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## REVIEW ARTICLE

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# FENTANYL - INDUCED COUGH - PATHOPHYSIOLOGY AND PREVENTION

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### Abstract

Many reports have demonstrated that intravenous administration of a bolus of fentanyl at induction of anesthesia can cause coughing with varying degrees. This cough can be benign, but sometimes it causes undesirable side effects including an increase in intraabdominal, intracranial or intraocular pressure. Many studies demonstrated that the incidence and severity of fentanyl-induced cough could be related to age, ethnicity, history of smoking, as well as to the rate, route, dose and concentration of fentanyl administered. This cough was described by several mechanisms including an inhibition of central sympathetic system leading to vagal predominance, reflex bronchoconstriction after the stimulation of tracheobronchial tree receptors, or histamine release. The efficacy of several measures to avoid fentanyl-induced cough have been demonstrated, and several anesthetics adjuncts can be given prior to fentanyl administration aiming at decreasing this unwanted side effect.

### Introduction

Fentanyl and its derivatives sufentanil, alfentanil, and recently remifentanil are the most frequently used opioids in clinical anesthesia. These synthetic potent opioids derived from phenylpiperidine are primarily administered for their analgesic effect especially prior to induction of anesthesia. They are also used to produce sedation for many procedures including endoscopy, cardiac catheterization, lumbar puncture and bone marrow aspirate/biopsy in pediatric oncology patients, as well as in the management of chronic pain including cancer pain, and others.

Fentanyl, first synthesized in 1960, is a  $\mu$ -opioid receptor agonist and has clinical potency ratio 50 to 100 times that of morphine. It is characterized by its rapid onset, short duration of action, profound dose-dependent analgesia, and cardiovascular stability mainly during laryngoscopy and endotracheal intubation, and is less likely to cause histamine release<sup>1,2</sup>.

As any other opioid, fentanyl has several side effects including nausea, constipation, dry mouth, somnolence, asthenia, hypoventilation, and apnea. Another important side effect is the fentanyl-induced cough. Many reports have demonstrated that a bolus of fentanyl at induction of

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anesthesia can cause coughing with varying degrees. Cough was also described after alfentanil, sufentanil, and remifentanil bolus administration at anesthesia induction<sup>3,4</sup>. This side effect can be transient, benign and self-limiting for most patients, but at times it can be spasmodic, explosive<sup>5</sup>, and life threatening<sup>6</sup>.

Fentanyl-induced cough should be avoided in patients who have potential for an increase in intracranial pressure such as cerebral aneurysms, arterio-venous malformation, cerebral tumor, or have already increased intracranial pressure such as ruptured cerebral aneurysms, and in patients with acute glaucoma, penetrating eye injuries, or dissecting aortic aneurysm. Although fentanyl-induced cough is not more frequent in chronic obstructive pulmonary disease or asthmatic patients<sup>7</sup>, it is wise to avoid cough in this group of patients who have hypersensitive airway.

### *Fentanyl-induced cough pathophysiology*

Cough is a well-integrated reflex resulting from mechanical and chemical stimulations of sensory receptors. The most likely receptors are the rapidly adapting pulmonary stretch receptors (RARs) with small diameter A delta myelinated fibers (localized mainly at the larynx) and the pulmonary and bronchial C-fiber receptors with nonmyelinated afferents. These fibers constitute the afferent limb which interacts with brainstem cough center, while the efferent limb consists of motor nerves that supply the muscles of coughing<sup>8</sup>. A new concept of the central regulatory system for cough reflex has been suggested. Cough-gating neurons, located in the ventrolateral nucleus tractus solitarius, play a crucial role in the generation of cough reflex. In fact, the second order relay neurons in the nucleus tractus solitarius receive peripheral tussigenic inputs. The cough-gating neurons, constituting the gating mechanism, integrate these afferents inputs and activate the central cough/respiratory pattern generator by producing triggering signals. Finally, the produced cough motor task is transmitted to the inspiratory and expiratory muscles through activation of respiratory motoneurons. The cough pattern generator in the brainstem appears to be identical to the respiratory pattern generator and

to function by reshaping of the discharge pattern of respiratory neurons<sup>9</sup>.

