

Effect of Equivalent Doses of Fentanyl, Sufentanil, and Remifentanil on the Incidence and Severity of Cough in Patients Undergoing Abdominal Surgery: A Prospective, Randomized, Double-Blind Study

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ABSTRACT

BACKGROUND: Fentanyl congeners have been found to induce cough during induction of general anesthesia. Studies of fentanyl and sufentanil have found incidence rates of 28% to 65% and 15%, respectively. However, no study has assessed the occurrence of cough induced by remifentanil.

OBJECTIVE: The aim of this study was to assess the effect of equivalent doses of fentanyl, sufentanil, and remifentanil on cough.

METHODS: Patients rated American Society of Anesthesiologists class I or II of either sex, aged 18 to 60 years, who were scheduled for elective abdominal surgery with general anesthesia were randomly and equally assigned to 3 groups using a computer-generated table of random numbers. The patients received equivalent doses of fentanyl 2 $\mu\text{g}/\text{kg}$, sufentanil 0.2 $\mu\text{g}/\text{kg}$, or remifentanil 2 $\mu\text{g}/\text{kg}$ via IV push. Vital signs (systolic blood pressure [SBP], heart rate [HR], and oxygen saturation via pulse oximetry [SpO_2]) and the occurrence and severity of cough were recorded for 2 minutes after drug administration by an anesthesiologist who was blinded to the drug treatment. The severity of cough was graded as none (0), mild (1–2), moderate (3–5), or severe (>5).

RESULTS: A total of 315 Chinese patients (197 women, 118 men; mean [SD] age, 37.9 [10.4] years) were approached for enrollment and assigned to 3 groups of 105 patients each; all patients completed the study protocol. The 3 treatment groups were similar in terms of demographic characteristics and type of abdominal surgery. The incidence of cough was significantly greater in the remifentanil group (57 [54.3%] patients) than in the fentanyl group (35 [33.3%]; $P < 0.01$) or the sufentanil group (32 [30.5%]; $P < 0.01$). The severity of cough was significantly greater in the remifentanil group (severe, moderate, mild, none: 24, 7, 26, 48) than in the fentanyl (7, 9, 19, 70; $P < 0.01$) or sufentanil group (4, 2, 26, 73; $P < 0.01$). In all 3 groups, when the patients coughed, significant increases were observed in their SBP (128 [12]–139 [16] mm Hg; $P < 0.01$) and HR (74 [10]–87 [16] beats/min; $P < 0.01$). Within 2 minutes after drug administration, 62 patients (59%) in the remifentanil group

experienced hypoxemia ($\text{SpO}_2 < 90\%$) necessitating manually assisted mask ventilation, while no patients experienced hypoxemia in the fentanyl or sufentanil group. Three patients (2.9%) in the remifentanil group experienced muscle rigidity and deterioration of SBP, HR, and SpO_2 . No other adverse events were recorded.

CONCLUSION: Remifentanil was associated with a significantly greater incidence and severity of cough than equivalent doses of fentanyl or sufentanil. Fentanyl and sufentanil appeared comparable in these Chinese patients undergoing abdominal surgery. (*Curr Ther Res Clin Exp.* 2008;69:480–487) © 2008 Excerpta Medica Inc.

KEY WORDS: cough, incidence, severity, fentanyl, sufentanil, remifentanil.

INTRODUCTION

Coughing is undesirable in patients with some coexisting conditions, including increased intracranial pressure, open eye injury, dissecting aortic aneurysm, pneumothorax, and reactive airway disease.¹ Fentanyl and sufentanil have been associated with general anesthesia-induced cough. The incidence of fentanyl-induced cough has been found to vary from 28% to 65%.^{1–4} The incidence of sufentanil-induced cough was reported to be 15% after a bolus of sufentanil 0.3 $\mu\text{g}/\text{kg}$ over 5 seconds.⁵ However, a search of MEDLINE (1956–August 2007) using the terms *remifentanil*, *incidence*, and *cough*, *coughing*, or *tussive effect* yielded no results.

In an unpublished preliminary study that was intended to determine the necessary data for sample size calculations in the present study, we observed that the incidence of sufentanil-induced cough was 30% after a bolus of sufentanil 0.2 $\mu\text{g}/\text{kg}$ administered via IV push and that remifentanil might also evoke cough. We designed a prospective, randomized, double-blind study to compare the incidence and severity of cough induced by equivalent doses of fentanyl, sufentanil, and remifentanil.

