Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by *iv* fentanyl

[Le salbutamol, la béclométhasone ou le chromoglycate de sodium suppriment la toux causée par le fentanyl iv]

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Purpose: Fentanyl, a synthetic opioid, is a popular choice amongst anesthesiologists in the operating room. Preinduction *iv* fentanyl bolus is associated with coughing in 28–45% of patients. Coughing due to fentanyl is not always benign and at times may be explosive requiring immediate intervention. We have studied the role of aerosol inhalation of salbutamol, beclomethasone and sodium chromoglycate in preventing fentanyl induced coughing and have compared their efficacy.

Methods: Two hundred patients aged 18–60 yr, undergoing elective laparoscopic cholecystectomy were randomized into four groups of 50 each. Group I served as control, while Groups II, III and IV received an aerosol inhalation of salbutamol, beclomethasone or sodium chromoglycate 15 min prior to entering the operating room. Following *iv* fentanyl (2 $\mu g \cdot kg^{-1}$) the incidence of cough was recorded and graded as mild (1–2), moderate (3–5) and severe (> 5) depending on the number of coughs observed. Results were analyzed using 'z' and Fischer's Exact test. A *P* value of ≤ 0.05 was considered significant.

Results: The incidence of cough was 28% in the control group, 6%, 0% and 4% in the salbutamol, beclomethasone and sodium chromoglycate groups respectively. Occurrence of cough was significantly low ($P \leq 0.05$) in the treatment groups, however the difference amongst the groups was not significant ($P \geq 0.05$).

Conclusion: The use of salbutamol, beclomethasone or sodium chromoglycate aerosol 15 min prior to *iv* fentanyl administration minimizes fentanyl-induced coughing.

Objectif : *Le fentanyl, un opioïde synthétique, est très utilisé par les anesthésiologistes en salle d'opération. L'administration iv d'un bolus de fentanyl avant l'induction de l'anesthésie est associée à de la toux chez 28-45 % des patients. Cette toux, pas toujours bénigne, peut parfois même être explosive et nécessiter une intervention immédiate. Nous avons étudié le rôle de l'inhalation de salbutamol, de béclométhasone et de chromoglycate de sodium en aérosols dans la prévention de la toux induite par le fentanyl et nous avons comparé leur efficacité.*

Méthode : *Deux cents patients de 18 à 60 ans, devant subir une cholécystectomie laparoscopique réglée ont été répartis au hasard en quatre groupes de 50. Le groupe I a servi de témoin, tandis que les groupes II, III et IV ont inhalé du salbutamol, de la béclométhasone ou du chromoglycate de sodium en aérosol, 15 min avant d'entrer dans la salle d'opération. Après l'administration iv de 2 $\mu g \cdot kg^{-1}$ de fentanyl, l'incidence de toux a été enregistrée et cotée comme légère (1-2), modérée (3-5) et sévère (> 5) selon le nombre d'accès de toux observés. Les résultats ont été analysés selon le test "Z" et le test exact de Fischer. Une valeur de $P \leq 0,05$ a été considérée significative.*

Résultats : *L'incidence de toux a été respectivement de 28 % dans le groupe témoin, 6 %, 0 % et 4 % dans les groupes de salbutamol, béclométhasone et chromoglycate de sodium. L'occurrence de toux a été significativement faible ($P \leq 0,05$) dans les groupes expérimentaux, même si la différence intergroupe n'a pas été significative ($P \geq 0,05$).*

Conclusion : *L'usage de salbutamol, de béclométhasone ou de chromoglycate de sodium en aérosol, 15 min avant l'administration iv de fentanyl, réduit la toux induite par le fentanyl.*

OPIOIDS have been administered for hundreds of years to allay anxiety and decrease pain associated with surgery. They are used as premedicants and analgesics perioperatively.[1] Fentanyl, a synthetic opioid, is a popular choice amongst anesthesiologists because of its quick onset, short duration of action, easy titrability, intense analgesia, cardiovascular stability and low

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histamine release.[2,3] A preinduction bolus of fentanyl is associated with coughing in 28–45% patients but this has not been considered a serious anesthetic complication.[4,5] Coughing due to fentanyl may not always be benign and brief, and at times, coughing can be explosive requiring immediate intervention on the operating table.[6] Further, coughing is known to be associated with increased intracranial, intra-occular and intra-abdominal pressures.

