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ORIGINAL ARTICLE

Effect of intravenous dezocine on fentanyl-induced cough during general anesthesia induction: a double-blinded, prospective, randomized, controlled trial

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Abstract
Purpose To evaluate the suppressive effect of intravenous dezocine on fentanyl-induced cough during the induction of general anesthesia.
Methods A total of 120 patients, American Society of Anesthesiologists (ASA) physical status I–II, were randomized into two equally sized groups ($n = 60$). These two groups were given either intravenous dezocine 0.1 mg/kg or a matching placebo (equal volume of 0.9% saline) 10 min before the induction of general anesthesia. Patients were induced with midazolam 0.1 mg/kg, fentanyl 5 μg/kg, propofol 1–1.5 mg/kg, and suxamethonium 1.5 mg/kg. The injection time of fentanyl was less than 2 s in all patients. The occurrence of cough was recorded 2 min after fentanyl bolus.
Results No patient in the dezocine group had cough, and 42 patients in the control group had cough. This difference was statistically different between these two groups ($P = 0.000$).
Conclusion These results demonstrate that intravenous dezocine 0.1 mg/kg 10 min prior to induction was effective in suppressing fentanyl-induced cough in our patients.

Keywords Fentanyl · Cough · Dezocine · General anesthesia · Suppress

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Introduction

Fentanyl, an opioid analgesic, is widely used as a pre-induction adjunct due to its intense analgesia, short duration of action, and cardiovascular stability, but cough as well as truncal rigidity elicited by fentanyl is undesirable. Cough induced during the induction of general anesthesia has the potential to elevate cerebral, ocular, or abdominal pressure, which may lead to a health-threatening condition in the patients [1]. Although fentanyl-induced cough is transient and not severe in most patients, the severity should not be ignored in patients with pneumothorax, cerebral aneurysm brain trauma, brain hernia, open eye injury, arterial aneurysm resection, and hypersensitive airway disease. Animal experiments have demonstrated that the use of a low-efficacy opioid in association with high-efficacy opioid will not only enhance the analgesic effect but also antagonize a number of undesirable adverse effects, such as pruritus and nausea caused by the higher efficacy opioid [2]. Pre-emptive fentanyl prior to the administration of fentanyl is able to effectively suppress fentanyl-induced cough [3]. Dezocine is an analgesic agent and a full agonist of κ-receptor and partial agonist of μ-receptor without classic μ-receptor dependence. As the effect of dezocine on fentanyl-induced cough is still unknown, we designed a prospective, randomized, double-blinded, and placebo controlled study to investigate the effect of dezocine on fentanyl-induced cough in patients during the induction of general anesthesia.

Patients and methods

Ethical approval for this study was provided by the Ethical Committee of the First Affiliated Hospital of Zhengzhou

University, Zhengzhou, Henan, China. Informed consent was obtained from all patients enrolled in this randomized, prospective, controlled study. A total of 120 American Society of Anesthesiologists (ASA) physical status I–II patients (age range 20–60 years, weight 45–90 kg) scheduled for elective surgery under general anesthesia were enrolled in this study. Exclusive criteria included known allergies, sinus bradycardia, severe neurological, respiratory or cardiovascular diseases, narcotic drug dependence and recent history of opioid application, a history of smoking, hepatic and renal dysfunction, gallbladder surgery, pregnancy, lactation and delivery surgery, upper airway infection within 2 weeks of surgery. Such conditions may cause spontaneous cough.

Patients meeting the inclusive criteria during the preanesthetic evaluation were randomly assigned into two groups of 60 patients each using a computer-generated table of random numbers.

