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Butorphanol suppresses fentanyl-induced cough during general anesthesia induction

A randomized, double-blinded, placebo-controlled clinical trial

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Abstract

Fentanyl-induced cough (FIC) is unwanted in the patients requiring stable induction of general anesthesia. This study was designed to evaluate the suppressive effects of butorphanol pretreatment on the incidence and severity of FIC during the induction of general anesthesia. A total of 315 patients of American Society of Anesthesiologists physical status I and II, scheduled for elective surgery under general anesthesia were randomized into 3 equally sized groups (n=0105). Two minutes before fentanyl bolus, group I received intravenously 5 mL normal saline, groups II and III received butorphanol 0.015 and 0.03 mg/kg (diluted with saline to 5 mL), respectively. Patients were then administrated with fentanyl 2.5 μg/kg within 5 s. The incidence and severity of FIC was recorded for 2 minutes after fentanyl bolus. During experimental period, the mean arterial pressure, heart rate, and peripheral capillary oxygen saturation (SpO_2) were recorded before the administration of butorphanol or normal saline (T0), 2 minutes (T1) after butorphanol injection, and 2 minutes (T2) after fentanyl injection. The incidence of FIC was 31.4% in group I, 11.4% in group II, and 3.8% in group III. Group III had a lowest incidence of FIC among 3 groups ($P<0.001$, vs group I; $P<0.05$, vs group II). The severe FIC was not observed in groups II and III, but was recoded from 6 patients in group I. At 2 minutes after fentanyl injection (T2), the mean arterial pressure was significantly higher in group I than that in groups II and III ($P<0.01$, vs group II; $P<0.05$, vs group III), but the values remained within safe limits. In conclusion, pretreatment with butorphanol could effectively and safely suppress FIC during anesthesia induction.

Abbreviations: ASA = American Society of Anesthesiologists, FIC = fentanyl-induced cough, HR = heart rate, MAP = mean arterial pressure, NIBP = noninvasive blood pressure, SpO_2 = peripheral capillary oxygen saturation.

Keywords: butorphanol, cough, fentanyl, general anesthesia

1. Introduction

Advantages, such as quick onset, short duration of action, intense analgesia, cardiovascular stability as well as low histamine release, make fentanyl widely used by anesthesiologists for induction and maintenance of general anesthesia.[1,2] However, intravenous bolus administration of fentanyl could elicit cough during induction, which is accompanied with increased intracranial, intraocular, and intra-abdominal pressure.[3] From our own experiences, the fentanyl-induced cough (FIC) is transient and self-limiting in most patients. But, FIC should be effectively prevented in certain patients who are suffering from open eye injury, pneumothorax, cerebral aneurysm, brain trauma, brain hernia, dissecting aneurysm, hypersensitive airway disease, nonfasting, and so on.[4,5] In some situations, severe FIC could even lead to life-threatening upper airway obstruction[6] and aspiration pneumonia[7] that require immediate intervention.

To date, various drugs have been used to reduce the incidence and severity of FIC. Among them, prototypical agonist-antagonist opioid analgesic agents, such as pentazocine and dezocine, have shown their efficacy in suppressing fentanyl- and sufentanyl-induced cough during general anesthesia induction with rarely adverse side effects.[8–11] Butorphanol is another agonist-antagonist opioid that is extensively used in clinical practice with more potent analgesic effect and a better pharmaceutical formulation. Besides, it has been used as the antitussive drug in animals.[12,13] However, there is no investigation regarding the effectiveness of butorphanol on preventing unwanted FIC. Hence, we designed this study to assess the effects of pretreatment with butorphanol on the incidence and severity of FIC during induction of general anesthesia.

2. Material and methods

This prospective, randomized, double-blinded, and placebo-controlled clinical trial was approved by the Institutional Medical Ethics Committee of Nanjing Medical University. After obtained written informed consents, 315 American Society of Anesthesiologists (ASA) physical status I–II patients of both

Editor: Kazuo Hanaoka.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:26(e3911)

Received: 6 April 2016 / Received in final form: 10 May 2016 / Accepted: 13 May 2016

http://dx.doi.org/10.1097/MD.0000000000003911

genders, aged 18–65 years and scheduled for elective surgery under general anesthesia were included in this trial. Exclusion criteria included pregnancy; impaired kidney or liver function; a history of chronic cough, asthma, smoking; upper respiratory tract infection, treatment with angiotensin converting enzyme inhibitors, bronchodilators, or steroids within the previous 2 weeks. Patients with increased intracranial, intraocular, or intra-abdominal pressures were also excluded.