Regarding the mechanism of cough induced by opioids, several hypotheses were implicated. The rapidly adapting receptors present on the mucosa of the proximal tracheobronchial airway can be stimulated by fentanyl causing bronchoconstriction and cough which can be suppressed by inhaled beta 2-agonists such as terbutaline<sup>10</sup> or salbutamol<sup>11</sup>. In addition, Tanaka et al. demonstrated that the topical application of citrate on C fibers of the airway induces cough in animals and humans<sup>12</sup>. Since fentanyl is available as citrate salts, citrate can stimulate C fibers (known also as J-receptors) present on the smooth muscles of trachea and bronchi releasing neuropeptides such as tachykinins or bradykinins responsible for the cough. These J receptors are accessible via pulmonary circulation and are very sensitive to chemical irritants<sup>13</sup>. The differences in the incidence and severity of cough among different opioids may be attributed to the amount of citrate in opioids<sup>14</sup>.

Histamine release is a possible cause for inducing cough by fentanyl, but this is not clear as fentanyl rarely causes histamine release in mast cells of the lungs. However, Argwal et al study showed that sodium chromoglycate, a mast cell stabilizer, led to a decrease in the incidence of fentanyl-induced cough<sup>11</sup>.

Fentanyl has been shown to enhance vagal activity while inhibiting sympathetic nervous system leading to reflex bronchoconstriction and cough<sup>15</sup>. Recently, it appears unlikely that the vagal system stimulation mediates fentanyl-induced cough as premedication by anticholinergic drugs as atropine does not decrease its incidence<sup>7,16</sup>.

Alternative hypothesis that should be verified by further studies is that the muscle rigidity produced by fentanyl can cause sudden adduction of vocal cords or supraglottic obstruction<sup>17</sup>, and a priming dose of vecuronium could decrease the incidence of fentanyl-induced cough<sup>7</sup>.

### *Incidence of fentanyl-induced cough*

The discrepancies in the incidence of fentanyl-induced cough may be related to age, ethnicity,

smoking, as well as to different doses, rates and routes of fentanyl administration.

1. Age: The incidence of fentanyl-induced cough is high in infants and children, even in small doses (1 µg/kg)<sup>18-20</sup>. This can be explained by an increase in irritant cough receptors<sup>17</sup>. However, Lin et al showed that age has no effect on the incidence of cough<sup>21</sup>.
2. Ethnicity: Fentanyl-induced cough may be more evident in Asian population than European one<sup>16,22</sup>. Schapermeier and Hopf demonstrated that the incidence of cough following intravenous (IV) fentanyl 1.5 µg/kg ranges between 3% and 6% in European patients<sup>22</sup> whereas Phua et al showed that this incidence is 28% using the same fentanyl dose in Asian patients<sup>16</sup>.
3. Smoking: There is a controversy regarding the implication of smoking in increasing the incidence of fentanyl-induced cough. Baley reported that fentanyl-induced cough was noticeable in smokers<sup>23</sup>. However, Dimitriou et al. demonstrated that the incidence of cough in the non-smoker and smoker group (more than 10 cigarettes per day) was similar after administration of 2-3 µg/kg of fentanyl during anesthesia induction<sup>24</sup>. Lin et al. demonstrated that light smoking may be a protective factor against fentanyl-induced cough. They showed that smokers who smoked fewer than 10 cigarettes per day have less fentanyl-induced cough than nonsmokers after administration of 2 µg /kg of fentanyl, but there was no difference between heavy smokers (more than 10 cigarettes per day) and non-smokers<sup>21</sup>. This can be explained by the inhibitory effects of nicotine on C fibers in current light smokers which are abolished in heavy smoker patients<sup>25</sup>.
4. Doses of injection: As shown in several previous studies, the incidence of fentanyl-induced cough increases proportionally with the doses. With a speed of injection of fentanyl less than 2 seconds at induction time, the cough incidence increased from 6.6% to 61% when fentanyl dose increased from 2 µg/kg to 4 µg/kg (table 1). All these doses were administered peripherally.
5. Speed of injection: Schapermeier and Hopf showed in their study that injection of 1.5 µg /kg of fentanyl over 2, 5 or 10 seconds leads to similar incidence of cough ranging from 3% to 6%, concluding that

the speed of injection does not affect the incidence of cough<sup>22</sup>. However, Lin et al showed that a longer injection time can reduce the incidence of fentanyl-induced cough. Fentanyl injection (2 µg/kg) induced cough in 18% of patients with an injection time less than 2 seconds; increasing injection time to 30 seconds yielded a drop in the incidence of evoked cough to 1.3%<sup>21</sup>. This can be explained by less chance of fentanyl to reach the threshold of plasma concentration as the mean time of fentanyl to reach the peak plasma concentration is 15 seconds<sup>25</sup>. In another study, Lin et al study showed that administration of 2.5 µg /kg of fentanyl over two seconds can reach 65 %<sup>17</sup>.