Patients schedule for surgery were unpremedicated and had fasted. Upon arrival at the operating room, patients were cannulated with an intravenous (IV) cannula (22G) on the dorsum of the right forearm. Monitoring of each patient was accomplished by electrocardiogram, non-invasive blood pressure [systolic (SBP) and diastolic blood pressure (DBP)], pulse oximetry (SpO_2), and end-tidal carbon dioxide measurement (M1205A; Philips, Eindhoven, the Netherlands). All patients were randomly assigned to receive either dezocine 0.1 mg/kg or a matching placebo (equal volume of 0.9% saline) 10 min before the induction of anesthesia. The application of anesthesia was standardized in the two groups. The patients were first induced with midazolam 0.1 mg/kg, fentanyl 5 μg/kg, propofol 1–1.5 mg/kg, and suxamethonium 1.5 mg/kg. The injection time of fentanyl was limited to under 2 s; propofol and suxamethonium were administered 2 min later, after the fentanyl bolus. All medications were provided by the hospital pharmacy (dezocine: SN10042021; Yangtze River Pharmaceutical, Co., Jiangsun, China; fentanyl: SN100302 Yichang Humanwell Pharmaceutical Co., Hubei, China), identical, and administered intravenously.

A blinded observer, who had no knowledge of the premedication given to the patients, recorded the occurrences of coughing 2 min after administration of the fentanyl bolus. It has been reported that cough occurs within 1 min of the fentanyl bolus iv [4], so we choose 2 min after the administration of the fentanyl bolus. SBP, DBP, heart rate (HR), and SpO_2 were recorded before the administration of dezocine or normal saline (T0) and 2 min (T1) later after fentanyl injection. Assisted mask ventilation oxygen was applied if desaturation was observed (SpO_2 <89%). Other side effects related to fentanyl and dezocine, such as truncal rigidity and apnea, were also recorded after the fentanyl injection.

All data were reported as the mean ± standard deviation (SD) or as percentages. The demographic data were analyzed with the unpaired Student's t test. Comparison between two groups was performed for overall incidence of cough by Fisher's exact test with Bonferroni correction. General linear model repeated-measures analyses were applied to compare differences of vital signs between groups before and after the fentanyl injection. The software package SPSS ver. 14.0 (SPSS, Chicago, IL) was used for statistical analysis. A $P < 0.05$ was considered to be statistically significant.

Results

All patients completed this study as required by the protocol. The demographic data were compared in both groups, and no statistically significant difference between the two groups was found with regard to sex, age, and weight. (Table 1). The hemodynamic data (BP, HR, and SpO_2) were also simila,r and there was no significant difference between groups in the baseline value or after fentanyl injection (Table 2). No patient in the dezocine group had cough, and 42 patients in the placebo group (0 vs. 70%) had cough; this difference was statistically significant ($P = 0.000$) (Table 3). None of the patients suffered from hypoxemia (SpO_2 <89%), desaturation, apnea, truncal rigidity, or other adverse effects after fentanyl injection.

Discussion

Cough is an intense body reflex irritation, and it may cause instantaneous changes in the internal environment of a patient on perioperative anesthesia. Tweed and Dakin reported cases requiring immediate tracheal intubation for excessive cough prior to the induction of general anesthesia [5]. In our study, dezocine completely suppressed fentanyl-induced cough. The incidence of cough elicited by fentanyl during general anesthesia induction has been reported to vary between 18 and 65% [6]. The incidence of fentanyl-induced cough among our patients was 70%, which may

Table 1 Patient characteristics

Patient characteristics	Dezocine group ($n = 60$)	Placebo group ($n = 60$)	P value
Age (years)	46.6 ± 10.3	48.2 ± 10.6	0.4
Sex (Male/female)	36/24	32/28	0.5
Weight (kg)	63.5 ± 7.6	64.6 ± 9.5	0.5

Values are mean ± SD. No statistical difference was observed between dezocine and placebo groups

Table 2 Changes in vital signs after treatment in both groups

Group	SBP (mmHg)		DBP (mmHg)		HR (bpm)		SpO_2 (%)	
	T0	T1	T0	T1	T0	T1	T0	T1
Dezocine	117.6 ± 17.3	118.5 ± 15.1	69.3 ± 10.4	69.6 ± 13.3	77.7 ± 10.4	76.9 ± 10.6	98.4 ± 1.8	98.8 ± 1.4
Placebo	117.6 ± 14.3	114.3 ± 16.3	72.7 ± 9.6	73.9 ± 11.2	80.63 ± 9.6	79.3 ± 11.0	98.4 ± 1.5	98.3 ± 1.5

SBP Systolic blood pressure, DBP diastolic blood pressure, *HR* heart rate, *SpO_2* pulse oximeter oxygen saturation, *T0* Time before administration of dezocine or normal saline injection, *T1* 2 min after fentanyl injection