Patients were randomly assigned to 3 groups of 105 patients each. Randomization was achieved by use of computer-generated random codes that were placed in consecutively numbered, opaque envelopes. Drugs were prepared in unlabeled 10 mL syringes outside the operating room by an anesthesiologist who was not involved in the induction of anesthesia.

None of the patients received any premedication. After the patients arrived, the operating room, a 20-gauge cannula was inserted into the dorsum of their hands and connected to a T-connector for drug administration. Standard monitors, including noninvasive arterial pressure, heart rate (HR), electrocardiography, and peripheral capillary oxygen saturation (SpO_2) were applied. Oxygen gas flow at 2 L/min was given via a facial mask and ringer lactate was infused at a rate of 4–6 mL/min.

After preoxygenation for 2 minutes, the pretreatment drug, butorphanol (#15081532, Hengrui, China) or saline was given. Group I received 5 mL saline; group II received butorphanol 0.015 mg/kg; group III received butorphanol 0.03 mg/kg. The butorphanol patients in groups II and III received were diluted with saline to 5 mL. Two minutes after infusion, fentanyl 2.5 μg/kg was administered through the peripheral venous line within 5 s. The incidence and severity of cough were observed continuously by another anesthesiologist who was blinded to group allocation for 2 minutes, as the cough generally happens within this period. Patients also were not aware of the pretreatment drug. The severity of cough was graded, based on the numbers of cough, as none (0), mild (1–2), moderate (3–4), and severe (5 or more). Mean arterial pressure (MAP), HR, and SpO_2 were recorded before the administration of butorphanol or normal saline (T0), 2 minutes (T1) later after butorphanol injection, and 2 minutes (T2) later after fentanyl injection. If SpO_2 dropped below 94%, manually assisted mask ventilation with oxygen was applied immediately. Then midazolam (0.05 mg/kg), etomidate (0.3 mg/kg), and rocuronium (0.6 mg/kg) were given to facilitate tracheal intubation.

In a pilot study, the incidence of FIC was 30% in 50 patients. We estimated that 96 patients in each group would be required to detect a 50% reduction in the incidence of cough with 80% power at a significance of $P < 0.05$. We factored in a 10% dropout rate and enrolled 105 patients in each group.

All statistical analyses were performed with GraphPad Prism 5.0 software (GraphPad Software Inc, San Diego, CA). Continuous variables are presented as mean ± standard deviation (SD). Parameters, such as age and weight, were compared among the groups using 1-way analysis of variance (ANOVA) followed by Turkey post-hoc test. MAP, HR, and SpO_2 at different time points were compared by using *2-way ANOVA* followed by Bonferroni post-hoc test. Categorized variables were described as frequency and analyzed by chi-square test or Fisher's exact test. Severity of FIC were presented as ranked data (none, mild, moderate, and severe) and compared by Mann–Whitney U test. P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Demographic characteristics

In the present study, 330 patients were recruited and 15 patients were excluded, as they met the exclusion criteria. Therefore, a total of 315 patients were randomized into 3 groups of 105 each and included in the final analyses (Fig. 1). The demographic characteristics, such as age, gender, body weight, and ASA physical status, were similar among the 3 groups (Table 1).

3.2. Incidence and severity of FIC

As shown in Table 2, the incidence of FIC in group I was significantly higher than that in groups II and III (31.4% vs 11.4% and 3.8%; $P < 0.001$, vs group II; $P < 0.001$, vs group III). Group II had a significantly higher incidence of FIC than group III ($P < 0.05$, vs group III). The severe FIC was not observed in group II and III, but was recoded from 6 patients in group I. The overall severity level of FIC in group I was also much higher than that in group II and III ($P < 0.001$, vs group II; $P < 0.001$, vs group III). Group III had the lowest severity of FIC among all the groups.

3.3. Vital signs

At 2 minutes after fentanyl injection (T2), the MAP was significantly higher in group I than that in group II and group III ($P < 0.01$, vs group II; $P < 0.05$, vs group III) (Fig. 2A). There was no difference in the HR data at 3 time points among the 3 groups (Fig. 2B). SpO_2 of all 3 groups at T2 time point were significantly lower than their levels at T1 time point ($P < 0.001$ in all 3 groups T2 vs T1), but there's no significant difference among 3 groups at T2 time point (Fig. 2C). None of patients suffered from hypoxemia ($SpO_2 < 90\%$) during this study.