6. Route of administration: The different routes of fentanyl administration have been evaluated in different studies. High incidence of fentanyl-induced cough has been observed when fentanyl was given at a high dose and via a central line. Bohrer et al. showed that IV administration of large dose of fentanyl 7 µg /kg via a central line causes cough with an incidence reaching 45%. vs 2.7% when the same dose was given peripherally, which can explain the direct fentanyl stimulation of the pulmonary chemoreflexes<sup>13</sup>.

### *Onset of fentanyl-induced cough*

In addition to the pharmacokinetic property of fentanyl, the dose, speed of injection, and route of administration contribute to the onset time of cough. Chen et al study showed that the rate of fentanyl injection through the same peripheral venous access at the same dose may affect both the incidence and onset time of cough. At the same dose and injection rate of fentanyl, forearm venous access of injection resulted in earlier onset of cough than lower limb venous access with a similar incidence<sup>26</sup>. In two other studies, the onset of cough was 9 seconds when 7 µg/kg fentanyl bolus was administered via a central line<sup>13</sup> and 42±8 seconds when 5 µg /kg was injected over 5 seconds peripherally<sup>10</sup>.

### *Pharmacological intervention to reduce fentanyl-induced cough*

Table 1

*Incidence of cough after fentanyl administration through peripheral line and summary of effective methods to prevent it. The articles are listed as per increasing fentanyl doses.*

References	Number of cases per group	Fentanyl dose ( $\mu\text{g}/\text{kg}$ )	Time of injection (seconds)	Incidence of cough after fentanyl (control) (%)	Medications to prevent cough	Incidence of cough after medication (%)
Lida et al, 2009 <sup>53</sup> .	106	1 3 5	NA	6.6 22.5 44.3	No intervention	
Phua et al. 1991 <sup>16</sup> .	50	1.5	NA	28	Atropine (0.01mg/kg) Morphine (0.2mg/kg) Midazolam (7.5mg)	30 6 40
Chung-Chang et al. 2007 <sup>35</sup> .	180	1.5	5	21.6	Ketamine (0.15mg/kg)	7.2
Hornig et al. 2007 <sup>36</sup> .	150	2	<2	38.7	Clonidine (2 $\mu\text{g}/\text{kg}$ )	17.3
Lin et al. 2005 <sup>21</sup> .	150	~2	<2 15 30	18 8 1.3	No intervention	
Lin et al. 2007 <sup>44</sup> .	108 (fentanyl group)/80 (Dexamethasone group)	~2	2	21.3	Dexamethasone 10mg)	6.3
Argwal et al. 2003 <sup>11</sup> .	50	2	5	28	One puff Salbutamol One puff Beclomethasone One puff Sodium chromoglycate	6 0 4
Qing et al. 2010 <sup>46</sup> .	93	2	2	22.6	Pentazocine (0.5mg/kg)	4.3
Hung et al. 2010 <sup>51</sup> .	200	~2	NA	18.5	Preemptive fentanyl dose 25 $\mu\text{g}$	7.5
Tang et al. 2010 <sup>49</sup> .	30	2.5	1.5 $\pm$ 0.3	80 (Intralipid 0.15ml/kg)	Propofol (1mg/kg) Propofol (1.5mg/kg) Propofol (2mg/kg)	40 6.7 3.3
Lin et al. 2004 <sup>17</sup> .	31	2.5	2	65	Lidocaine (2mg/kg) Ephedrine (5mg): Propofol (0.6mg/kg):	14 21 37
Yu et al. 2012 <sup>40</sup> .	110	3	NA	40.9	Midazolam (0.6mg/kg) Dexmedetomidine (0.6 $\mu\text{g}/\text{kg}$ ) Midazolam(0.6mg/kg)+dex(0.6 $\mu\text{g}/\text{kg}$ )	63.6 22.7 0
Pandey et al. 2004 <sup>31</sup> .	251	3	NA	34.22	Lidocaine (1.5mg/kg):	13.1
Pandey et al. 2005 <sup>32</sup> .	80	3	NA	35	Lidocaine (0.5mg/kg): Lidocaine (1mg/kg): Lidocaine (1.5mg/kg):	13.75 15 13.75
Yu et al. 2007 <sup>19</sup> .	50	3	3-5	32	Dilution of fentanyl from 50 $\mu\text{g}/\text{ml}$ to 25 $\mu\text{g}/\text{ml}$ 50 $\mu\text{g}/\text{ml}$ to 10 $\mu\text{g}/\text{ml}$ 50 $\mu\text{g}/\text{ml}$ to 10 $\mu\text{g}/\text{ml}$ + prolonged time to injection	16 12 2
Liang et al. 2012 <sup>37</sup> .	100	4	<2	61	Dexmedetomidine (0.5 $\mu\text{g}/\text{kg}$ ): Dexmedetomidine (1mcg/kg):	40 18
Lui et al. 1996 <sup>10</sup> .	30	5	NA	43	Terbutaline (5mg):	3
Sun et al. 2011 <sup>47</sup> .	60	5	<2	70	Dezocine (0.1mg/kg)	0
Bohrer et al. 1990 <sup>13</sup> .	37	7	1	2.7	No intervention	

