective suppression of cough during tracheal intubation ranges between 1.5 to 2.0 $mg \cdot kg^{-1}$ and the duration of cough suppression was reported to last about five to eight minutes in previous studies.[5,9,10] The effect of *iv* lidocaine on suppression of cough during endotracheal intubation increased in a dose-dependent man-

TABLE I Demographic data

Groups	*I (n = 80)*	*II (n = 80)*	*III (n = 80)*	*IV (n = 80)*
Age (yr)	40.31 ± 13.11	42.96 ± 12.59	41.66 ± 11.54	42.00 ± 12.65
Weight (kg)	55.91 ± 7.49	55.27 ± 7.17	57.09 ± 4.19	56.59 ± 7.12
Male/female (*n*)	52/28	53/27	55/25	51/29

P = not significant between groups.

TABLE II Fentanyl-induced cough and its severity among the groups

Groups	*No. of patients*	*No cough*	*Incidence and severity of cough*				*%*
			Mild	*Moderate*	*Severe*	*Total*	
I	80	69	7 (63.6%)	3 (27.3%)	1 (9%)	11	13.75
II	80	68	8 (66.7%)	4 (33.3%)	0 (0%)	12	15.00
III	80	69	7 (63.6%)	4 (36.4%)	0 (0%)	11	13.75
IV	80	52*	21 (75%)	6 (21.4%)	1 (3.6%)	28*	35.00*

* *P* value < 0.05 (Placebo *vs* Groups I, II, and III).

ner and correlated well with plasma levels. Administration of *iv* lidocaine 2.0 mg·kg^{-1} one to five minutes before intubation suppressed the cough reflex significantly in a group of patients under nitrous oxide-halothane anesthesia whose ages ranged between 15 to 55 yr and who did not receive a muscle relaxant.[10] In our previous study we evaluated the effect of lidocaine on fentanyl-induced cough with a fixed dose of 1.5 mg·kg^{-1}. Lidocaine 1.5 mg·kg^{-1} administered one minute prior to fentanyl significantly reduced the incidence of cough from 34.22% to 13.14% (absolute risk reduction of 21.08% and relative risk reduction of 62%).[11] In the present study we used increasing doses of lidocaine to evaluate its suppressive effect on fentanyl-induced cough. The results demonstrate that all doses reduced the incidence of cough, but that there is no significant difference between treatment groups.

The mechanisms of fentanyl-induced cough are not well understood but various theories have been proposed. Fentanyl has been shown to inhibit central sympathetic outflow causing vagal predominance, inducing cough and reflex bronchoconstriction.[1,12,13] Effective suppression of the cough response from 43% to 3% after terbutaline and salbutamol (selective beta$_2$-adrenergic bronchodilator) inhalation supports the concept of bronchoconstriction.[12] The rapid response of the reflex and efficacy of morphine in preventing cough suggests that a pulmonary chemoreflex is also the likely mechanism, mediated by either irritant-receptors (rapidly adapting receptors) or by vagal C fibre receptors in close proximity to pulmonary vessels (juxta capillary receptors). On the other hand, suppression of cough with betamethasone inhalation supports the trigger stimulus and bronchial hyperirritability theory.[1,2,12] Histamine release from mast cells in the lungs (though this appears unlikely as fentanyl rarely causes histamine release) or constriction of the tracheal smooth muscles (by release of tachykinins from sensory nerve endings due to citrate in fentanyl citrate) and the possible stimulation of irritant receptors following deformation of the tracheobronchial wall triggering the cough are other plausible explanations.[1,3,14,15]

The mechanisms by which lidocaine suppresses cough are not known but it has been proposed that depression of brain stem functions by lidocaine may be responsible for cough suppression. An alternate mechanism is that lidocaine may act by anesthetizing peripheral cough receptors in the trachea and hypopharynx.[8]

In conclusion, our study suggests that *iv* lidocaine 0.5 mg·kg^{-1} is the minimal dose to suppress fentanyl-induced cough when administered one minute prior to fentanyl. Any further increase in the lidocaine dose does not reduce the incidence and severity of fentanyl-induced cough.

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