PATIENTS AND METHODS

This study was conducted at the Jinling Hospital, Nanjing University, Nanjing, China, between August 2007 and March 2008. The study protocol was approved by the ethics committee of Jinling Hospital. Written informed consent was obtained from all patients before study enrollment.

Patients rated American Society of Anesthesiologists class I or II of either sex, aged 18 to 60 years, who were scheduled for elective abdominal surgery with general anesthesia were eligible for the study. Exclusion criteria were as follows: weight >20% above ideal; impaired kidney or liver function; the presence of a gastric tube; a history of asthma, chronic cough, or smoking; upper respiratory tract infection in the previous 2 weeks; and recent treatment with angiotensin-converting enzyme inhibitors, bronchodilators, or corticosteroids.

One investigator (J.-G.X.) evaluated all inclusion/exclusion criteria and randomized the patients to 1 of 3 groups using a computer-generated table of random numbers to receive fentanyl (50 $\mu\text{g}/\text{mL}$; Renfu Co., Hubei, China), sufentanil (50 $\mu\text{g}/\text{mL}$; Renfu Co.), or remifentanil (1000 $\mu\text{g}/\text{bottle}$; Renfu Co.). The same investigator was responsible for drug preparation. The allocation sequences were contained in a set of

sealed envelopes, and the other investigators and patients involved in the study were blinded to treatment assignment.

Sufentanil and remifentanil were diluted with normal saline to 10 mL and 20 mL, respectively, whereas fentanyl was not diluted. Each drug preparation was the same volume and all were colorless and odorless. All administrations were conducted via 5-second IV push. By reducing the minimal alveolar concentration of isoflurane, the potency ratios of fentanyl, sufentanil, and remifentanil were nearly 1:10:1⁶⁻⁹; fentanyl 2 µg/kg (50 µg/mL), sufentanil 0.2 µg/kg (5 µg/mL), or remifentanil 2 µg/kg (50 µg/mL) was administered via IV push.

No premedication was allowed. In the operating room, venous access to the median cubital vein was established with a 20G IV cannula that was connected to a venous transfusion tubing via a 3-way joint. Electrocardiogram and oxygen saturation via pulse oximetry (SpO₂) were monitored, and a radial artery cannula was inserted to monitor blood pressure (BP). The mean (SD) vertical distance between the drip bottle and the median cubital vein was 90 (5) cm. With the controller of the IV fluid running rate fully opened, the drug was administered at a relatively constant rate via IV push within 5 seconds by an investigator (J.-C.S.) who had been trained in controlling the administration rate. A stopwatch was used to monitor the time between drug administration and the onset of coughing.

In an unpublished preliminary study of 90 patients using a 3-minute observation period, all coughing occurred within 1 minute after study drug administration, and a decrease in SpO₂ to <90% usually occurred within 2 minutes in 72% of patients in the remifentanil group. When SpO₂ decreased to <90%, manually-assisted mask ventilation with pure oxygen was to be applied immediately. Consequently, 2 minutes was chosen as the observation period in the present study. Atropine 0.5 mg IV was administered immediately if the heart rate (HR) was <50 beats/min. The primary outcome was the incidence of cough and the secondary outcome was the severity of cough, which was graded as none (0), mild (1–2), moderate (3–5), or severe (>5).^{2,5} All evaluators were trained in the grading technique at the same time.

Systolic BP (SBP), HR, and SpO₂ were recorded before drug administration. The lowest SpO₂ within 2 minutes after drug administration was recorded in all patients; and the highest SBP and HR within 2 minutes were recorded in patients who coughed. SpO₂ was also recorded when a patient required manually assisted mask ventilation.

STATISTICAL ANALYSIS

We conducted a preliminary study using the same protocol as the present study in 3 groups of 30 patients each. The results of the study were not published. Eleven patients (37%) in the fentanyl group, 9 (30%) in the sufentanil group, and 16 (53%) in the remifentanil group coughed. With an $\alpha = 0.05$, $\beta = 0.1$, maximal percentage = 55%, and minimal percentage = 30%, this analysis suggested that 97 patients were needed in each group. To allow for possible dropouts prior to study initiation, it was determined that 105 patients would be enrolled in each group.

Values are reported as mean (SD), median (range), or number (%). The binary variables, including the incidence of cough, were compared using the Fisher exact test

with Bonferroni correction. Ranked variables (including the severity of cough) or non-normally distributed variables were compared using the Kruskal-Wallis H test followed by the Dunn test for post hoc multiple comparisons. Normally distributed variables were compared using 1-way analysis of variance followed by the least significant difference test or paired *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 315 patients were approached for enrollment (197 women, 118 men; mean [SD] age, 37.9 [10.4] years) and randomly assigned to 3 groups of 105 patients each. The 3 treatment groups were similar in terms of demographic characteristics and type of surgery (Table I). All the enrolled patients completed the study protocol.