NA (Not available)

Several pharmacological interventions were done to decrease this side-effect with varying success.

1. Lidocaine: IV lidocaine has been demonstrated to decrease airway reflexes including cough reflex during tracheal intubation<sup>27</sup>, extubation<sup>28</sup>, and bronchography<sup>29</sup>. As a proposed mechanism, lidocaine can act centrally by depression of brainstem functions or peripherally by blocking tracheal and hypo-pharyngeal cough receptors<sup>30</sup>. Pandey and co-authors demonstrated that 1.5 mg/kg of lidocaine administered one minute before 3 µg/kg of fentanyl can decrease significantly the incidence of cough<sup>31</sup>. In a dose-response study, he demonstrated that administration of a low dose of lidocaine (0.5 mg/kg IV) over 5 seconds, one minute prior to an induction bolus of fentanyl 3 µg/kg, is effective in decreasing fentanyl-induced cough and that increasing lidocaine dose up to 1.5 mg/kg does not reduce the incidence and severity of fentanyl-induced cough<sup>32</sup>. Lin et al showed the administration of lidocaine 2 mg/kg one minute before fentanyl 2.5 µg/kg over 2 seconds at induction can suppress cough reflex<sup>17</sup>. A recent meta-analysis showed that lidocaine reduces the incidence and severity of fentanyl-induced cough, and that the lowest effective dose of lidocaine for preventing the prevalence of cough was 0.5 mg/kg. No severe adverse effects were reported<sup>33</sup>.

2. Beta 2-adrenergic receptors: As previously mentioned, one of the proposed mechanisms for fentanyl-induced cough is fentanyl-triggered bronchoconstriction. Ephedrine, a sympathomimetic drug that acts as a bronchodilator, can be safely administered intravenously at a small dose (5 mg) in healthy patients, but it is relatively contraindicated in patients with severe hypertension or coronary artery disease<sup>17</sup>. Other beta-2 adrenergic receptor agonists such as nebulized terbutaline<sup>10</sup> and salbutamol<sup>11</sup> were effective in decreasing the incidence of fentanyl-induced cough.

3. Ketamine: It has been also demonstrated that excitatory amino acids and N-methyl - D-aspartate (NMDA) receptor agonists present in the larynx, lungs and airways are capable of stimulating cough reflex<sup>34</sup>; ketamine, an NMDA receptor antagonist, characterized by its potent analgesic and bronchodilator effect has been used as premedication

with a dose of 0.15 mg/kg and was effective in decreasing the incidence of fentanyl-induced cough and delaying its onset<sup>35</sup>.

4. Alpha 2-adrenoreceptor agonist: Clonidine, an alpha 2-adrenoreceptor agonist known by its analgesic, anxiolytic, and sedative effects, is widely used as premedication before surgery. Horng and co-authors demonstrated that premedication with 2 µg/kg of clonidine followed 2 minutes later by administration of 2 µg/kg of fentanyl within 2 seconds decreases the incidence of cough from 38.7% to 17.3%<sup>36</sup>. Recently, the usage of dexmedetomidine, a highly selective alpha 2-adrenoreceptor agonist at doses of 0.5 µg/kg and 1 µg/kg has been effective in reducing cough when 4 µg/kg of fentanyl was injected in less than 2 seconds without causing major cardiovascular instability. However, the severity and onset of time of cough were not affected<sup>37</sup>. The mechanism by which these alpha 2-agonists decrease cough is unclear. It could be attributed to the sedative and broncho-relaxant properties as for ketamine, midazolam and propofol<sup>38</sup>. Hung speculated that clonidine suppresses opioid-induced cough by reducing opioid-induced muscle rigidity that causes the sudden adduction of the vocal cords or supraglottic obstruction<sup>39</sup>. Yu et al. showed that the premedication with dexmedetomidine 0.6 µg/kg and midazolam 0.06 mg/kg, 2 minutes before injecting fentanyl 3 µg/kg within 2 seconds, suppresses completely fentanyl-induced cough, while an incidence of 22.7% was observed after the administration of 0.6 µg/kg of dexmedetomidine alone<sup>40</sup>.