The various mechanisms proposed to explain fentanyl-induced cough are: inhibition of central sympathetic outflow leading to vagal predominance,[7] histamine release, deformation of the tracheobronchial wall stimulating the irritant receptors leading to reflex bronchoconstriction and cough.[8,9] Salbutamol, beclomethasone and sodium chromoglycate are used routinely in the management of bronchospasm. Therefore, we postulated that aerosol inhalation of these drugs would prevent fentanyl-induced cough.

Material and methods

Following approval from Institutional Research and Ethical Committees, informed consent was obtained from all patients included in this randomized, prospective and controlled study.

Two hundred ASA I and II patients of either sex, aged between 18–60 yr, scheduled for elective laparoscopic cholecystectomy under general anesthesia were randomly assigned into four groups of 50 each using a computer generated table of random numbers. Group I served as control and did not receive any treatment while patients belonging to Groups II, III and IV inhaled one metered aerosol puff of salbutamol, beclomethasone or sodium chromoglycate 15 min prior to entering the operating room. Patients having a history of chronic obstructive airway disease, an upper respiratory infection in the last two weeks, chronic smoking or recent intake of angiotensin converting enzyme inhibitors, bronchodilators or steroids were excluded from the study.

In the operating room venous access was established. Monitoring consisted of electrocardiogram, non-invasive blood pressure, oxygen saturation and capnography. A fentanyl bolus of 2 $\mu g \cdot kg^{-1}$ was given *iv* over a period of five seconds following which the incidence of cough, if any, was recorded by another anesthesiologist who was blinded to drug therapy. Depending upon the number of coughs observed it was graded as mild (1–2), moderate (3–5) and severe (> 5). Induction of anesthesia was commenced once cough subsided.

Considering the expected incidence of cough following *iv* fentanyl to be 35% and assuming a reduction up to 10% following any of the treatments and a power of 80%, the minimum sample size required in each group was 43. Anticipating some variability in reduction we included 50 patients in each group. Patients' characteristics were compared by unpaired Student's t test. Comparisons between groups were performed for overall incidence of coughing by 'z' test. Coughing was further compared separately at various levels of severity by Fischer's Exact test. A $P < 0.05$ was considered significant.

Results

The demographic data were comparable in the four groups (Table I). Fourteen (28%) patients had cough in the control group (Group I). Three (6%) patients had cough in the salbutamol group (II) and two (4%) patients had cough in the sodium chromoglycate group (IV). None of the patients in the beclomethasone group (III) had any cough. Severe cough was not observed in any of the treatment groups. The total incidence of cough was significantly higher ($P \leq 0.05$) in the control group when compared to any of the treatment groups (Table II). However, no significant difference in the incidence of cough was observed in the three treatment groups.

Discussion

All bronchodilators, when given as an aerosol, result in a rapid onset of action and deposition of more then 10% of the drug in the lungs leading to effective bronchodilatation.[10] We observed that a metered dose of salbutamol (B_2 adrenergic agonist), beclomethasone (corticosteroid) and sodium chromoglycate (mast call stabilizer) significantly reduced the incidence of cough evoked by *iv* bolus of 2 $\mu g \cdot kg^{-1}$ fentanyl.