4. Discussion

In this study, we found that preemptive infusion of butorphanol 0.015 and 0.03 mg/kg 2 minutes before fentanyl bolus administration effectively and safely reduced the incidence and severity of FIC during general anesthesia induction. Besides, butorphanol showed capacity to prevent the elevated blood pressure that may be induced by cough reflex after fentanyl injection, although the highest MAP was still within safe limits. The drop of SpO_2 in all 3 groups was supposed to be due to fentanyl-induced respiratory depression.

As reported, the incidence of FIC varies over a wide range from 2.7% to 80%.[14,15] Here, we found the incidence of FIC in group I and our former pilot study in which patients did not receive the preemptive butorphanol were both around 30%. The discrepancy among various studies may primarily depend on the doses and concentration of fentanyl injected, the rates, and the routes of injection. However, 2 recently published meta-analysis results support our finding. Kim et al.[16] assessed 28 articles which focused on pharmacological and nonpharmacological prevention of FIC including 5660 patients in intervention groups and 3188 patients in control group. They concluded that the overall incidence of FIC in control group was approximately 31.4%. Another meta-analysis (2370 patients) according to the effects of preemptive small dose fentanyl on the incidence of FIC found that 31.0% of patients without priming fentanyl experienced FIC.[17]

Up to now, the exact mechanism for FIC remains unclear, but some theories have been proposed to explain this phenomenon.