5. Dexamethasone: Tachykinin release stimulates the rapidly activating receptors either directly by contracting smooth muscles or indirectly by inducing histamine release from airway mast cells. It has been reported that dexamethasone can stabilize mast cells<sup>41</sup> and reduce tachykinin-induced bronchoconstriction in guinea pigs, but this needs more investigation in humans<sup>42</sup>. In addition, it has been reported that dexamethasone stimulates neutral endopeptidase which reverses the enhanced airway reactivity of airway epithelial cells<sup>43</sup>. Lin et al study showed that 10 mg of dexamethasone 5 min prior to injection of fentanyl 100 µg/kg in 40-69 kg patient or 150 µg/kg in a 70-90 kg patient

reduces the incidence of fentanyl-induced cough<sup>44</sup>. Yu and coauthors demonstrated also that 10 mg of dexamethasone can decrease cough from 26.5% to 6.5% when remifentanyl was used and reached a target concentration of 5 ng/ml<sup>45</sup>.

6. Agonist-antagonist opioid: Recently, pentazocine, an agonist of kappa and sigma receptors and a weak antagonist of  $\mu$ -receptors, has been shown to be effective in decreasing cough. Qing et al. showed that 0.5 mg/kg of pentazocine given 5 min prior to administration of 2  $\mu$ g/kg of fentanyl over 2 seconds decreases the incidence of cough from 22.6% to 4.3%<sup>46</sup>. Also, dezocine, a full antagonist-kappa receptor and partial agonist-mu receptor, was used to decrease cough when administered at a dose of 0.1 mg/kg 10 minutes prior to injection of 5  $\mu$ g /kg of fentanyl; however, more studies are needed to clarify the effects and mechanisms of action of dezocine in suppressing fentanyl-induced cough<sup>47</sup>.
7. Propofol: This drug is known to have a bronchodilator effect<sup>38,48</sup>, and priming doses ranging from 1 mg/kg to 2 mg/kg administered before anesthesia induction were effective in suppressing the cough<sup>49</sup>. However, Lin et al observed that premedication with 0.6 mg/kg of propofol could not inhibit fentanyl-induced cough<sup>17</sup>.
8. Priming doses of fentanyl: It has been shown that a priming fentanyl dose of 0.5  $\mu$ g/kg<sup>50</sup> or preemptive use of 25  $\mu$ g fentanyl administered 1 minute prior to 125  $\mu$ g or 150  $\mu$ g of fentanyl<sup>51</sup> could suppress

effectively the cough. The preemptive dose of fentanyl releases neurotransmitters that do not reach the threshold to cause cough. However, after a larger dose of fentanyl, there will be an exhaustion of these neurotransmitters resulting in a lower incidence of cough<sup>50</sup>.

9. Dilution of fentanyl: Yu et al found that fentanyl diluted from 50  $\mu$ g/ml to 25  $\mu$ g/ml and 10  $\mu$ g/ml injected over 3-5 seconds reduces the incidence of cough, and that administration of 3  $\mu$ g/kg of fentanyl diluted to 10  $\mu$ g/ml combined with a prolonged injection time to 30 seconds eliminates completely fentanyl-induced cough<sup>19</sup>.
10. Non-therapeutic modalities: Ambesh et al. reported a significantly reduced cough (32% to 4%) induced by 2.5  $\mu$ g/kg of fentanyl if a huffing maneuver was done before induction of anesthesia<sup>52</sup>.

## Conclusion

Cough with varying degrees of severity can be caused by intravenous administration of fentanyl bolus at induction of anesthesia. Although most of the time benign, it can be sometimes associated with undesirable side effects. In order to decrease its incidence and severity, the route, rate, dose, and concentration of fentanyl injection should be taken into consideration, and several adjuncts can be given prior to fentanyl administration.

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