The incidence of cough was significantly greater in the remifentanyl group (57 [54.3%]) than in the fentanyl group (35 [33.3%]; $P < 0.01$) or the sufentanil group (32 [30.5%]; $P < 0.01$). The severity of cough was significantly greater in the remifentanyl group (none, mild, moderate, severe: 48, 26, 7, 24, respectively) compared with the fentanyl (70, 19, 9, 7; $P < 0.01$) or the sufentanil group (73, 26, 2, 4; $P < 0.01$). The incidence and severity of cough between the fentanyl and the sufentanil groups were not significantly different. The time to onset of cough for the sufentanil group (24.0 [4.3] seconds) was significantly longer than that for the fentanyl (19.7 [3.3]; $P < 0.01$) or remifentanyl groups (18.6 [3.2]; $P < 0.01$) (Table II).

In all 3 groups, when the patients coughed, significant increases occurred in their SBP (128 [12]–139 [16] mm Hg; $P < 0.01$) and HR (74 [10]–87 [16] beats/min; $P < 0.01$).

Median (range) SpO₂ decreased significantly after drug administration in all 3 groups (remifentanyl, 8% [1–10]; fentanyl, 2% [0–6]; sufentanil, 3% [0–8]; all, $P <$

Table I. Baseline demographic and clinical characteristics of the study patients (N = 315).*

Characteristic	Fentanyl (n = 105)	Sufentanil (n = 105)	Remifentanyl (n = 105)
Age, mean (SD), y	37.6 (10.3)	39.1 (10.0)	37.2 (10.9)
Sex, no. (%)			
Female	64 (61)	65 (62)	68 (65)
Male	41 (39)	40 (38)	37 (35)
Height, mean (SD), cm	166.5 (7.5)	165.6 (7.2)	164.7 (6.9)
Weight, mean (SD), kg	62.0 (7.6)	61.2 (7.3)	60.1 (8.5)
Abdominal surgery, no. (%)			
Lower	66 (63)	59 (56)	62 (59)
Upper	39 (37)	46 (44)	43 (41)

*No significant between-group differences were found.

Table II. Incidence, severity, and time to onset of cough after receiving a single administration of fentanyl, sufentanil, or remifentanil (N = 315).

Characteristic	Fentanyl (n = 105)	Sufentanil (n = 105)	Remifentanil (n = 105)
Incidence, no. (%)	35 (33.3)	32 (30.5)	57 (54.3)*
Severity, no. (%) [†]			
None	70 (66.7)	73 (69.5)	48 (45.7)
Mild	19 (18.1)	26 (24.8)	26 (24.8)
Moderate	9 (8.6)	2 (1.9)	7 (6.7)
Severe	7 (6.7)	4 (3.8)	24 (22.9)*
Time to onset, mean (SD), s	19.7 (3.3)	24.0 (4.3) [†]	18.6 (3.2)

* $P < 0.01$ versus the fentanyl and sufentanil groups.

[†]Severity was based on the following score scale: none, 0; mild, 1 to 2; moderate, 3 to 5; severe, >5 .^{2,5}

* $P < 0.01$ versus the fentanyl and remifentanil groups.

0.01). The decrease was significantly greater in the remifentanil group compared with the fentanyl and sufentanil groups (both, $P < 0.01$) (Table III). Within 2 minutes after drug administration, 62 patients (59%) in the remifentanil group experienced hypoxemia ($\text{SpO}_2 < 90\%$) that necessitated manually-assisted mask ventilation; no patients in the fentanyl or sufentanil group experienced hypoxemia.

Three patients in the remifentanil group experienced noticeable muscle rigidity but did not cough. One of them, a 42-year-old female (baseline height, 165 cm; weight, 65 kg; BP, 116/63 mm Hg; HR, 72 beats/min; and SpO_2 , 99%) experienced bradycardia. One minute after remifentanil injection, her BP, HR, and SpO_2 decreased to 85/50 mm Hg, 45 beats/min, and 90%, respectively. Atropine 0.5 mg IV was administered; however, manually-assisted mask ventilation was difficult, possibly due to muscle rigidity. Rocuronium bromide 50 mg was administered immediately, and BP, HR, and SpO_2 recovered 1 minute later. The other 2 patients (48-year-old male, 169 cm, 70 kg; 30-year-old female, 160 cm, 60 kg) experienced increases in BP (150/76–207/101 and 131/66–176/89 mm Hg, respectively) and HR (85–108 and

Table III. Median (range) oxygen saturation via pulse oximetry (SpO_2) at baseline and after receiving fentanyl, sufentanil, or remifentanil (N = 315).