No statistical difference was observed between the dezocine and placebo groups

Table 3 Incidence of coughing in both groups

Group	Total (*n*)	Cough (*n*)	Ratio (%)
Dezocine	60	0	0
Placebo	60	42	70

P value = 0.000 (dezocine vs. placebo group)

due to the small sample size in our study and the fast injection of fentanyl. The injection time of fentanyl is an important factor that affects cough frequency [7]. The threshold of fentanyl-induced cough may be readily reached with a rapid intravenous injection. Many factors have been associated with fentanyl-induced cough, such as drug dosage and concentration, order of drug administration, intravenous injection rate and site [8], individual physical condition, age, sex, weight, disease history, smoking, and family genetics. A number of techniques have been applied to reduce the incidence of fentanyl-induced cough, including the use of betamethasone (8.3 vs. 35%), dexamethasone (6.3 vs. 21.3%) [9], ephedrine (21 vs. 65%) [10], lidocaine (13.1%) [11], ketamine (7.2 vs. 21.6%) [12], and propofol (6.7%) [13], a change the order of administering the drugs, the speed of fentanyl administration, and fentanyl concentration. The use of the drugs in these earlier studies was unable to completely prevent fentanyl-induced cough, and some of them are very limited in terms of their clinical application. For example, betamethasone and dexamethasone are steroids and should be used under strict conditions; ephedrine can cause hemodynamic changes; lidocaine does not have a significant influence on the severity of cough; ketamine is scarcely used in adult general anesthesia, especially in patients with hypertension, elevation of intracranial pressure, and intraocular pressure. In a study involving the pre-injection of propofol as a measure to suppress fentanyl-induced cough, the incidence of cough in the propofol group (recommended dose 1.5 mg/kg) was approximately 6.7% [13]. An overdose of propofol may cause fluctuation of hemodynamics. Patients who are sensitive to the effects of muscle relaxants cannot be given vecuronium bromide early, as breathing difficulties may arise. Other research has suggested that prolongation of the effective duration of fentanyl and dilution of the fentanyl dose before administration are not convenient practices in some emergent situations. In our study, dezocine had the effect of analgesia and had a synergistic effect on fentanyl; as such, it was able to completely prevent cough. In a subsequent study, we found that dezocine suppressed the fentanyl induced cough just before the fentanyl bolus, thereby removing the necessity to wait 10 min before administering the fentanyl. Consequently, it may be possible to use dezocine as an advance analgesia. The limitation of the study is we did not compare the severity of cough between the two groups [14] because we observed no cough in dezocine group; therefore we just recorded the incidence of cough despite the severity.

The mechanisms of fentanyl-induced cough have been reported to be opioid receptors [15], C-fiber receptors, rapidly adapting pulmonary stretch receptors, histamine, and the citrate in fentanyl injection fluid.

Dezocine is a new bridge central amino tetralin, a mixed opioid agonist/antagonist analgesic, a completely κ-receptor agonist, and a partial μ-receptor agonist without classic μ-receptor dependence liability. As a result of various countries' drugs admittance system, dezocine may not be accessed in every country and available for use in all hospitals. However, dezocine is widely applied as an advance and postoperative pain analgesic agent in many countries. The results of animal experiments have demonstrated that the use of a low-efficacy opioid in association with a high-efficacy opioid will not only enhance the analgesic effect but also antagonize some of undesirable side effects, such as pruritus and nausea, of the higher efficacy opioid. This double benefit effect may due to the opioid receptors agonized and antagonized. In has been reported that pre-emptive fentanyl 25 μg (0.5 ml) 1 min before the administration of fentanyl 125 or 150 μg significantly reduced the incidence of fentanyl-induced cough in both pre-emptive groups [3.5% for the 125 μg fentanyl group and 7.5% for the 150 μg fentanyl group compared to the saline group (18.5%)]. The frequency along with dosage implies that partial μ receptor agonists did not reach the cough threshold, indicating that partial μ pre-agonized receptors cannot

completely suppress cough. Dezocine therefore suppresses fentanyl-induced cough by other mechanisms.