In our study, fentanyl (2 $\mu g \cdot kg^{-1}$) induced cough in 28% of control patients. Bohrer *et al.*, in a study of 150 patients undergoing coronary artery bypass grafting, observed a 45% incidence of cough when fentanyl (7 $\mu g \cdot kg^{-1}$) was administered via a central venous catheter.[5] The higher incidence could be due to the larger dose and the central route used by Bohrer *et al.* Lui *et al.* reported a 46% incidence of fentanyl-induced cough using a dose of 5 $\mu g \cdot kg^{-1}$.[11] In another study, Phua *et al.* observed a 28% incidence of cough following 1.5 $\mu g \cdot kg^{-1}$ *iv* fentanyl injected through a peripheral venous cannula.[6] The latter observations are similar to our finding.

Various mechanisms have been proposed to explain fentanyl-induced cough. Fentanyl has been shown to inhibit central sympathetic outflow causing activation of the vagus nerve, inducing cough and reflex bronchoconstriction.[7] Lui *et al.* hypothesized that fentanyl-induced cough is due to bronchoconstriction.[11] They evaluated the effects of nebulized terbutaline (B_2 ago-

TABLE I Patient characteristics

	Control (Group I; n = 50)	*Salbutamol (Group II; n = 50)*	*Beclomethasone (Group III, n = 50)*	*Na chromoglycate (Group IV; n = 50)*
Age (yr)	36.2 ± 9.1	37 ± 7.4	39 ± 8.4	34.5 ± 8.2
Sex (M / F)	18 / 32	16 / 34	14 / 36	15 / 35
Weight (kg)	61 ± 12	58 ± 09	60.6 ± 09	56 ± 10
Height (cm)	160 ± 07	158 ± 08	155 ± 09	164 ± 06

TABLE II Severity of cough following a 2 $\mu g \cdot kg^{-1}$ bolus of fentanyl

Study Groups	*No. of patients (n)*	*Incidence of coughing*						*Statistical significance by "z" test*	*Power*
		None	*Mild*	*Moderate*	*Severe*	*Total*	*%*		
I. Control	50	36	8	3	3	14*	28		
II. Salbutamol	50	47	2	1	0	3	6	$P < 0.003$	84
III. Beclomethasone	50	50	0	0	0	0	0	$P < 0.001$	98
IV. Sodium chromogycate	50	48	2	0	0	2	4	$P < 0.001$	91

*Denotes $P < 0.05$

nist) and concluded that terbutaline inhalation effectively suppressed the cough response from 43% to 3%. Salbutamol inhalation causes bronchodilation and is also an effective antitussive agent both in normal and asthmatic patients. Inhalation of a metered dose of salbutamol significantly decreased the incidence of cough in our study.

In humans, fentanyl constricts the tracheal smooth muscle and hence the irritant receptors nearby may be stimulated following deformation of the tracheobronchial wall.[9] These receptors, when stimulated, can trigger the cough reflex via the vagal afferent pathway. We used corticosteroid (beclomethasone) inhalation therapy as it is known to reduce bronchial hyperirritability, mucosal edema and also to suppress the inflammatory response to trigger stimuli.[12] None of the patients who received beclomethasone inhalation had any cough following a preinduction bolus of *iv* fentanyl.

Histamine release in humans from lung mast cells is a possible mechanism of fentanyl-induced cough, though this appears very unlikely as fentanyl rarely causes histamine release.[13] Sodium chromoglycate inhibits degranulation of mast cells triggered by various stimuli. The release of histamine, leukotrienes, interleukins and other inflammatory mediators from mast cells may be responsible for coughing. Metered dose inhalation of sodium chromoglycate significantly decreased the incidence of cough in our study.

We conclude that pretreatment with salbutamol, beclomethasone or sodium chromoglycate aerosol prior to a 2 $\mu g \cdot kg^{-1}$ *iv* fentanyl bolus reduces the incidence of cough. Therefore, we recommend that all patients likely to experience adverse events associated with fentanyl-induced cough should receive a metered dose of one of these drugs by inhalation 15 min prior to induction of anesthesia.

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