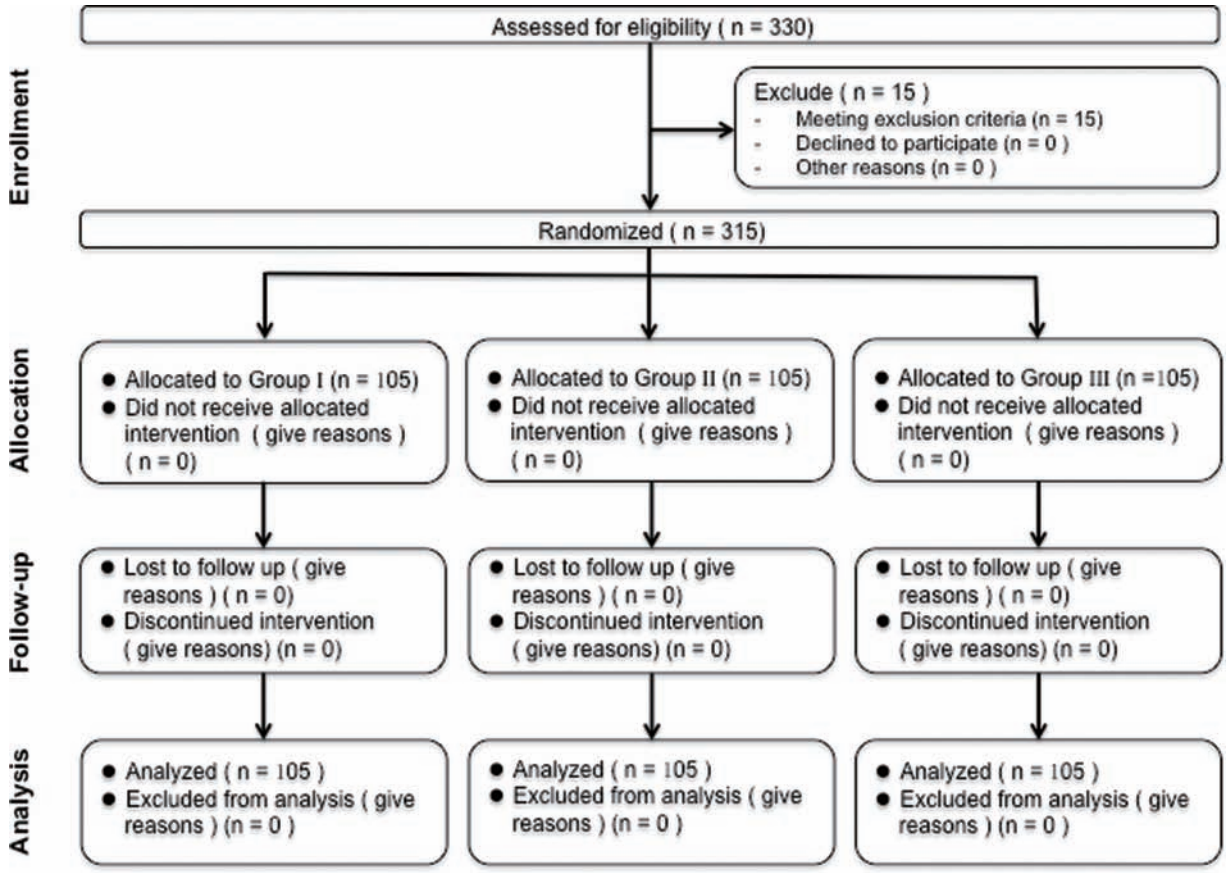

Figure 1. Patient flow (according to the consort chart).

After bolus injection, fentanyl could inhibit central sympathetic outflow, and the relatively vagal predominance may induce cough and reflex bronchoconstriction.[18,19] Besides, fentanyl-induced tracheal smooth muscle constriction could elicit pulmonary chemoreflexes mediated by rapidly adapting receptors (irritant receptors) or vagal C-fiber receptors (also known as J or juxtacapillary receptors) located in close proximity to pulmonary vessels and which then contributes to FIC.[14,20,21] In addition, substances like histamine and neuropeptides, released by an action on prejunctional μ-opioid receptors after fentanyl administration,[22] the sudden adduction of the vocal cords or supraglottic obstruction caused by opioid-induced muscle rigidity,[18] and the relative fluctuation in plasma fentanyl concentration during injection[17] also play important roles in the occurrence of FIC.

According to the possible mechanisms, many pharmacological interventions have been used to prevent FIC, including lidocaine,[23,24] ephedrine,[25] α_2-receptor agonist (clonidine and dexmedetomidine),[26,27] dexamethasone,[28] ketamine,[29] and propofol.[30,31] Though the medicines mentioned earlier could partly reduce the incidence of cough, some unexpected side effects, such as arrhythmia, cardiovascular depression, respiratory depression, bradycardia, and hyper- or hypotension, have occurred during drug administration. However, it is noteworthy that the prototypical agonist-antagonist opioid analgesic agents, such as pentazocine and dezocine showed their high efficacy in reducing the incidence of fentanyl and/or sufentanyl-induced cough without obviously adverse side effects.[8–11]

Butorphanol is another agonist-antagonist opioid with a published affinity for opioid receptors in vitro of 1:4:25 (μ:δ:κ).[32,33] It is proven to be with more potent analgesic effect and a better pharmaceutical formulation and has also been extensively used for perioperative analgesia over the world. What's more, it is also used as the antitussive drug in animals.[12,13] Here, we demonstrated that butorphanol could effectively and safely suppress the FIC with the most prominent

Table 1

Demographic data.

	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*P*
Age, y	39.7 ± 13.8	41.1 ± 14.0	39.3 ± 12.9	0.59
Gender (M/F)	55/50	63/42	57/48	0.51
Weight, kg	63.5 ± 9.6	62.3 ± 9.8	63.3 ± 10.0	0.62
ASA (I/II)	70/35	66/39	75/30	0.42

Values are expressed as the number of patients or mean ± SD. M = male, F = female.

Table 2

Incidence and severity of fentanyl-induced cough.

Severity	Group I (n = 105)	Group II*** (n = 105)	Group III***# (n = 105)
None	72	93	101
Mild	20	11	4
Moderate	7	1	0
Severe	6	0	0
Incidence n, %	33 (31.4%)	12 (11.4%)***	4 (3.8%)***#

Values are expressed as the number of patients or frequency.
Incidence of fentanyl-induced cough: ***$P < 0.001$, compared to group I; #$P < 0.05$, compared to group II.
Severity of fentanyl-induced cough: ***$P < .001$, compared to group I; #$P < 0.05$, compared to group II.