Characteristic	Fentanyl (n = 105)	Sufentanil (n = 105)	Remifentanil (n = 105)
Baseline SpO_2 , %	99 (97–100)	99 (97–100)	99 (97–100)
Lowest SpO_2 , %	97 (92–100)*	96 (91–100)*	90 (90–99)* [†]
Decrease in SpO_2 , %	2 (0–6)	3 (0–8)	8 (1–10) [†]

* $P < 0.01$ versus baseline.

[†] $P < 0.01$ versus the fentanyl and sufentanil groups.

70–89 beats/min) and a decrease in SpO₂ (100%–95% and 97%–91%). No other adverse events were recorded.

DISCUSSION

Various mechanisms have been proposed to explain fentanyl-induced cough. A pulmonary chemo reflex mediated by either vagal C-fiber receptors in close proximity to pulmonary vessels^{6,10,11} (juxtacapillary receptors) or by irritant receptors (rapidly adapting receptors) has been suggested.^{4,6} Opioid-induced histamine release¹² and muscle rigidity leading to sudden adduction of the vocal cords or supraglottic obstruction by soft tissue¹³ have also been suggested. These mechanisms might explain why fentanyl congeners are associated with cough in the present study. However, the explanation for the significantly longer time to onset of sufentanil-induced cough remains unclear.

In one study by Agarwal et al,² fentanyl 2 µg/kg administered via a peripheral venous catheter over a period of 5 seconds elicited cough in 28% of patients undergoing elective laparoscopic cholecystectomy. Pandey et al¹⁴ found that 35% of elective surgery patients coughed after receiving fentanyl 3 µg/kg through a peripheral venous catheter. Lin et al¹ observed a 65% incidence of cough in elective surgery patients following administration of fentanyl 2.5 µg/kg IV via a freely running peripheral venous catheter within 2 seconds. In the present study, the incidence of fentanyl-induced cough was 33%. Different doses, administration routes, and administration rate might explain the discrepancy in the incidence of cough between these studies.

In another study by Agarwal et al,⁵ sufentanil 0.3 µg/kg administered via a peripheral catheter on the dorsum of the hand over 5 seconds was associated with cough in 15% of the patients and the severity of sufentanil-induced cough was significantly less than that of fentanyl ($P = 0.039$). However, we found the incidence of cough with sufentanil was 30% and the severity of cough in the sufentanil group was similar to that of the fentanyl group. The differing results between the 2 studies might be due to differences in doses, concentrations, administration routes, administration rate, sample size, or race; whether the drugs were diluted with normal saline or water prior to injection; and whether or not the patients were premedicated.

Coughing is associated with acute increases in BP, HR, and intracranial, intraocular, and intra-abdominal pressure.² In the present study, coughing was associated with increases in BP and HR. SpO₂ decreased after drug administration in each group, with the greatest SpO₂ decrease occurring in the remifentanyl group. The greatest effect occurred with remifentanyl at ~1.3 minutes,¹⁵ while the greatest effect with fentanyl was at 3.6 minutes and with sufentanil at 5.6 minutes.¹⁶

Remifentanyl was reported to induce tonic-clonic activity in an otherwise healthy adult.¹⁷ In the present study, 3 patients in the remifentanyl group had muscle rigidity. Intravenous administration of remifentanyl has been associated with decreases in BP, HR, carbon monoxide, and myocardial contractility.^{18,19} In the present study, 1 patient had significant bradycardia and required treatment with atropine, and 2 patients had increased BP and HR and decreased SpO₂. Thomson et al²⁰ reported that 10% of the patients with an intravenous administration of fentanyl 50 to 100 µg/kg for anesthesia

induction experienced hyperdynamic cardiovascular effects due to activation of central sympathetic nerves. Because IV push administration of remifentanyl might elicit these severe adverse events, such as muscle rigidity or myocardial contractility, it should be used cautiously or avoided in clinical practice. Therefore, though we performed the present study using sufficient safety monitoring, the use of IV push administration of remifentanyl was a major limitation in the study protocol. Further studies are needed to explore the mechanisms of the differences in the incidence and severity of cough among fentanyl congeners.

CONCLUSION

Remifentanyl was associated with a greater incidence and severity of cough than fentanyl or sufentanyl, while sufentanyl and fentanyl appeared comparable in this study in patients undergoing abdominal surgery.

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