In the context of fentanyl-induced cough, we speculate that the possible mechanism of dezocine suppressing fentanyl-induced cough could be as follows. (1) dezocine is a partial μ-receptor agonist that either causes no cough or possibly induces cough when above the cough threshold; it also occupies the μ-receptor, preventing the combination of fentanyl with μ-receptor. (2) Dezocine agonizes κ receptors, which in turn antagonize fentanyl-activated μ receptors, thereby inducing cough. (3) Dezocine counteracts the action of fentanyl by a central gating mechanism of cough suppression, predominantly via C-fibers receptors. (4) Dezocine inhibits the release of histamine by antagonizing and suppressing cough reflex. Some researchers have proposed that opioid receptors exist in the brain and spinal cord and that the differences in intensity of the analgesic and side effects of narcotic drugs are related to opioid receptors in different parts of brain. In 1990, Karlsson and his co-workers [16] found that opioid drugs affected μ and κ receptors on guinea pig trachea and bronchial trees, resulting in inhibition of bronchial cough and reflex contraction of the role. In this case, it is not impossible to surmise that opioid receptors also exist in humans and mediate the antitussive effect.

Conclusions

Our results demonstrate that IV dezocine 0.1 mg/kg 10 min before fentanyl is an effective and clinically feasible method for suppressing fentanyl-induced cough during general anesthesia induction.

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References

1. Yu M-S, Kim JY, Kim HY. Intravenous dexamethasone pretreatment reduces remifentanil induced cough. Korean J Anesthesiol. 2011;60(6):403–7.
2. Morgan D, Cook CD, Smith MA, Picker MJ. An examination of the interactions between the antinociceptive effects of morphine and various m-opioids: the role of intrinsic efficacy and stimulus intensity. Anesth Analg. 1999;88:407–13.
3. Hung KC, Chen CW, Lin VCH, Weng HC, Hsieh SW. The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. Anaesthesia. 2010;65(1):4–7.
4. Lui PW, Hsing CH, Chu YC. Terbutaline inhalation suppresses fentanyl-induced coughing. Can J Anaesth. 1996;43(12):1216–9.
5. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. Anesth Analg. 2001;92(6):1442–3.
6. Ambesh SP, Singh N, Gupta D, Singh PK, Singh U. A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study. Brit J Anaesth. 2010;104(1):40–3.
7. Lin JA, Yeh CC, Lee MS, Wu CT, Lin SL, Wong CS. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. Anesth Analg. 2005;101(3):670–4.
8. Chen YM, Chen WT, Liang SW, Gu MN. Intravenous injection rate and site of fentanyl affect the incidence and onset time of fentanyl-induced cough. Nan Fang Yi Ke Da Xue Xue Bao. 2009;29(2):339–40.
9. Lin JA, Chen FC, Lee MS, Horng HC, Cherng CH, Yeh CC, Wong CS. Intravenous dexamethasone pretreatment reduces fentanyl-induced cough. J Formos Med Assoc. 2007;106(8):649–55.
10. Lin CS, Sun WZ, CHan WH, LIn CJ, Yeh HM, Mok MS. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Can J Anaesth. 2005;52(2):207.
11. Pandey CK, Raza M, Ranjan R, Lakra A, Agarwal A, Singh U, Singh RB, Singh PK. Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. Anesth Analg. 2004;99(6):1696–8 (table of contents).
12. Yeh CC, Wu CT, Huh BK, Lee MS, Lin SL, Sheen MJ, Wong CS. Premedication with intravenous low-dose ketamine suppresses fentanyl-induced cough. J Clin Anesth. 2007;19(1):53–6.
13. Tang Q, Qian Y, Zhang Q, Yang J, Wang Z. 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(2):121–4.
14. Cho HB, Kwak HJ, Park SY, Kim JY. Comparison of the incidence and severity of cough after alfentanil and remifentanil injection. Acta Anaesthesiol Scand. 2010;54(6):717–20.
15. Gharagozlou P, Demirci H, Clark JD, Lameh J. Activation profiles of opioid ligands in HEK cells expressing delta opioid receptors. BMC Neurosci. 2002;3:19.
16. 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(2):863–8.