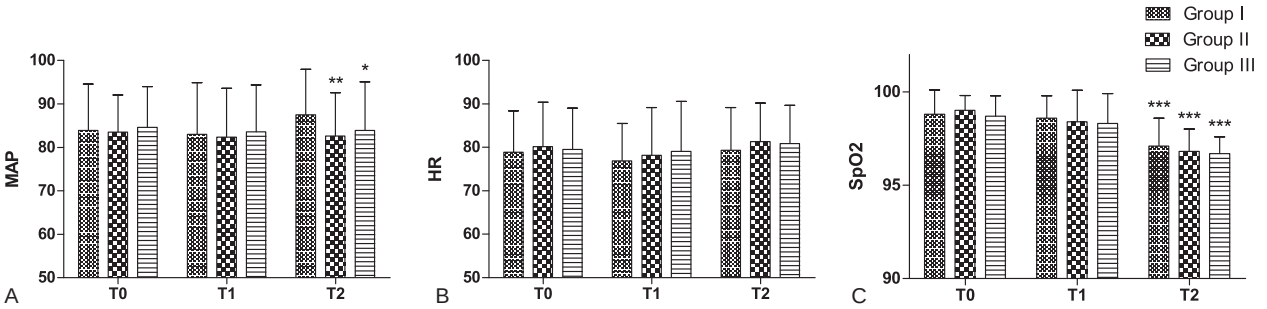

Figure 2. Changes of MAP, HR, and SpO_2 during study period. (A) MAP at different time points. *$P < 0.05$, **$P < 0.01$, compared to group I (B) HR at different time points. (C) SpO_2 at different time points. ***$P < 0.001$, compared to their own levels at T1 time point. T0, time before administration of butorphanol or saline; T1, 2 minutes after butorphanol or saline injection; T2, 2 minutes after fentanyl injection; MAP, mean arterial pressure; HR, heart rate; SpO_2, peripheral capillary oxygen saturation.

effect at a dose of 0.03 mg/kg. We speculate that the possible mechanism of butorphanol suppressing FIC could be as follows: first, butorphanol has an excellent central nervous system penetration due to its high lipid solubility. The preemptive use of butorphanol could inhibit the cough reflex by directly inhibiting the cough center neurons in the medulla. Second, since Butorphanol is a partial μ-receptor agonist, priming use of butorphanol may result in depletion of neurotransmitters in peripheral nerve fibers. Besides, it can also occupy the μ-receptor, which is responsible for cough, preventing the later combination of fentanyl with related μ-receptor. Third, butorphanol may exert its antitussive effects by activating δ- and κ-receptor through central or peripheral mechanisms, which have been demonstrated in rats and guinea pigs.[34–36]

There are 2 limitations in our study. First, the main outcome measures (incidence and severity) were subjective, but we did not find other more accurate and convenient monitoring indicators in the previous clinical studies. Secondly, our study provides evidence for the efficacy of butorphanol in suppressing FIC in clinical practice; but we did not verify the exact mechanisms by which fentanyl induces cough and butorphanol prevents FIC. Hence, more animal and basic experiments are warranted.

In conclusion, we suggest that using a priming dose of butorphanol 0.03 mg/kg is a feasible, effective, and safe method to suppress FIC during the induction of general anesthesia in clinical practice.

Acknowledgments

The authors thank all nursing staff in operating rooms and wards for their efforts and performance during this study.

References

[1] Grell FL, Koons RA, Denson JS. Fentanyl in anesthesia: a report of 500 cases. Anesth Analg 1970;49:523–32.
[2] Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiology 1984;61:731–55.
[3] McCool FD. Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 suppl):48s–53s.
[4] Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. Anesth Analg 2001;92:1442–3.
[5] Uvelin A, Rakic G. Guidelines for prevention of fentanyl-induced cough. Acta Anaesth Scand 2009;53:1228–9.
[6] Ambesh SP, Singh N, Srivastava K. Fentanyl induced coughing caused life-threatening airway obstruction in a patient with arteriovenous malformation of tongue and hypopharynx. Internet J Anesthesiol 2009;20:
[7] Lim KJ, Lee SK, Lee HM, et al. Aspiration pneumonia caused by fentanyl-induced cough—a case report. Korean J Anesthesiol 2013; 65:251–3.
[8] Ai Q, Hu Y, Wang Y, et al. Pentazocine pretreatment suppresses fentanyl-induced cough. Pharmacol Rep 2010;62:747–50.
[9] Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. Pharmacol Rep 2015;67:52–5.
[10] Sun ZT, Yang CY, Cui Z, et al. Effect of intravenous dezocine on fentanyl-induced cough during general anesthesia induction: a double-blinded, prospective, randomized, controlled trial. J Anesth 2011;25:860–3.
[11] Xu Y, Zhu Y, Wang S, et al. Dezocine attenuates fentanyl-induced cough in a dose-dependent manner—a randomized controlled trial. Int J Clin Exp Med 2015;8:6091–6.
[12] Cavanagh RL, Gylys JA, Bierwagen ME. Antitussive properties of butorphanol. Arch Int Pharmacodyn Ther 1976;220:258–68.
[13] Christie GJ, Strom PW, Rourke JE. Butorphanol tartrate: a new antitussive agent for use in dogs. Vet Med Small Anim Clin 1980;75:1559–62.

[14] Bohrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. Anaesthesia 1990;45:18–21.
[15] Tang Q, Qian Y, Zhang Q, et al. Effects of different priming doses of propofol on fentanyl-induced cough during anesthesia induction: a preliminary randomized controlled study. Ups J Med Sci 2010;115:121–4.
[16] Kim JE, Min SK, Chae YJ, et al. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis. J Anesth 2014;28:257–66.
[17] Du BX, Cao L, Zhao WL, et al. Pre-emptive small dose of fentanyl suppresses fentanyl-induced cough: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2014;7:826–36.
[18] Agarwal A, Azim A, Ambesh S, et al. Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. Can J Anaesth 2003;50:297–300.
[19] Lui PW, Hsing CH, Chu YC. Terbutaline inhalation suppresses fentanyl-induced coughing. Can J Anaesth 1996;43:1216–9.
[20] Yasuda I, Hirano T, Yusa T, et al. Tracheal constriction by morphine and by fentanyl in man. Anesthesiology 1978;49:117–9.
[21] Kamei J, Nakanishi Y, Asato M, et al. Fentanyl enhances the excitability of rapidly adapting receptors to cause cough via the enhancement of histamine release in the airways. Cough (London, England) 2013;9:3.
[22] Phua WT, Teh BT, Jong W, et al. Tussive effect of a fentanyl bolus. Can J Anaesth 1991;38:330–4.
[23] Pandey CK, Raza M, Ranjan R, et al. Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. Anesth Analg 2004;99:1696–8.
[24] Gecaj-Gashi A, Nikolova-Todorova Z, Ismaili-Jaha V, et al. Intravenous lidocaine suppresses fentanyl-induced cough in Children. Cough (London, England) 2013;9:20.
[25] Lin CS, Sun WZ, Chan WH, et al. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Can J Anaesth 2004;51:654–9.
[26] Hung KC. The possible mechanism of clonidine to suppress fentanyl-induced coughing. Acta Anaesthesiol Scand 2009;53:1227–8.
[27] Yu J, Lu Y, Dong C, et al. Premedication with intravenous dexmedetomidine-midazolam suppresses fentanyl-induced cough. Irish J Med Sci 2012;181:517–20.
[28] Lin JA, Chen FC, Lee MS, et al. Intravenous dexamethasone pretreatment reduces fentanyl-induced cough. J Formosan Med Associat 2007;106:649–55.
[29] Yeh CC, Wu CT, Huh BK, et al. Premedication with intravenous low-dose ketamine suppresses fentanyl-induced cough. J Clin Anesth 2007;19:53–6.
[30] Firouzian A, Emadi SA, Baradari AG, et al. Can low dose of propofol effectively suppress fentanyl-induced cough during induction of anaesthesia? A double blind randomized controlled trial. J Anaesthesiol Clin Pharmacol 2015;31:522–5.
[31] Sedighinejad A, Naderi Nabi B, Haghighi M, et al. Propofol is effective to depress fentanyl-induced cough during induction of anesthesia. Anesth Pain Med 2013;2:170–3.
[32] Chang KJ, Hazum E, Cuatrecasas P. Novel opiate binding sites selective for benzomorphan drugs. Proc Natl Acad Sci U S A 1981;78:4141–5.
[33] Commiskey S, Fan LW, Ho IK, et al. Butorphanol: effects of a prototypical agonist-antagonist analgesic on kappa-opioid receptors. J Pharmacol Sci 2005;98:109–16.
[34] Kamei J, Tanihara H, Kasuya Y. Antitussive effects of two specific kappa-opioid agonists, U-50,488H and U-62,066E, in rats. Eur J Pharmacol 1990;187:281–6.
[35] Kotzer CJ, Hay DW, Dondio G, et al. The antitussive activity of delta-opioid receptor stimulation in guinea pigs. J Pharmacol Exp Ther 2000;292:803–9.
[36] Karlsson JA, Lanner AS, Persson CG. Airway opioid receptors mediate inhibition of cough and reflex bronchoconstriction in guinea pigs. J Pharmacol Exp Ther 1990;252:863–8.